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The harmful health effects of recreational ecstasy: a systematic review of observational evidence

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Abstract

The harmful health effects of recreational ecstasy: a systematic review of observational evidence

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Objectives: To investigate the harmful health effects of taking ecstasy (3,4-methylenedioxymethamphetamine, MDMA) for recreational purposes.
Data sources: MEDLINE, EMBASE, PsycINFO and Web of Knowledge were searched. Additional information on deaths was collected from the General Mortality Register (GMR) and the Special Mortality Register collated by the National Programme on Substance Abuse Deaths (np-SAD).
Review methods: Studies were categorised according to design, with systematic research syntheses (Level I evidence) the most valid and least open to bias. Where Level I evidence was not available, controlled observational studies (Level II evidence) were systematically reviewed. If neither Level I nor Level II evidence was available, uncontrolled case series and case reports (Level III evidence) were systematically surveyed. Data were extracted by one reviewer and a sample checked by a second. The heterogeneity of Level II evidence was addressed by undertaking stratified analyses for current and former ecstasy users and comparing them either with control groups using other illegal drugs but not ecstasy (polydrug controls) or with controls naïve to illegal drugs (drug-naïve controls). Statistical heterogeneity was minimised by using a random-effects model throughout and investigated using study-level regression analysis (metaregression).
Results: Five Level I syntheses were identified; for each it was difficult to ascertain the exact methods adopted and evidence included. Small but significant deficits for ecstasy users compared to controls were reported in areas relating to attention, memory, psychomotor speed, executive systems functioning, and self-reported depressive symptoms. Data from Level II studies were directly pooled for seven individual outcomes, suggesting that ecstasy users performed worse than controls on common measures of immediate and delayed verbal recall (RAVLT, RBMT, digit span). No difference was seen in IQ (NART). The 915 outcome measures identified in Level II studies were analysed in broad domains: immediate and delayed verbal and visual memory, working memory, two measures of attention, three measures of executive function, perceptual organisation, self-rated depression, memory and anxiety, and impulsivity measured objectively and subjectively. Ecstasy users performed significantly worse than polydrug controls in 13/16 domains and significantly worse than drug-naïve controls in 7/12 domains for which sufficient data were available. The largest, most consistent exposure effects were seen in meta-analyses of memory (especially verbal and working memory, with less marked effects seen in visual memory). Former ecstasy users frequently showed deficits that matched or exceeded those seen amongst current users. At aggregate level, the effects do not appear to be dose-related, but are variably confounded by other drug use, particularly alcohol. Of Level III evidence, in the 10 years to 2006, the np-SAD and the GMR recorded an average of around 50 drug-related deaths per year involving ecstasy; it was the sole drug implicated in around 10 cases per year. Retrospective case series, based on hospital emergency department records, reported a death rate of 0–2% from emergency admissions related to ecstasy. Two major syndromes are most commonly reported as the immediate cause of death in fatal cases: hyperthermia and hyponatraemia.
Conclusions: A broad range of relatively low-quality literature suggests that recreational use of ecstasy is associated with significant deficits in neurocognitive function (particularly immediate and delayed verbal

memory) and increased psychopathological symptoms. The clinical significance of the exposure effect in individual cases will be variable but, on average, deficits are likely to be relatively small. Ecstasy is associated with a range of acute harms but appears to be a rare cause of death in isolation.

Contents

Glossary and list of abbreviations

Glossary

Aneurysm Localised, blood-filled dilatation of a blood vessel.

Angiitis Inflammation of blood vessels.

Anuria Absence of urine output.

Arteriovenous Relating to the blood vessels – arteries and veins.

Bruxism Tooth grinding.

Co-drug use Use of more than one drug on the same occasion.

Diplopia Double vision.

Disseminated intravascular coagulopathy A pathological process whereby systemic blood starts to coagulate throughout the body.

Ecological fallacy A recognised error in the interpretation of statistical data, whereby inferences about the nature of individuals are based solely upon aggregate statistics collected for the group to which those individuals belong.

Glaucoma Increased pressure within the eye.

Hemiparesis Paralysis affecting one side of the body.

Heterogeneity Difference in nature.

Hyperpyrexia Exceptionally high fever.

Hyperthermia Abnormally high body temperature, heat stroke.

Hyponatraemia Decrease in blood sodium concentration below the normal range.

Keratopathy Damage to, or dysfunction or abnormality of the cornea.

Mediastinum The central compartment of the thoracic cavity, containing the heart.

Myopia Short-sightedness.

Necrosis Cell death.

Neurocognitive deficit Reduction or impairment of mental processes relating to thinking, learning or judgement.

Nystagmus Involuntary rapid eyeball movements.

Oedema Excessive fluid in the tissue of the body causing swelling.

Pneumomediastinum Air or gas in the mediastinum, usually resulting from a ruptured bleb on the surface of the lung.

Pneumopericardium Air between the heart and the membrane around it (pericardium).

Pneumothorax Air or gas in the space around the lungs, usually resulting from an air leak from the lungs and leading to lung collapse.

Polydrug use Use of multiple types of drugs.

Psychodysleptic Hallucinogenic.

Psychopathology Behaviours or experiences that are indicative of psychological impairment.

Psychosis Experience of loss of contact with reality which may be marked by hallucinations, agitated behaviour and delusions.

Rhabdomyolysis The destruction of skeletal muscle cells.

continued

Snowball sampling A sampling method whereby initial contacts recruit others to take part in the study, and so on.

Sympathomimetic Mimicking the effects of the sympathetic nervous system.

Tachycardia Rapid heart beat.

Tentorial herniation Brain tissue pushing through the tentorium as a result of brain swelling.

Trismus Disturbance of nerves leading to spasm in jaw muscles and difficulty opening the mouth.

Wolff–Parkinson–White syndrome A heart condition involving pre-excitement of the ventricles.

Abbreviations

A&E	accident and emergency
ANCOVA	analysis of covariance
ARF	acute renal failure
CI	confidence interval
DIC	disseminated intravascular coagulopathy
DRD	drug-related death
EM	effect measure
ETLD	estimated total lifetime dose
ETLE	estimated total lifetime exposure
GHB	gamma-hydroxybutyric acid
GMR	General Mortality Register
HTA	Health Technology Assessment
IQ	intelligence quotient
LSD	lysergic acid diethylamide, 'acid'
MA	methamphetamine, 'crystal meth'
MBDB	3,4-methylenedioxy-phenyl-*N*-methylbutanamine
MDA	3,4-methylenedioxyamphetamine
MDEA	3,4-methylenedioxy-*N*-ethyl amphetamine, 'Eve'
MDMA	3,4-methylenedioxy-methamphetamine, ecstasy
MOOSE	meta-analysis of observational studies in epidemiology
np-SAD	National Programme on Substance Abuse Deaths
OR	odds ratio
PMA	paramethoxyamphetamine
REM	rapid eye movement
SD	standard deviation
SMD	standardised mean difference
WMD	weighted mean difference
XTC	ecstasy

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table. However, please note that, because of their large number, all abbreviations relating to outcome measures from contributing studies are defined in Appendix 5.

Executive summary

Background

Street drugs known as 'ecstasy' have been sold for about 20 years in the UK. The active substance that such tablets contain – or purport to contain – is 3,4-methylenedioxymethamphetamine (MDMA). Shortly after consumption, MDMA releases chemicals in the brain that tend to bring about a sense of euphoria, exhilaration and increased intimacy with others. It is thought to be the third most commonly used illegal drug in the UK after cannabis and cocaine, with estimates suggesting that between 500,000 and 2 million tablets are consumed each week. Most people who take ecstasy also use other legal and illegal drugs, sometimes at the same time. Ecstasy is commonly taken in nightclubs and at parties and is very often associated with extended sessions of dancing.

Along with the pleasurable effects sought by users of MDMA, it has become clear that the drug can cause a range of unintended harms. In the short term, a range of adverse events have been reported – some fatal – and consumption of MDMA may also have long-term consequences, especially with regard to users' mental health.

Objectives

This review aims to address the question: 'What are the harmful health effects of taking ecstasy (MDMA) for recreational use?' It does not examine the harmful indirect and/or social effects, such as effects on driving and road traffic accidents and the consequences of any effect MDMA may have on sexual behaviour.

Methods

The following databases were searched using a comprehensive search syntax: MEDLINE, EMBASE, PsycINFO (run 19 September 2007) and Web of Knowledge (run 7 October 2007). The search outputs were considered against pre-specified inclusion/exclusion criteria; the full text of all papers that could not confidently be excluded on title and abstract alone was then retrieved and screened. Only studies published in English were included. Meeting abstracts were included only if sufficient methodological details were given to allow appraisal of study quality. Studies were categorised according to a hierarchy of research design, with systematic research syntheses (Level I evidence) being preferred as the most valid and least open to bias. Where Level I evidence was not available, controlled observational studies (Level II evidence) were systematically reviewed. If neither Level I nor Level II evidence was available, uncontrolled case series and case reports (Level III evidence) were systematically surveyed. Data extraction was undertaken by one reviewer and a sample checked by a second.

Synthesising Level II evidence posed substantial challenges due to the heterogeneity of the included studies, the number and range of outcome measures reported, the multiplicity of comparisons (differing ecstasy exposures, differing comparator groups) and outcomes, repeated measures and the observational nature of the data. Analyses were stratified for current and former ecstasy users, with separate analyses for control groups using other illegal drugs but not ecstasy (*polydrug controls*) or controls naïve to illegal drugs (*drug-naïve controls)*. Random-effects meta-analyses were used throughout. Heterogeneity was also explored through study-level regression analysis (meta-regression). Where a sufficient number of studies had reported identical outcomes, they were meta-analysed on their original scale. Other outcome measures were grouped into broad domains and effect sizes expressed as standardised mean differences in order to combine data derived from multiple instruments. Objective and self-reported outcome measures within each domain were analysed separately.

For the Level III evidence, only narrative synthesis was possible.

Results

Of 4394 papers identified by our searches, 795 were reviewed in full and 422 met the inclusion

criteria. Five systematic syntheses, 110 controlled observational studies and 307 uncontrolled studies were included. The controlled observational studies exclusively investigated the chronic harms, mainly neurocognitive and psychopathological, associated with ecstasy use. Sixteen case series based on national and regional registries and databases were concerned with deaths from ecstasy (nine were UK based). Additional information on deaths was available from the General Mortality Register (GMR) and the Special Mortality Register collated by the National Programme on Substance Abuse Deaths (np-SAD). The remaining case series and case reports concerned both fatal and non-fatal acute harms.

Most of the included studies were small and subject to biases in selection of subjects and controls, measurement and reporting of confounders and outcomes.

Previous research syntheses (Level I evidence)

For each identified Level I synthesis, it was difficult to ascertain the exact methods adopted and evidence included. Three reviews reported worse performance for ecstasy users compared to controls in a variety of neurocognitive domains (attention, verbal learning and memory, non-verbal learning and memory, motor/psychomotor speed, executive systems functioning, short- and long-term memory). A fourth study reviewed self-reported depressive symptoms and found that ecstasy users had increased levels compared to controls. The final synthesis was primarily concerned with the acute intoxication effects of ecstasy rather than health harms. In all analyses, the effect sizes seen were considered to be small.

Controlled observational studies (Level II evidence)

Of the 110 controlled observational studies included, there was one prospective study, the Netherlands XTC Toxicity (NeXT) study, which recruited a cohort of participants likely to start using ecstasy and followed them for a year. Those who started using ecstasy were then compared to a group of matched controls who had remained ecstasy-naïve. Ecstasy-exposed participants had poorer performance in some memory tests, although the absolute test scores for both cohorts were comfortably within the normal range. Other tests suggested an association between ecstasy exposure and certain aspects of sensation-seeking, but there was no evidence of an effect on depression or impulsivity. The cumulative dose of ecstasy consumed was small (median 3–6 tablets).

The remaining Level II evidence consisted of cross-sectional studies only. Data were directly pooled for seven individual outcomes. Six were common measures of immediate and delayed verbal recall, in which ecstasy users performed significantly worse than polydrug controls. Effect sizes appeared to be small, with the mean scores for each group falling within the normal range for the instrument concerned. No difference was seen between ecstasy users and polydrug and drug-naïve controls in the remaining measure, IQ.

A total of 915 outcome measures were grouped into broad outcome domains as suggested in the literature and after consultation with expert advisers. For 16 of these meta-outcomes, there were sufficient data for meta-analysis: immediate and delayed verbal and visual memory, working memory, sustained and focused attention, three measures of executive function (planning, response inhibition and shifting), perceptual organisation, self-rated depression, memory, and anxiety and impulsivity measured objectively and subjectively. Ecstasy users performed significantly worse than polydrug controls on all outcome domains with the exception of executive function (response inhibition and shifting) and objective measures of impulsivity. Fewer comparisons were possible with drug-naïve controls, with statistically significant effects seen for verbal and working memory and self-rated measures of depression, memory and impulsivity. With both control groups, former ecstasy users frequently showed deficits that matched or exceeded those seen among current users.

The small effect sizes seen were not consistently modified by any study-level demographic variables. There was little evidence of a dose–response effect: studies reporting heavier average use of ecstasy did not provide more extreme effect measures than those consisting of lighter users, and there was no demonstrable effect of length of abstinence from ecstasy. When assessing the impact of inter-arm differences on results, no consistent effect was seen for imbalances in age or gender. However, in several cases, it appeared that imbalances in intelligence between cohorts may have been important. Use of other drugs also appeared to modify effects: alcohol consumption proved the most consistent effect modifier, with increased exposure in ecstasy-exposed populations apparently reducing the magnitude of deficits across a range of neurocognitive outcomes.

For the remaining outcome domains, there were insufficient data for quantitative synthesis and the results were summarised narratively. For psychopathological symptoms, there was a significant deficit for ecstasy users compared to polydrug controls in the obsessive–compulsive domain only, with greater deficits seen in comparison to drug-naïve controls. In a few studies, ecstasy users have been shown to have higher levels of subjectively rated aggression than drug-naïve controls. It was not possible to draw clear conclusions about the possible effects of ecstasy consumption on dental health, loneliness, motor function or sleep disturbance.

Case series and case reports (Level III evidence)

Registry data from the np-SAD and GMR are not directly comparable due to differences in data sources and recording of drug use. The GMR (1993–2006) suggests that there were, on average, 17 deaths a year where ecstasy was recorded as the sole drug involved (2.5% of all deaths ascribed to a single drug) and another 33 per year where it was reported as co-drug use. Ecstasy-associated deaths appear to have increased up to 2001 but to have stabilised thereafter. In the 10 years to 2006, the np-SAD recorded an average of 50 drug-related deaths in which ecstasy was present (69 in 2006; 5% of the total for the year). Ecstasy was believed to be the sole drug implicated in an average of 10 deaths annually over the same time period. According to this registry, the typical victim of an ecstasy death is an employed white male in his twenties, who is a known drug user co-using a number of other substances. Nearly half of ecstasy-related deaths occur on a Saturday or Sunday night.

Published case series and case reports document a wide range of fatal and non-fatal acute harms, often very selectively. Two major syndromes are most commonly reported as the immediate cause of death in fatal cases: hyperthermia (with consequences including disseminated intravascular coagulation, rhabdomyolysis and acute liver and renal failure) and hyponatraemia (commonly presenting with confusion and seizures due to cerebral oedema). Ecstasy users presenting with hyponatraemia have invariably consumed a large amount of water. We found 41 deaths relating to hyperthermia reported in the literature and 10 from hyponatraemia (all women).

Other acute harms associated with fatal cases include cardiovascular dysfunction, neurological dysfunction (seizures and haemorrhage) and suicide. Acute renal failure and subacute liver failure can occur without association with hyperthermia. All these presentations were also seen in non-fatal cases, alongside an additional range of symptoms including acute psychiatric effects, urinary retention and respiratory problems including pneumothorax and pneumomediastinum.

There are difficulties in estimating taken dose of MDMA from the available literature, and it is not clear why some people seem to have acute, even fatal, reactions to doses that are commonly tolerated in others.

Discussion

The evidence we identified for this review provides a fairly consistent picture of deficits in neurocognitive function for ecstasy users compared to ecstasy-naïve controls. Although the effects are consistent and strong for some measures, particularly verbal and working memory, the effect sizes generally appear to be small: where single outcome measures were pooled, the mean scores of all participants tended to fall within normal ranges for the instrument in question and, where multiple measures were pooled, the estimated effect sizes were typically in the range that would be classified as ‘small’.

However, there are substantial shortcomings in the methodological quality of the studies analysed. Because none of the studies was blinded, observer or measurement bias may account for some of the apparent effect. There is a suggestion of publication bias in some analyses, and we saw clear evidence of selective reporting of outcomes.

Selection bias is an inevitable problem: due to the observational nature of all relevant evidence, there is no guarantee that the cohorts being compared were not subject to differences in areas other than exposure to ecstasy. This effect will have been exaggerated in those studies comparing ecstasy-exposed participants to drug-naïve controls; in these instances, it is impossible to isolate the effect of ecstasy exposure from the impact of other substances. Within-study imbalances in intelligence and the use of other substances, particularly alcohol, appeared to explain some of the effects seen. We suggest that the apparently beneficial effect of alcohol consumption may be explained in two ways: either alcohol may mitigate the hyperthermic effects of ecstasy in the acute setting, attenuating damage to the brain, or ecstasy users

who co-use alcohol may represent a population of more casual ecstasy takers than those who tend not to drink.

Although the NeXT study suggests that small deficits in memory may be secondary to ecstasy exposure, all other included studies were cross-sectional in nature; without evidence of the temporal relationship between exposure and outcome, it is difficult to draw any causal inferences.

We did not find any studies directly investigating the quality of life of participants, and we found no attempts to assess the clinical meaningfulness of any inter-cohort differences. The clinical significance of any exposure effect is thus uncertain; it seems unlikely that these deficits significantly impair the average ecstasy user's everyday functioning or quality of life. However, our methods are unlikely to have identified subgroups that may be particularly susceptible to ecstasy. In addition, it is difficult to know how representative the studies are of the ecstasy-using population as a whole. Generalising the findings is therefore problematic.

Ecstasy is associated with a wide range of acute harms, but remains a rare cause of death when reported as the sole drug associated with death related to drug use. Hyperthermia and hyponatraemia and their consequences are the commonest causes of death, but a wide range of other acute fatal and non-fatal harms are reported. Due to the poor quality of the available evidence, it is not possible to quantify the risk of acute harms in any meaningful way.

Research recommendations

Large, population-based, prospective studies are required to examine the time relationship between ecstasy exposure and neurocognitive deficits and psychopathological symptoms.

Further research synthesis of the social and other indirect health harms of ecstasy would provide a more complete picture. Similar synthesis of the health harms of amphetamines generally would provide a useful comparison.

Future cross-sectional studies will only add to the evidence-base if they are large, as representative as possible of the ecstasy-using population, use well-validated outcome measures, measure outcomes as objectively as possible with researchers blind to the ecstasy-using status of their subjects, report on all outcomes used, and provide complete documentation of possible effect modifiers. Cohorts should be matched for baseline factors, including IQ and exposure to alcohol.

The heterogeneity of outcome measures used by different investigators is unhelpful: consensus on the most appropriate instruments to use should be sought. Investigators should collect data directly reflecting the quality of life of participants and/or attempt to assess the clinical meaningfulness of any inter-cohort differences.

A registry of adverse events related to illegal intoxicants presenting to medical services (akin to the 'yellow card' system for prescription medicines) would enable useful estimation of the incidence of harmful effects of ecstasy in comparison to other substances.

Future case reports of acute harms of ecstasy are unlikely to contribute valuable information to the evidence-base. Where novel findings are presented, care should be taken to report toxicological findings confirming the precise identity of the substance(s) consumed by the individual(s) in question.

Chapter 1
Aims and background

Review question

What are the harmful health effects of taking 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) for recreational use?

Pharmacology

'Ecstasy' is the common street-name for drugs that contain – or purport to contain – 3,4-methylenedioxymethamphetamine (MDMA) as their active ingredient. Following the convention of Gowing *et al.*,[1] the term *ecstasy* is used here to denote the drug as it is sold on the street (with composition unknown), whereas MDMA refers to the known chemical substance.

MDMA is a synthetic chemical belonging to the amphetamine family. Several chemically closely related substances are also commonly used as recreational drugs:

- amphetamine ('speed', 'whizz')
- methamphetamine (MA; 'crystal meth')
- paramethoxyamphetamine (PMA)
- 3,4-methylenedioxyamphetamine (MDA)
- 3,4-methylenedioxy-*N*-ethylamphetamine (MDEA; 'Eve')
- 3,4-methylenedioxy-phenyl-*N*-methylbutanamine (MBDB).

Drugs sold as 'ecstasy' frequently contain one or more of these substances, instead of or in addition to MDMA.[2] Another street-drug, gamma-hydroxybutyric acid (GHB) is colloquially known as 'liquid ecstasy', despite being pharmacologically very different from this group. GHB is outside the scope of this review.

The intended effects for which ecstasy users take the drug are described in terms of euphoria, exhilaration and a sense of increased intimacy and empathy with others,[3] effects that have been reproduced by administration of MDMA in laboratory conditions.[4] The neuropharmacological mechanisms by which these effects are produced involve the release of extracellular serotonin (5-HT) and dopamine,[5] neurotransmitters that are commonly associated with the mood and pleasure systems of the brain.

On ingestion, MDMA is rapidly absorbed and first effects are felt 30–60 minutes later, peaking at 60–120 minutes.[6,7] Psychoactive effects last for 2 to 4 hours although MDMA remains detectable in the blood much longer, with a half-life of 6 to 8 hours.[6]

In controlled conditions in humans, cardiovascular effects are evident at doses of MDMA of 1.0 mg/kg or higher.[6] Heart-rate rises to a peak of an average of 20–30 beats per minute higher than baseline approximately an hour after consumption of doses similar to those taken recreationally.[8–10] Blood pressure increases over a similar period: systolic blood pressure rises by 25–40 mmHg and diastolic blood pressure by 10–20 mmHg.[8–10] Body temperature also rises (by 0.3–1.0°C), but this effect is less immediate, with a peak several hours after consumption.[8,10,11] Body temperature increase is related to ambient temperature, which may be more pronounced in club settings.[6] These responses mimic those of the sympathetic nervous system, and may be exacerbated by the environmental conditions under which ecstasy is typically taken – in clubs or parties, with loud music, flashing lights and long periods of dancing.[12] The apparently non-linear nature of MDMA pharmacokinetics has been emphasised; blood concentrations of MDMA rise disproportionately as dosage is increased.[13]

History

The first documentary record of the synthesis of MDMA is the 1912 German patent application of Merck pharmaceuticals, but there is no record of MDMA being tested in humans until 1960, and no commercial application was identified for the substance by Merck, or any other manufacturer.[14] In the 1970s, some use was made by mental-health professionals in west coast USA to enhance empathy, lower defensive barriers and enhance intimacy among people in psychotherapy.[7] Following very sporadic reports in the 1970s, recreational use of MDMA became more widespread during the 1980s.[15] The term 'ecstasy'

first appeared in print in reference to MDMA in 1985[16] and in the British media in 1987.[17]

The US Drug Enforcement Administration classified MDMA as a Schedule 1 controlled substance with effect from 1 July 1985.[18] In the UK, it had already been criminalised; a statutory instrument of 1977, without naming MDMA in particular, categorised all ring-substituted phenethylamines as Class A substances under the Misuse of Drugs Act,[19] a classification that has remained in place.

In the late 1980s and early 1990s, consumption of ecstasy became strongly associated with a widespread culture of dance parties ('raves'),[20] characterised by loud music, extensive light shows and marathon dancing sessions.[21] As the 1990s progressed, ecstasy retained its strong association with dance music, although the scene moved into nightclubs, partly as a result of legislation that sought to prevent raves taking place.[22]

Administration, purity, dose and price

Ecstasy is usually taken orally in pill form. The price of ecstasy has reduced dramatically over recent years, from an average of more than £15 per tablet in 1993 to around £5 in 2003.[23] Most recent figures show that the trend is continuing, with a median price of £3 per tablet in 2006, although prices vary regionally and may be as little as £1.[24] Over a similar period, the average MDMA content of a tablet has also reduced – though not to the same degree – falling from 100 mg in 1993 to approximately 75 mg in 2001.[25]

Most ecstasy used in the UK is sourced from the Netherlands or Belgium.[26] Ecstasy tablets as sold on the street contain a variable amount of MDMA, and tablets which look the same, sharing logos, may have very different compositions in terms of the amount and type of drug they contain.[27] Analysis of the content of drugs purporting to be ecstasy tablets seized by the police in 2006 showed the amount of MDMA ranging from none to around 120 mg.[27] MDMA was the main drug in the vast majority of cases, but other active substances were dominant in a small proportion of tablets (MDEA 0.04%, MDA < 0.01%, other amphetamines 0.2%, piperazines 1.5%). Some tablets also contain MDEA, MDA or amphetamine in addition to MDMA. Ecstasy tablets may also be 'cut' with unrelated substances. Some of these are pharmacologically weak (e.g. caffeine, paracetamol – 0.06% of tablets seized in 2006 contained no controlled drug[26]); however, there have also been reports of stronger psychoactive substances (e.g. atropine, opiates, phenylbutanamine and dextromethorphan).[2] In 2004, it was suggested that, following a period in the 1990s during which ecstasy tablets were relatively unlikely to contain MDMA as their sole active ingredient, tablets had become rather more 'pure' at around the turn of the millennium.[2] One US source suggests that any such effect may have been short lived: tablets analysed in 2005–7 appeared to have approximately a one-in-three chance of containing only MDMA, MDMA along with other active ingredients, or no MDMA at all.[27] Such variations in dose, along with difficulties in obtaining accurate self-reported consumption, cause difficulties in estimating lifetime use, although many studies attempt to do this.

Usage

In the UK, reported MDMA consumption has remained relatively stable over the past decade, with around 2% of 16–59-year-olds reporting ecstasy use in the preceding 12 months.[28] Use is higher among young people, with a 1996 meta-analysis of general population surveys about use among 16–24-year-olds suggesting that 7% [95% confidence interval (CI) 6.1–7.8] had used ecstasy in the previous year, and 3% (95% CI 2.4–3.6) had used it in the previous month.[29] This makes it the third most used illegal drug in the UK after cannabis and cocaine. Among people regularly attending raves and nightclubs, the number of people ever having used ecstasy may be as high as 80–90%.[30,31]It has been estimated that somewhere between 500,000 and 2 million doses of MDMA are consumed each week in the UK.[32]

The overwhelming pattern of ecstasy usage is as part of polydrug consumption (use of more than one drug) and co-use (mixed consumption of two or more drugs on the same occasion).[31,33] In a 2003 survey of UK users (recruited through an advertisement in a dance music publication), ecstasy-using respondents also reported extensive concomitant use of alcohol (88% of users reported consumption on one or more occasions in conjunction with ecstasy), amphetamines (83%), cannabis (82%), cocaine (58%) and amyl nitrate (51%), and there was also some use of lysergic acid diethylamide (LSD), ketamine, fluoxetine, crack cocaine, herbal highs and sildenafil. In addition,

various substances were used in the 'comedown' period following ecstasy consumption, most notably cannabis (82%), alcohol (60%), benzodiazepines (18%) and heroin (2%).

As a result of these factors, together with the unknown composition of pills bought as ecstasy, it is not possible to isolate exposure to MDMA in particular in any individual history or in characteristics across cohorts. Even if there were such a thing as an identifiable group of individuals whose ecstasy consumption alone distinguished them from the general population, it would still be impossible to ascertain to which chemicals they had been exposed, and at what dosage.

Safety

Reports from investigators assessing the psychotherapeutic potential of MDMA in 1986 suggested that the drug was 'apparently physically safe', despite some 'undesirable' effects.[34] Within a year of such claims, the first reports of ecstasy-related deaths appeared in the medical literature.[35] In the UK, the first reported fatalities came in 1991.[36,37] At around the same time, concerns about long-term neuropsychiatric sequelae of ecstasy use began to be expressed in the popular press.[38] The issue of ecstasy safety made a dramatic impression on the popular imagination with the death of Leah Betts, who died after taking a single ecstasy tablet during her eighteenth birthday party in late 1995. However, it has been suggested that fatalities related to ecstasy use receive a disproportionate amount of attention in the media, particularly if the victim is young and female.[39] An assessment of the number of newspaper reports of drug-related deaths in Scotland in the 1990s compared to Registrar General records of deaths approached a 1 : 1 ratio for ecstasy, while for other drugs the ratio was much higher (for example, for heroin there was one newspaper report for every five deaths; for cocaine 1 : 8; for amphetamines 1 : 3; and for paracetamol 1 : 265).[39]

This review assesses the published evidence of the incidence and impacts of adverse health effects of recreational consumption of MDMA.

Chapter 2
Methods

Review methods

The review proceeded according to a prespecified protocol, which is reproduced in full as Appendix 2. Departures from the planned protocol are acknowledged in the following description of methods. Except where otherwise specified, the general methods of the review followed the guidance on the conduct of systematic reviews published by the Centre for Reviews and Dissemination.[40]

Identification of evidence

The search strategy comprised the following main elements:

- searching of electronic databases
- contact with experts in the field
- scrutiny of bibliographies of retrieved papers.

Search strategy for electronic databases

A comprehensive search syntax using indexed keywords (e.g. MeSH, EMTREE) and free-text terms was developed. The search strategy is shown in full in Appendix 3.

Databases searched

The following electronic databases were searched: MEDLINE, EMBASE and PsycINFO (all via DIALOG DATASTAR); Web of Knowledge.

Inclusion of relevant evidence

The outputs of searches were considered against the prespecified inclusion/exclusion criteria, with a sample of citations screened by a second reviewer, to appraise the validity of assessment. Studies that could confidently be identified as not meeting eligibility criteria on the basis of title and abstract were excluded. The full texts of all other papers were obtained, and assessed to ascertain whether they fulfilled the inclusion criteria. As a result of the volume of material retrieved, it was not possible to satisfy our protocol requirement that each potentially relevant paper would be reviewed for inclusion by two reviewers; however, a sample of inclusion decisions was checked by a second reviewer, with good agreement.

Inclusion/exclusion criteria

The relevance of all evidence was appraised with respect to the following criteria:

Population

Included:

- Users of recreational drugs in the UK or in populations relevant to the UK.

Excluded:

- Animal studies.
- Non-drug-using volunteers enrolled in prospective research.

Exposures

Included:

- Recreational use of substances shown to or believed by the investigator(s) to contain MDMA.

Excluded:

- Use of street drugs shown not to or believed by the investigator(s) not to contain MDMA, whether referred to as 'ecstasy' or not.
- Therapeutic use of MDMA.
- Generic drug-using populations in which it is not possible to isolate a subgroup with exposure to MDMA in particular.

Comparators

Where comparative evidence was reviewed, studies with comparator arm(s) meeting the following characteristics were considered eligible:

Included:

- Recreational users of drugs other than MDMA.
- Non-drug-users.

Outcomes

Included:

- Death.
- Acute, clinically observable health harms.
- Long-term, clinically observable health harms.

Excluded:

- Surrogate measures of harm (e.g. neuroimaging studies, biochemical markers), where there is no explicit correlation to observed effect.

- Biochemical indices of MDMA consumption (e.g. testing for MDMA use in blood or hair samples).
- Studies reporting therapeutic measures for adverse events without providing data on individuals suffering such complications.
- Subjective measures of psychostimulation (i.e. studies of the drug's intended short-term intoxicative effects).
- Indirect harms, e.g.
  - accidental injury where ecstasy consumption is detected/implicated
  - health consequences of high-risk sexual behaviour contributed to by ecstasy consumption
  - birth defects secondary to maternal exposure to MDMA.

Papers in languages other than English

Only studies published in English were included in the review.

Meeting abstracts

Reports published as meeting abstracts were included in the review only if sufficient methodological details were reported to allow critical appraisal of study quality.

Methods of analysis/synthesis

General approach

Initially, all included evidence was reviewed to establish a taxonomy of reported outcomes. For each outcome, the available evidence was categorised in a predefined hierarchy of research design:

- *Level I* Pre-existing systematic research syntheses (systematic reviews, meta-analyses, syntheses of qualitative data)
- *Level II* Controlled observational studies (cohort studies, case–control studies, etc.)
- *Level III* Uncontrolled observational evidence (case reports and case series).

Where adequately designed and conducted, Level I evidence was preferred.

Where no adequate Level I evidence was identified for a given outcome, any Level II evidence was systematically reviewed. The quality of research was appraised and described, and findings were reported. Where possible and appropriate, quantitative synthesis of study outcomes was also undertaken (for methods, see Quantitative synthesis of Level II data: general approach, below).

Where neither Level I nor Level II evidence was available, Level III evidence was systematically surveyed.

Critical appraisal

Level I evidence

Level I evidence was appraised with reference to a bespoke quality-assessment instrument (*Table 1*), which was adapted from the recommendations of the MOOSE (meta-analysis of observational studies in epidemiology) proposal.[41]

Level II evidence

Level II evidence was appraised with reference to a bespoke quality-assessment instrument (*Table 2*), which was constructed with reference to recommendations made by Levine and colleagues,[42] Downs and Black, [43] the NHS Centre for Reviews and Dissemination [40] and Mallen and co-workers. [44]

Level III evidence

Because a very large amount of Level III evidence was identified and there were few methodological characteristics with which it could be distinguished (i.e. all such evidence was, by definition, of a poor quality), no formal critical appraisal was undertaken.

Data extraction

Data were extracted using a bespoke database. Because of the very large volume of material retrieved, it was not possible to satisfy our protocol requirement that all data extraction would be double-checked by a second reviewer; however, the data extracted from the 20 studies on which our syntheses relied most heavily were checked by a second reviewer. There were no major errors, and minor errors were corrected. Data extraction tables have not been reproduced in this report because they would run to many hundreds of pages. Details are available from the authors.

Quantitative synthesis of Level II data: general approach

In deciding the approach to the meta-analysis of outcomes of the included studies, a number of aspects of this dataset need to be considered:

- substantial heterogeneity in the design, risk of bias, population and definition of ecstasy and control exposures
- the wide range and large number of outcome measures reported (in total, 915 different outcome measures were identified in the evidence-base)

TABLE 1 *Level I evidence: appraisal instrument*

Item	Possible responses	Notes
1. Is study defined as a systematic review in title?	Yes	
	No	
2. Are study aims clearly described and focused?	Yes	
	No	
3. Do study objectives describe population, study design, exposure?	Completely	Full details of population, study design, exposure
	Partially	Some details
	No	
4. Search strategy supplied (or available) and appropriate?	Yes	Details of databases searched and search terms used
	No	
5. Additional sources used?	Yes	For example, author contact or hand searching
	No	
	Can't tell	
6. Double data extraction?	Yes	Either double-data entry or one reviewer recording data with second reviewer checking each datapoint
	No	
	Can't tell	
7. Assessment of study quality?	Yes	List instruments used in notes
	No	
	Can't tell	
8. Assessment of heterogeneity?	Appropriate	List methods used
	Not appropriate	
	Not done	
9. Results pooled?	Yes	List methods used
	No	
10. Pooling appropriate?	Yes	Assessment of synthesis methods (fixed- vs random-effects models, etc.)
	No	
	NA	
11. Subgroups considered in pooling?	Yes	Either separate or stratified analyses
	No	
	NA	
12. Results of pooling presented as forest plots?	All	
	Some	
	None	
	NA	
13. Strengths and weaknesses of review discussed?	Yes	
	No	
14. Potential biases of review discussed?	Yes	
	No	

NA, not applicable.

TABLE 2 *Level II evidence: appraisal instrument*

Item	Possible responses	Notes
1. Are study aims clearly described and focused?	Yes	
	No	
2. Is study design (controlled, observational) appropriate to answer these aims?	Yes	
	No	If Q1 and Q2 are both answered 'No', then *stop here*
3. Was study prospective?	Prospective	
	Cross-sectional	
	Ambidirectional	
4. Exposure to MDMA	Quantified	Sufficient to analyse exposure history and estimate total lifetime exposure
	Partial	Some details, but insufficient to quantify total lifetime exposure
	Inadequate	Not possible to ascertain exposure history
5. Exposure to other substances	Quantified	Sufficient to analyse exposure history and estimate total lifetime exposure
	Reported	Some details, but insufficient to quantify total lifetime exposure
	Partial	Select if exposure to important substances is not reported, and list in notes
	NR	
6. Are there explicit inclusion and exclusion criteria for study?	Partial	Some indication of eligibililty criteria, but incomplete information
	No	
	Can't tell	
	Yes	
7. How has sample been recruited?	Advertising	Note where, if stated
	Direct approach	For example, individuals approached in club
	Other	Describe
	Snowball	
	NR	
8. From where has MDMA cohort(s) (or cases in case–control studies) been recruited?	Club	
	University	
	Community	
	Health-care system	
	Other	Please note
	Mixture	More than one of these categories
9. From where has control cohort(s) been recruited?	Club	
	University	
	Community	
	Health-care system	
	Other	Please note
	Mixture	More than one of these categories
10. Are sample characteristics adequately described?	Partial	Some details, but important information missing
	No	
	Yes	For example, age and gender; depending on outcome, others – e.g. intelligence – may be important; SDs for continuous variables

TABLE 2 *Level II evidence: appraisal instrument (continued)*

Item	Possible responses	Notes
11. Are there significant differences between cohorts?	Yes	Significance testing should be undertaken, where possible, if authors have not reported this
	No	
	Can't tell	
12. Do analyses attempt to control for confounders?	Yes – matched cohorts	Cohorts are matched on important confounders
	Yes – adjusted analyses	For example, exposure to other substance included as a covariate in effect size calculations (ANCOVA; other regression)
	Yes – stratified analyses	
	Partial	Note any shortcomings in approach adopted
	No	
	Can't tell	
	NA	
13. Is there a power calculation?	Yes	
	No	
	Can't tell	
14. Is sample size sufficient?	Yes	Only answer 'Yes' if sample size fulfils criteria of explicit power calculation
	No	Only answer 'No' if there is an explicit power calculation but sample size does not fulfil criteria
	Not analysed	All other cases
15. Is primary outcome measure objective?	Objective	
	Subjective	Includes all self-reported measures; however, note if measured according to validated instrument
16. Are secondary outcome measures objective?	Objective	
	Subjective	
	Mixed	
17. Were outcome assessors blind to exposure status?	Yes	
	No	
	Can't tell	
	NA	
18. Are dose–response relationships considered?	Yes	
	No	
	Can't tell	
19. Is temporal relationship correct?	No	Outcome precedes exposure
	Can't tell	
	Yes	Exposure shown to precede outcome, enabling causal inference
20. Are drop-out rates similar between MDMA cohort and controls?	Yes	
	No	
	Can't tell	
	NA	Will be the case for most retrospective study designs

ANCOVA, analysis of covariance; NA, not applicable; NR, not reported; SD, standard deviation.

- substantial level of multiplicity:
  - multiple comparisons, i.e. inclusion of more than one ecstasy exposure (e.g. heavy ecstasy users versus light ecstasy users versus ecstasy-naïve controls; current ecstasy users versus former ecstasy users versus ecstasy-naïve controls) or more than one control arm (e.g. ecstasy users versus polydrug-using controls versus drug-naïve controls) in a single study
  - multiple outcomes, i.e. inclusion of more than one outcome measure assessing a given outcome domain within a single study, either through the reporting of several relevant subscales from a single instrument (e.g. individual immediate memory trials from the RAVLT) or through the reporting of several relevant measures (e.g. the RAVLT and the RBMT)
  - repeated measures, i.e. comparison between exposure and control over more than one time point (e.g. follow-up over a period of abstinence, with repeated measurements at regular intervals)
- observational basis of comparisons.

Collectively these issues pose a substantial methodological challenge to the application of standard meta-analysis methods. Our methodological approach to each of these issues is discussed below.

Substantial (clinical) heterogeneity

Four strategies were employed to minimise the potential problem of heterogeneity. First, separate meta-analyses were conducted according to the types of control groups in included studies (ecstasy users versus polydrug-using controls without exposure to ecstasy; ecstasy users versus drug-naïve controls). Throughout this document, the term *polydrug controls* is used to refer to control groups in which some or all of the participants had a history of exposure to illegal drugs other than ecstasy. In contrast, *drug-naïve controls* are those who have no experience of illegal substances, although most will have a history of alcohol consumption and/or tobacco smoking. Three studies[45–47] were excluded from analysis because they provided insufficient information on whether control participants had exposure to other substances; hence, it could not be ascertained to which of our analyses data should contribute. Several studies were designed to compare ecstasy-exposed participants with separate polydrug and drug-naïve control arms; in these instances, the relevant comparisons are included in each meta-analysis, as appropriate. Second, each meta-analysis was, where possible, stratified to distinguish between current ecstasy users and former users. Third, a random-effects meta-analysis was used throughout, thereby explicitly recognising that the separate studies may be estimating different effect sizes of ecstasy exposure. Last, study-level regression ('metaregression') was used to explore the statistical heterogeneity across studies. The association between the exposure effect size and population [e.g. mean age, sex and baseline intelligence quotient (IQ)] and ecstasy exposure characteristics (e.g. duration and frequency of usage) was examined univariately.

Range and number of outcomes

To rationalise the range and diversity of outcomes reported, a pre-hoc decision was made to focus and synthesise the results according to a series of domains, representing key areas of interest. The underlying principle was to maximise parsimony, i.e. to reduce the heterogeneous evidence-base to as few meta-outcomes as could be sensibly delineated. The categorisation of outcomes into domains was initially defined by the reviewers, with particular reference to the textbooks of Lezak *et al*.,[48] Hersen *et al*.[49] and Strauss *et al*.[50] In the particular areas of executive function and attention, we were guided by conceptual models – based on principal components analyses – proposed by Miyake *et al*.[51] and Mirsky *et al*.[52] respectively. These categories were reviewed and, where necessary, revised by our expert advisory group. Where outcome domains featured some objective measures and some self-reported measures, these were analysed separately.

To combine studies using different outcome measures within each domain, effect sizes were expressed as a standardised mean difference (SMD). The SMD expresses the size of the exposure effect of ecstasy in each study relative to the variability observed in that study. Accordingly, for a given study i,

$$d_i = \frac{m_{1i} - m_{2i}}{s_i}, \qquad (1)$$

where m_{1i} and m_{2i} represent the reported means in ecstasy-exposed and control cohorts, respectively, and s_i is the pooled standard deviation across both groups, estimated as,

$$s_i = \sqrt{\frac{(n_{1i}-1)\mathrm{SD}_{1i}^2 + (n_{2i}-1)\mathrm{SD}_{2i}^2}{N_i - 2}}, \qquad (2)$$

where n_{1i}, n_{2i} and N_i represent the sample sizes of ecstasy-exposed, control and combined cohorts respectively, and the reported standard deviations of measurements in ecstasy-exposed and control groups are SD_{1i} and SD_{2i}. To pool SMDs, it is necessary to derive the standard error, which is estimated as follows:

$$SE(d_i) = \sqrt{\frac{N_i}{n_{1i}n_{2i}} + \frac{d_i^2}{2(N_i - 2)}} \,. \quad (3)$$

The method assumes that the differences in standard deviations among studies reflect differences in measurement scales and not real differences in variability among study populations.

Multiplicity

Multiple comparisons

To include studies with multiple comparison arms within a conventional meta-analysis, it is first necessary to decompose the data in question to a series of pairwise comparisons (so A versus B versus C becomes A versus C and B versus C, assuming C is the common comparator). However, it would be inappropriate to treat each such comparison as an independent unit of analysis, by entering all datapoints into a single meta-analysis, because to do so is effectively to double-count data from the shared comparator (that is to say: if A versus C and B versus C are entered into the same analysis, then the data representing C effectively appears twice) (see Section 16.5.4 of the Cochrane Handbook for Systematic Reviews of Interventions[49]).

To minimise this unit-of-analysis error, we have adopted two different approaches:

- Our primary approach was to include each pairwise comparison in our analyses, but to adjust the size of the shared comparator to reflect the number of comparisons in which it is involved. For example, if a trial compared 100 current ecstasy users and 100 former ecstasy users with 100 ecstasy-naïve controls, we assumed that half of the control group was committed to each comparison. Accordingly, two comparisons would be entered into the meta-analysis: 100 current ecstasy users versus 50 ecstasy-naïve controls and 100 former ecstasy users versus 50 ecstasy-naïve controls. For dichotomous outcomes, both the number of events and the total number of participants is halved; for continuous outcomes, it is only necessary to adjust the total number of participants (in turn, this decreases the precision of each effect estimate, because the sample size feeds into the calculation of standard error, and ensures that each individual comparison will have reduced weight in the meta-analysis).
- Another approach to the same problem is to pool all relevant datapoints to provide a single unit of analysis for the pairwise comparison of interest. Using the same example as above, a meta-arm of 200 current and former ecstasy users would be compared to the 100 control participants. For dichotomous data, event numbers are simply added; for continuous outcomes, the mean for the combined arm is estimated as the weighted mean from the multiple separate arms (where the numbers in each arm provide the weights), and the standard deviation for the combined arm is calculated according to the usual formula (an extension of equation (2), above, accounting for a combination of more than two estimates):

$$s_c = \sqrt{\frac{\sum_{i=1}^{k}(n_i - 1)s_i^2}{\sum_{i=1}^{k}(n_i - 1)}} \,, \quad (4)$$

where i indexes a total of k arms being combined, n_i is the number of participants in each arm, and s_i is the standard deviation for that arm.

The disadvantage of this latter approach is that inter-arm heterogeneity – which, in itself, may be informative – is obscured. In particular, it is difficult to perform metaregression on analyses constructed in this way, because covariates of interest would also have to be pooled, with the likely effect that any influence of variables of interest on overall effect will be disguised. For example, in the case previously put forward, it would not make sense to investigate the effects of duration of abstinence on exposure effect, when two groups with very different profiles have been conflated.

In each instance, our primary analysis is based on the separate pairwise approach. However, we recognise that this method only partially overcomes the unit-of-analysis error (because the resulting comparisons remain correlated).[53] Therefore, we also performed sensitivity analyses, adopting the second aggregation method, to investigate whether our choice of approach had any notable influence on results.

Multiple outcomes

Methods are available for synthesising multiple outcome measures in a single meta-analysis.[54–56] The benefit of such methods is that they take into account the level of correlation that exists between outcomes from the same study in the analysis. On the other hand, these methods are complex, and may obscure within-study heterogeneity, which may be important. For these reasons, this approach was not pursued.

Instead, we derived single units of analysis by pooling domain-related outcomes into a single 'omnibus' domain-specific outcome. Deriving these estimates was a four-stage procedure:

1. All potentially relevant outcome measures were screened to ensure no duplicate data content. For example, if a study reported a series of subtests along with an index score that had been categorised as relevant to the domain of interest, the index score only was included in our analysis. Wherever second-order manipulations of subscores were reported (e.g. a Stroop test in which interference effect was reported as time in interference trial minus time in simple naming), those measures were not included if the individual subscores on which they were based were already part of the dataset. In the event that such second-order measures were the only relevant datapoints extracted from a study (in the above example, where interference effect is reported without raw trial times), there would be no double-counting of data, so such datapoints were included.
2. Data for each individual outcome measure were adjusted to reflect the multiplicity of comparisons (as described in Multiple comparisons, above).
3. Each individual measure was expressed in terms of SMD (see Range and number of outcomes, above).
4. For each comparison, a weighted average of all SMDs was calculated, using the precision of the estimates as the weighting factor (this could be seen as a sub-meta-analysis, adopting a fixed-effects model with inverse variance weighting).

This method assumes that the correlation between outcomes is uninformative (as described above for multiple comparisons). However, assuming a relatively conservative correlation between outcomes of 0.5 and based on three or four domain-specific outcomes, it estimated that our method will overestimate the precision of the omnibus outcome estimate by only some 10 to 15%.[57]

We believe this approach should provide a more informative – and less biased – estimate of effect than those available in some previous meta-analyses of the effects of ecstasy exposure which, when faced with a multiplicity of outcomes, have simply selected a single outcome as most representative of the domain in question.[58,59] This approach not only discards potentially informative data but also relies very heavily on the assumption that the reviewer's choice of outcome is truly representative of the domain in question.

Other reviewers have adopted a similar approach to ours, basing their analyses on multiple outcomes 'aggregated … to produce an average effect size'.[60,61] However, in each instance, the methods used to pool separate outcomes are not described.

Repeated measures

A relatively small subset of studies reported repeated measurements of an outcome of interest (e.g. over a period of abstinence,[62,63] or before and after an experimental procedure[64]). In such cases, we have entered only the first measurement taken into our quantitative syntheses. An exception to this principle was made for a few studies in which measurements had been taken in users experiencing the acute and/or subacute effects of ecstasy consumption, and then a subsequent measurement recorded when such effects had worn off. In these instances, the later measurement – which more properly captures the long-term effects of ecstasy exposure – was used. Previous meta-analyses have explicitly[61] or presumably[58–60] taken a similar approach. An alternative approach would have been to use an effect estimate based on time-to-event analysis (such as hazard ratio). However, no such analyses were reported.

Observational basis of comparisons

Because of the observational nature of the included studies, potential confounders (e.g. participant age, exposure to legal and illegal drugs other than ecstasy) are highly unlikely to be equally distributed across the exposure and control arms. Dependent on direction and magnitude, within-study confounder imbalances are likely either to overestimate or to underestimate any underlying exposure effect. This asymmetric distribution of confounders has not been explicitly considered in previous meta-analyses of the effects of ecstasy. Using an extension of an analytic approach recently described by Trowman *et al.*,[65] we used

metaregression similar to analysis of covariance (ANCOVA) to explore the evidence for important confounding of effect, and to 'adjust' the exposure effect size for potential imbalance in confounder distribution between exposure and control groups:

> observed difference = exposure effect + ($\beta \times$ difference in confounder).

The output of particular interest is the constant ('exposure effect'), which represents the 'true' effect of the exposure after accounting for baseline differences in confounders between the arms of individual studies. When the difference in confounder is 0, this value is equivalent to unadjusted exposure effect size. This can be seen clearly when the relationship is plotted on a graph as the point at which the estimated regression line intersects the *y*-axis.

Quantitative synthesis of Level II data: technical approach

Primary meta-analyses

We used random-effects meta-analyses (DerSimonian and Laird model[66]) only, regardless of any statistical evidence of inter-study homogeneity. Heterogeneity was explored by visualisation of results and, in statistical terms, by calculation of both Cochran's *Q* (compared to a chi-squared distribution)[67] and the I^2-statistic.[68,69] Small-study effects (including publication bias) were visualised using funnel plots and quantified using Egger's test.[70] Analyses were conducted using bespoke software, written in Visual Basic for Applications and applied in both Microsoft Access and Microsoft Excel. Stata 9.1 was used to verify the accuracy of analyses (`metan` command) and to assess small-study effects (`metabias` command).

Metaregression

Metaregression was undertaken using Stata 9.1 (`metareg` command). The method of moments model was used for all metaregressions because, although the restricted maximum likelihood estimator is generally recommended in this situation,[71,72] our methods extended to using the outputs of metaregression analyses to calculate adjusted effect estimates (see Observational basis of comparisons, above). Therefore, it was important for us to compare the outputs of metaregressions with our original meta-analyses, and the method of moments model is identical to a classical random-effects meta-analysis when the effect of the covariate is zero. Because of inconsistencies in the evidence-base, it was not possible to undertake multivariate analyses, so regressions were conducted solely on a univariate basis.

The metaregression analyses presented in our results fall into three categories:

- 'Classical' metaregression, in which the covariate is a study-level characteristic (e.g. average age of all participants, average IQ of all participants).
- Dose–response analyses, in which the covariate is one of several estimates of ecstasy exposure in the ecstasy arm [e.g. estimated total lifetime dose (ETLD), duration of use].
- Exploration of inter-arm confounding, in which the covariate is a measure of the difference between cohorts in any one of several characteristics other than exposure to ecstasy (e.g. difference in age, difference in exposure to other substances). Two methods were used to quantify asymmetry in drug exposure. First, differences were calculated on an absolute scale: difference in ETLD of the substance in question, calculated according to uniform units (joints of cannabis, grams of amphetamine and cocaine, units of alcohol). In meta-analyses comparing ecstasy-exposed populations with drug-naïve controls (for whom the ETLD of illegal substances is, by definition, nil), this variable becomes a simple index of consumption in the ecstasy-using arm. Second, because ETLD is only reported by a minority of studies, the SMD between arms was calculated using any one of several drug exposure variables. Standardised difference scores for drug consumption were based on the highest ranking measure available in each study according to the following hierarchy:
  - ETLD (amount of the substance ever taken; any quantitative unit)
  - estimated total lifetime exposure (number of occasions on which the substance has ever been taken)
  - dose over a specified period (e.g. estimated amount taken in past 12 months)
  - frequency (e.g. number of occasions taken per month)
  - typical dose (amount of substance taken per occasion)
  - exposure score (average score on a bespoke ordinal scale)
  - duration of use (length of history of exposure to the substance).

  Because single values cannot be manipulated in the same way as inter-arm differences,

standardised differences in drug exposure were only calculated for meta-analyses comparing ecstasy-exposed populations with polydrug controls. In comparisons with drug-naïve controls, these covariates were omitted from analysis.

Throughout this document, the term 'confounder' is used to refer to any variable that, while unrelated to the outcomes of interest, may potentially have an influence on observed effect. In some cases, the assumption of independence may be an inaccurate one, and it may be more correct to use the term 'effect modifier', to emphasise that there is a causal interaction between the variable and the outcome. However, it is not possible for us to disentangle such relationships on the basis of the evidence-base available to us.

Chapter 3
Results

The papers identified by literature searches, screened against the inclusion criteria and finally included in the review are shown in *Figure 1*, together with the reasons for exclusion of the rest.

Although we were not able to integrate new findings in our review, we performed updated literature searches on 28 February 2008. Of 289 new citations returned, 44 appeared – on the basis of title or abstract alone – as though they might be relevant to the content of this project; these references are given in Appendix 4. We recommend that any future update of this review considers this evidence for inclusion.

Previous syntheses (Level I)

We identified five previous systematic reviews and/or meta-analyses. One reported on self-reported depressive symptomatology in ecstasy users[56] and three were concerned with the chronic neurocognitive effects of ecstasy.[58–60,73,74] The fifth review discussed the acute subjective effects of ecstasy associated with intoxication and was not considered further.[74]

Methods

The characteristics and methods of the identified studies are summarised in *Table 3*.

Findings

Depressive symptomatology

The meta-analysis by Sumnall and Cole 2005[58] of self-reported depressive symptomatology in community samples of ecstasy users found a significantly increased level of depressive symptoms in ecstasy users compared to a mix of polydrug and drug-naïve controls – 22 studies, effect size 0.31 (95% CI 0.18–0.44; $p < 0.001$). The authors state that they used polydrug controls where available rather than drug-naïve controls, but do not specify more detail. Weighted metaregression analysis showed that estimated lifetime ecstasy use, but not duration of use, dose per episode or abstention period, predicted effect size and that this effect remained after partially controlling for alcohol, amphetamine and cannabis. The effect size for studies was significant using the Beck Depression Inventory (BDI) (0.48; 95% CI 0.29–0.66; $p < 0.001$) and the Symptom Checklist-90-revised (SCL-90R) (0.26; 95% CI 0.02–0.50; $p < 0.05$), but using the original SCL-90 it was not. Metaregression also showed decreasing effect size as study size increased: only studies with fewer than 40 subjects produced a significant effect size (16/22). As the funnel plot was significantly asymmetrical, publication bias is likely in this review and is identified as an issue by the authors. There is no narrative synthesis or quality assessment of the studies and the methods of the included studies are unclear.

Memory and neurocognition

Three previous syntheses have conducted meta-analyses based on systematic identification of studies.[59,60,73] None provide a critique of the quality of the included studies.

Kalechstein *et al.*[73] reported that in their 'lenient' group of studies ($n = 23$), exposure to MDMA, was associated with poorer performance in each of the neurocognitive domains: attention [SMD (Cohen's d) = 0.40], verbal learning and memory (0.73), non-verbal learning and memory (0.58), motor/psychomotor speed (0.55) and executive systems functioning (0.52) ($p < 0.001$ for each domain). It is not clear what the matched controls were in terms of other drug use. For the more stringent group of studies ($n = 11$), results were similar, with verbal learning and memory still showing the greatest effect (SMD = 0.85). No narrative synthesis of the studies was included, so no detail of the quality of the included studies is available.

The effect sizes of Verbaten[59] are based on comparisons between the highest ecstasy-using group and a non-ecstasy-using control from each of the 10 included studies. For short-term memory, the mean effect size of –1.15 remained significant after controlling for lifetime exposure to ecstasy (–0.95; $p < 0.01$) and cannabis use (–0.67; $p < 0.01$). For long-term memory, the mean effect size of –1.25 remained significant after controlling for lifetime ecstasy consumption, but not after controlling for lifetime cannabis use (–1.15; $p > 0.05$). For sustained attention-processing speed, the mean effect size of 0.41 ($p < 0.01$) remained

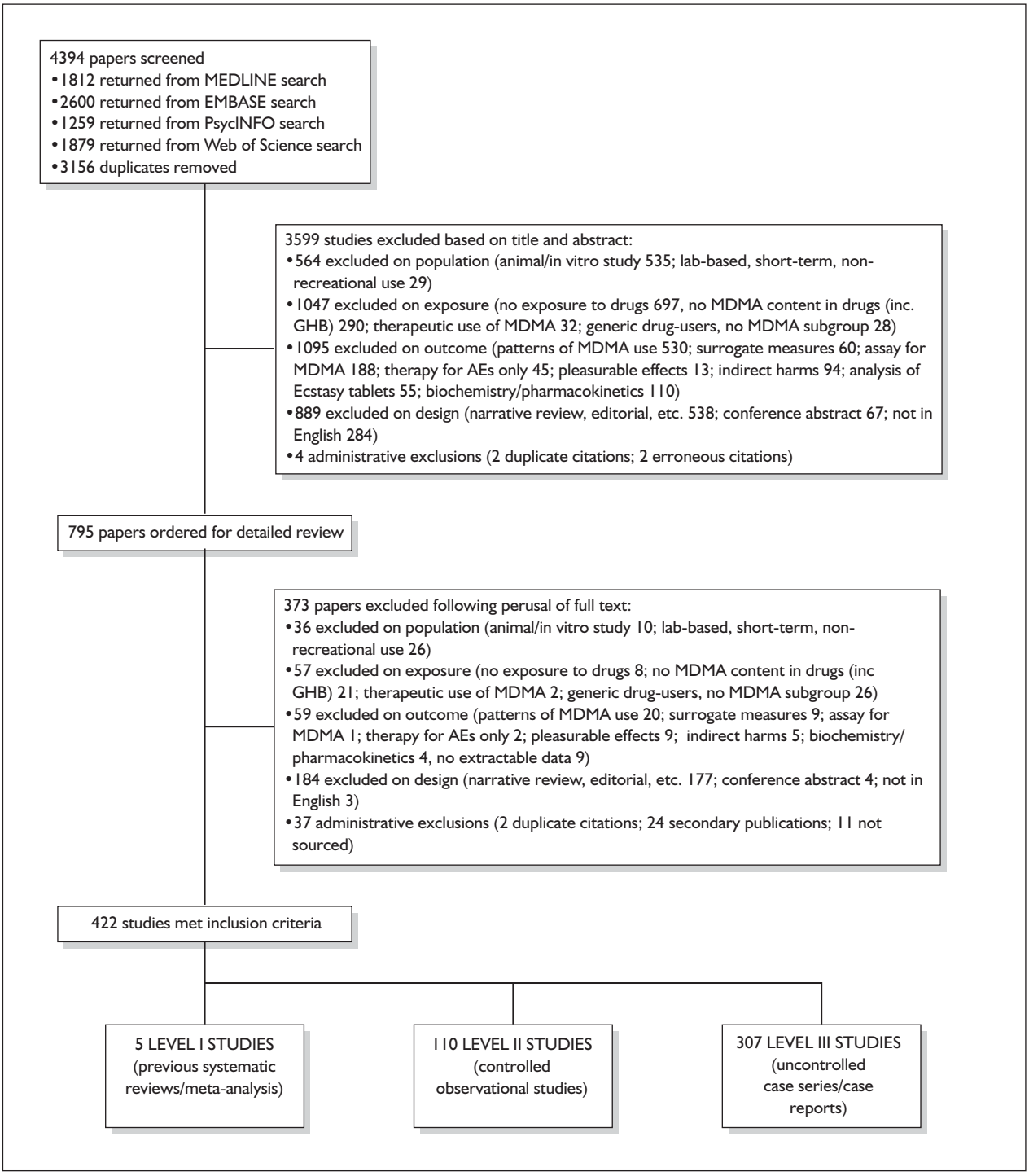

FIGURE 1 *Review flowchart. AEs, adverse events.*

significant after controlling for lifetime ecstasy consumption. For attention performance, the mean effect size of –0.82 remained significant after controlling for lifetime ecstasy consumption and lifetime cannabis consumption.

Laws and Kokkalis[60] provide an updated meta-analysis for Verbaten[59] of 28 studies. On short-term memory, ecstasy users performed worse than controls in 22 of 25 studies (SMD –0.63; 95% CI –0.91 to –0.41). For long-term memory, ecstasy users performed worse than controls in 17 of 19 studies (SMD –0.87; 95%CI –1.38 to –0.45). Ecstasy users performed worse than controls on verbal memory (SMD –1.00; 95% CI –1.45 to –0.59) and visual memory (SMD –0.27; 95% CI

TABLE 3 *Level I evidence: methods of included syntheses*

Paper	Search strategy	Inclusion/exclusion criteria	Research question	Meta-analysis?
Sumnall and Cole 2005[54]	Web of Knowledge, PsycINFO, MAPS MDMA databases searched 1914–2004 Ecstasy, MDMA, human, self-report, depressive, depression Reference lists of retrieved articles searched, experts consulted for unpublished data	Inclusion: self-reported depressive symptomatology using validated measures in community samples of ecstasy users 25 studies identified	To quantify self-reported depressive symptomatology in substance misusers reporting ecstasy use	Yes
Verbaten 2003[55]	PsycINFO and MEDLINE searched 1975–2002, search terms not mentioned	Inclusion: *n*, mean and SD reported for all dependent variables; subjects drug free for at least a week 10 studies included	Existence and strength of effect of neurocognitive damage from ecstasy use; evidence for a dose–response effect	Yes – regression for lifetime exposure
Laws and Kokkalis 2007[56]	MEDLINE, Google Scholar, PsycINFO, National Institute on Drug Abuse, Erowid using MDMA, memory, ecstasy, cogniti*, neuropsych* Reference lists of retrieved articles and core on-line journals searched	Inclusion: studies contained relevant memory subtest data for an appropriate non-MDMA-using control group that could be used to derive an effect size 28 studies identified	Impact of recreational MDMA use on memory – updating Verbaten's review	Yes – no forest plots presented, fixed- and random-effects models used, subgroup analyses for studies addressing confounders
Kalechstein *et al*. 2007[69]	PsycINFO and MEDLINE searched using MDMA, neurocognition, neuropsychology, cognition	Lenient group inclusion: measures of neurocognition, matched controls 23 studies included Stringent group inclusion: as above plus controls similar in age, education/premorbid IQ, MDMA users not treatment-seeking and abstinent at time of assessment 11 studies included	To quantify the association between neurocognition and MDMA misuse	Yes, but no forest plots, summary measures only reported in tables

MDMA, 3,4-methylenedioxymethamphetamine (ecstasy).

–0.55 to –0.03). While the effect size was larger for long-term than short-term memory, this difference was not significant. Deficits were significantly greater for verbal than for visual memory. No significant differences in effect sizes were observed when comparing drug-naïve with non-naïve controls. There was no effect of lifetime exposure to ecstasy or cannabis use on effect sizes.

Conclusions

None of these studies was judged to have exactly the same focus as our review and, in each case, it was difficult to ascertain the exact methods adopted in the review. This lack of detail may be the result of constraints imposed by journals on article length. A particular problem was identifying what evidence had been included in quantitative

syntheses. For these reasons, we concluded that it would not be appropriate to rely on these previous reviews alone for any outcomes of interest. Accordingly, our review of Level II evidence includes all the outcomes on which previous reviewers have reported. We compare our results with theirs in Chapter 4 (Strength and consistency of effect).

Controlled (Level II) evidence (chronic harms)

Assessment of the quality of studies

This section of the review uses data from 110 studies. Aside from data derived from the Netherlands XTC toxicity study (NeXT), which will be discussed separately, all studies assessed the effects of ecstasy in people who already had a history of ecstasy use. Virtually all studies, therefore, provide only cross-sectional data from a group of ecstasy-exposed subjects compared to a control group without or with minimal ecstasy exposure.

Recruitment

Recruiting users of illegal drugs for research studies is challenging and authors have used various methods. Some subjects have been recruited from those attending programmes in drug addiction centres or admitted to long-term rehabilitation programmes, which include urine monitoring for MDMA and other drug use. Other studies recruited active users at raves/dance parties, while others used advertising either in specialist media or via their research institution. The snowball technique has been used extensively: participants initially recruited are encouraged to recruit others by word of mouth. These methods are very likely to provide a non-representative sample of ecstasy users. The samples chosen could reflect subjects with a high proportion of problems associated with ecstasy use (in those already in drug addiction programmes) or those who share certain characteristics unrelated to ecstasy use, such as those who choose to respond to an advertisement. The extent to which results from any of these studies can be generalised to the whole ecstasy-using population is therefore uncertain.

Recruitment of the control group may also lead to bias in the result. Often the control group comprised individuals from the research establishment who reported no illicit drug use. These may be students at a university or health-care workers. Such individuals may be reluctant to report illegal drug use and are also likely to differ systematically from the ecstasy users in other ways, such as socioeconomic status and educational attainment. In some studies, urine samples were screened during the study period, so that self-reported recent drug use could be objectively validated.

Study size

In the majority of studies, a power calculation was not performed. Without a power calculation it is not known what chance the study had of detecting a difference between groups, if a true difference exists. Given the very small sample size of many of these studies, it has to be assumed that the chance of declaring false-negative findings (type 2 error) is high. This point is especially relevant where authors have reported that ecstasy-using groups did not differ from controls in terms of baseline characteristics.

Confounding

Given the lack of randomised and other prospective studies, a major issue for this review was the extent to which confounding variables could be identified and controlled for in the included studies. Some sought to control for potential confounding by matching of groups, stratifying patients according to variables thought to be important, such as amount of ecstasy use (e.g. Dafters *et al.*[75]), or by conducting analyses using potentially important variables as covariates (e.g. Heffernan *et al.*[76]). Many studies, however, did not control for the effect of differing prior exposure, or other confounders, in either the design or the analysis plan. Studies also varied in the extent to which they quantified prior exposure to ecstasy and other drugs. In some, an estimate of total lifetime exposure was made by the authors or sufficient data were presented to enable an estimate to be made.

A limitation around the use of studies describing matched groups is that there is no uniformity amongst the variables considered important to match. One study (Back-Madruga *et al.*[46]), which describes groups as matched, actually uses historical archival controls in which ecstasy use was not questioned. In most cases, matching has been restricted to basic demographic variables, but some also include educational attainment, IQ, socioeconomic variables and concomitant drug use. However, in 27 studies, the analyses had not been adjusted to account for potential confounders. For example, Butler and Montgomery[77] found that impulsivity and risk taking was greater in ecstasy users than in non-users and further that risk-taking scores were higher amongst high ecstasy users than low ecstasy users. However, there were significant

differences in the use of cocaine, amphetamines and LSD between the groups which were not allowed for in the analysis and so the extent to which this result can be attributed to ecstasy use is uncertain. Similarly, another analysis of depressive symptomatology reports an 'Ecstasy using' cohort whose history, when compared to that of controls, featured significantly more consumption of alcohol, nicotine, cannabis, psilocybin, amphetamine, LSD, amyl nitrate, ketamine, cocaine and opiates[78] but did not attempt to adjust the results to account for these differences. Attributing harmful health effects to MDMA use rather than to other drugs is therefore extremely difficult.[79]

Using only cross-sectional data also limits the extent to which effects can be attributed to a possible cause, as the causal association, should there be one, can go in either direction. For example, a group of studies have noted that novelty-seeking behaviour is stronger among ecstasy users; in these cross-sectional studies the explanation could equally well be either that ecstasy leads to such behaviour or that individuals who already exhibit that behaviour are more likely to use ecstasy.

A small number of studies obtained cross-sectional data and then followed patients up for a period of days to several years to obtain further data. We have classified such studies as 'ambidirectional' because, although they have a prospective component (observing different groups over time), the original exposure precedes enrolment into the study and the results may be confounded by factors that were present on enrolment.

Disappointingly, we were compelled to exclude one of the very few prospective studies in this area (Lieb *et al.*[80]) from our review because it only reports results from a cohort exposed to 'ecstasy, amphetamine or related compounds' (contact with the authors failed to elicit data limited to those exposed to ecstasy only). Similarly, the longitudinal follow-up study by Daumann *et al.*[81] conflates the use of ecstasy and amphetamine for follow-up measurements (though not for baseline data, which are included in our review). We appreciate that such classifications are more reflective of common usage patterns; additionally, this means that they are more practical to adopt from a study recruitment perspective. However, it is very difficult to make use of such data in a policy-making context because it is impossible to disentangle the contributions of the various substances to the reported results.

Dose-related effects

Determining any dose-related effects of MDMA is more problematic than with prescribed medication in clinical trials or other studies for a number of reasons. Illegal drugs are not produced with pharmaceutical quality assurance procedures and there is ample evidence of great variability in the dose of MDMA contained in available tablets. Consequently, there is no assurance of the dose taken by participants even if they can recall accurately the number of tablets they have taken. Aside from variability in content of the desired active drug there is also variability in content of contaminants, some of which may exert a pharmacological action. Participants in these studies are perhaps also more likely than patients in clinical trials to have inaccurate recall or to lie about their drug consumption. Any claims for a dose effect must therefore be interpreted very cautiously.

Despite this caution, a number of studies attempt to investigate the suggestion that long-term harm from ecstasy use is associated with heavy use rather than low episodic use. There is variation in the thresholds that different researchers have set for low and high use, but all estimates are based on self-reported use and are subject to recall bias, particularly where use over a number of years is recorded.

Abstinent period

To maximise a study's ability to distinguish long-term effects from acute and subacute sequelae of drug consumption, it is important to ensure that participants are tested after a period of abstinence long enough to rule out any residual effects of their last dose(s). We did not routinely extract information about the extent of abstinence required by each study before testing, or the means by which compliance with such criteria was verified. However, we note that studies varied widely in this respect. For example, Gerra *et al.*[82] required participants to have ceased consumption of illegal drugs 3 weeks before testing, and used urine screening three times a week to ensure compliance. In another study, the same author ensured abstinence over a 12-month period by the same method. At the other end of the spectrum, Quednow *et al.*[83] relied upon subjects' self-declaration that they were drug free for 3 days before participation in the study.

Blinding

Many studies do not state whether the researchers carrying out the assessments were blinded to the exposure status of the participant.

Outcome measures and reporting bias

A feature of the dataset for this review is the large number and diverse range of outcome measures that researchers have assessed. In many cases the outcomes assessed are subjective and rely on the participants' self-report of a characteristic. In some cases well-established outcome measures are used, whereas in others the validation of the assessment tool is less clear. Studies assessing personality dimensions and mood tended to make use of subjective measures, while those assessing memory and cognitive function made greater use of objective measures. In many cases the studies did not identify a primary outcome measure but subjected the range of data to statistical analyses and hypothesis tests. In most cases no adjustment to significance level has been made for the multitude of hypothesis tests conducted, and the findings of such studies should be regarded as exploratory and hypothesis generating.

In addition, studies have not always reported all outcomes investigated, but have included only those which yielded positive results. Together with the uncertain, but often large, number of outcomes investigated, this selective reporting adds to the interpretation difficulties and increases the likelihood that many results are chance findings.

The Netherlands XTC Toxicity Study

The Netherlands XTC toxicity study is the only study meeting the inclusion criteria for this review that provided data which can truly be described as prospective. A number of objective tests were employed to assess different aspects of memory and visuospatial functioning, and although references are provided it is not clear to what extent the measurement tools used have been validated. Statistically significant differences between the groups were only observed for measures of verbal memory. A large number of statistical comparisons have been made and it would be a moot point to discuss whether the p-values used to declare significance should have been adjusted to reflect this. The authors also chose to use one-tailed tests as they hypothesised that ecstasy use could have been associated only with impaired performance and not with enhanced performance. It would have been more conservative to have used two-tailed tests, keeping $p < 0.05$ constant as the level at which to declare statistical significance. The conclusion that exposure to even a low dose of MDMA may impair verbal memory has recently been challenged. It was noted that the difference in scores between the groups arose because the increased performance on retest was greater in the ecstasy-naïve group than in the incident ecstasy-using group, i.e. verbal memory test scores numerically increased in both groups but to a lesser degree in the ecstasy group. The scores remained within the normal range. There is some debate as to whether the relative decline in scores is attributable to ecstasy affecting verbal memory in a way that serves to blunt the benefit of a retest some 18 months after the initial test. The conclusion that these effects are apparent even after a low cumulative dose has also been challenged as the range of ecstasy use was reported as 0.5–70 tablets. In response to this challenge the authors present some sensitivity analysis excluding four subjects (approximately 7% of the sample) who used in excess of 10 tablets, yielding a new group mean consumption of 1.95 tablets (range 0.5–6), which was found to have little effect on the results. Dose of ecstasy per occasion was also considered briefly with data presented showing that 95% of users took no more than two tablets per occasion and that during the period of study the mean dose of MDMA per tablet was 78 mg. The authors conducted logistic regression analysis which showed an increased risk of a decline in a verbal learning test with increased consumption.

The strength of the Netherlands XTC toxicity study is the prospective nature whereby a cohort of ecstasy-naïve subjects was followed up for around 2 years. The sampling methods resulted in a study population that is probably not representative of the general population of young people, but the varied situations from which recruitment occurred and the fact that both the eventual ecstasy-using and the control groups came from this same sample make this study stand out from many of the others. It presents a range of objective cognitive measures, and subjective mood and personality measures.

Although many potential confounders are possible, the authors attempt to identify these and adjust their analysis accordingly. The principal concerns are centred on the direction of results in both the active and control groups in one of only three measures out of a possible 12 that were statistically significant, and the relatively large p-values associated with these in the context of multiple one-tailed hypothesis tests.

Results: the Netherlands XTC Toxicity (NeXT) study

Methods

This study started in 2002 with the aims of examining:

- the causality of ecstasy use in observed brain pathology in humans
- the long-term course of brain pathology in ecstasy users
- the clinical relevance of observed brain pathology in ecstasy users.

The study design included three arms:

- a cross-sectional study of heavy users of ecstasy and controls using varying amounts of other drugs
- a prospective cohort study of subjects who were ecstasy-naïve at recruitment but had a high risk for future first ecstasy use
- a retrospective cohort study of lifetime ecstasy users with matched controls.

As this study is the only one we have identified that has included prospective data, we report its methodology and results separately from the rest of the Level II evidence that is purely cross-sectional in nature.

We have identified nine publications from the whole study. Two[84,85] describe the methodology, including a detailed assessment of the recruitment techniques,[85] particularly the possibility that the investigators' approach encouraged the drug-naïve subjects to start using ecstasy. Two more publications[86,87] report findings from the cross-sectional study; one presents qualitative data from older ecstasy users[86] and the other presents neuroimaging data (functional magnetic resonance imaging),[87] which are not included in this review. A third report from the cross-sectional arm, identified through an update search and also not fully included in this review, presents cognitive effects in 71 subjects with a spectrum of drug-using histories using a range of instruments. The remaining four publications present results from the prospective cohort arm; two of these report functional magnetic resonance imaging data and are not included in this review,[88,89] whereas the others report cognitive[90] and depression, impulsivity and sensation-seeking[91] data. To date, no publications have been identified that report findings from the retrospective cohort study of lifetime ecstasy users and matched controls identified from a pre-existing longitudinal study in the Netherlands.

Recruitment
Subjects were recruited to both the cross-sectional and the prospective arms by website, an internet campaign, snowball sampling and site sampling at a variety of locations (dance events, youth fairs, universities, etc.). For the prospective arm, subjects were asked about their future intention to use ecstasy and included only if they had a high probability of intending to use ecstasy in the near future. Subjects were paid for their participation in the various assessments.

Follow-up
Subjects in the prospective arm completed further questionnaires on drug use at 3-monthly intervals for a year. The main outcomes were assessed at three time points: after recruitment (i.e. before first ecstasy use), shortly after first ecstasy use for those who started using ecstasy and 12–24 months after baseline assessment in all ecstasy-users and in a sample of those who remained ecstasy-naïve.

Measuring exposure to ecstasy
Ecstasy exposure was assessed initially by questionnaire. Subjects were asked to abstain from drug use for 2 weeks before testing and from alcohol for 1 week before testing. Abstinence was checked by urinalysis and prior exposure to ecstasy and other amphetamines was checked by hair analysis.

Neuropsychological and psychopathological outcomes
Included outcome measures were: working memory/executive functioning, verbal and visual memory, visuospatial functioning, verbal intelligence, depression (BDI), impulsivity (Barratt Impulsiveness Scale; BIS) and Spannings Behoefte Lijst (SBL; Dutch version of the Sensation-Seeking Scale).

Results of the prospective study
One hundred and eighty-eight ecstasy-naïve subjects who were considering ecstasy use in the near future and preferably had at least one friend currently using ecstasy, were recruited over a 2-year period from April 2002 to April 2004. All 188 underwent initial assessment; 158 completed all the follow-up questionnaires of whom 64 said they had started ecstasy use since inclusion in the study and 59 of these 64 participated in the follow-up assessment session, 16–19 months after the initial assessment, together with 61 of the 94 subjects who said they had not used ecstasy, matched for age, sex and IQ (Dutch Adult Reading Test). Subjects were young (average age 21 years) with slightly more women (57%).

At initial assessment, there were no significant differences between those who started using ecstasy and those who did not in terms of age, sex, IQ,

educational status and the consumption of other drugs (alcohol, tobacco, amphetamine and cocaine) with the exception of cannabis (greater in those who started using ecstasy, mean joints per week 48.8 versus 17.2, $p < 0.05$ Mann–Whitney test). There were also no significant differences in any of the neuropsychological or psychopathological tests between the two groups at baseline.[86,87] The mean cumulative dose of ecstasy in those who started using it was three or six tablets, depending on which paper you read.

Baseline total scores for depression (BDI), impulsivity (BIS) and sensation-seeking (SBL) did not predict incident ecstasy use, even after controlling for years of education and alcohol, cannabis and cocaine use.[87] At follow-up, there were significant differences between those using ecstasy and the ecstasy-naïve subjects in three of the subscales of the SBL: experience-seeking (β-coefficient 1.76; 95% CI 0.09–3.42), disinhibition (β-coefficient 3.31; 95% CI 1.74–4.88) and general sensation-seeking (β-coefficient 0.54; 95% CI 0.20–0.87) even after correcting for baseline scores. After correcting for potential confounders, ecstasy use had a significant effect on only the SBL general score and the disinhibition subscale. Cannabis use in the last year had a positive predictive value on future ecstasy use [odds ratio (OR) 1.30; 95% CI 1.08–1.56]. The thrill- and adventure-seeking subscale unexpectedly had a negative predictive value on future first ecstasy use (OR 0.95; 95% CI 0.91–1.00).

At follow-up approximately a year later, there was a significant difference in the change in scores (follow-up minus initial) between those subjects stating that they had started using ecstasy (mean cumulative dose three tablets) and those who remained ecstasy-naïve for immediate and delayed verbal memory (0.86 versus 3.90, $p = 0.03$; –0.52 versus 0.65, $p = 0.03$ respectively). A higher proportion of the ecstasy-using group showed a decline in verbal recognition (22.4% versus 6.7%, $p = 0.02$). The effect of ecstasy use on delayed verbal memory remained after controlling for cocaine and amphetamine use. All other neuropsychological tests showed no significant differences. The ecstasy-naïve subjects showed a normal retest effect, but this was not demonstrated in the ecstasy-using group even after controlling for other drug use.[92] Overall test performance for all subjects remained within the normal range of an age- and sex-comparable general population (indeed, all the RAVLT memory scores for which differences were found represent very high-functioning performance, when compared with norms).

In conclusion, the only prospective study we have identified for this review found that a low cumulative dose of ecstasy is associated with a (small) decline in verbal memory and may increase certain aspects of sensation seeking, but is not associated with depression or impulsivity.

Syntheses: individual outcome measures

In the first instance, we searched the assembled evidence-base for outcome data that had been reported by multiple studies using the same instruments and the same scales. We identified seven outcome measures that were reported with enough consistency to be meta-analysed without further transformation in a meaningful number of studies. With the exception of the National Adult Reading Test IQ, all of these outcomes were measures of verbal memory and could only be analysed in comparisons between ecstasy users and polydrug controls.

The results of these syntheses are summarised in *Table 4*. Note that effect measures are presented as weighted mean differences, meaning that the estimated effect reflects the difference between comparators on the original measurement scale.

Measures of verbal memory showed an average deficit for ecstasy-exposed populations of sufficient magnitude that the null hypothesis of no inter-cohort difference could be rejected at conventional levels of statistical significance (i.e. $p < 0.05$), with the exception of the immediate prose recall score from the Rivermead Behavioural Memory Test, which fell only marginally short ($p = 0.052$).

There was no detectable difference between populations in the National Adult Reading Test IQ, in comparisons between ecstasy users and drug-naïve controls or in comparisons between ecstasy users and polydrug controls.

Full details of these analyses are set out in the following section.

Rey Auditory Verbal Learning Test verbal recall (immediate) – MDMA users versus polydrug controls

The Rey Auditory Verbal Learning Test (RAVLT) is one of the most widely used neuropsychological assessment instruments in our evidence-base. Amongst a broad range of subscales reflecting immediate memory, the most commonly reported was the sum of items remembered across all five initial trials in the test. These data are shown and

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TABLE 4 *Individual outcome measures: summary of meta-analysis results*

	Current ecstasy users vs controls				Former ecstasy users vs controls				All ecstasy-exposed vs controls			
	n	**MD**	**(95% CI)**	***p***	***n***	**MD**	**(95% CI)**	***p***	***n***	**MD**	**(95% CI)**	***p***
MDMA users vs polydrug controls												
RAVLT verbal recall (immediate)	8	−3.912	(−7.124 to −0.700)	0.017	2	−5.497	(−17.216 to 6.221)	0.358	8	−4.049	(−6.994 to −1.105)	0.007
RAVLT verbal recall (delayed)	7	−3.727	(−6.784 to −0.671)	< 0.001	1	−3.000	(−5.435 to −0.565)	–	7	−1.173	(−1.770 to −0.575)	< 0.001
RBMT prose recall (immediate)	6	−0.340	(−1.198 to 0.518)	0.437	4	−1.436	(−2.638 to −0.234)	0.019	6	−0.657	(−1.308 to −0.006)	0.048
RBMT prose recall (delayed)	6	−0.441	(−1.195 to 0.314)	0.252	4	−1.726	(−2.890 to −0.563)	0.004	6	−0.769	(−1.407 to −0.131)	0.018
Digit span (forwards)	5	−0.449	(−0.817 to −0.080)	0.017	1	−0.270	(−1.123 to 0.583)	–	5	−0.421	(−0.759 to −0.082)	0.015
Digit span (backwards)	6	−0.626	(−1.081 to −0.170)	0.007	0	–	–	–	6	−0.626	(−1.081 to −0.170)	0.007
IQ (National Adult Reading Test)	13	0.002	(−0.953 to 0.957)	0.996	5	−2.745	(−5.299 to −0.191)	0.035	13	−0.321	(−1.248 to 0.606)	0.498
MDMA users vs drug-naïve controls												
IQ (National Adult Reading Test)	6	−0.372	(−1.657 to 0.913)	0.570	2	−1.174	(−4.501 to 2.153)	0.489	6	−0.474	(−1.618 to 0.670)	0.417

MD, mean difference; MDMA, 3,4-methylenedioxymethamphetamine (ecstasy); RAVLT, Rey Auditory Verbal Learning Test; RBMT, Rivermead Behavioural Memory Test.

synthesised using a random-effects meta-analysis in *Figure 2*. We include one study[91] for which reported data are based on the Dutch translation of the test.

The evidence for worse performance in ecstasy-exposed populations is strong, with a mean difference of around four items. This difference equates to slightly more than half a standard deviation in the normative population (the norm for those aged 20–29 is 56.1 items; SD 7.3).[92]

Sensitivity analysis with aggregated comparisons for each study provides a mean difference estimated at –3.758 (95% CI –7.126 to –0.391), suggesting that our primary analysis may marginally overestimate the difference between populations. More notable than this slight reduction in effect estimate is the revised hypothesis test: whereas, in the primary analysis, evidence is strong for a difference between populations ($p = 0.007$), the sensitivity analysis provides a p-value that, while still comfortably within the bounds of conventional statistical significance, is somewhat less compelling ($p = 0.029$).

There is no evidence of small-study bias in this dataset (Egger's $p = 0.336$), and the funnel plot (not shown) had an unremarkable appearance.

Sufficient data were available to attempt metaregression analyses for 15 covariates, shown in *Table 5*. There was no evidence of a dose–response effect per se (see *Figure 88* in Appendix 7). There was the suggestion of an association between duration of use and extent of memory deficit, with those who had used ecstasy for the longest performing worst, relative to their respective controls. However, this trend was not strong enough to achieve conventional statistical significance.

For metaregressions assessing the influence of confounding (inter-arm asymmetry), significant results were seen for age, gender and cocaine exposure. For age (*Figure 3*), a positive coefficient was estimated, suggesting that the younger the ecstasy users were in comparison to controls, the worse their relative performance in the memory test.

The effect of gender imbalance is shown in *Figure 4*. It can be seen that the plot is characterised by a number of studies in which gender distribution is well balanced (six of the datapoints appear on or close to the graph's y-axis). Aside from these studies, it appears to be the case that a negative inter-arm gender difference (indicating that the proportion of males was lower in the ecstasy-exposed arm than in the polydrug controls) is associated with little or no difference between arms in memory performance. Conversely, those studies in which greatest difference was seen between populations were also those in which ecstasy-exposed arms had a greater proportion of men than their respective control groups. These findings may not be a surprise because women are often found to score more highly in the RAVLT than men.[48]

Figure 5 depicts the influence of imbalances in cocaine exposure on measured memory performance. If the model estimated in this analysis were to be accepted, confounding by exposure to cocaine would account for most of the difference between cohorts. The adjusted estimate of mean difference (i.e. the difference that would be expected if groups were perfectly matched for cocaine exposure) is –1.669 (95% CI –5.294 to 1.955). Under this model, the evidence for an underlying difference in populations appears weak ($p = 0.367$).

Rey Auditory Verbal Learning Test verbal recall (delayed) – MDMA users versus polydrug controls

In addition to the estimate of immediate memory, we were able to synthesise one RAVLT subscale reflecting delayed verbal memory: items remembered in trial 8. Seven studies provided data on this outcome measure. Details are presented, along with a random-effects meta-analysis, in *Figure 6*.

The results of this analysis reflect those obtained for RAVLT immediate memory (see *Figure 2*) fairly closely. Ecstasy-exposed individuals are estimated to recall a little over one item fewer than polydrug controls. Again, this difference equates to approximately half a standard deviation in the normative population (the norm for those aged 20–29 years is 11.3 items; SD 2.3).[92] The probability of such results occurring if there were no underlying difference between cohorts is very small ($p < 0.001$).

Sensitivity analysis with single, pooled comparisons for each study provides a mean difference estimated at –1.134 (95% CI –1.805 to –0.463), which is extremely close to the primary analysis.

Egger's test for small-study bias falls some way short of significance ($p = 0.145$); nevertheless, we note that the funnel plot for this dataset (*Figure 7*) shows that the most extreme effect estimates tended to come from the least precise studies.

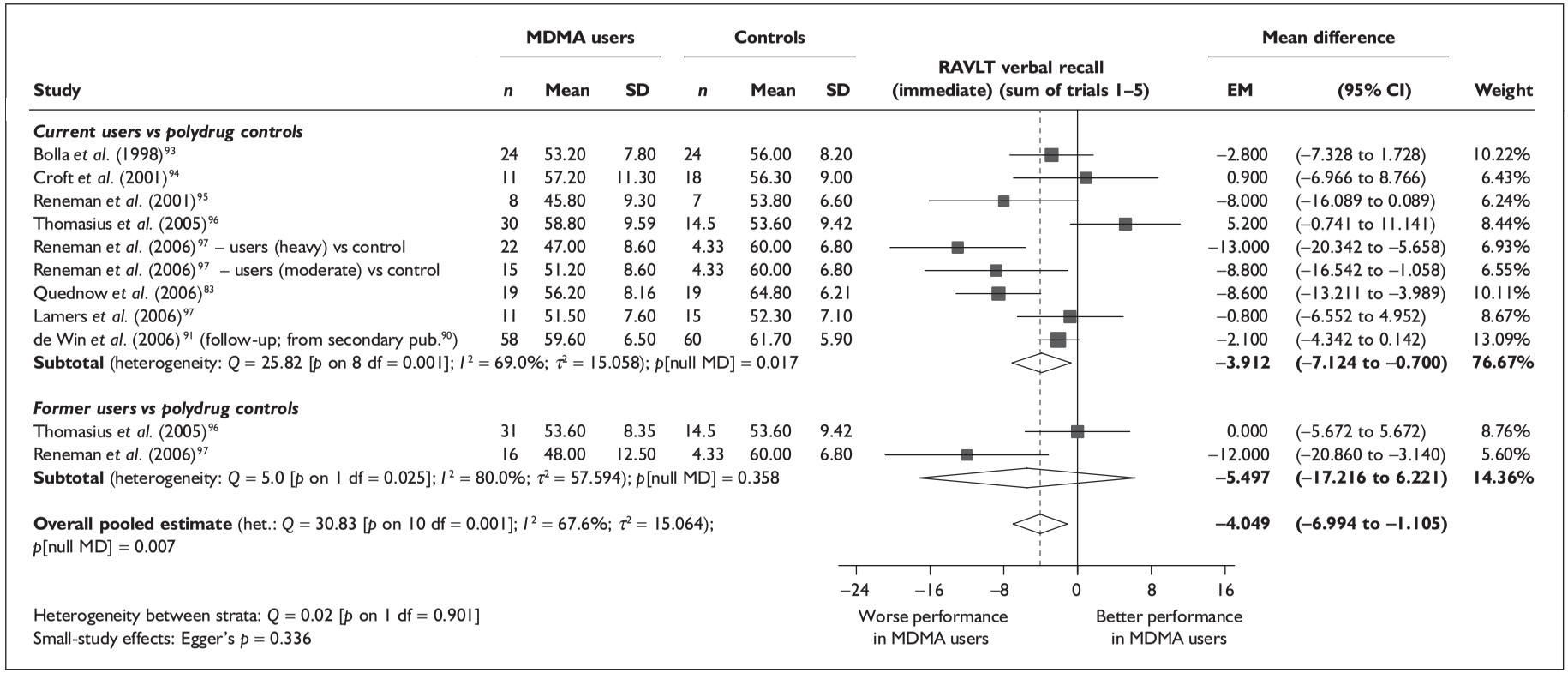

FIGURE 2 *Rey Auditory Verbal Learning Test (RAVLT) verbal recall (immediate) (sum of trials 1–5) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

TABLE 5 *Rey Auditory Verbal Learning Test (RAVLT) verbal recall (immediate) (sum of trials 1–5) – ecstasy users versus polydrug controls: univariate metaregression results*

	Effect modification				Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**WMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	11	−1.167	(−2.466 to 0.132)	0.078			
Sex (% male)	10	−10.092	(−31.899 to 11.715)	0.364			
IQ	5	0.418	(−0.729 to 1.565)	0.475			
Education (years)	5	1.901	(−0.208 to 4.010)	0.077			
Characteristics of ecstasy exposure							
ETLD (tablets)	9	0.003	(−0.010 to 0.015)	0.689			
ETLE (occasions)	< 5						
Period since last consumption (days)	5	0.010	(−0.028 to 0.048)	0.599			
Duration of ecstasy use (days)	7	−0.003	(−0.007 to 0.000)	0.074			
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	11	1.617	(0.028–3.206)	0.046	−2.958	(−5.867 to −0.048)	0.046
Sex (% male)	10	−20.519	(−36.621 to −4.416)	0.013	−3.299	(−5.887 to −0.710)	0.013
Baseline intelligence measures (SMD)	6	4.105	(−6.271 to 14.480)	0.438	−1.030	(−6.432 to 4.373)	0.709
Education (years)	5	1.375	(−1.313 to 4.064)	0.316	−2.486	(−6.560 to 1.588)	0.232
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	10	−3.629	(−7.875 to 0.618)	0.094	−3.022	(−6.603 to 0.558)	0.098
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	10	2.475	(−10.178 to 15.127)	0.701	−5.773	(−13.948 to 2.403)	0.166
Exposure to cocaine (ETLD)	< 5						
Exposure to cocaine (SMD)	9	−6.003	(−11.127 to −0.880)	0.022	−1.669	(−5.294 to 1.955)	0.367
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	9	−5.439	(−16.520 to 5.643)	0.336	−4.424	(−8.369 to −0.480)	0.028

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference; WMD, weighted mean difference.

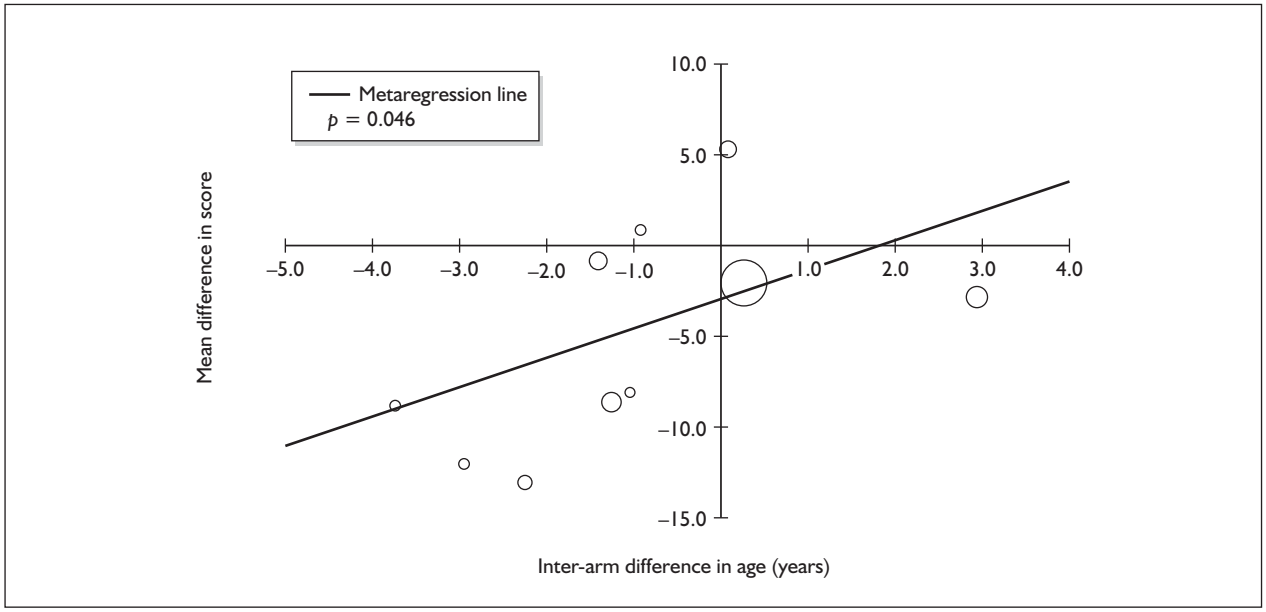

FIGURE 3 *Rey Auditory Verbal Learning Test (RAVLT) verbal recall (immediate) (sum of trials 1–5) – ecstasy users versu.polydrug controls: mean difference in score against inter-arm asymmetry in age.*

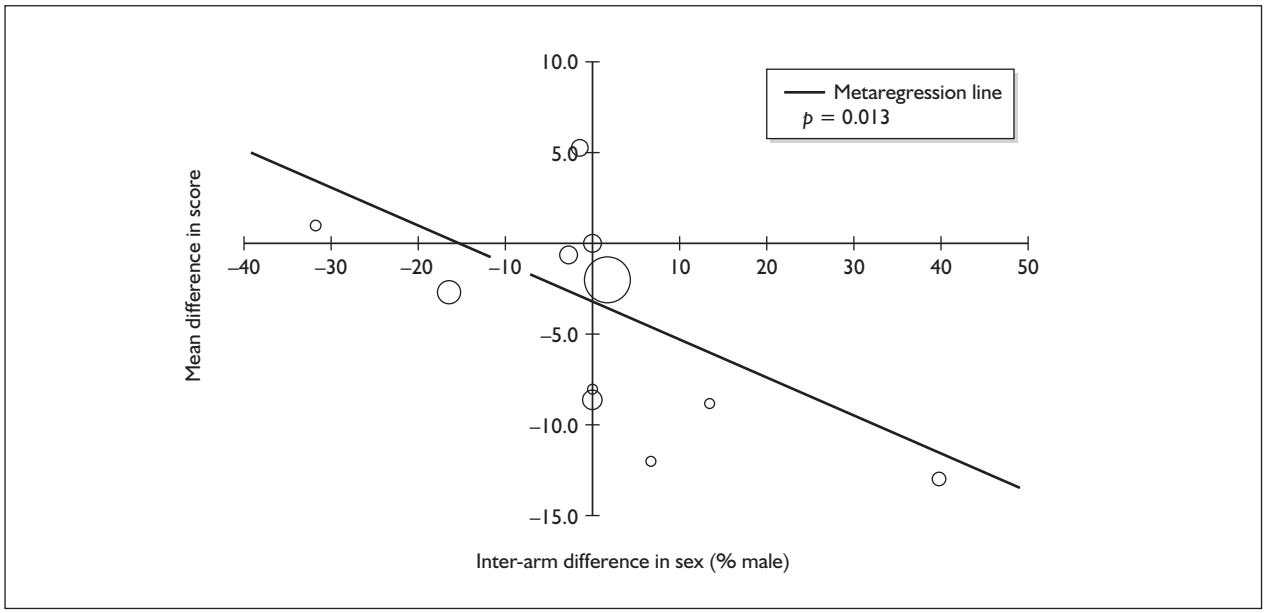

FIGURE 4 *Rey Auditory Verbal Learning Test (RAVLT) verbal recall (immediate) (sum of trials 1–5) – ecstasy users versus polydrug controls: mean difference in score against inter-arm asymmetry in gender.*

Sufficient data were available to attempt metaregression analyses for 13 covariates, shown in *Table 6*. There was a weak suggestion of a dose–response effect, with more extreme effects seen in participants with greater ETLD of ecstasy. However, this finding is based on a small and – visually, at least – not especially convincing dataset (see *Figure 89* in Appendix 7).

The one metaregression that did produce a p-value < 0.05 was that using asymmetry in baseline intelligence as covariate (*Figure 8*). However, the negative coefficient means that the direction of this effect is counterintuitive, suggesting that greater memory deficits can be expected whenever ecstasy-exposed cohorts are *more* intelligent than their comparators. It is difficult to explain this finding, so it is tempting to infer a Type I error, especially in the context of multiple testing.

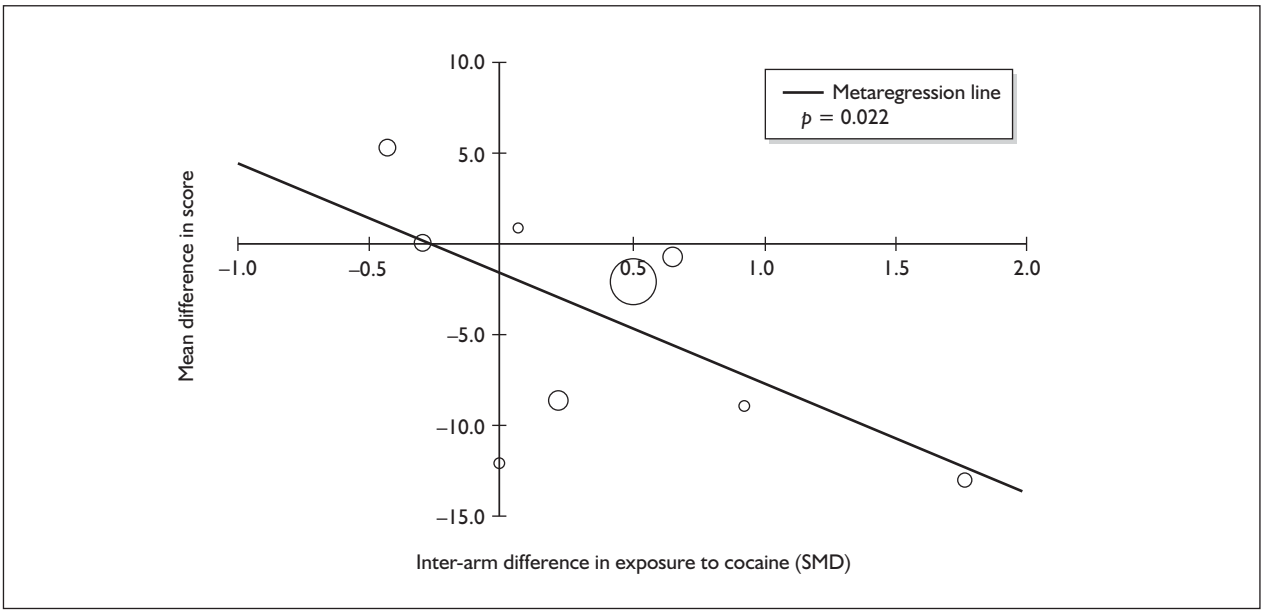

FIGURE 5 *Rey Auditory Verbal Learning Test (RAVLT) verbal recall (immediate) (sum of trials 1–5) – ecstasy users versus polydrug controls: mean difference in score against inter-arm asymmetry in cocaine exposure (standardised mean difference).*

Rivermead Behavioural Memory Test prose recall (immediate) – MDMA users versus polydrug controls

The Rivermead Behavioural Memory Test (RBMT) is another instrument that is well represented in the assembled evidence-base. In particular, the prose (story) recall test was administered by enough investigators to make meta-analysis possible for both immediate and delayed memory (for the latter, see next section).

In total, this analysis includes 12 comparisons, drawn from six different studies (eight comparisons from six studies providing data for current ecstasy users and four comparisons from four studies providing data for former ecstasy users). One study was excluded from analysis because it presented only scaled scores.[101] We included data from the 2006 study by Reneman *et al.*,[97] which presents results as the sum of two consecutive administrations of the test, by halving the reported figures (although this may not provide an accurate estimate of dispersion).

When meta-analysed (*Figure 9*), these data suggest that ecstasy-exposed cohorts recall an average of two-thirds of an item fewer than polydrug controls. It should be noted that there is a fairly wide range of performance, with control group scores ranging from 4.3 to 9.5. Sensitivity analysis using the aggregated data approach generated a comparable effect estimate (MD –0.720); however – because this approach was, in this instance, subject to greater uncertainty than the primary analysis – the evidence for an exposure effect has a less statistically robust appearance [95% CI –1.572 to 0.133; p(null MD) = 0.098]. There is no evidence of small-study bias in this dataset (Egger's $p = 0.332$), and the funnel plot (not shown) had an unremarkable appearance.

Sufficient data were available to attempt metaregression analyses for 12 covariates; details are shown in *Table 7*, with those analyses with results that achieved or approached conventional levels of significance discussed in detail below. There was no evidence of a dose–response effect (see *Figure 90* in Appendix 7).

The most statistically robust – and intuitively appealing – metaregression assesses the relationship between baseline intelligence imbalances and RBMT performance, as shown in *Figure 10*. The positive coefficient implies that, the greater the extent to which ecstasy users outperformed ecstasy-naïve participants on intelligence measures, the less they could be expected to suffer in comparison to controls when it came to the outcome of interest. This strongly suggests that the apparent exposure effect is confounded by this variable. The intercept of the metaregression – which, in an analysis of this type, provides an adjusted estimate of effect size accounting for the influence of the covariate – is, at –0.471 (95% CI –1.126 to 0.183), somewhat reduced compared to the primary analysis. More notably still, the hypothesis test assessing the evidence against a null effect appears much weaker

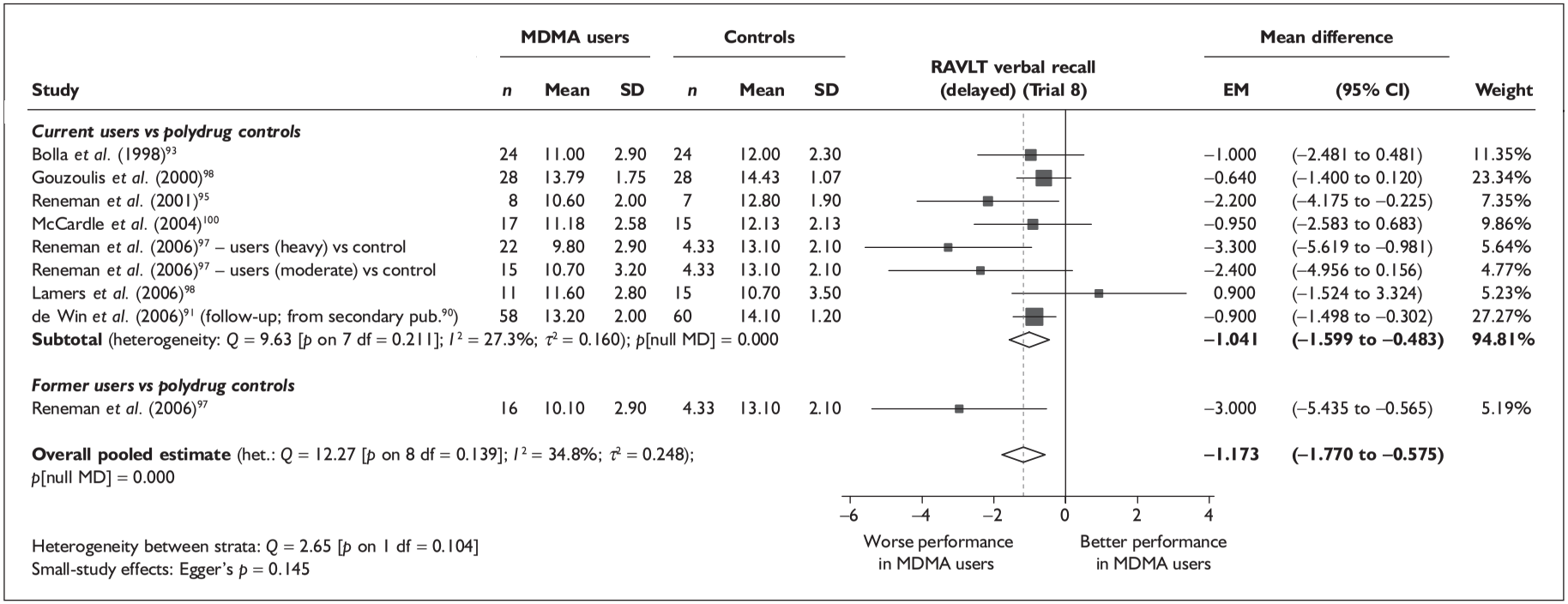

FIGURE 6 *Rey Auditory Verbal Learning Test (RAVLT) verbal recall (delayed) (trial 8) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

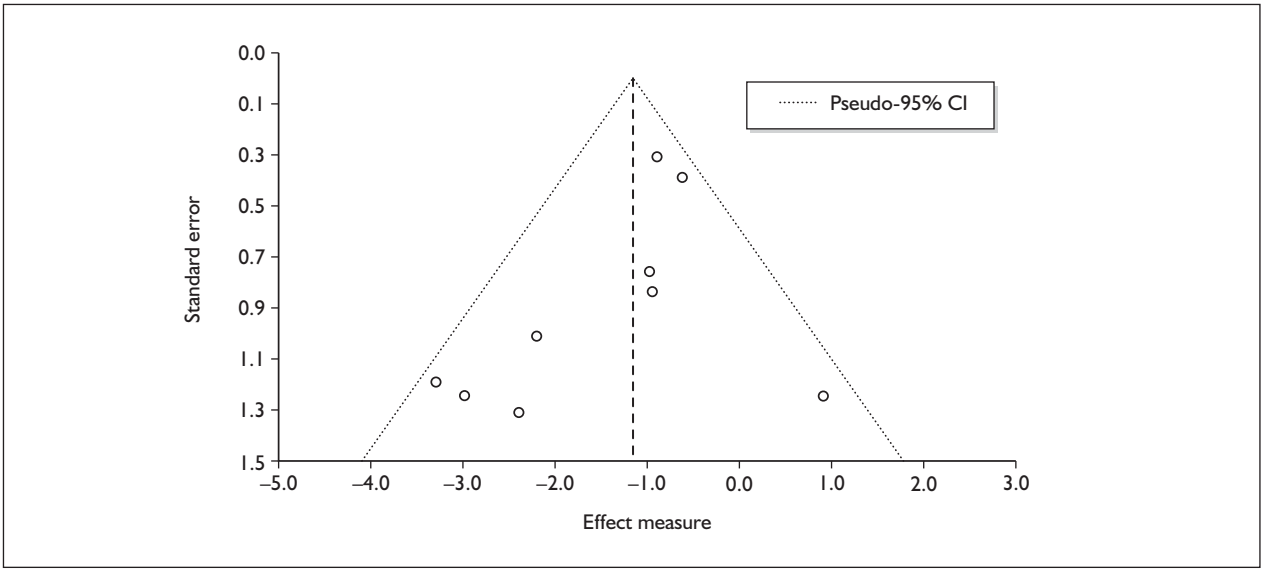

FIGURE 7 *Rey Auditory Verbal Learning Test (RAVLT) verbal recall (delayed) (trial 8) – ecstasy users versus polydrug controls: funnel plot.*

($p = 0.158$). According to this model, then, the apparent difference between cohorts is at least partially ascribable to unequal intelligence status.

The second metaregression producing results that would, conventionally, be considered statistically significant covaries asymmetry in exposure to alcohol against the outcome of interest. The relationship between these variables is depicted in *Figure 11*. While, at first glance, this looks like a relatively strong association, it should be noted that a positive correlation is estimated, suggesting that those studies in which ecstasy-exposed participants exhibited better memory performance were those in which ecstasy users drank *more* alcohol than controls.

Rivermead Behavioural Memory Test prose recall (delayed) – MDMA users versus polydrug controls

This analysis includes the same 12 comparisons from six studies described for immediate recall, above. Once more, the study by Zakzanis *et al.*[101] was excluded, and the datapoints from Reneman *et al.*[97] were halved.

When meta-analysed (*Figure 12*), these data provide a very similar picture to that seen in the synthesis of immediate recall data (*Figure 9*), suggesting that ecstasy-exposed cohorts recall an average of around three-quarters of an item fewer than polydrug controls. Again, a fairly wide range of performance was seen, with control group scores ranging from 3.85 to 8.95. Sensitivity analysis using the aggregated data approach generated a similar effect estimate and, in this instance, the reanalysis retained an exposure effect that would conventionally be considered statistically significant [MD –0.864; 95% CI –1.688 to –0.039; p(null MD) = 0.040].

There is no evidence of small-study bias in this dataset (Egger's $p = 0.571$), and the funnel plot (not shown) had an unremarkable appearance.

Sufficient data were available to attempt metaregression analyses for 12 covariates; details are shown in *Table 8*, with those analyses with results that achieved or approached conventional levels of significance discussed in detail below. There was no evidence of a dose–response effect (see *Figure 91* in Appendix 7).

A pronounced positive correlation was found between baseline intelligence imbalances and RBMT delayed memory performance, as shown in *Figure 13*. This association – which closely reflects the results for RBMT immediate memory (see *Figure 10*) – suggests that results may be at least partially explained by asymmetry in intelligence. However, even when results are adjusted for this confounding, fairly strong evidence of an underlying exposure effect remains ($p = 0.026$).

The effects of confounding in exposure to amphetamines and alcohol are shown in *Figures 14* and *15* respectively. Once again, these findings are reminiscent of the results seen in equivalent metaregressions for RBMT immediate memory. In both cases, a fairly strong positive correlation is seen, again suggesting that the studies in which ecstasy users also had additional exposure to other

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TABLE 6 *Rey Auditory Verbal Learning Test (RAVLT) verbal recall (delayed) (trial 8) – ecstasy users versus polydrug controls: univariate metaregression results*

	Effect modification				Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**WMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	9	−0.183	(−0.398 to 0.032)	0.084			
Sex (% male)	9	−1.138	(−5.829 to 3.553)	0.584			
IQ	5	0.034	(−0.420 to 0.488)	0.826			
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	6	−0.002	(−0.006 to 0.001)	0.155			
ETLE (occasions)	< 5						
Period since last consumption (days)	5	0.001	(−0.017 to 0.018)	0.931			
Duration of ecstasy use (days)	8	−0.001	(−0.001 to 0.000)	0.104			
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	9	0.293	(−0.123 to 0.710)	0.140	−1.090	(−1.724 to −0.456)	0.005
Sex (% male)	9	−4.338	(−10.024 to 1.347)	0.114	−1.055	(−1.692 to −0.418)	0.006
Baseline intelligence measures (SMD)	7	−2.034	(−3.977 to −0.091)	0.043	−2.082	(−3.271 to −0.893)	0.006
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	8	−0.776	(−1.850 to 0.297)	0.127	−0.743	(−1.668 to 0.182)	0.097
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	7	0.352	(−2.677 to 3.381)	0.777	−1.770	(−4.025 to 0.484)	0.100
Exposure to cocaine (ETLD)	< 5						
Exposure to cocaine (SMD)	6	−0.918	(−3.963 to 2.128)	0.450	−0.796	(−3.328 to 1.737)	0.432
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	7	0.978	(−1.469 to 3.425)	0.351	−1.768	(−3.173 to −0.362)	0.023

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference; WMD, weighted mean difference.

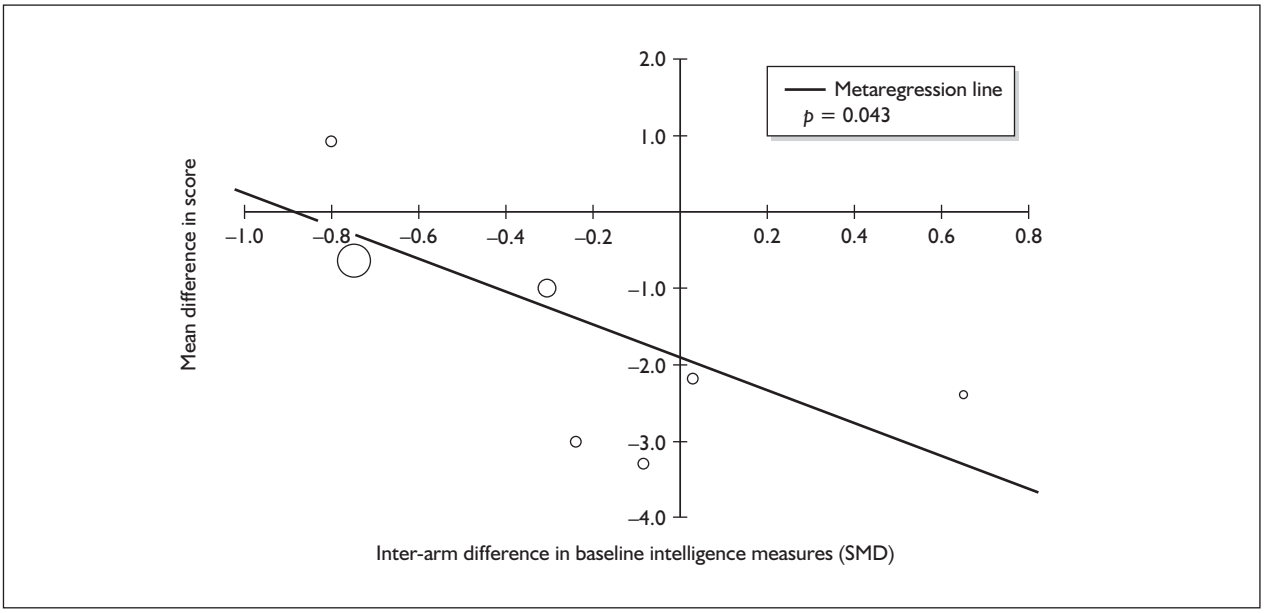


FIGURE 8 *Rey Auditory Verbal Learning Test (RAVLT) verbal recall (delayed) (trial 8) – ecstasy users versus polydrug controls: mean difference in score against inter-arm asymmetry in baseline intelligence measures (standardised mean difference).*

substances, when compared to controls, were also those studies in which they performed best on the RBMT.

Because the analyses for immediate and delayed memory as measured by the RBMT are based on the same studies, and have very similar results, it is not a surprise to see analogous pictures emerging in metaregression analyses. With this in mind, it should be emphasised that the repetition of surprising results does not necessarily lend further credence to them. If the first paradoxical result-set is dismissed as a Type I error – that is to say, the apparently suggestive results have occurred by chance variation – then one might expect to see that artefactual pattern repeated in other analyses that are based on closely related data.

Digit span (forwards) – MDMA users versus polydrug controls

We identified seven comparisons, drawn from five studies, in which a forwards digit span was used to assess differences in verbal memory between ecstasy users and polydrug controls (six comparisons from five studies providing data for current ecstasy users and a single comparison providing data for former ecstasy users). The digit span data reported by de Win and colleagues[90,91] was excluded from this analysis, because the investigators had used modified methods (with three instead of two series of digits per length), leading to scores that were not directly comparable with the other studies.

A random-effects meta-analysis of the identified data (*Figure 16*) suggests that ecstasy users have an average span of approximately 0.4 digits less than polydrug controls. This effect is just strong enough to achieve conventional statistical significance. Sensitivity analysis using the aggregated data approach generated a very similar effect estimate [MD –0.412; 95% CI –0.746 to –0.078; p(null MD) = 0.016].

None of the average scores recorded by ecstasy users or controls are outside the normal range for this test (Lezak *et al.*[48] refer to any span of six or higher as 'well within normal limits').

There is no evidence of small-study bias in this dataset (Egger's $p = 0.945$), and the funnel plot (not shown) had an unremarkable appearance.

The small size of the dataset meant that we were able to attempt metaregression analyses for only five covariates, none of which provided any significant results. Details are shown in *Table 9*. There was no evidence of a dose–response effect (see *Figure 92* in Appendix 7).

Digit span (backwards) – MDMA users versus polydrug controls

We identified eight comparisons, drawn from six studies, in which a backwards digit span was used to assess differences in verbal memory between ecstasy users and polydrug controls (all data related to current ecstasy users). Once more, we excluded data from the studies by de Win's group,[90,91] because of their inconsistent methods.

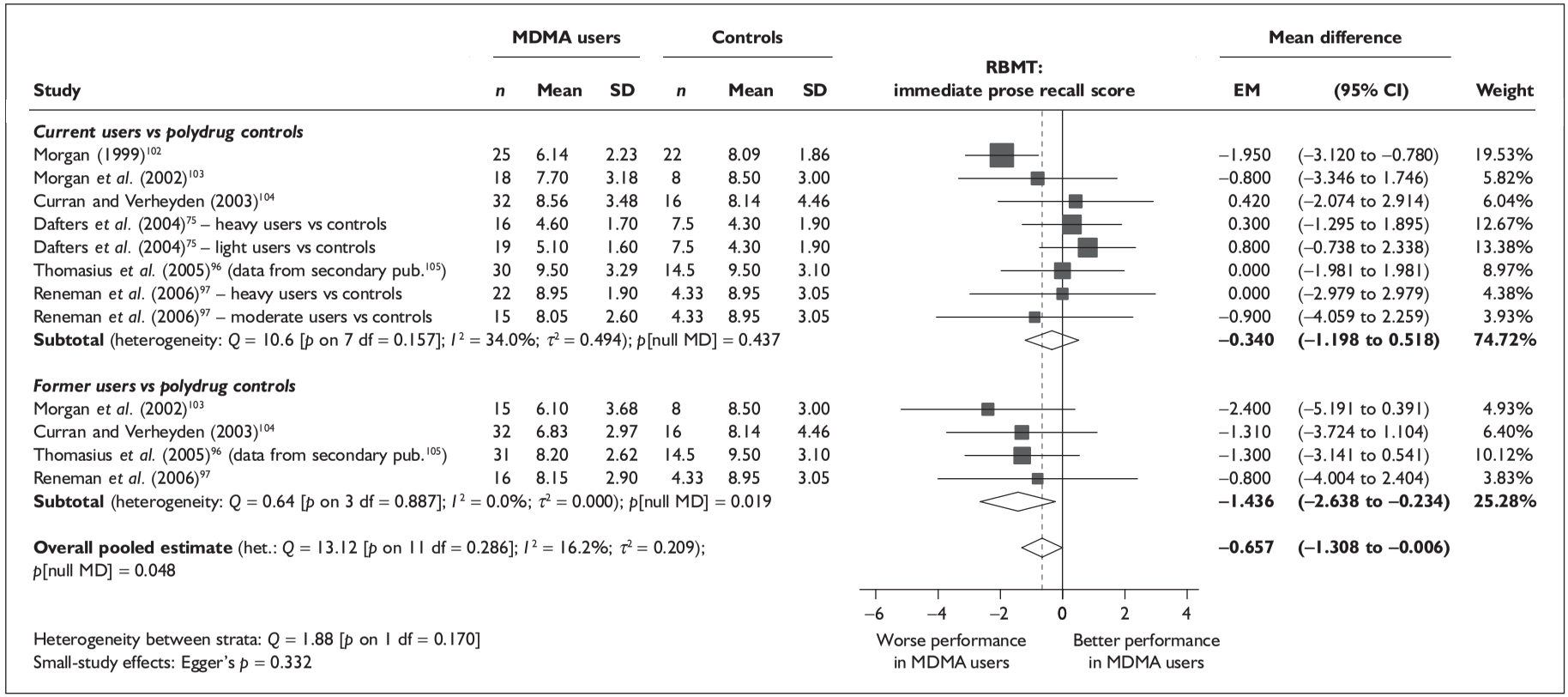


FIGURE 9 *Rivermead Behavioural Memory Test (RBMT) prose recall (immediate) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

TABLE 7 *Rivermead Behavioural Memory test (RBMT) prose recall (immediate) – ecstasy users versus polydrug controls: univariate metaregression results*

	Effect modification				Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**WMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	12	0.007	(−0.394 to 0.408)	0.974			
Sex (% male)	12	0.431	(−3.658 to 4.520)	0.836			
IQ	9	0.077	(−0.101 to 0.256)	0.398			
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	10	0.000	(−0.003 to 0.003)	0.995			
ETLE (occasions)	< 5						
Period since last consumption (days)	< 5						
Duration of ecstasy use (days)	6	0.002	(−0.004 to 0.009)	0.470			
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	12	0.088	(−0.286 to 0.461)	0.646	−0.691	(−1.379 to −0.002)	0.049
Sex (% male)	12	4.170	(−0.195 to 8.535)	0.061	−0.480	(−1.099 to 0.139)	0.128
Baseline intelligence measures (SMD)	10	1.656	(0.522−2.792)	0.004	−0.471	(−1.126 to 0.183)	0.158
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	12	−0.092	(−1.336 to 1.152)	0.885	−0.615	(−1.426 to 0.196)	0.137
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	11	1.784	(−0.074 to 3.642)	0.060	−1.848	(−3.592 to −0.105)	0.038
Exposure to cocaine (ETLD)	< 5						
Exposure to cocaine (SMD)	10	0.461	(−0.943 to 1.864)	0.520	−0.730	(−1.692 to 0.232)	0.137
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	12	1.263	(0.288–2.237)	0.011	−0.682	(−1.257 to −0.107)	0.020

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference; WMD, weighted mean difference

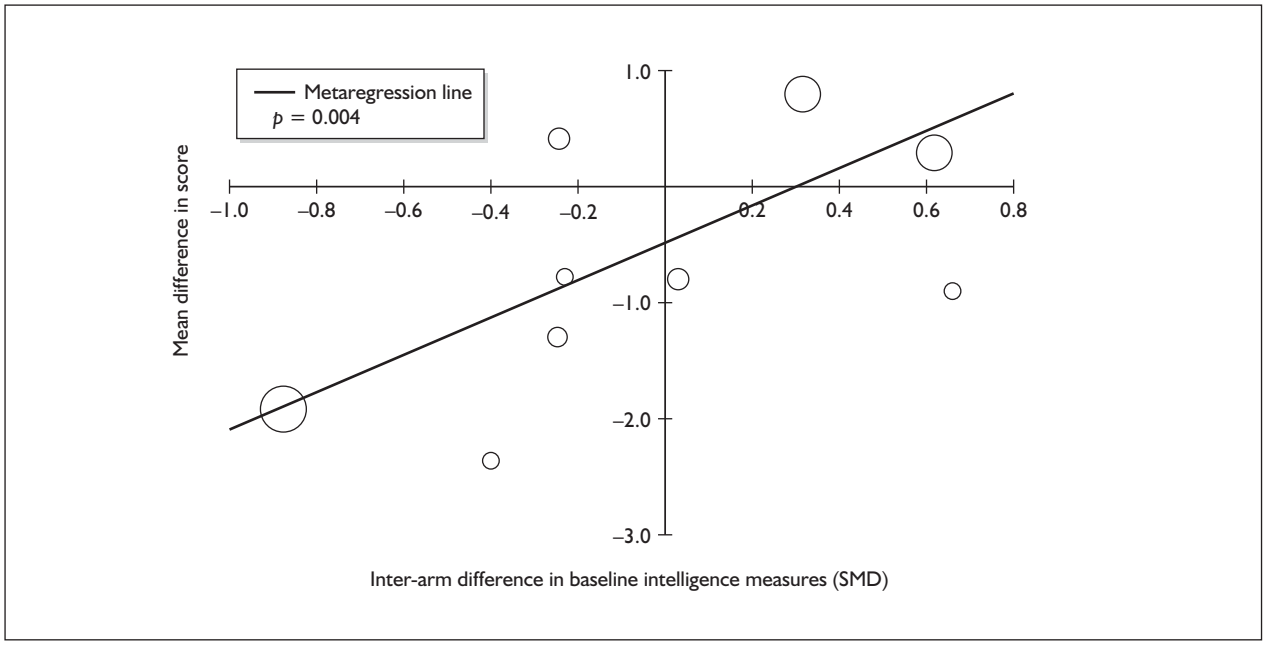


FIGURE 10 *Rivermead Behavioural Memory Test (RBMT) prose recall (immediate) – ecstasy users versus polydrug controls: mean difference in score against inter-arm asymmetry in baseline intelligence measures (standardised mean difference).*

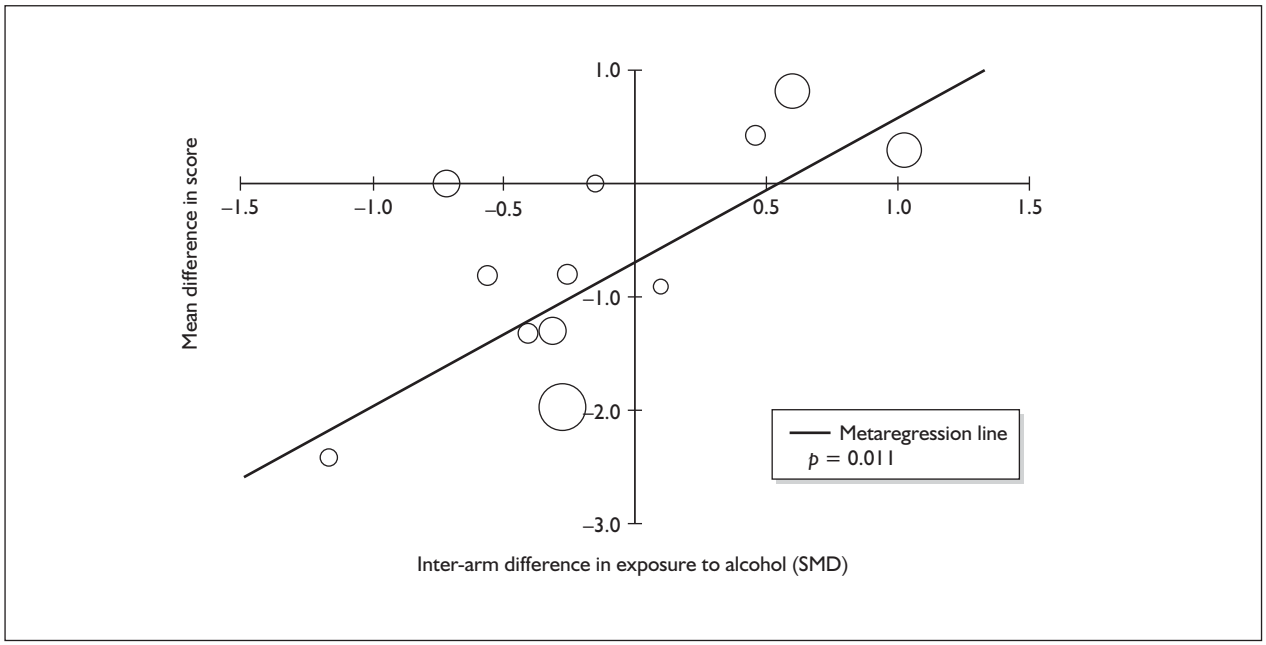


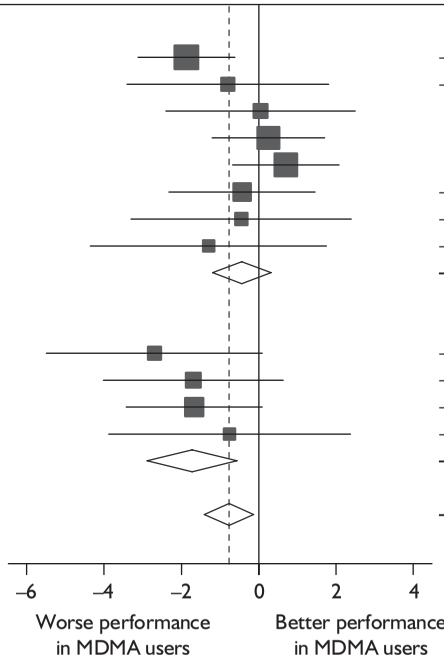
FIGURE 11 *Rivermead Behavioural Memory Test (RBMT) prose recall (immediate) – ecstasy users versus polydrug controls: mean difference in score against inter-arm asymmetry in exposure to alcohol (standardised mean difference).*

Meta-analysed results (*Figure 17*) are fairly similar to those seen in the forwards digit span, with a significant difference between ecstasy users and controls of about 0.6 digits. Again, all average scores appear to be within the normal range. Sensitivity analysis using the aggregated data approach generated a very similar effect estimate [MD –0.638; 95% CI –1.096 to –0.181; p(null MD) = 0.006].

There is no evidence of small-study bias in this dataset (Egger's $p = 0.416$), and the funnel plot (not shown) had an unremarkable appearance.

There were sufficient data to attempt metaregression analyses for seven covariates; details are shown in *Table 10*. None of the analyses provided significant results, and there was no evidence of a dose–response effect (see *Figure 93* in Appendix 7).

Study	MDMA users n	MDMA users Mean	MDMA users SD	Controls n	Controls Mean	Controls SD	RBMT: delayed prose recall score	Mean difference EM	Mean difference (95% CI)	Weight
Current users vs polydrug controls										
Morgan (1999)[102]	25	5.36	2.48	22	7.23	1.90		−1.870	(−3.125 to −0.615)	16.90%
Morgan *et al.* (2002)[103]	18	6.20	3.39	8	7.00	3.00		−0.800	(−3.404 to 1.804)	5.34%
Curran and Verheyden (2003)[104]	32	7.57	3.53	16	7.52	4.33		0.050	(−2.399 to 2.499)	5.96%
Dafters *et al.* (2004)[75] – heavy users vs controls	16	4.10	1.65	7.5	3.85	1.70		0.250	(−1.211 to 1.711)	13.72%
Dafters *et al.* (2004)[75] – light users vs controls	19	4.55	1.45	7.5	3.85	1.70		0.700	(−0.680 to 2.080)	14.86%
Thomasius *et al.* (2005)[96] (data from secondary pub.[105])	30	8.52	3.12	14.5	8.95	2.96		−0.430	(−2.320 to 1.460)	9.24%
Reneman *et al.* (2006)[97] – heavy users vs controls	22	7.20	1.95	4.33	7.65	2.90		−0.450	(−3.299 to 2.399)	4.55%
Reneman *et al.* (2006)[97] – moderate users vs controls	15	6.35	2.70	4.33	7.65	2.90		−1.300	(−4.353 to 1.753)	4.01%
Subtotal (heterogeneity: $Q = 8.99$ [p on 7 df = 0.253]; $I^2 = 22.2\%$; $\tau^2 = 0.256$); p[null MD] = 0.252								**−0.441**	**(−1.195 to 0.314)**	**74.57%**
Former users vs polydrug controls										
Morgan *et al.* (2002)[103]	15	4.30	3.68	8	7.00	3.00		−2.700	(−5.491 to 0.091)	4.72%
Curran and Verheyden (2003)[104]	32	5.83	2.73	16	7.52	4.33		−1.690	(−4.013 to 0.633)	6.53%
Thomasius *et al.* (2005)[96] (data from secondary pub.[105])	31	7.28	2.51	14.5	8.95	2.96		−1.670	(−3.431 to 0.091)	10.34%
Reneman *et al.* (2006)[97]	16	6.90	3.10	4.33	7.65	2.90		−0.750	(−3.875 to 2.375)	3.84%
Subtotal (heterogeneity: $Q = 0.85$ [p on 3 df = 0.838]; $I^2 = 0.0\%$; $\tau^2 = 0.000$); p[null MD] = 0.004								**−1.726**	**(−2.890 to -0.563)**	**25.43%**
Overall pooled estimate (het.: $Q = 13.34$ [p on 11 df = 0.272]; $I^2 = 17.5\%$; $\tau^2 = 0.217$); p[null MD] = 0.018								**−0.769**	**(−1.407 to −0.131)**	



Heterogeneity between strata: $Q = 3.5$ [p on 1df = 0.061]
Small-study effects: Egger's $p = 0.571$

FIGURE 12 *Rivermead Behavioural Memory Test (RBMT) prose recall (delayed) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

DOI: 10.3310/hta13060

TABLE 8 *Rivermead Behavioural Memory Test (RBMT) verbal recall (delayed) – ecstasy users versus polydrug controls: univariate metaregression results*

	Effect modification				Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**WMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	10	−0.260	(−0.805 to 0.285)	0.350			
Sex (% male)	12	−0.084	(−4.189 to 4.022)	0.968			
IQ	11	0.097	(−0.021 to 0.215)	0.108			
Education (years)	***< 5***						
Characteristics of ecstasy exposure:							
ETLD (tablets)	10	−0.001	(−0.004 to 0.002)	0.646			
ETLE (occasions)	< 5						
Period since last consumption (days)	< 5						
Duration of ecstasy use (days)	6	0.003	(−0.008 to 0.015)	0.569			
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	10	0.306	(−0.155 to 0.767)	0.193	−0.889	(−1.642 to −0.136)	0.021
Sex (% male)	12	4.119	(−2.129 to 10.367)	0.196	−0.533	(−1.280 to 0.214)	0.162
Baseline intelligence measures (SMD)	12	1.511	(0.366–2.657)	0.010	−0.668	(−1.256 to −0.079)	0.026
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	12	−0.115	(−1.686 to 1.456)	0.886	−0.783	(−1.622 to 0.056)	0.067
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	11	2.551	(0.491–4.612)	0.015	−2.874	(−4.926 to −0.822)	0.006
Exposure to cocaine (ETLD)	< 5						
Exposure to cocaine (SMD)	10	0.661	(−0.946 to 2.269)	0.420	−0.937	(−1.904 to 0.029)	0.057
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	12	1.379	(0.447–2.311)	0.004	−0.838	(−1.422 to −0.253)	0.005

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference; WMD, weighted mean difference.

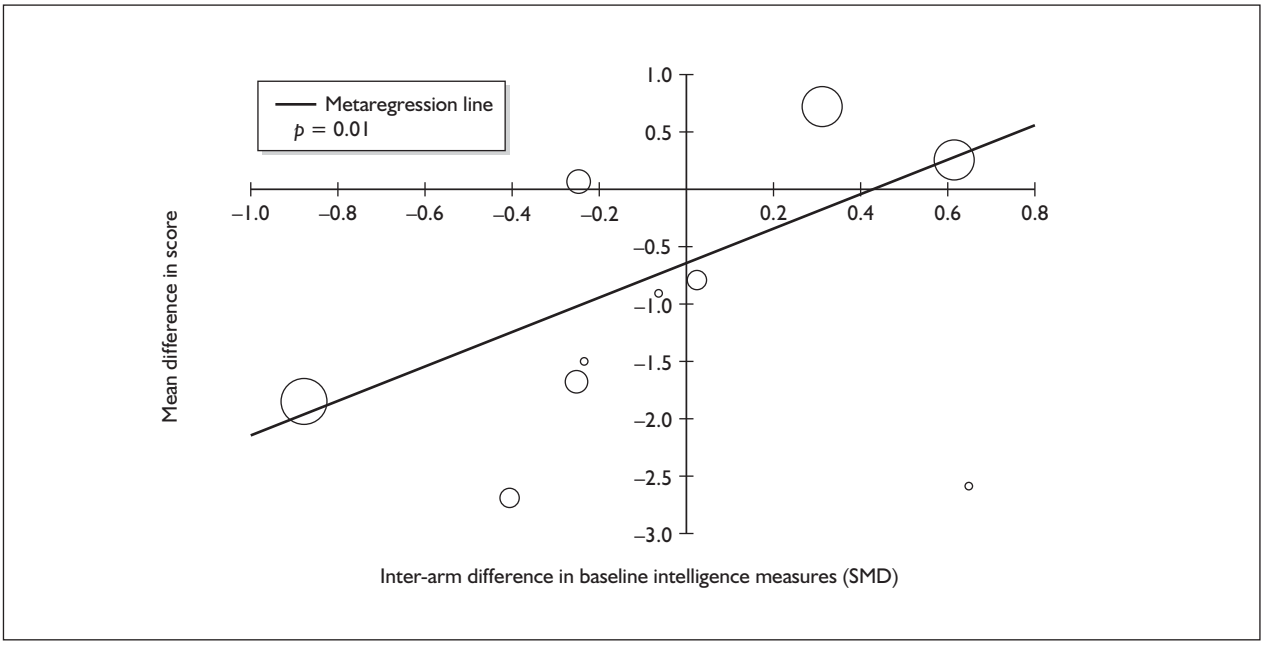


FIGURE 13 *Rivermead Behavioural Memory Test (RBMT) prose recall (delayed) – ecstasy users versus polydrug controls: mean difference in score against inter-arm asymmetry in baseline intelligence measures (standardised mean difference).*

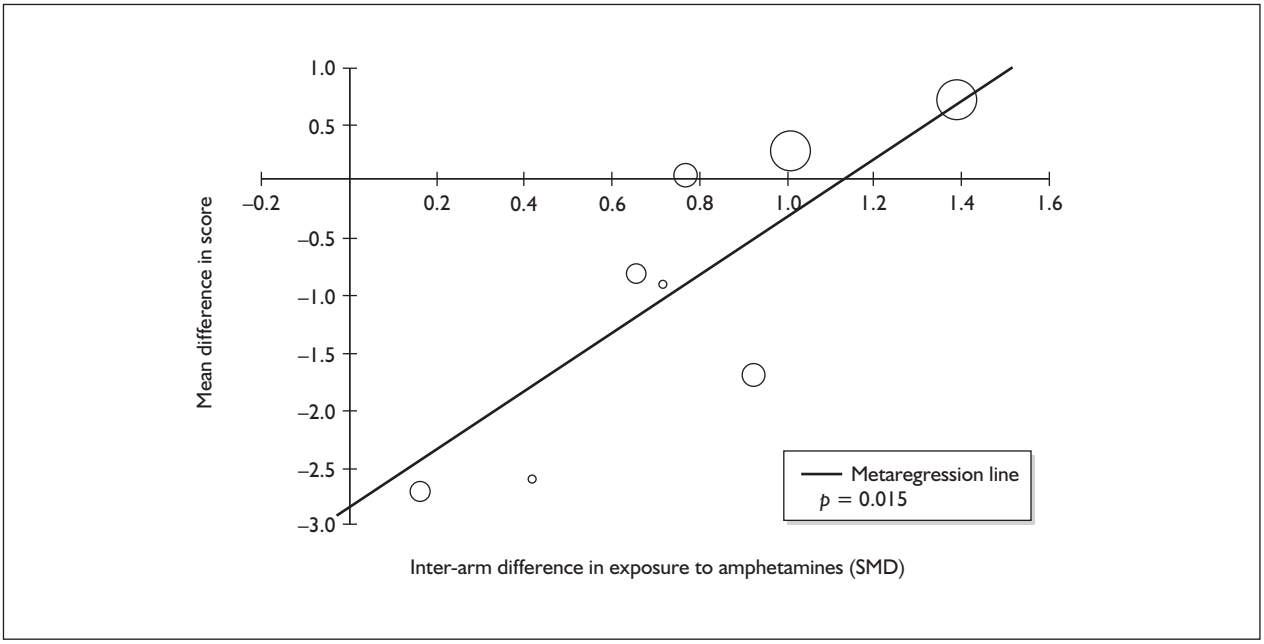


FIGURE 14 *Rivermead Behavioural Memory Test (RBMT) prose recall (delayed) – ecstasy users versus polydrug controls: mean difference in score against inter-arm asymmetry in exposure to amphetamines other than MDMA (standardised mean difference).*

IQ (National Adult Reading Test) – MDMA users versus polydrug controls

Of all the measures in the assembled evidence-base, the most frequently reported was IQ as measured by the National Adult Reading Test (it should be noted that we include here studies using foreign-language translations of the test). In the majority of cases, investigators did not present these data as outcomes of interest in their own studies, but rather used them to estimate the underlying intelligence of their participants (the most notable reason for doing so being to ensure a reasonable balance between cohorts). Nevertheless, we have included the National Adult Reading Test as an outcome measure of interest in our analyses because we believed it was reasonable to look for differences between populations with regard to this measure. Of course, if the assumptions underpinning most investigators' use of the test are correct, then we would hope to see no difference between ecstasy-exposed and ecstasy-naïve populations.

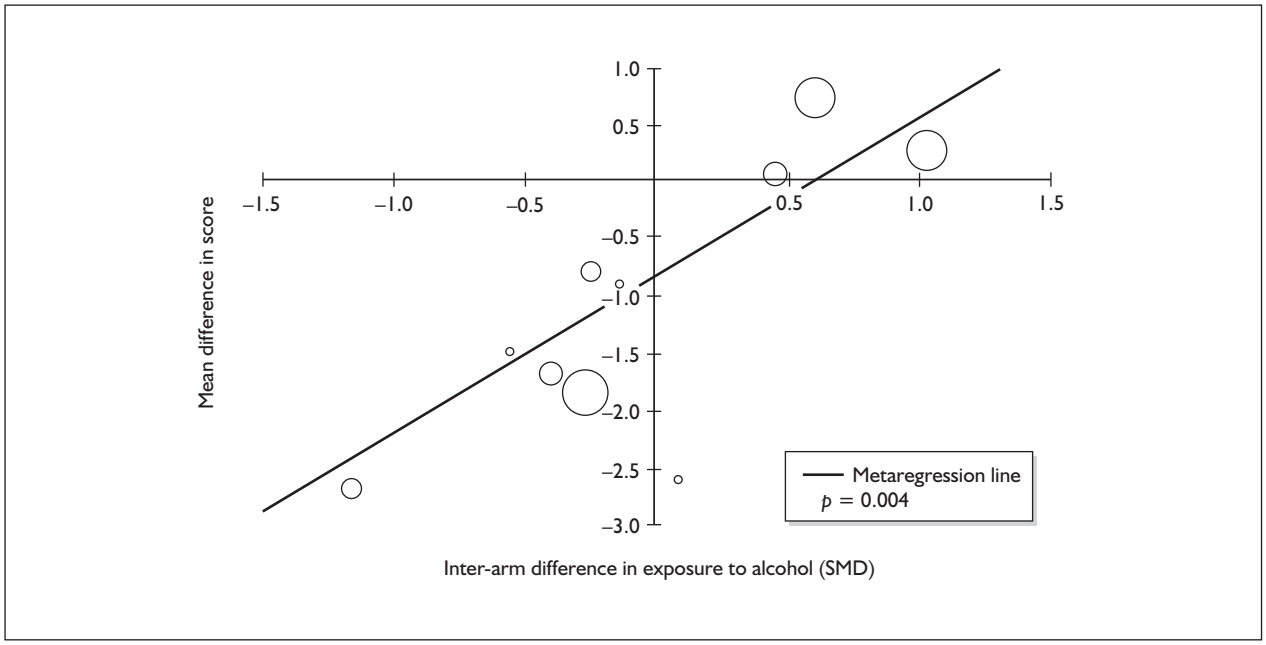


FIGURE 15 *Rivermead Behavioural Memory Test (RBMT) prose recall (delayed) – ecstasy users versus polydrug controls: mean difference in score against inter-arm asymmetry in exposure to alcohol (standardised mean difference).*

Figure 18 shows our random-effects meta-analysis of these data. It suggests that, while the IQs of ecstasy-exposed individuals were rated an average of 0.321 points lower than those of polydrug controls, this is unlikely to represent a significant difference ($p = 0.498$). Interestingly, the evidence of lower IQ scores among ecstasy users was somewhat stronger in the ex-users' stratum: former users had IQs an average of 2.75 points lower than controls, with reasonable evidence against a null effect ($p = 0.035$). It should be noted that this finding is based on a relatively small number of studies, so high susceptibility to Type I error may be inferred. In comparisons between current ecstasy users and polydrug controls, the difference between groups was very nearly zero.

Sensitivity analysis with single, pooled comparisons for each study suggests that our primary analysis may very slightly underestimate the discrepancy between cohorts (by less than 0.1 of an IQ point: MD 0.418; 95% CI –1.614 to 0.778). As might be expected, the evidence of a difference between cohorts is equally weak in this analysis ($p = 0.493$).

There is no evidence of small-study bias in this dataset (Egger's $p = 0.862$), and the funnel plot (not shown) had an unremarkable appearance.

In total, sufficient data were available to attempt metaregression analyses for 16 covariates; details are shown in *Table 11*. It should be noted that, in other analyses in this review, we have used baseline intelligence measures as an explanatory variable in metaregression analyses. In this instance, where the intelligence of study participants is the response variable of interest, these covariates have been excluded.

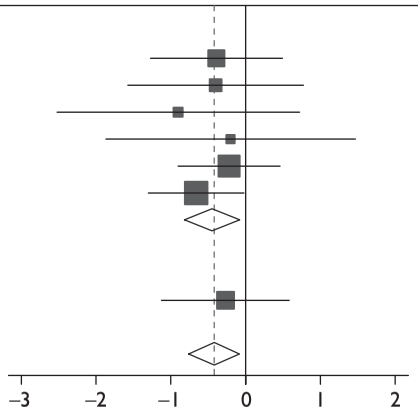
There was no evidence of a dose–response effect: cohorts with high exposure to ecstasy were no more disadvantaged against controls than those who had consumed comparatively little (see *Figure 94* in Appendix 7).

Figure 19 compares mean difference in IQ with asymmetry in the amount of alcohol exposure between study arms. It should be noted that this analysis generates a positive coefficient, suggesting that those studies in which higher IQs were found in the ecstasy-exposed participants were those in which ecstasy users drank *more* alcohol than controls. However, because this dataset shows a reasonable balance across the spectrum of imbalance of alcohol exposure, this variable has little influence on the estimated average effect of ecstasy exposure: the adjusted mean difference is less than 0.1 IQ points greater (–0.506; 95% CI –1.540 to 0.529), and just as consistent with a null difference ($p = 0.338$).

IQ (National Adult Reading Test) – MDMA users versus drug-naïve controls

As in the comparison with polydrug controls, we included studies using foreign-language translations of the test.

Study	MDMA users n	MDMA users Mean	MDMA users SD	Controls n	Controls Mean	Controls SD	Digit span (forwards)	Mean difference EM	Mean difference (95% CI)	Weight
Current users vs polydrug controls										
Gouzoulis *et al.* (2000)[99]	28	8.54	1.84	28	8.93	1.51		−0.390	(−1.272 to 0.492)	14.73%
Croft *et al.* (2001)[94]	11	9.20	1.60	18	9.60	1.50		−0.400	(−1.572 to 0.772)	8.33%
Halpern *et al.* (2004)[106] – heavy users vs controls	11	9.00	2.00	8	9.90	1.60		−0.900	(−2.521 to 0.721)	4.36%
Halpern *et al.* (2004)[106] – moderate users vs controls	12	9.70	2.20	8	9.90	1.60		−0.200	(−1.867 to 1.467)	4.12%
Wareing *et al.* (2004)[107]	42	6.52	1.23	15.5	6.74	1.15		−0.220	(−0.903 to 0.463)	24.57%
McCardle *et al.* (2004)[100]	17	6.41	0.87	15	7.07	0.96		−0.660	(−1.298 to −0.022)	28.14%
Subtotal (heterogeneity: Q = 1.26 [p on 5 df = 0.939]; I^2 = 0.0%; τ^2 = 0.000); p[MD = 0] = 0.017								**−0.449**	**(−0.817 to −0.080)**	**84.26%**
Former users vs polydrug controls										
Wareing *et al.* (2004)[107]	17	6.47	1.33	15.5	6.74	1.15		−0.270	(−1.123 to 0.583)	15.74%
Overall pooled estimate (het.: Q = 1.4 [p on 6 df = 0.966]; I^2 = 0.0%; τ^2 = 0.000); p[MD = 0] = 0.015								**−0.421**	**(−0.759 to −0.082)**	



Heterogeneity between strata: Q = 0.14 [p on 1 df = 0.706]
Small study effects: Egger's p = 0.945

FIGURE 16 *Digit span (forwards) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

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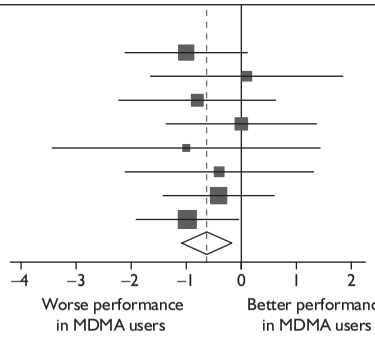
TABLE 9 *Digit span (forwards) – ecstasy users versus polydrug controls: univariate metaregression results*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**WMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	5	0.059	(−0.186 to 0.304)	0.636			
Sex (% male)	< 5						
IQ	< 5						
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	< 5						
ETLE (occasions)	< 5						
Period since last consumption (days)	< 5						
Duration of ecstasy use (days)	< 5						
Frequency of ecstasy use (occasions/ months)	< 5						
Inter-arm differences							
Age (years)	5	0.020	(−0.216 to 0.256)	0.867	−0.402	(−0.762 to −0.041)	0.029
Sex (% male)	< 5						
Baseline intelligence measures (SMD)	5	0.723	(−1.860 to 3.306)	0.583	0.049	(−1.327 to 1.426)	0.944
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	< 5						
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	< 5						
Exposure to cocaine (ETLD)	< 5						
Exposure to cocaine (SMD)	< 5						
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	< 5						

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference; WMD, weighted mean difference.

Study	MDMA users n	MDMA users Mean	MDMA users SD	Controls n	Controls Mean	Controls SD	Digit span (backwards)	Mean difference EM	Mean difference (95% CI)	Weight
Current users vs polydrug controls										
Gouzoulis *et al.* (2000)[99]	28	7.00	2.34	28	8.00	1.87		−1.000	(−2.109 to 0.109)	16.86%
Croft *et al.* (2001)[94]	11	8.00	2.60	18	7.90	1.80		0.100	(−1.647 to 1.847)	6.80%
Gouzoulis *et al.* (2003)[108] – heavy users vs controls	30	8.00	2.30	15	8.80	2.30		−0.800	(−2.226 to 0.626)	10.21%
Gouzoulis *et al.* (2003)[108] – moderate users vs controls	30	8.80	2.00	15	8.80	2.30		0.000	(−1.366 to 1.366)	11.12%
Halpern *et al.* (2004)[106] – heavy users vs controls	11	8.10	3.30	8	9.10	2.10		−1.000	(−3.433 to 1.433)	3.51%
Halpern *et al.* (2004)[106] – moderate users vs controls	12	8.70	1.60	8	9.10	2.10		−0.400	(−2.114 to 1.314)	7.07%
McCardle *et al.* (2004)[100]	17	5.12	1.65	15	5.53	1.25		−0.410	(−1.418 to 0.598)	20.44%
Reay *et al.* (2006)[109]	15	5.61	1.19	15	6.59	1.40		−0.980	(−1.910 to −0.050)	24.00%
Overall pooled estimate (het.: $Q = 2.85$ [p on 7 df = 0.898]; $I^2 = 0.0\%$; $\tau^2 = 0.000$); p[MD = 0] = 0.007								**−0.626**	**(−1.081 to −0.170)**	



Small-study effects: Egger's $p = 0.416$

FIGURE 17 *Digit span (backwards) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

DOI: 10.3310/hta13060

TABLE 10 *Digit span (backwards) – ecstasy users versus polydrug controls: univariate metaregression results*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**WMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	6	0.082	(−0.250 to 0.414)	0.628			
Sex (% male)	6	2.416	(−1.974 to 6.806)	0.281			
IQ	< 5						
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	< 5						
ETLE (occasions)	< 5						
Period since last consumption (day)	< 5						
Duration of ecstasy use (day)	5	−0.001	(−0.002 to 0.001)	0.309			
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	6	−0.149	(−0.395 to 0.098)	0.237	−0.541	(−1.044 to −0.038)	0.035
Sex (% male)	6	−2.492	(−6.390 to 1.406)	0.210	−0.642	(−1.125 to −0.160)	0.009
Baseline intelligence measures (SMD)	5	1.172	(−0.737 to 3.081)	0.229	−0.127	(−1.191 to 0.937)	0.815
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	6	0.220	(−0.558 to 0.998)	0.580	−0.826	(−1.672 to 0.021)	0.056
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	< 5						
Exposure to cocaine (ETLD)	< 5						
Exposure to cocaine (SMD)	< 5						
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	< 5						

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference; WMD, weighted mean difference.

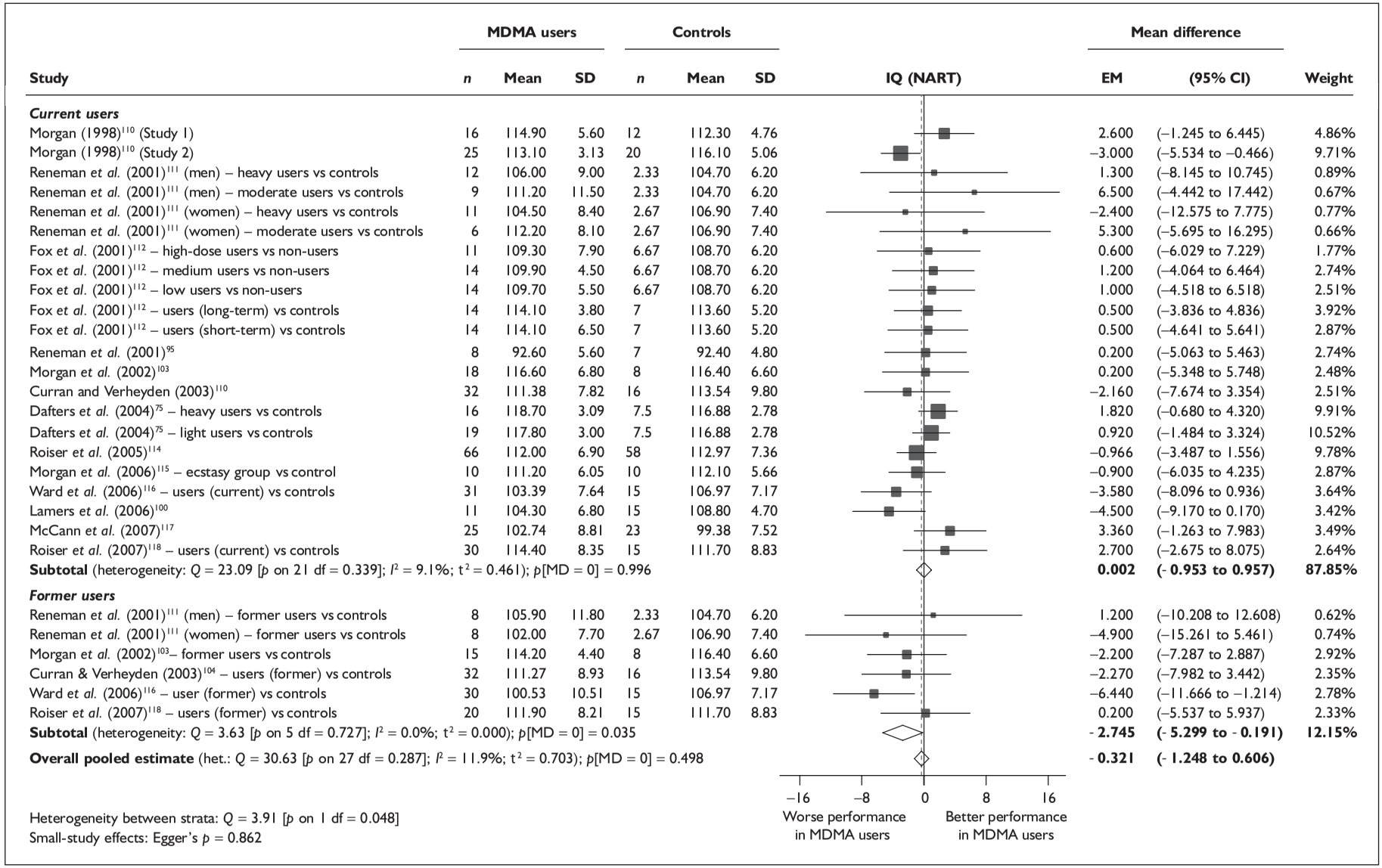


FIGURE 18 *IQ (National Adult Reading Test) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

DOI: 10.3310/hta13060

TABLE 9 *IQ (National Adult Reading Test) – ecstasy users versus polydrug controls: univariate metaregression results*

	Effect modification				Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**WMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	28	0.080	(−0.401 to 0.561)	0.744			
Sex (% male)	28	−2.720	(−8.875 to 3.434)	0.386			
IQ							
Education (years)	12	−1.017	(−3.443 to 1.410)	0.411			
Characteristics of ecstasy exposure							
ETLD (tablets)	19	0.001	(−0.003 to 0.005)	0.646			
ETLE (occasions)	< 5						
Period since last consumption (days)	21	−0.001	(−0.005 to 0.003)	0.643			
Duration of ecstasy use (days)	17	−0.001	(−0.004 to 0.002)	0.620			
Frequency of ecstasy use (occasions/month)	6	−0.107	(−1.440 to 1.227)	0.875			
Inter-arm differences							
Age (years)	28	−0.152	(−0.574 to 0.271)	0.481	−0.303	(−1.254 to 0.647)	0.532
Sex (% male)	28	0.715	(−4.922 to 6.353)	0.804	−0.364	(−1.374 to 0.645)	0.479
Baseline intelligence measures (SMD)							
Education (years)	12	−0.780	(−2.641 to 1.082)	0.412	−2.343	(−5.793 to 1.108)	0.183
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	21	0.691	(−0.106 to 1.488)	0.089	−0.414	(−1.442 to 0.614)	0.430
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	20	0.285	(−1.616 to 2.185)	0.769	−0.227	(−1.720 to 1.266)	0.766
Exposure to cocaine (ETLD)	< 5						
Exposure to cocaine (SMD)	17	−0.103	(−1.710 to 1.503)	0.900	−0.210	(−2.006 to 1.585)	0.818
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	21	1.918	(0.142–3.694)	0.034	−0.506	(−1.540 to 0.529)	0.338

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference; WMD, weighted mean difference.

Figure 20 shows our random-effects meta-analysis of these data. It shows an extremely similar picture to that seen in the comparison with polydrug controls. Ecstasy-exposed individuals' IQs rated an average of 0.474 points lower than those of polydrug controls, but this is unlikely to represent a significant difference ($p = 0.417$). Again, ex-users appear more disadvantaged than current users although, in this case, the former users' stratum is even more underpowered (comprising only two datapoints). In the comparison between current ecstasy users and controls, a non-significant average difference of less than 0.4 IQ points was seen.

Sensitivity analysis with single, pooled comparisons for each study generated results very similar to those of the primary analysis (MD –0.491; 95% CI –1.755 to 0.772; null effect $p = 0.446$).

There is no evidence of small-study bias in this dataset (Egger's $p = 0.992$), and the funnel plot (not shown) had an unremarkable appearance.

Sufficient data were available to attempt metaregression analyses for nine covariates; details are shown in *Table 12*. Once more, we excluded intelligence measures as explanatory variables. None of the analyses were able to provide a statistically convincing explanation of the heterogeneity seen amongst base-case effect estimates. There was no evidence of a dose–response effect (see *Figure 95*, in Appendix 7).

Syntheses: controlled (Level II) evidence – composite measures

We identified a total of 915 discrete outcome measures, measured according to 135 different instruments, among the Level II evidence. These were mapped into a series of 38 domains ('meta-outcomes'). Full details of the mapping, along with abbreviations by which instruments are referred to in this section, are provided in Appendix 5.

Of the 38 outcome domains, 16 represented small collections of data that were not amenable to any form of synthesis, either because they comprised measures that were too general to fit among our domains (e.g. measures that sought to tap 'memory' as a single construct) or because they examined single, specific factors that could not be combined with other items in the evidence-base (e.g. 'orientation'). These data were not analysed further. A further six meta-outcomes were identified as sensible units of analysis, but provided insufficient data for meaningful quantitative synthesis; these are considered in Other Level II outcome measures (see p.133).

The remainder of available data – mapped into a total of 16 composite domains – was sufficiently complete to make meta-analysis possible. It was possible to derive an effect estimate for ecstasy users compared to polydrug controls in all 16 cases, and for ecstasy users compared to drug-naïve controls in 11 of the domains. These analyses are summarised in *Tables 13* and *14*, respectively.

Ecstasy users compared to polydrug controls

In 12 of 16 domains analysed, a significant effect of ecstasy exposure was seen ($p < 0.05$ against the null hypothesis of no exposure effect). Estimated effect sizes ranged from 0.143 to 0.509, with most estimates falling between 0.15 and 0.4. According to Cohen's rule of thumb,[119] such differences can be considered to fall in the range of 'small' effects, with some approaching 'medium' effect sizes.

The only domain in which an effect greater than 0.5 SD was found was that of self-rated memory. This is based on a small sample of studies ($n = 5$) reporting a collection of subjective outcome measures, both factors that would tend to increase uncertainty in the finding. Self-rated measures of impulsivity and anxiety also suggested a comparatively pronounced effect.

Among objective measures, the largest effects were seen in the domains of working memory (SMD –0.391; 95% CI –0.589 to –0.192), delayed verbal memory (SMD –0.377; 95% CI –0.498 to –0.257) and immediate verbal memory (SMD –0.332; 95% CI –0.451 to –0.214). For the outcomes we have categorised as relating to attention, we identified a significant inter-population difference in the 'focus–execute' component, but not for the 'sustain' component. Amongst our executive function meta-outcomes, an exposure effect was seen for the 'planning' component, but not for 'response inhibition' or 'shifting'.

Ecstasy users compared to drug-naïve controls

Eight of 12 domains analysed suggested a significant effect of ecstasy exposure, with estimated effect sizes ranging from 0.272 to 1.037. As in the polydrug-controlled comparisons, self-rated measures generated some of the most sizeable effect estimates, while the largest effects in objective measures were seen in the domains of immediate verbal memory (SMD –0.840; 95%

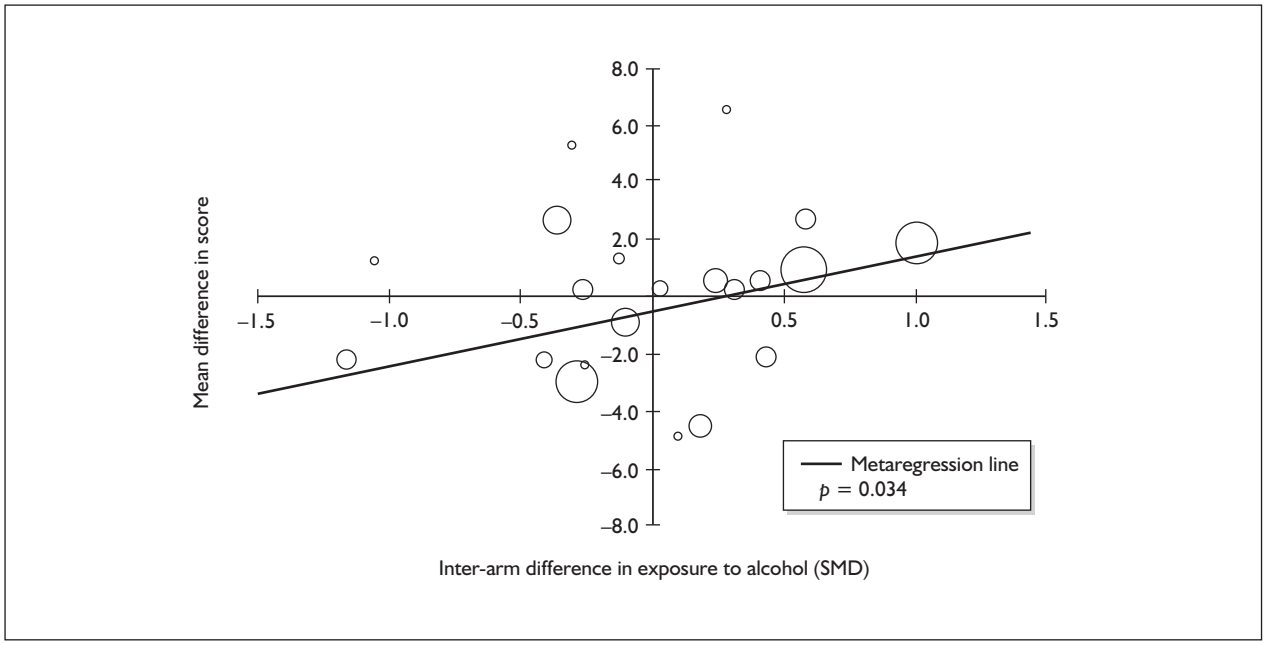


FIGURE 19 *IQ (National Adult Reading Test) – Ecstasy users versus polydrug controls: mean difference in IQ against inter-arm asymmetry in exposure to alcohol (standardised mean difference).*

CI –0.990 to –0.690) and delayed verbal memory (SMD –1.037; 95% CI –1.734 to –0.341).

Verbal memory (immediate) – MDMA users versus polydrug controls

The dataset assembled for this measure comprises 100 datapoints, representing a total of 40 pairwise comparisons, drawn from 27 different studies (35 comparisons from 27 studies providing data for current ecstasy users and five comparisons from five studies providing data for former ecstasy users). For data published in multiple studies originating from Liverpool John Moores University, data from a single publication[120] only were included in this analysis, because it was not possible to deduce the extent of duplicate reporting across the full range of papers. In total, 46 different outcome measures are included, the most common being RBMT: prose recall (10 datapoints), RAVLT: sum of trials 1–5 (10 datapoints) and digit span – backwards (five datapoints). The complete dataset is detailed in *Table 51*, in Appendix 6.

The meta-analysis (*Figure 21*) suggests that ecstasy-exposed cohorts tended to perform worse than polydrug controls by around one-third of a standard deviation, with strong evidence against the null hypothesis of no difference between groups ($p < 0.001$). The stratified analysis identified no difference in exposure effect between current and former ecstasy users.

To contextualise the magnitude of this difference, we note that, in the Zakzanis *et al*. study,[101] a standardised mean difference of precisely –0.332 SD was seen between arms as a result of current ecstasy users scoring 0.2 less than controls on the RBMT immediate prose recall test (1.5 versus 1.7; scaled scores).

A sensitivity analysis in which all individual arms were aggregated to provide single, study-level estimates of effect for each outcome measure before meta-analysis revealed a very similar result (SMD –0.339; 95% CI –0.444 to –0.234). This suggests that our primary analysis is robust to the assumptions underpinning the pooling of data.

There is little evidence of small-study bias, as indicated by Egger's test ($p = 0.330$); similarly, the funnel plot (*Figure 22*) shows no clear trend, although there may be a slight tendency for the least precise studies to produce the most extreme effect estimates.

Sufficient data were available to attempt metaregression analyses for 17 covariates; details are shown in *Table 15*. There was no evidence of a dose–response effect (see *Figure 96* in Appendix 7).

Figure 23 plots estimated effect size against average education level, showing that there is a tendency for differences in performance to diminish as education level increases. Notably, the four

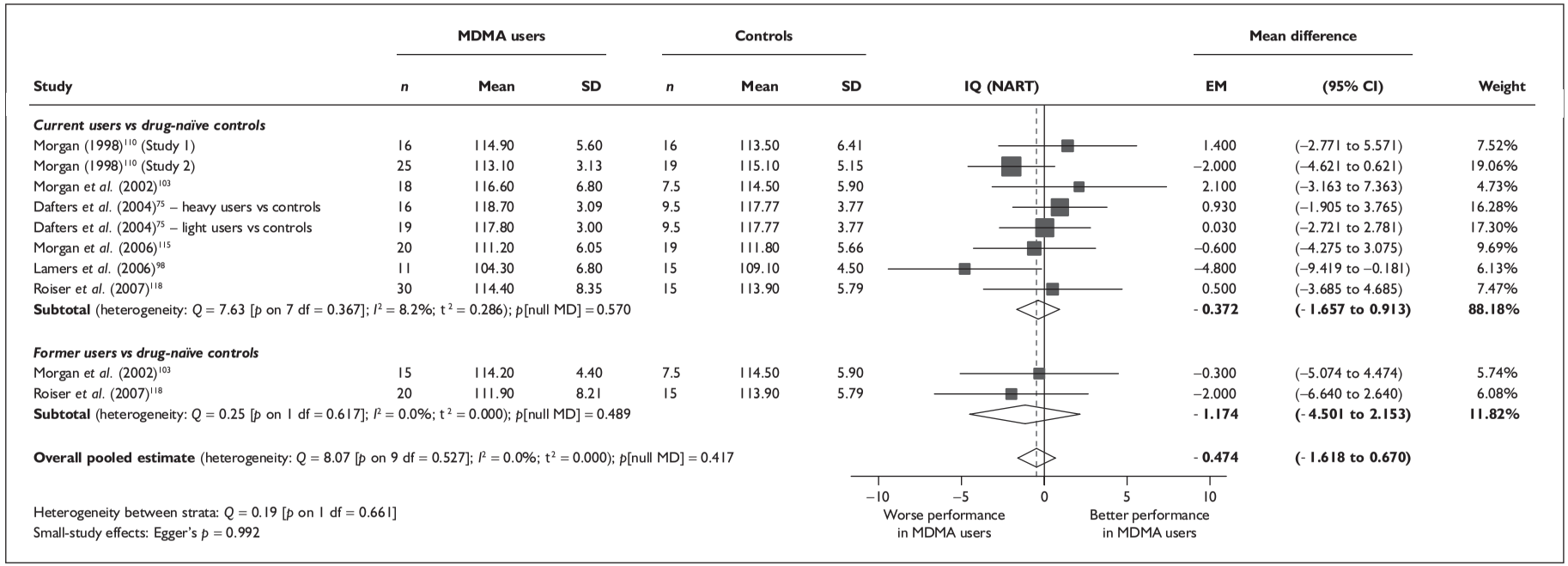


FIGURE 20 *IQ (National Adult Reading Test) – ecstasy users versus drug-naïve controls: random-effects meta-analysis.*

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TABLE 12 *IQ (National Adult Reading Test) – ecstasy users versus drug-naïve controls: univariate metaregression results*

	Effect modification				Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**WMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	8	−0.610	(−1.953 to 0.734)	0.374			
Sex (% male)	10	−12.053	(−31.529 to 7.424)	0.225			
IQ							
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	7	0.000	(−0.006 to 0.006)	0.963			
ETLE (occasions)	< 5						
Period since last consumption (days)	5	−0.002	(−0.008 to 0.004)	0.588			
Duration of ecstasy use (days)	< 5						
Frequency of ecstasy use (occasions/months)	< 5						
Inter-arm differences							
Age (years)	8	0.350	(−0.506 to 1.206)	0.423	−0.995	(−2.540 to 0.549)	0.207
Sex (% male)	10	−3.601	(−17.401 to 10.200)	0.609	−0.329	(−1.601 to 0.942)	0.612
Baseline intelligence measures (SMD)							
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to amphetamines (ETLD)	< 5						
Exposure to cocaine (ETLD)	< 5						
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	8	−0.682	(−2.828 to 1.463)	0.533	0.012	(−1.591 to 1.616)	0.988

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.; WMD, weighted mean difference.

TABLE 13 *Composite measures: summary of meta-analysis results (ecstasy users versus polydrug controls)*

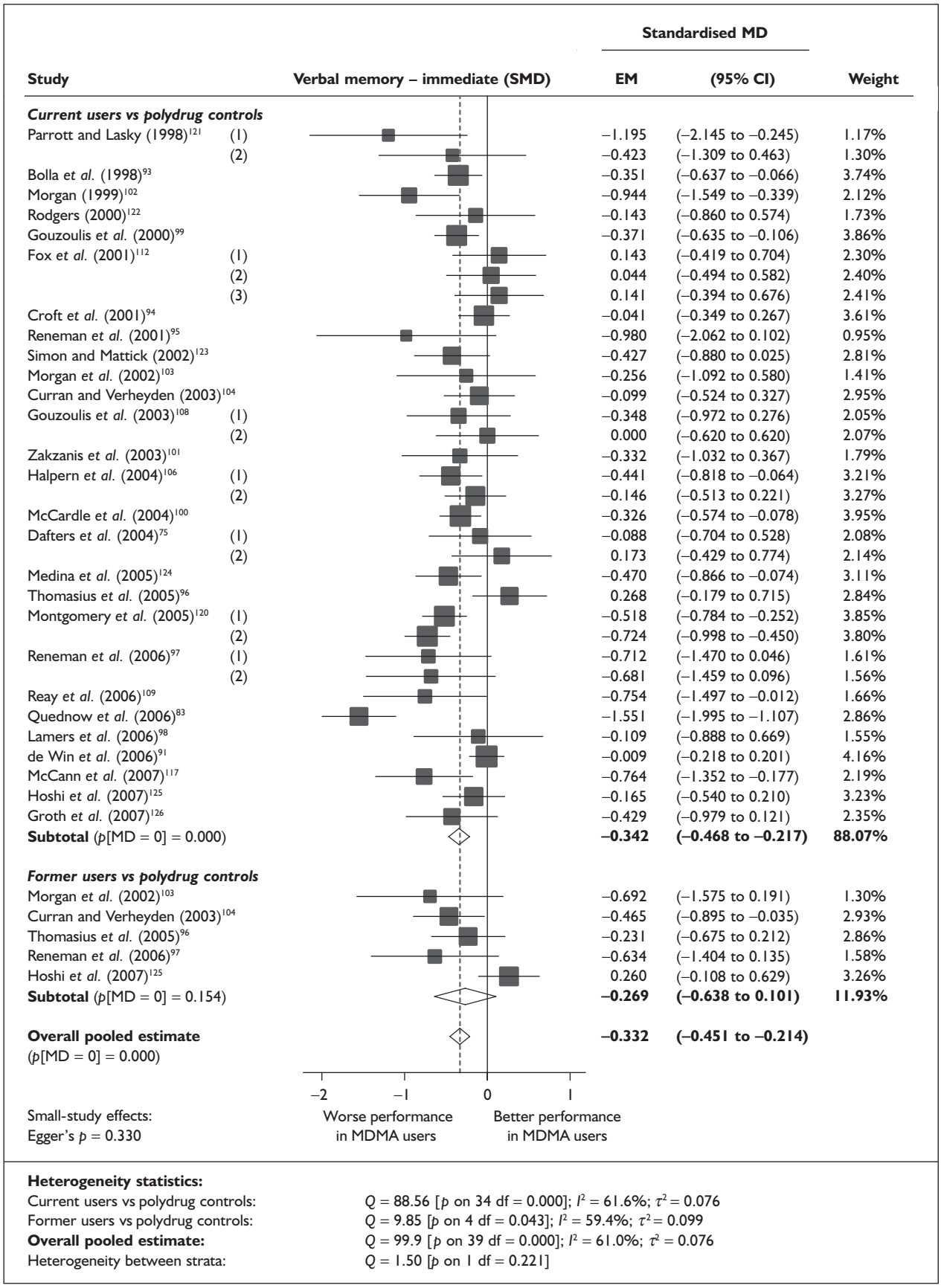
		Current ecstasy users versus controls			
		Studies	**EM**	**(95% CI)**	***p***
Verbal memory (immediate)	*Figure 21*	35	−0.342	(−0.468 to −0.217)	< 0.001
Verbal memory (delayed)	*Figure 27*	27	−0.357	(−0.495 to −0.220)	< 0.001
Visual memory (immediate)	*Figure 31*	19	−0.151	(−0.295 to −0.007)	0.040
Visual memory (delayed)	*Figure 38*	12	−0.180	(−0.327 to −0.034)	0.016
Working memory	*Figure 41*	19	−0.361	(−0.579 to −0.144)	0.001
Attention (focus–execute)	*Figure 46*	26	−0.240	(−0.351 to −0.128)	< 0.001
Attention (sustain)	*Figure 49*	8	−0.086	(−0.288 to 0.115)	0.401
Executive function (planning)	*Figure 54*	10	−0.150	(−0.291 to −0.010)	0.036
Executive function (response inhibition)	*Figure 57*	17	−0.133	(−0.360 to 0.093)	0.247
Executive function (shifting)	*Figure 61*	12	−0.199	(−0.516 to 0.118)	0.218
Perceptual organisation	*Figure 62*	19	−0.151	(−0.295 to −0.007)	0.040
Depression (self-rated)	*Figure 64*	33	−0.247	(−0.361 to −0.133)	< 0.001
Memory (self-rated)	*Figure 70*	8	−0.509	(−0.690 to −0.328)	< 0.001
Anxiety (self-rated)	*Figure 72*	27	−0.249	(−0.401 to −0.096)	0.001
Impulsivity (objective measures)	*Figure 76*	9	−0.247	(−0.495 to 0.001)	0.051
Impulsivity (subjective measures)	*Figure 81*	12	−0.387	(−0.643 to −0.130)	0.003

TABLE 14 *Composite measures: summary of meta-analysis results (ecstasy users versus drug-naïve controls)*

		Current ecstasy users versus controls			
		Studies	**EM**	**(95% CI)**	***p***
Verbal memory (immediate)	*Figure 25*	14	−0.852	(−1.031 to −0.672)	< 0.001
Verbal memory (delayed)	*Figure 29*	14	−1.114	(−1.994 to −0.233)	0.013
Visual memory (immediate)	*Figure 37*	6	−0.177	(−0.489 to 0.135)	0.266
Visual memory (delayed)	*Figure 39*	6	−0.409	(−1.244 to 0.426)	0.337
Working memory	*Figure 45*	6	−0.459	(−0.862 to −0.056)	0.025
Attention (focus–execute)	*Figure 48*	14	−0.254	(−0.422 to −0.085)	0.003
Attention (sustain)					
Executive function (planning)					
Executive function (response inhibition)	*Figure 59*	8	−0.137	(−0.348 to 0.074)	0.204
Executive function (shifting)					
Perceptual organisation					
Depression (self-rated)	*Figure 66*	27	−0.538	(−0.785 to −0.292)	< 0.001
Memory (self-rated)					
Anxiety (self-rated)	*Figure 74*	22	−0.323	(−0.425 to −0.222)	< 0.001
Impulsivity (objective measures)	*Figure 79*	9	−0.392	(−0.682 to −0.102)	0.008
Impulsivity (subjective measures)	*Figure 83*	8	−0.780	(−1.096 to −0.465)	< 0.001

Former ecstasy users versus controls				All ecstasy exposed versus controls			
Studies	**EM**	**(95%CI)**	***p***	**Studies**	**EM**	**(95% CI)**	***p***
5	−0.269	(−0.638 to 0.101)	0.154	40	−0.332	(−0.451 to −0.214)	< 0.001
5	−0.468	(−0.720 to −0.216)	< 0.001	32	−0.377	(−0.498 to −0.257)	< 0.001
3	−0.064	(−0.277 to 0.149)	0.557	22	−0.143	(−0.270 to −0.016)	0.027
2	−0.213	(−0.647 to 0.221)	0.336	14	−0.184	(−0.323 to −0.045)	0.010
3	−0.649	(−0.960 to −0.337)	< 0.001	22	−0.391	(−0.589 to −0.192)	< 0.001
4	−0.157	(−0.324 to 0.010)	0.065	30	−0.226	(−0.323 to −0.130)	< 0.001
3	0.136	(−0.608 to 0.880)	0.719	11	−0.029	(−0.238 to 0.180)	0.784
0	–	–	–	11	−0.176	(−0.324 to −0.028)	0.020
3	0.120	(−0.238 to 0.477)	0.512	20	−0.103	(−0.303 to 0.097)	0.314
0	–	–	–	13	−0.184	(−0.483 to 0.115)	0.228
3	−0.064	(−0.277 to 0.149)	0.557	22	−0.143	(−0.270 to −0.016)	0.027
5	−0.503	(−0.804 to −0.202)	0.001	38	−0.272	(−0.377 to −0.167)	< 0.001
0	–	–	–	8	−0.509	(−0.690 to −0.328)	< 0.001
5	−0.380	(−0.673 to −0.086)	0.011	32	−0.263	(−0.396 to −0.130)	< 0.001
0	–	–	–	10	−0.200	(−0.417 to 0.017)	0.071
2	−0.437	(−0.889 to 0.015)	0.058	14	−0.394	(−0.616 to −0.173)	< 0.001

Former ecstasy users versus controls				All ecstasy exposed versus controls			
Studies	**EM**	**(95% CI)**	***p***	**Studies**	**EM**	**(95% CI)**	***p***
4	−0.792	(−1.053 to −0.531)	< 0.001	18	−0.840	(−0.990 to −0.690)	< 0.001
4	−0.732	(−1.044 to −0.421)	< 0.001	18	−1.037	(−1.734 to −0.341)	0.004
0	–	–	–	7	−0.173	(−0.418 to 0.071)	0.165
2	−0.283	(−0.705 to 0.139)	0.189	8	−0.366	(−1.014 to 0.283)	0.269
0	–	–	–	7	−0.505	(−0.868 to −0.143)	0.006
2	−0.436	(−0.852 to −0.019)	0.040	16	−0.272	(−0.424 to −0.120)	< 0.001
				4	0.159	(−0.180 to 0.498)	0.358
2	0.123	(−0.265 to 0.511)	0.534	10	−0.088	(−0.282 to 0.105)	0.371
4	−0.853	(−1.211 to −0.494)	< 0.001	31	−0.573	(−0.803 to −0.343)	< 0.001
3	−0.571	(−0.977 to −0.165)	0.006	25	−0.338	(−0.437 to −0.239)	< 0.001
0	–	–	–	10	−0.333	(−0.594 to −0.072)	0.012
0	–	–	–	9	−0.778	(−1.058 to −0.499)	< 0.001



Heterogeneity statistics:

Current users vs polydrug controls: $Q = 88.56$ [p on 34 df = 0.000]; $I^2 = 61.6\%$; $\tau^2 = 0.076$

Former users vs polydrug controls: $Q = 9.85$ [p on 4 df = 0.043]; $I^2 = 59.4\%$; $\tau^2 = 0.099$

Overall pooled estimate: $Q = 99.9$ [p on 39 df = 0.000]; $I^2 = 61.0\%$; $\tau^2 = 0.076$

Heterogeneity between strata: $Q = 1.50$ [p on 1 df = 0.221]

FIGURE 21 *Verbal memory – immediate (composite measure) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

comparisons in this dataset estimating the greatest deficit for ecstasy users are also those in which participants have the lowest average education levels. If this model were to be believed, one would not expect to see a difference between cohorts if it could be assumed that a study's participants had received around 15½ years of education. However, the dataset is a restricted one: only 12 of the 40 pairwise comparisons available in the full meta-analysis provide covariate data (although the estimated effect size in this subgroup is comparable to that seen in the full analysis: SMD –0.371; 95% CI –0.659 to –0.083).

Figure 24 plots estimated effect size against inter-arm asymmetry in intelligence. The fact that most comparisons are located in the 'south-west' quadrant of the plot shows that, in the majority of studies, ecstasy-exposed participants not only performed worse in the memory tasks but also were less intelligent than controls. Conversely, the effect size is smaller (indeed, in several cases suggesting an advantage for the ecstasy users), when intelligence measures favour those cohorts. The regression analysis suggests that there may be a general trend for worse performance in those studies in which ecstasy users had lower intelligence scores than controls. However, even if this model is to be believed, asymmetry in intelligence does not explain differences between cohorts entirely, and the evidence for worse performance in ecstasy-exposed cohorts remains strong (adjusted effect estimate: SMD –0.240; 95% CI –0.384 to –0.096; $p = 0.003$).

Verbal memory (immediate) – MDMA users versus drug-naïve controls

The dataset assembled for this measure comprises 41 datapoints, representing a total of 18 pairwise comparisons, drawn from 12 different studies (14 comparisons from 12 studies providing data for current ecstasy users and four comparisons from four studies providing data for former ecstasy users). Twenty different outcome measures are included, the most common being RBMT: prose recall (seven datapoints), digit span – backwards (six datapoints) and RAVLT: sum of trials 1–5 (five datapoints). The complete dataset is detailed in *Table 52* in Appendix 6.

When this dataset was meta-analysed (*Figure 25*), both current and former ecstasy users tended to perform worse than drug-naïve controls by around 0.8 of a standard deviation, with strong evidence against the null hypothesis of no difference between groups ($p < 0.001$). According to Cohen's rule of thumb, this would qualify as a 'large' inter-population difference. To give an indication of the magnitude of this standardised difference in real terms, the datapoint from Morgan's 1999 study[102] appears relatively typical of the pattern of results seen here. In this study, current ecstasy users recalled an average of 1.95 fewer items than drug-naïve controls in the immediate prose recall task of the RBMT (SMD –0.852).

The stratified analysis identified no difference in exposure effect between current and former ecstasy users.

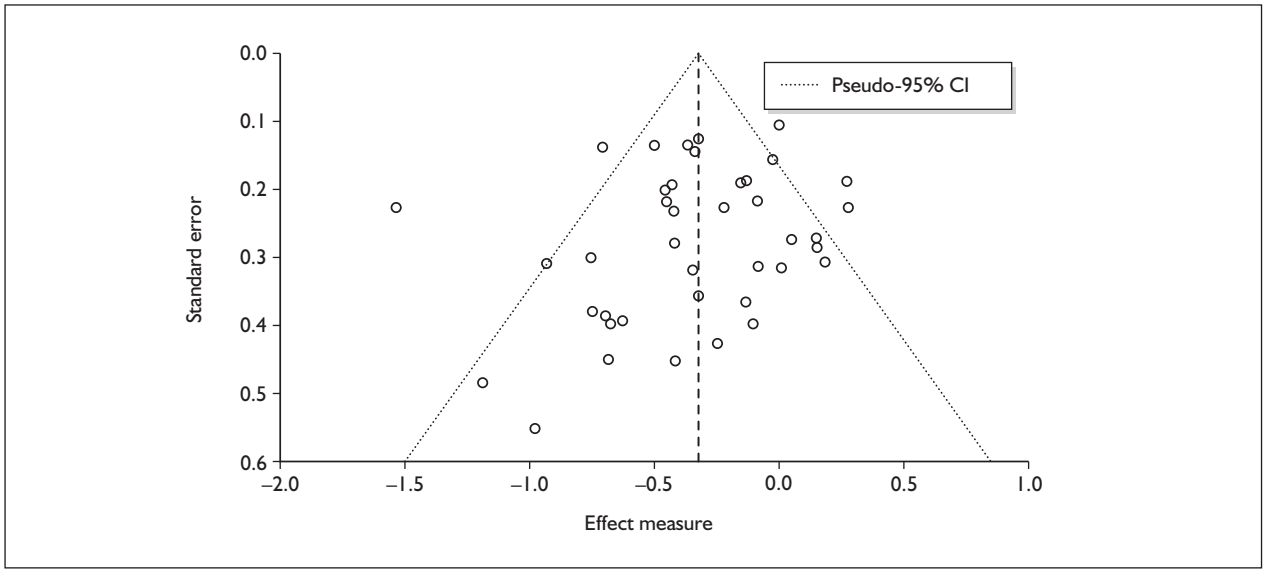


FIGURE 22 *Verbal memory – immediate (composite measure) – ecstasy users versus polydrug controls: funnel plot.*

TABLE 15 *Verbal memory – immediate (composite measure) – ecstasy users versus polydrug controls: univariate metaregression results*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (year)	36	0.022	(−0.029 to 0.074)	0.395			
Sex (% male)	36	−0.304	(−0.924 to 0.317)	0.337			
IQ	18	0.032	(−0.011 to 0.076)	0.145			
Education (years)	12	0.295	(0.085–0.506)	0.006			
Characteristics of ecstasy exposure							
ETLD (tablets)	20	0.000	(−0.001 to 0.001)	0.586			
ETLE (occasions)	6	0.001	(−0.001 to 0.003)	0.190			
Period since last consumption (days)	17	0.000	(0.000–0.001)	0.244			
duration of ecstasy use (days)	24	0.000	(0.000–0.000)	0.874			
Frequency of ecstasy use (occasions/month)	10	0.102	(−0.044 to 0.249)	0.171			
Inter-arm differences							
Age (years)	36	0.034	(−0.025 to 0.093)	0.256	−0.321	(−0.452 to −0.189)	0.000
Sex (% male)	36	−0.191	(−1.109 to 0.728)	0.684	−0.310	(−0.441 to −0.178)	0.000
Baseline intelligence measures (SMD)	30	0.356	(0.067–0.645)	0.016	−0.240	(−0.384 to −0.096)	0.001
Education (years)	12	−0.028	(−0.309 to 0.253)	0.847	−0.402	(−0.833 to 0.029)	0.067
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	26	−0.166	(−0.344 to 0.011)	0.066	−0.184	(−0.315 to −0.053)	0.006
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	23	−0.135	(−0.331 to 0.062)	0.180	−0.116	(−0.272 to 0.040)	0.146
Exposure to cocaine (ETLD)	6	−0.001	(−0.003 to 0.001)	0.210	−0.112	(−0.318 to 0.094)	0.287
Exposure to cocaine (SMD)	19	−0.242	(−0.555 to 0.070)	0.129	−0.131	(−0.307 to 0.046)	0.147
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	23	−0.005	(−0.232 to 0.222)	0.966	−0.250	(−0.390 to −0.111)	0.000

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

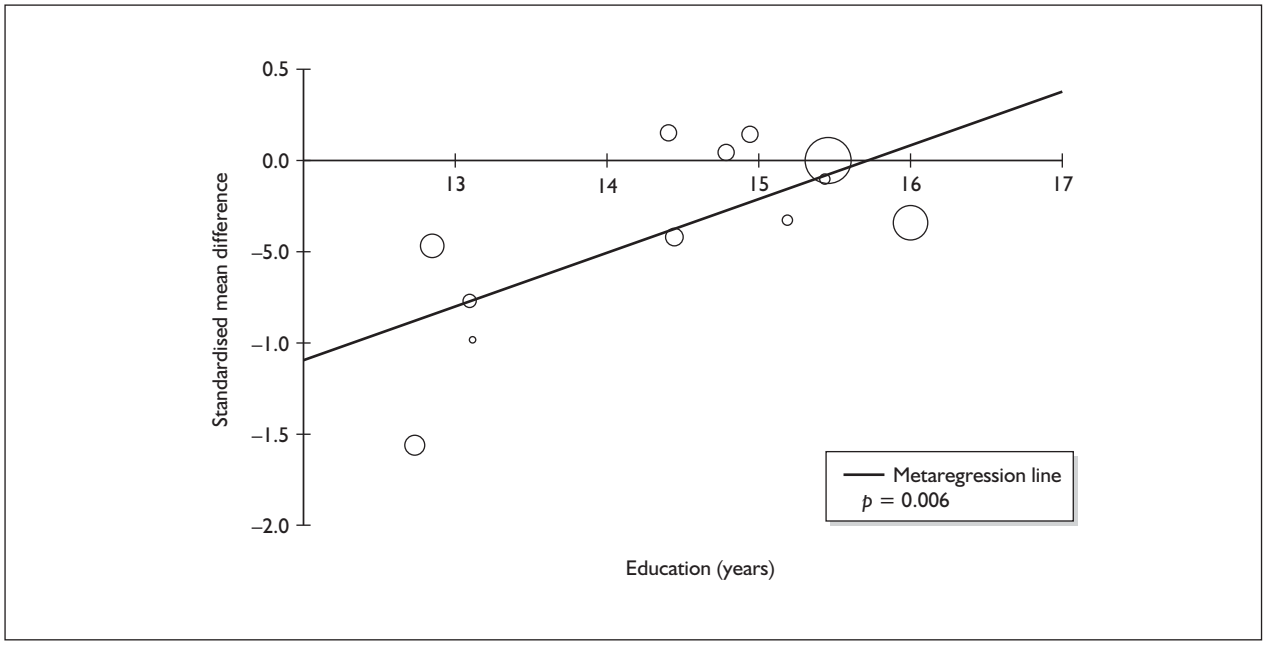


FIGURE 23 *Verbal memory – immediate (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against education of participants (average value across all cohorts).*

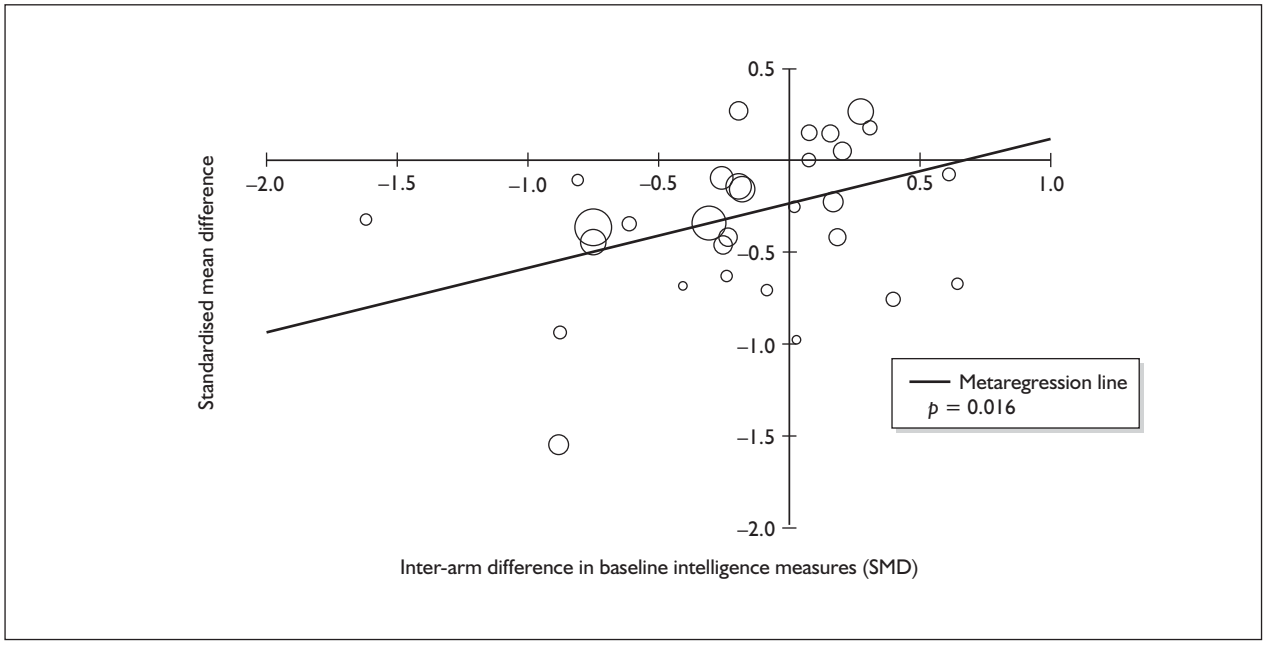


FIGURE 24 *Verbal memory – immediate (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against inter-arm asymmetry in baseline intelligence measures (standardised mean difference).*

Sensitivity analysis with aggregated comparisons for each study suggested that our primary analysis may underestimate the difference between populations by around 0.1 SD [revised SMD –0.959; 95% CI –1.285 to –0.633; p(null SMD) < 0.001].

There is some evidence of small-study bias (Egger's p=0.023). The funnel plot for this dataset (*Figure 26*) shows that the four estimates with the highest precision provide a smaller-than-average estimate of exposure effect and, conversely, that those datapoints suggesting greatest difference between cohorts tend to be amongst those that are subject to the greatest uncertainty. Accordingly, one might conclude that, had every relevant test ever undertaken been available to this meta-analysis, the

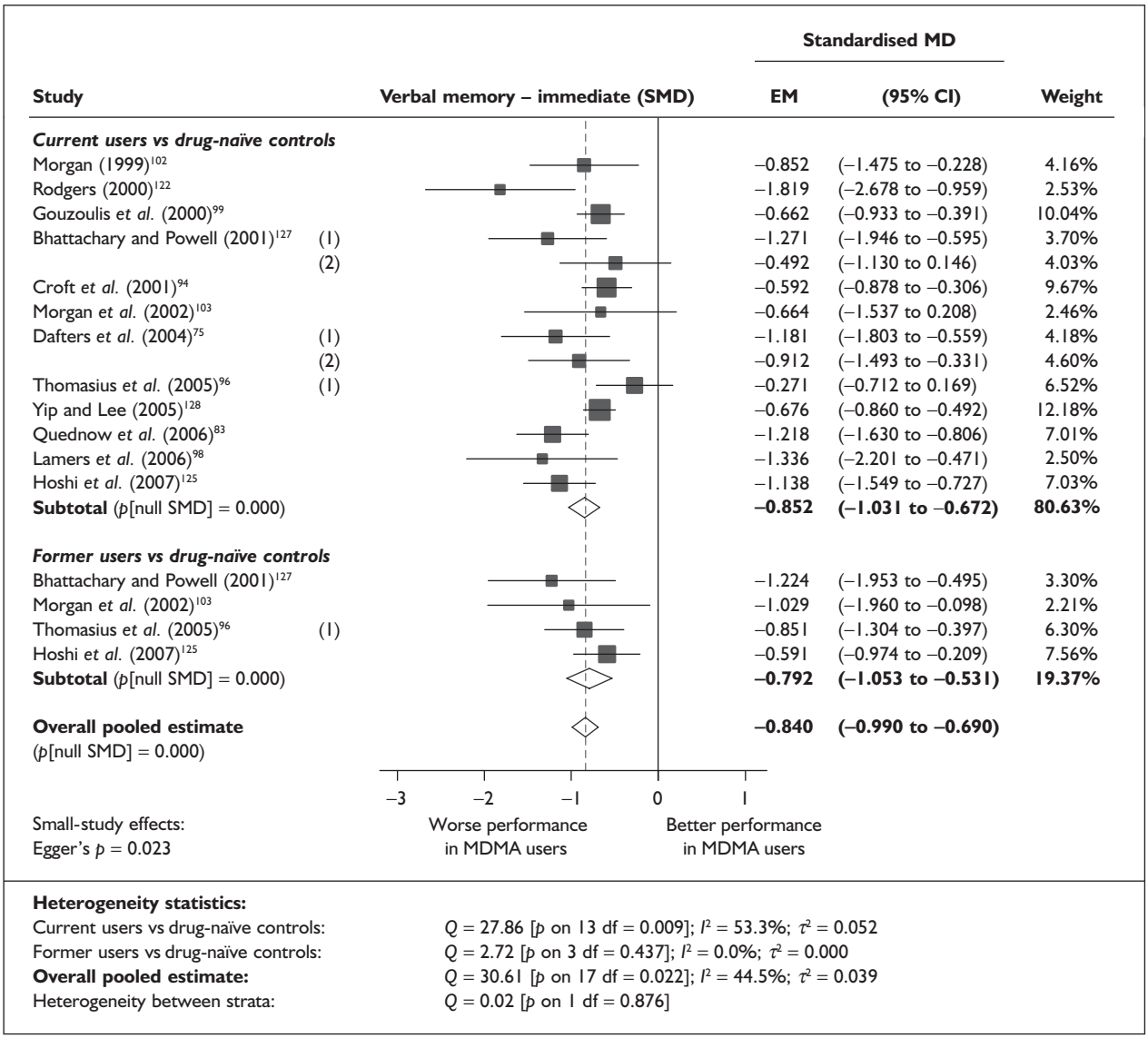


FIGURE 25 *Verbal memory – immediate (composite measure) – ecstasy users versus drug-naïve controls: random-effects meta-analysis.*

estimated exposure effect may have been somewhat lower.

Sufficient data were available to attempt metaregression analyses for 10 covariates; details are shown in *Table 16*. None of the metaregressions generated results that achieved or approached conventional levels of significance, and there was no evidence of a dose–response effect (see *Figure 97* in Appendix 7).

Verbal memory (delayed) – MDMA users versus polydrug controls

The dataset assembled for this measure comprises 49 datapoints, representing a total of 32 pairwise comparisons, drawn from 22 different studies (27 comparisons from 22 studies providing data for current ecstasy users and five comparisons from five studies providing data for former ecstasy users). Twenty-two different outcome measures are included, the most common being RBMT: prose recall (10 datapoints), RAVLT: trial 8 (seven datapoints) and Buschke: overall score (four datapoints). The complete dataset is detailed in *Table 53* in Appendix 6.

The meta-analysis, shown in *Figure 27*, suggests that ecstasy-exposed individuals' long-term verbal memory is worse than that of polydrug controls by a little under 0.4 SD. According to Cohen's guidelines, this would probably be thought of as somewhere between a 'small' and a 'medium' difference. The effect might appear to be greater in former ecstasy users, whom controls outperformed by almost 0.5 SD (a 'medium' difference, according to Cohen). However, there is insufficient evidence to reject a null hypothesis of homogeneous strata ($p = 0.533$). Sensitivity analysis with single, pooled

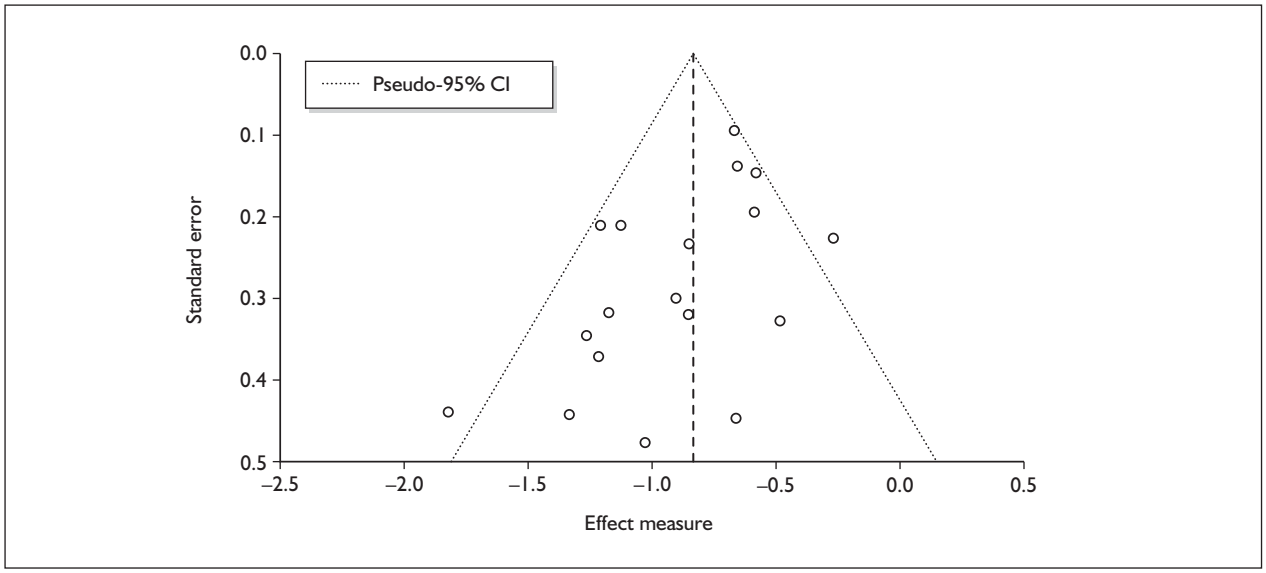


FIGURE 26 *Verbal memory – immediate (composite measure) – ecstasy users versus drug-naïve controls: funnel plot.*

comparisons for each study provides a SMD estimated at –0.402 [95% CI –0.515 to –0.288; p(null SMD) < 0.001], which is extremely close to the primary analysis.

To translate these findings back into a more easily interpretable scale, it may be useful to return to the raw data on which the analysis was based, to see which individual datapoints are closest to the calculated average. For the comparison between current users and controls, a relatively typical datapoint is the WMS-III delayed memory index score from the study by Groth *et al.*,[126] in which the ecstasy-using cohort registered lower scores than polydrug controls by an average of 3.8 points (108.4 versus 112.2; SMD –0.356). Where former users were compared to controls, the most representative datapoint was that from Curran and Verheyden,[104] where the difference between cohorts was 1.69 items on the RBMT delayed prose recall test (5.825 versus 7.515; SMD –0.506).

There is no evidence of small-study bias in this dataset (Egger's $p = 0.254$), and the funnel plot (not shown) had an unremarkable appearance.

Sufficient data were available to attempt metaregression analyses for 15 covariates; details are shown in *Table 15*. There was no evidence of a dose–response effect (see *Figure 98* in Appendix 7).

Figure 28 plots estimated effect size against average education level, showing that there is a tendency for differences in performance to diminish as education level rises. This is a very similar picture to that seen for immediate verbal memory (see *Figure 23*). It should be noted, however, that both analyses are based on fairly restricted datasets.

Verbal memory (delayed) – MDMA users versus drug-naïve controls

The dataset assembled for this measure comprises 28 datapoints, representing a total of 20 pairwise comparisons, drawn from 12 different studies (15 comparisons from 12 studies providing data for current ecstasy users and five comparisons from four studies providing data for former ecstasy users). Fifteen different outcome measures are included, the most common being RBMT: prose recall (seven datapoints), prose retained (three datapoints) and prose recall (three datapoints). The complete dataset is detailed in *Table 54* in Appendix 6.

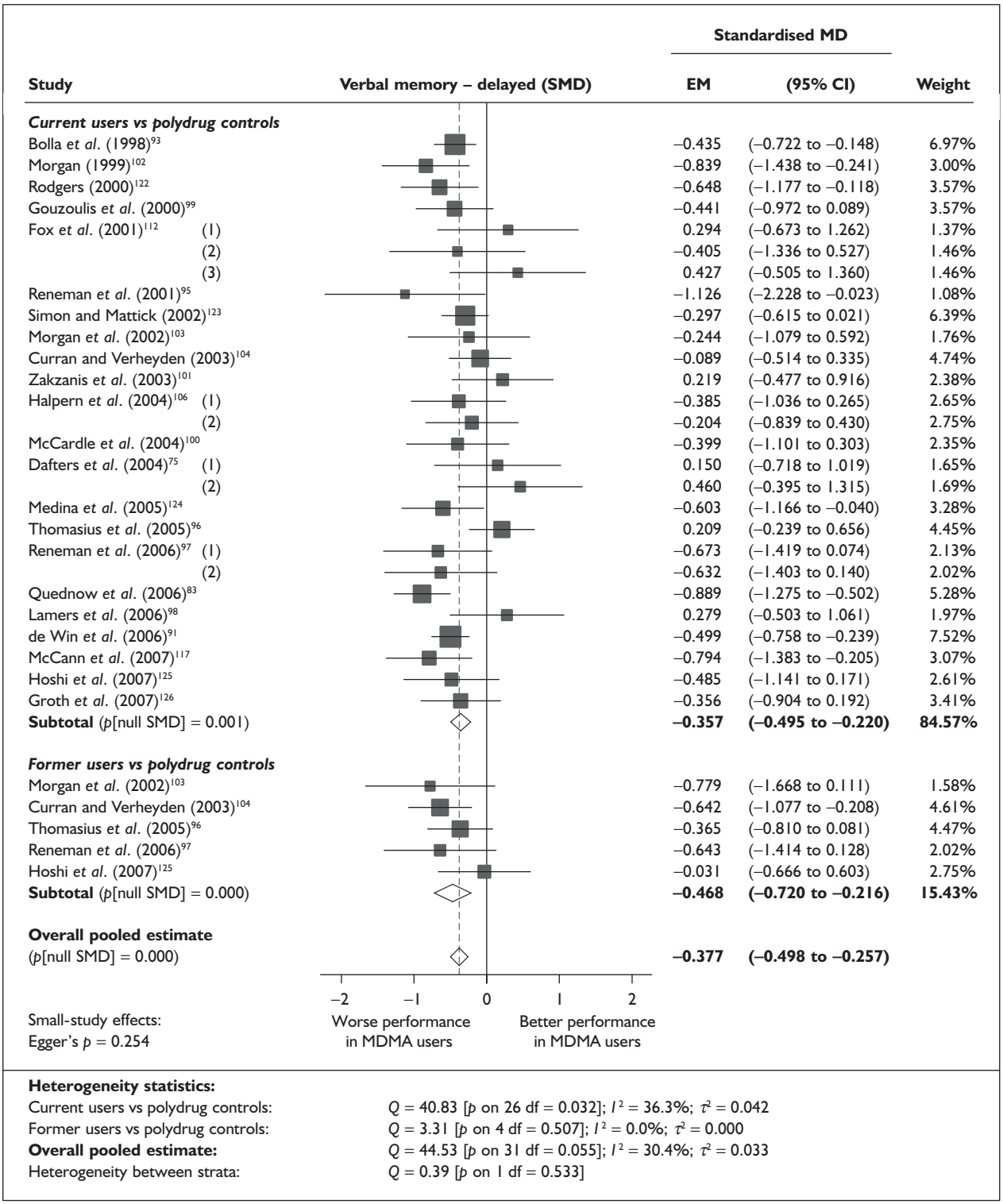
In the meta-analysis (*Figure 29*), ecstasy-exposed individuals' delayed verbal memory is estimated to be inferior to that of drug-naïve controls by very nearly 1 SD. However, the forest plot shows very clearly that one effect estimate – that from Yip and Lee's study[128] – is entirely atypical of results from other studies. If this single datapoint is excluded from the meta-analysis, the estimated SMD falls to –0.717 (95% CI –0.915 to –0.518); however, the evidence for an overall exposure effect remains strong ($p < 0.001$).

Yip and Lee's anomalous datapoint represents a composite of two subtests from the RAVLT, in both of which the performance of ecstasy-exposed participants was less than half the

TABLE 16 *Verbal memory – immediate (composite measure) – ecstasy users versus drug-naïve controls: univariate metaregression results*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	18	−0.009	(−0.060 to 0.042)	0.733			
Sex (% male)	17	−0.269	(−1.053 to 0.515)	0.501			
IQ	11	−0.003	(−0.034 to 0.029)	0.855			
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	11	0.000	(−0.001 to 0.001)	0.969			
ETLE (occasions)	< 5						
Period since last consumption (days)	7	0.000	(0.000–0.001)	0.352			
Duration of ecstasy use (days)	7	0.000	(0.000–0.000)	0.096			
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	18	0.011	(−0.079 to 0.102)	0.810	−0.849	(−1.009 to −0.690)	0.000
Sex (% male)	17	−2.024	(−5.506 to 1.459)	0.255	−0.870	(−1.037 to −0.702)	0.000
Baseline intelligence measures (SMD)	16	0.047	(−0.439 to 0.533)	0.850	−0.828	(−1.012 to −0.645)	0.000
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to amphetamines (ETLD)	< 5						
Exposure to cocaine (ETLD)	5	−0.003	(−0.007 to 0.001)	0.139	−0.525	(−0.854 to −0.196)	0.002
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	14	−0.182	(−0.544 to 0.180)	0.325	−0.747	(−0.962 to −0.532)	0.000

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.



Heterogeneity statistics:

Current users vs polydrug controls:	$Q = 40.83$ [p on 26 df = 0.032]; $I^2 = 36.3\%$; $\tau^2 = 0.042$
Former users vs polydrug controls:	$Q = 3.31$ [p on 4 df = 0.507]; $I^2 = 0.0\%$; $\tau^2 = 0.000$
Overall pooled estimate:	$Q = 44.53$ [p on 31 df = 0.055]; $I^2 = 30.4\%$; $\tau^2 = 0.033$
Heterogeneity between strata:	$Q = 0.39$ [p on 1 df = 0.533]

FIGURE 27 *Verbal memory – delayed (composite measure) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

standard achieved by drug-naïve controls. There are a number of possible explanations for this extreme result. First, it should be noted that the outlying datapoints are those based on the Chinese version of the RAVLT; this is the only study in the evidence-base to rely on this instrument, the validity and characteristics of which are unclear to us. Second, it is possible that there are environmental and/or genetic factors that make ecstasy exposure effects unusual – or, at least, difficult to generalise to a UK context – in a Hong Kong Chinese population. Third, the authors' description of the population from which their cohorts were drawn implies that Hong Kong

TABLE 17 *Verbal memory – delayed (composite measure) – Ecstasy users v. polydrug controls: Univariate metaregression results*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	30	−0.019	(−0.069 to 0.031)	0.454			
Sex (% male)	30	−0.253	(−0.852 to 0.346)	0.407			
IQ	18	0.033	(−0.007 to 0.072)	0.103			
Education (years)	12	0.177	(0.011–0.344)	0.037			
Characteristics of ecstasy exposure							
ETLD (tablets)	17	0.000	(0.000 – 0.001)	0.649			
ETLE (occasions)	6	−0.001	(−0.004 to 0.002)	0.600			
Period since last consumption (days)	17	0.000	(−0.001 to 0.001)	0.599			
Duration of ecstasy use (days)	21	0.000	(0.000 – 0.000)	0.994			
Frequency of ecstasy use (occasions/month)	7	0.045	(−0.184 to 0.273)	0.702			
Inter-arm differences							
Age (years)	30	0.042	(−0.015 to 0.099)	0.152	−0.395	(−0.524 to −0.267)	0.000
Sex (% male)	30	−0.201	(−1.238 to 0.837)	0.705	−0.378	(−0.508 to −0.248)	0.000
Baseline intelligence measures (SMD)	28	0.082	(−0.222 to 0.385)	0.598	−0.323	(−0.480 to −0.167)	0.000
Education (years)	12	0.027	(−0.207 to 0.260)	0.824	−0.374	(−0.707 to −0.040)	0.028
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	23	−0.134	(−0.374 to 0.106)	0.275	−0.365	(−0.518 to −0.213)	0.000
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	21	0.078	(−0.258 to 0.414)	0.649	−0.417	(−0.677 to −0.158)	0.002
Exposure to cocaine (ETLD)	5	0.000	(−0.003 to 0.002)	0.763	−0.100	(−0.541 to 0.341)	0.657
Exposure to cocaine (SMD)	18	−0.121	(−0.494 to 0.252)	0.525	−0.327	(−0.557 to −0.096)	0.005
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	21	0.086	(−0.173 to 0.344)	0.517	−0.358	(−0.507 to −0.210)	0.000

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

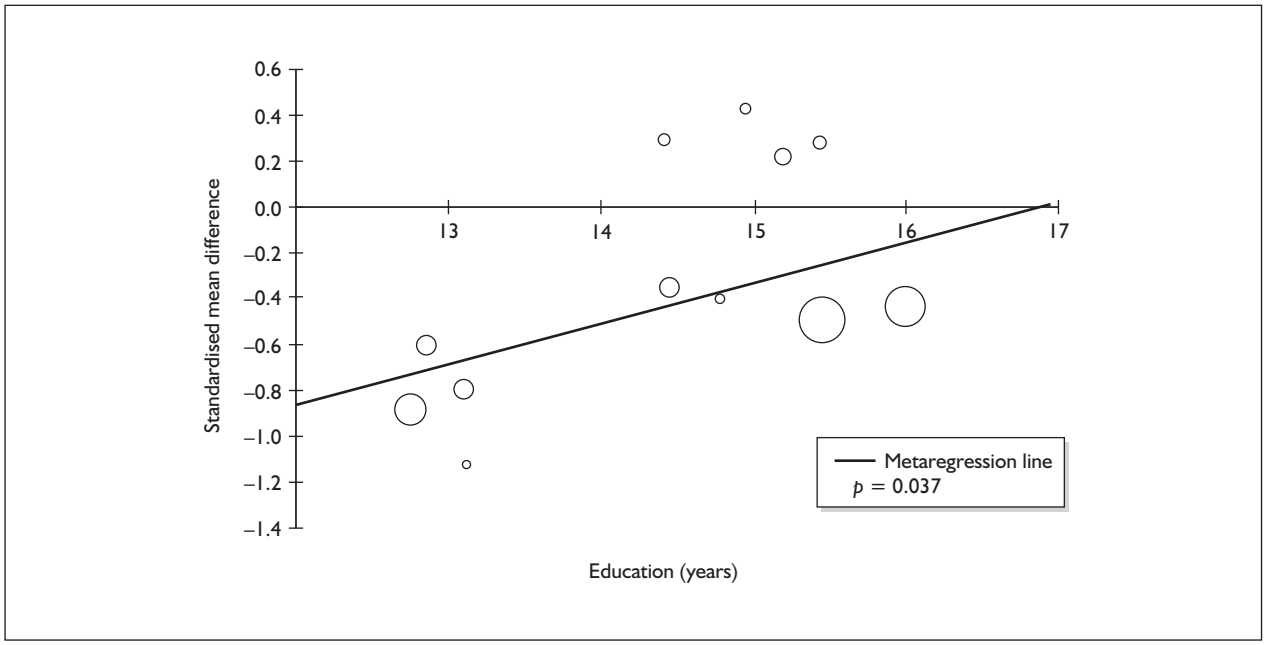


FIGURE 28 *Verbal memory – delayed (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against education of participants (average value across all cohorts).*

clubbers use ecstasy and other drugs in a markedly different way to the patterns seen elsewhere. They claim to have recruited relatively uncontaminated ecstasy-using and control cohorts, excluding participants with exposure to other substances, including tobacco and alcohol (more than one drink per week). The fact that nearly two-thirds of potential participants were excluded for violating these criteria would tend to enhance such claims; most other included studies had broad eligibility rules, and appear to have included most or all prospective participants. Accordingly, it could be argued that – although it remains subject to all the limitations of the observational paradigm – Yip and Lee's study overcomes some of the confounding seen in other research, with exposure to ecstasy providing the only clearly observable difference between cohorts. Nevertheless, it would be a substantial step to extend this argument to the suggestion that Yip and Lee's estimate provides a 'true' exposure effect, while the additional confounding inherent in other studies serves drastically to underestimate the real difference.

Unsurprisingly, this outlying estimate has a substantial effect on calculated heterogeneity statistics. With Yip and Lee's data included, tests reveal an extremely heterogeneous dataset ($p < 0.001$; $I^2 = 96.0\%$), whereas reanalysis without the anomalous estimate reveals a picture that suggests a much more homogeneous dataset ($p = 0.047$; $I^2 = 39.6\%$). Similarly, initial tests are strongly suggestive of interstratum heterogeneity ($p = 0.003$) but, on closer inspection, it becomes clear that this result is driven entirely by the single atypical estimate from Yip and Lee's study: the reanalysis without this datapoint is wholly consistent with a homogeneous effect across strata ($p = 0.595$).

Sensitivity analysis with single, pooled comparisons for each study provides a mean difference estimated at –1.253 (95% CI –1.936 to –0.571). This may appear to be a relatively substantial discrepancy from the primary analysis; however, further analysis reveals that this is because the aggregated approach is affected to an even greater extent by Yip and Lee's outlying estimate (without this datapoint, the sensitivity analysis generates a pooled estimate of –0.745; 95% CI –0.991 to –0.499, which is close to the primary analysis).

Returning to the raw data on which the analysis was based, the individual datapoints that are closest to the calculated averages are – for the full dataset including Yip and Lee – the RBMT prose recall subscore reported by Dafters and colleagues[75] [in which heavy ecstasy users scored an average of 1.85 less than controls (SMD –0.979)], and – for the restricted dataset without the outlying estimate – the delayed (trial 8) RAVLT recall score from Lamers *et al.*[98] [in which the deficit for ecstasy users is estimated at 1.5 items (SMD –0.701)].

When applied to the full dataset, Egger's test suggested that there was no evidence of small-

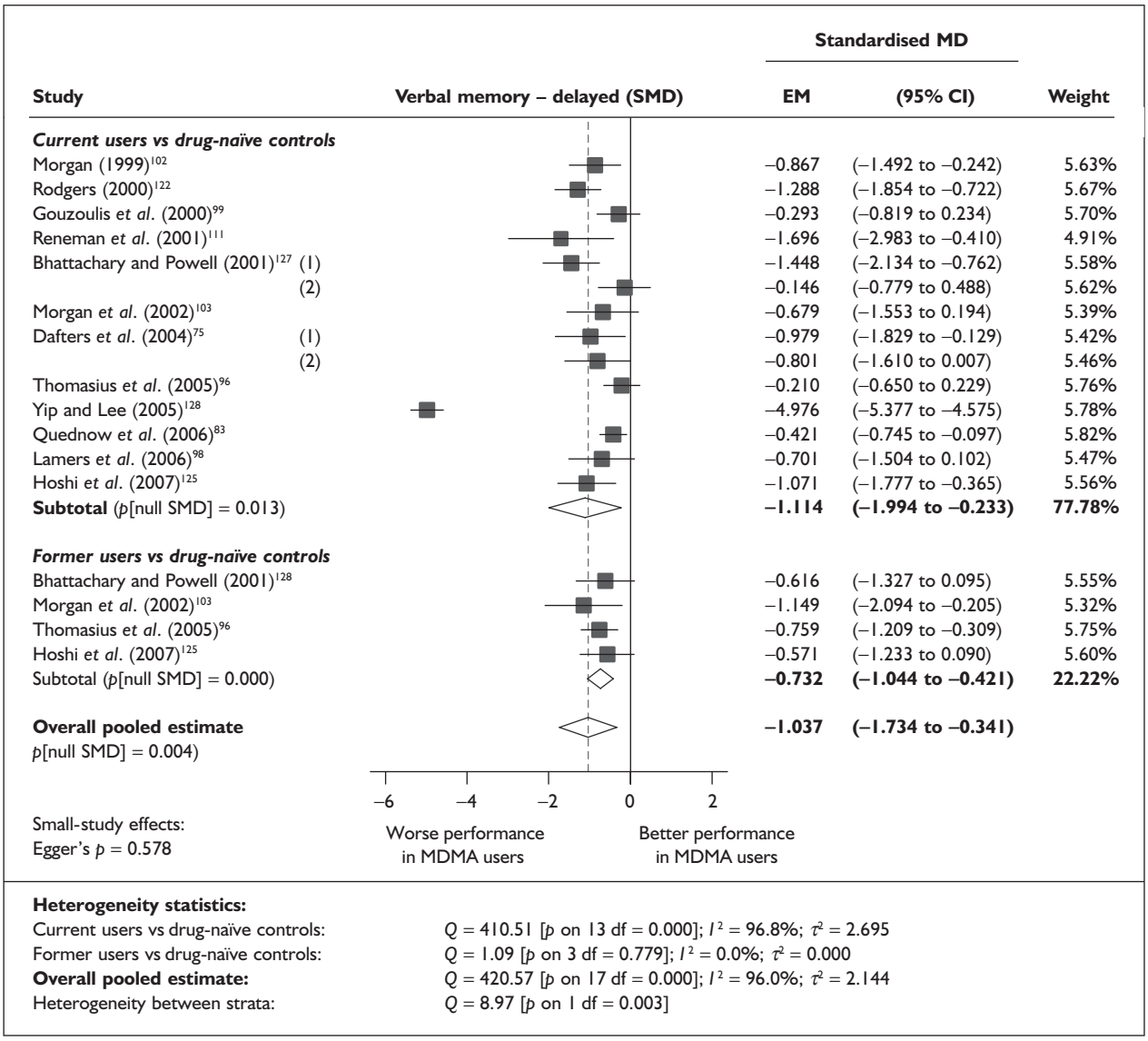


FIGURE 29 *Verbal memory – delayed (composite measure) – ecstasy users versus drug-naïve controls: random-effects meta-analysis.*

study bias in this dataset ($p = 0.578$). Once more, however, this result is substantially affected by the single outlying estimate: if Yip and Lee's data are excluded, then Egger's test returns a p-value of 0.021, suggesting that the null hypothesis of no small-study effect is difficult to support. The trend for more precise studies to estimate a smaller difference can be clearly visualised in the funnel plot for this dataset (*Figure 30*), as can the distorting influence of Yip and Lee's study.

Sufficient data were available to attempt metaregression analyses for 13 covariates (*Table 18*); none provided significant results, and there was no evidence of a dose–response effect (see *Figure 99* in Appendix 7).

Visual memory (immediate) – MDMA users versus polydrug controls

The dataset assembled for this measure comprises 66 datapoints, representing a total of 22 pairwise comparisons, drawn from 16 different studies (19 comparisons from 16 studies providing data for current ecstasy users and three comparisons from three studies providing data for former ecstasy users). Forty-one different outcome measures are included, the most common being Corsi Block: span (six datapoints), Corsi Block: span plus one (five datapoints) and WMS-R: visual reproduction (four datapoints). The complete dataset is detailed in *Table 55* in Appendix 6.

The meta-analysis (*Figure 31*) suggests that ecstasy-exposed cohorts performed worse than controls by a small, but nonetheless significant, margin. Sensitivity analysis using the aggregated data approach generated very similar results [SMD −0.126; 95% CI −0.233 to −0.020; p(null SMD) = 0.020]. The inter-population difference appears to be even smaller in the former-ecstasy-using stratum; however, the hypothesis test for interstratum heterogeneity provides no statistical justification for supposing the participants belong to different distributions.

The small magnitude of this standardised difference becomes apparent when one compares the pooled estimate with the raw data on which the meta-analysis is based. For example, in Bolla *et al.*,[93] ecstasy users scored an average of 0.2 less than controls in WMS-R figural memory (7.3 versus 7.5; SMD −0.166) and, in the spatial recognition task in Fox *et al.*,[130] there was an additional response latency of 110 milliseconds in the ecstasy-exposed cohort (2.4 seconds versus 2.29 seconds; SMD −0.168).

There is no evidence of small-study bias in this dataset (Egger's $p = 0.523$), and the funnel plot (not shown) had an unremarkable appearance.

Sufficient data were available to attempt metaregression analyses for 17 covariates; details are shown in *Table 19*. There was no evidence of a dose–response effect (see *Figure 100* in Appendix 7).

Figure 32 plots memory performance against average age (classical metaregression, with covariate measured across all participants). It appears that the most marked deficit for ecstasy users may be found when populations with lower average age are assessed (it is notable that the eight lowest effect estimates appear amongst the youngest cohorts). In contrast, inter-arm differences, apparently, tend to be minimal in older cohorts.

There may also be a gender effect in evidence: *Figure 33* plots the outcome of interest against the gender composition of the populations under analysis (classical metaregression, with covariate measured across all participants). It shows that deficits were greatest in ecstasy-using cohorts that were predominantly made up of men. It is noticeable that the two datapoints contributed by comparisons of 100% male populations are those suggesting the greatest underperformance in ecstasy users.

For differential covariates, a very strong positive correlation was found between immediate visual memory outcomes and baseline asymmetry in intelligence, suggesting that good performance in these tests can be expected wherever one cohort has an advantage over the other in intelligence. This relationship is clear in *Figure 34*, which plots the variables against each other. It can be seen that datapoints representing worst performance in ecstasy users tend to be those in which they were less intelligent than controls whereas, in studies

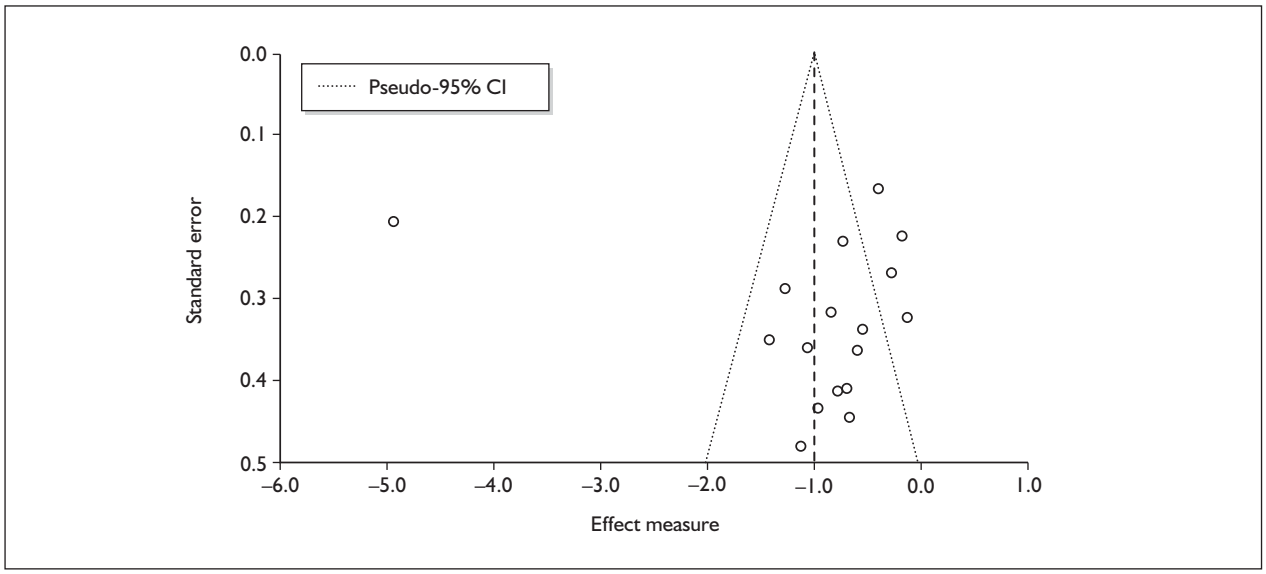


FIGURE 30 *Verbal memory – delayed (composite measure) – ecstasy users versus drug-naïve controls: funnel plot.*

TABLE 18 *Verbal memory – delayed (composite measure) – ecstasy users versus drug-naïve controls: univariate metaregression results*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	18	−0.118	(−0.319 to 0.082)	0.246			
Sex (% male)	17	0.396	(−0.563 to 1.355)	0.419			
IQ	11	−0.014	(−0.047 to 0.018)	0.387			
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	11	0.002	(−0.002 to 0.005)	0.290			
ETLE (occasions)	< 5						
Period since last consumption (days)	8	0.001	(−0.004 to 0.005)	0.684			
Duration of ecstasy use (days)	7	0.001	(0.000–0.003)	0.126			
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	18	0.085	(−0.343 to 0.513)	0.697	−1.083	(−1.814 to −0.352)	0.004
Sex (% male)	17	−2.030	(−5.560 to 1.499)	0.260	−0.703	(−0.898 to −0.509)	0.000
Baseline intelligence measures (SMD)	16	−0.545	(−2.812 to 1.722)	0.638	−1.073	(−1.926 to −0.219)	0.014
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to amphetamines (ETLD)	< 5						
Exposure to cocaine (ETLD)	< 5						
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	13	0.057	(−0.364 to 0.477)	0.792	−0.740	(−1.021 to −0.460)	0.000

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

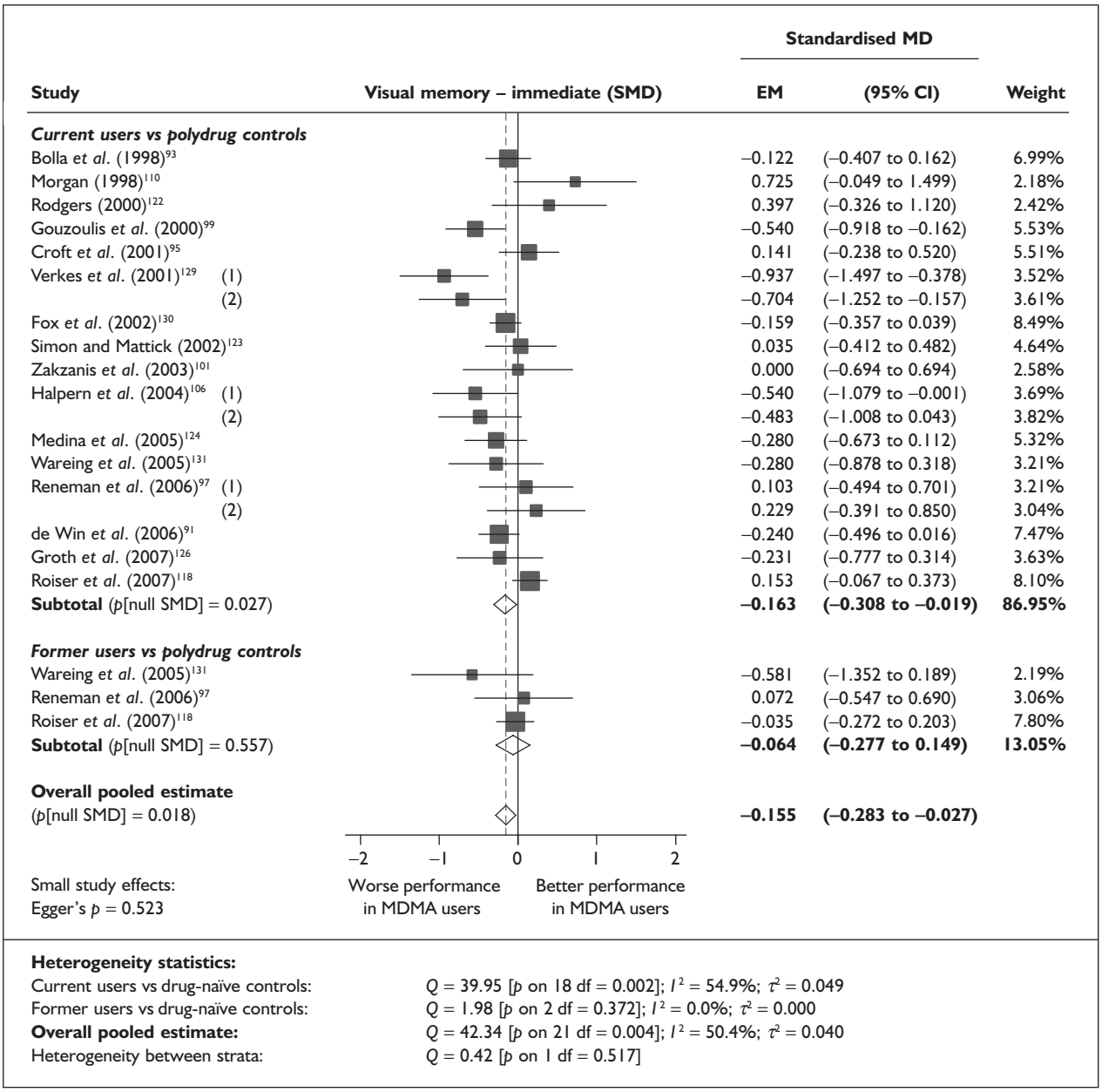


FIGURE 31 *Visual memory – immediate (composite measure) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

in which ecstasy users were more intelligent than controls, they could be expected to match or outperform controls in the memory tests. We note that a similar – albeit slightly less compelling – picture was seen in the equivalent metaregression for the analogous measure of verbal memory (see *Figure 24*).

This model suggests that the small exposure effect seen in the primary analysis is ascribable entirely to baseline imbalances in intelligence: when accounting for this confounding, the adjusted SMD is estimated at –0.028 (95%CI –0.148 to 0.092), which is consistent with a null effect ($p = 0.623$). This can be clearly seen in *Figure 34*, because the metaregression line passes almost directly through the origin of the graph.

In addition to the absolute effect of age (see *Figure 32*), inter-population asymmetry in age may also have an effect on observed results. *Figure 35* shows that this effect has a negative coefficient, suggesting that worse performance by ecstasy-exposed cohorts is seen when they are older than their control groups.

Figure 36 shows the effect of differential amphetamine exposure on observed results. Although there appears to be a trend associating poorer performance with increased exposure

TABLE 19 *Visual memory – immediate (composite measure) – ecstasy users versus polydrug controls: univariate metaregression results*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	20	0.062	(0.011–0.113)	0.017			
Sex (% male)	18	−1.002	(−1.851 to −0.152)	0.021			
IQ	6	0.010	(−0.049 to 0.068)	0.740			
Education (years)	7	0.028	(−0.117 to 0.173)	0.705			
Characteristics of ecstasy exposure							
ETLD (tablets)	17	0.000	(−0.001 to 0.000)	0.382			
ETLE (occasions)	< 5						
Period since last consumption (days)	11	0.000	(−0.001 to 0.001)	0.782			
Duration of ecstasy use (days)	15	0.000	(0.000–0.000)	0.986			
Frequency of ecstasy use (occasions/month)	6	0.015	(−0.077 to 0.107)	0.752			
Inter-arm differences							
Age (years)	20	−0.060	(−0.117 to −0.003)	0.040	−0.124	(−0.247 to −0.002)	0.047
Sex (% male)	18	−0.250	(−1.314 to 0.814)	0.645	−0.109	(−0.249 to 0.032)	0.129
Baseline intelligence measures (SMD)	15	0.422	(0.174–0.670)	0.001	−0.028	(−0.137 to 0.081)	0.614
Education (years)	7	−0.020	(−0.177 to 0.138)	0.808	−0.237	(−0.463 to −0.012)	0.039
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	15	−0.028	(−0.360 to 0.304)	0.868	−0.117	(−0.321 to 0.086)	0.259
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	12	−0.215	(−0.426 to −0.004)	0.046	0.022	(−0.092 to 0.136)	0.704
Exposure to cocaine (ETLD)	< 5						
Exposure to cocaine (SMD)	10	−0.091	(−0.402 to 0.219)	0.564	0.002	(−0.216 to 0.221)	0.984
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	14	0.013	(−0.344 to 0.371)	0.941	−0.096	(−0.258 to 0.066)	0.246

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

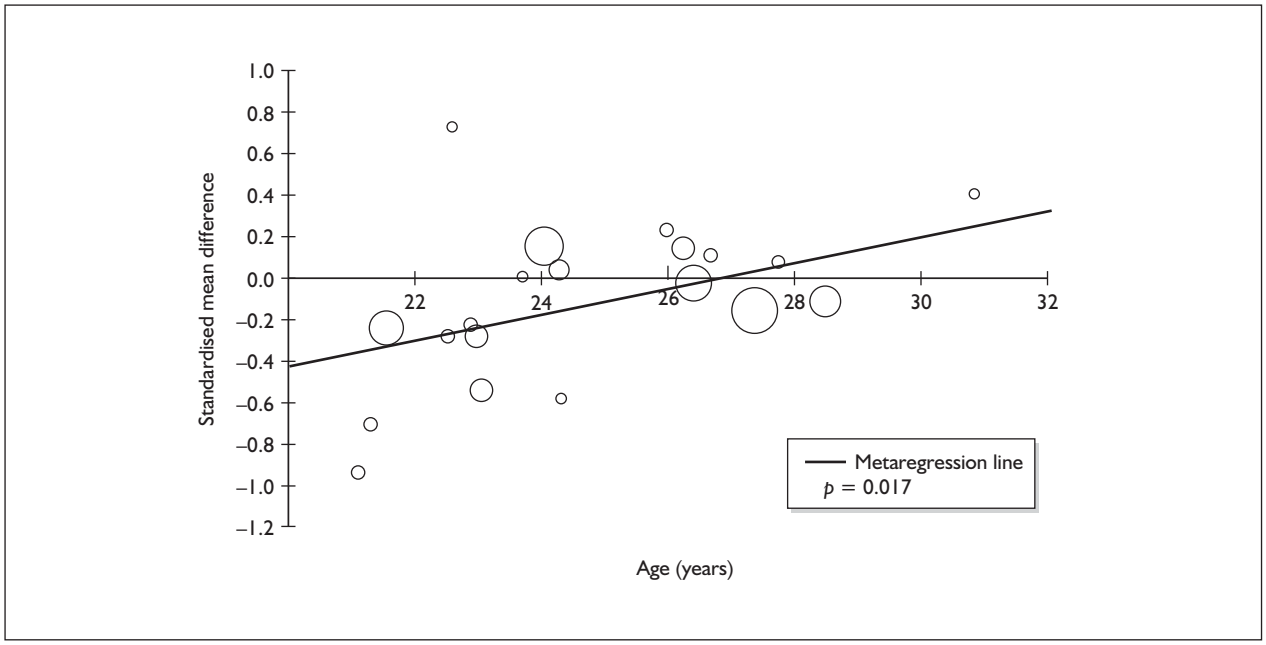


FIGURE 32 *Visual memory – immediate (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against average age (all participants).*

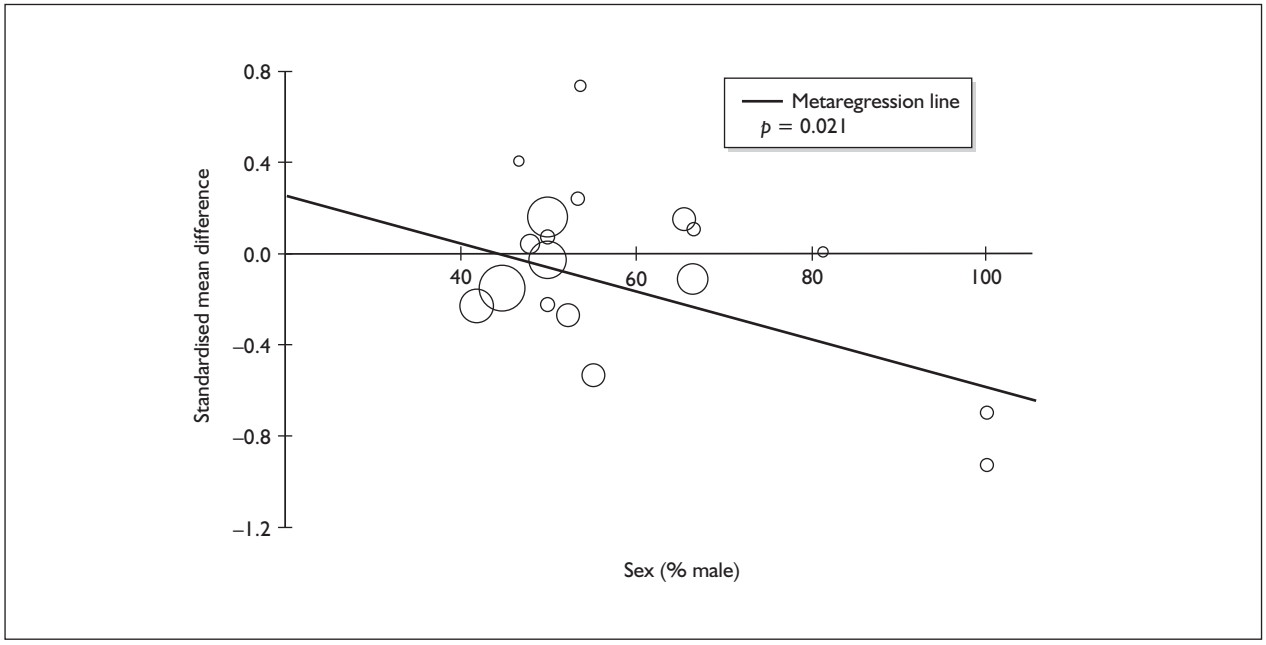


FIGURE 33 *Visual memory – immediate (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against gender (across all participants).*

asymmetry (i.e. ecstasy users taking more amphetamines than controls), it should be noted that a single datapoint is exerting considerable leverage on this analysis. The bubble on the left-hand side of the plot represents the study by Roiser *et al.*,[118] in which there was substantially greater exposure to amphetamines in the control group than in the current ecstasy users. If this single datapoint is excluded from the evidence-base, the apparent association with outcome disappears entirely ($p = 0.379$).

Visual memory (immediate) – MDMA users versus drug-naïve controls

The dataset assembled for this measure comprises 25 datapoints, representing a total of seven

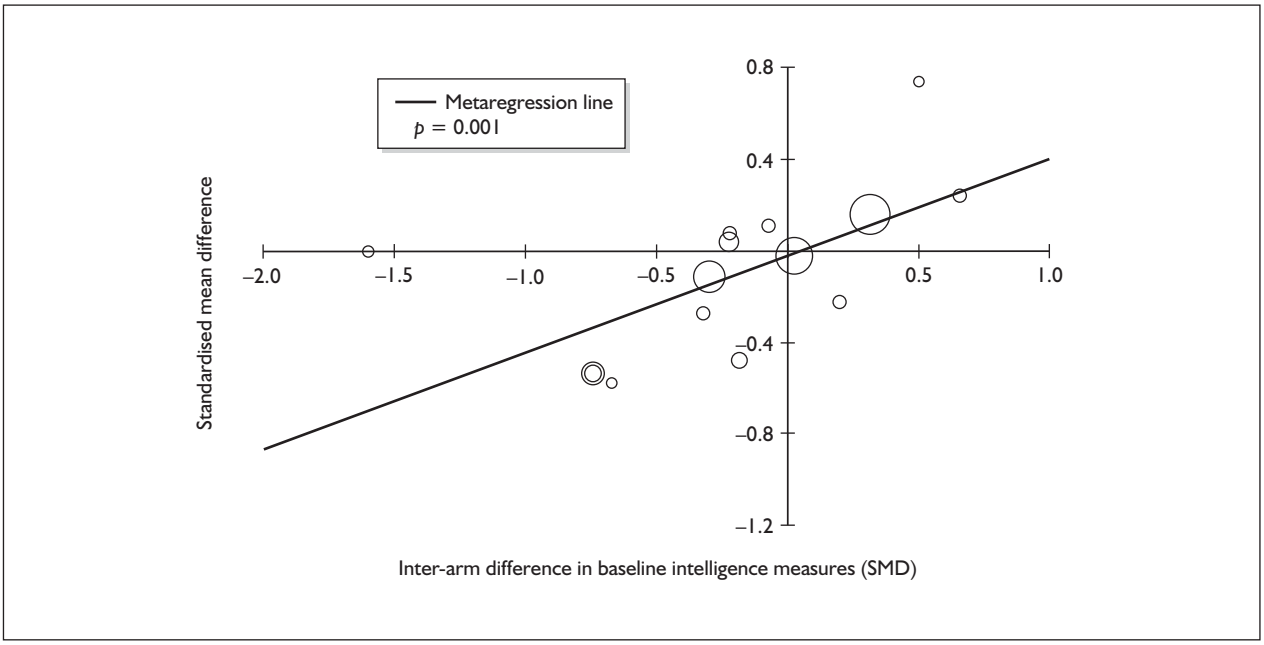


FIGURE 34 *Visual memory – immediate (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against inter-arm asymmetry in baseline intelligence measures.*

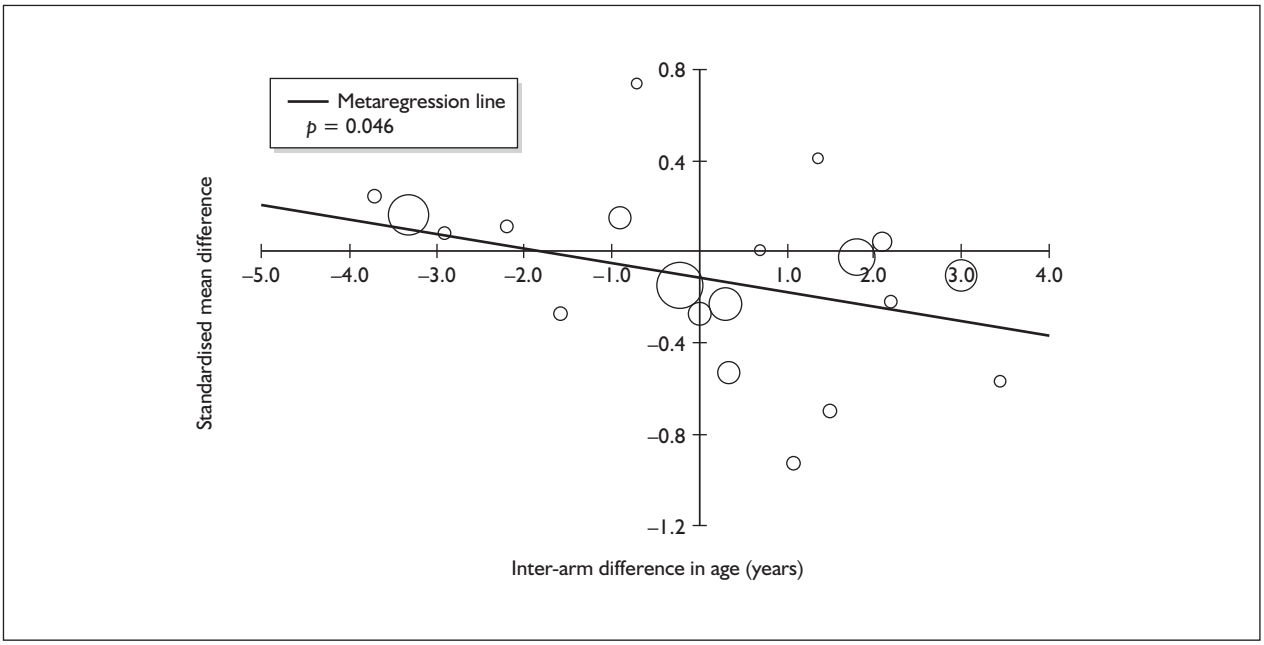


FIGURE 35 *Visual memory – immediate (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against inter-arm asymmetry in age.*

pairwise comparisons, drawn from six different studies (six comparisons from six studies providing data for current ecstasy users and one comparison from one study providing data for former ecstasy users). Seventeen different outcome measures are included, the most common being PRM: latency (two datapoints), PRM: correct (two datapoints) and CANTAB DMTS: simultaneous–latency (two datapoints). The complete dataset is detailed in *Table 56* in Appendix 6.

When meta-analysed (*Figure 37*), these data suggest that there is little evidence of an exposure effect in this area. The effect estimate is noticeably similar to that seen in the comparison with polydrug controls (see *Figure 31*) but, in this instance, the

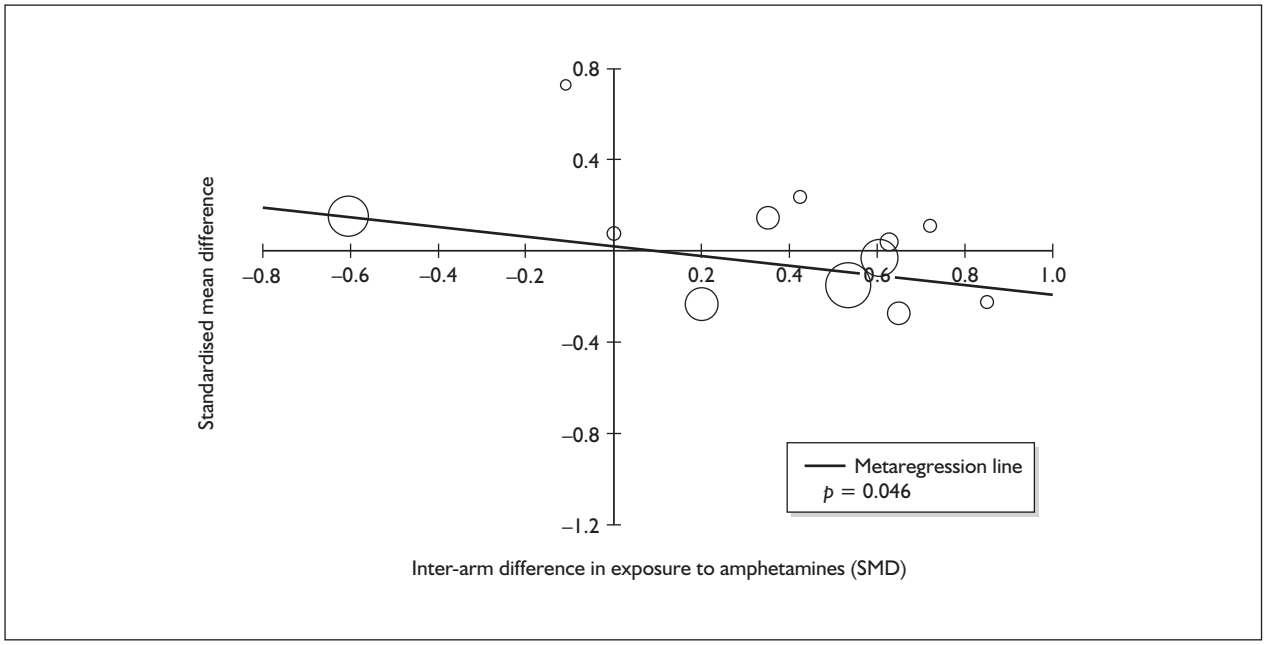


FIGURE 36 *Visual memory – immediate (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against inter-arm asymmetry in exposure to amphetamines other than MDMA.*

analysis is based on a smaller dataset, and is subject to greater uncertainty. Sensitivity analysis using the aggregated data approach did not produced markedly different findings [SMD –0.132; 95% CI –0.294 to 0.029; p(null SMD) = 0.107].

There is no evidence of small-study bias in this dataset (Egger's $p = 0.921$), and the funnel plot (not shown) had an unremarkable appearance.

Sufficient data were available to attempt metaregression analyses for six covariates; details are shown in *Table 20.* None of the analyses were able to provide a statistically convincing explanation of the heterogeneity seen amongst base-case effect estimates. Both covariates relating to gender distribution generated p-values approaching 0.05; however, little credence can be given to these findings, in the context of multiple testing with very limited ($n = 6$) datasets. There was no evidence of a dose–response effect (see *Figure 101* in Appendix 7).

Visual memory (delayed) – MDMA users versus polydrug controls

The dataset assembled for this measure comprises 22 datapoints, representing a total of 14 pairwise comparisons, drawn from 10 different studies (12 comparisons from 10 studies providing data for current ecstasy users and two comparisons from two studies providing data for former ecstasy users). Ten different outcome measures are included, the most common being WMS-R: visual reproduction (five datapoints), R-OCFT: total score (four datapoints) and WMS-R: visual paired associates (two datapoints). The complete dataset is detailed in *Table 57* in Appendix 6.

When meta-analysed (*Figure 38*), these data are strongly reminiscent of the immediate visual memory findings discussed above (see *Figure 31*), with ecstasy-exposed individuals apparently subject to a small but significant deficit in performance. Once more, sensitivity analysis using the aggregated data approach generated extremely similar results [SMD –0.186; 95% CI –0.325 to –0.047; p(null SMD) = 0.009].

A typical datapoint feeding this analysis is found in Reneman *et al.*,[93] in which the WMS-R visual reproduction score was a single point lower in the ecstasy-exposed arm than in the controls (35.4 versus 36.4; SMD –0.187).

There is no evidence of small-study bias in this dataset (Egger's $p = 0.173$), and the funnel plot (not shown) had an unremarkable appearance.

Sufficient data were available to attempt metaregression analyses for nine covariates; details are shown in *Table 21*. None of the analyses were able to provide a statistically convincing explanation of the heterogeneity seen amongst base-case effect estimates, and there was no evidence of a dose–response effect (see *Figure 102* in Appendix 7).

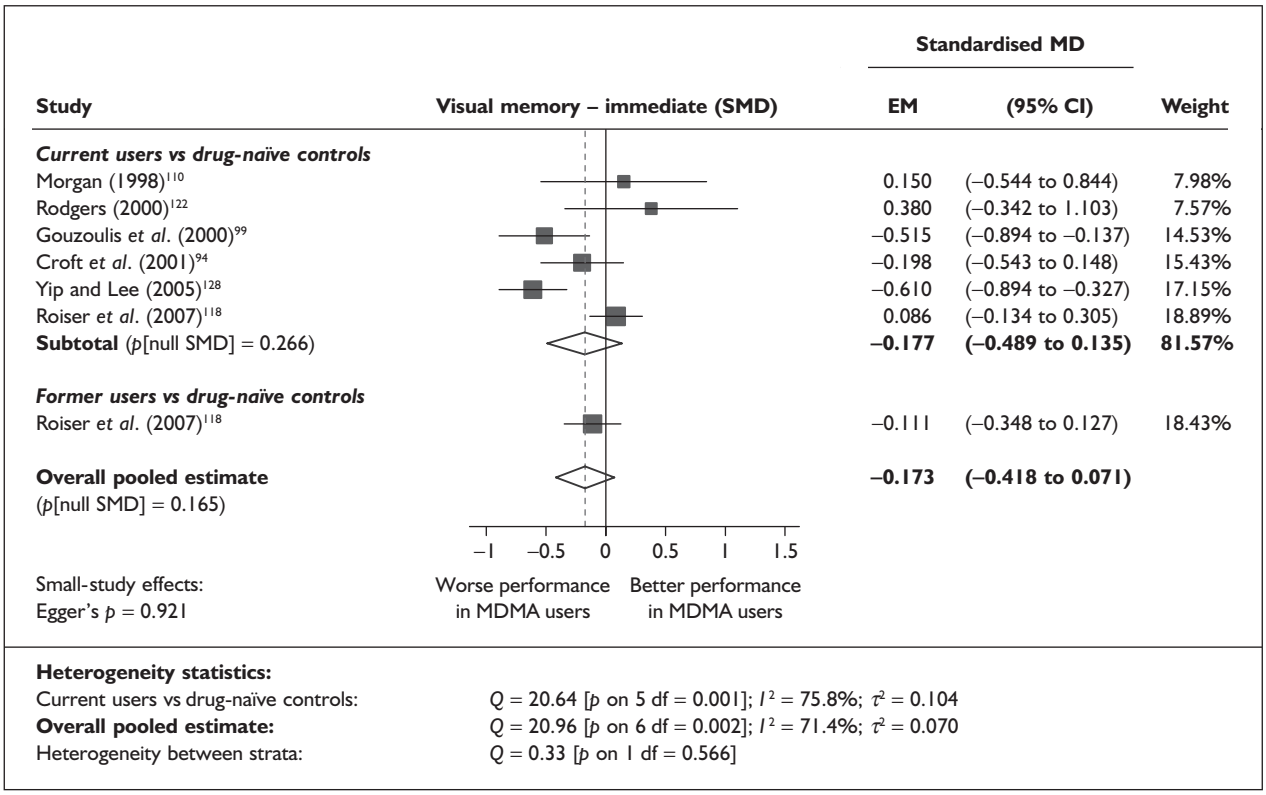


FIGURE 37 *Visual memory – immediate (composite measure) – ecstasy users versus drug-naïve controls: random-effects meta-analysis.*

Visual memory (delayed) – MDMA users versus drug-naïve controls

The dataset assembled for this measure comprises 11 datapoints, representing a total of seven pairwise comparisons, drawn from five different studies (five comparisons from five studies providing data for current ecstasy users and two comparisons from two studies providing data for former ecstasy users). Six different outcome measures are included, the most common being R-OCFT: total score (three datapoints), PRM: correct (two datapoints), and PRM: latency (two datapoints). The complete dataset is detailed in *Table 58* in Appendix 6.

Meta-analysis (*Figure 39*) suggests that, although ecstasy exposure is associated with worse performance in the majority of cases, pooled results do not provide convincing evidence against the null hypothesis of no exposure effect. This is true of the two strata individually and of the overall pooled estimate.

As in the analogous measure of delayed verbal memory (see *Figure 29*), the forest plot shows that the effect estimate from Yip and Lee's study[128] is markedly atypical of results from other studies. If this single datapoint is excluded from the meta-analysis, results become much more suggestive of a homogeneous dataset ($Q = 5.68$; p on 6 df = 0.460; $I^2 = 0.0\%$). Without Yip and Lee's study,[128] the estimated SMD falls somewhat to –0.191 but, because the heterogeneity term in the random-effects model is much reduced, the estimate appears rather more precise (95% CI –0.423 to 0.041). The evidence for an overall exposure effect remains weak ($p = 0.460$).

Our initial sensitivity analysis, adopting single, aggregated comparisons for each study, generated an SMD estimated at –0.520 (95% CI –1.239 to 0.198), which is noticeably higher than that seen in the primary analysis. However, as previously, this discrepancy appears to be an artefact of the distortions of Yip and Lee's study: repeated sensitivity analysis excluding the outlier is closely comparable to the primary analysis using the restricted dataset [SMD –0.234; 95% CI –0.605 to 0.137; p(null SMD) = 0.216].

When applied to the full dataset, Egger's test suggested that evidence of small-study bias approached significance ($p = 0.053$). However, Yip and Lee's study is exerting considerable leverage in this analysis; reanalysis with the datapoint excluded is much more suggestive of an unbiased dataset ($p = 0.338$). The funnel plot for this analysis (*Figure 40*) is unlikely to cause concern about publication

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TABLE 20 *Visual memory – immediate (composite measure) – ecstasy users versus drug-naïve controls: univariate metaregression results*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	7	−0.009	(−0.098 to 0.080)	0.842			
Sex (% male)	6	−3.563	(−7.306 to 0.180)	0.062			
IQ	< 5						
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	6	0.000	(−0.001 to 0.001)	0.470			
ETLE (occasions)	< 5						
Period since last consumption (days)	< 5						
Duration of ecstasy use (days)	< 5						
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	7	−0.008	(−0.171 to 0.154)	0.921	−0.160	(−0.461 to 0.141)	0.297
Sex (% male)	6	4.394	(−0.407 to 9.194)	0.073	−0.112	(−0.282 to 0.059)	0.200
Baseline intelligence measures (SMD)	5	0.538	(−0.398 to 1.474)	0.260	−0.122	(−0.471 to 0.227)	0.493
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to amphetamines (ETLD)	< 5						
Exposure to cocaine (ETLD)	< 5						
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	< 5						

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

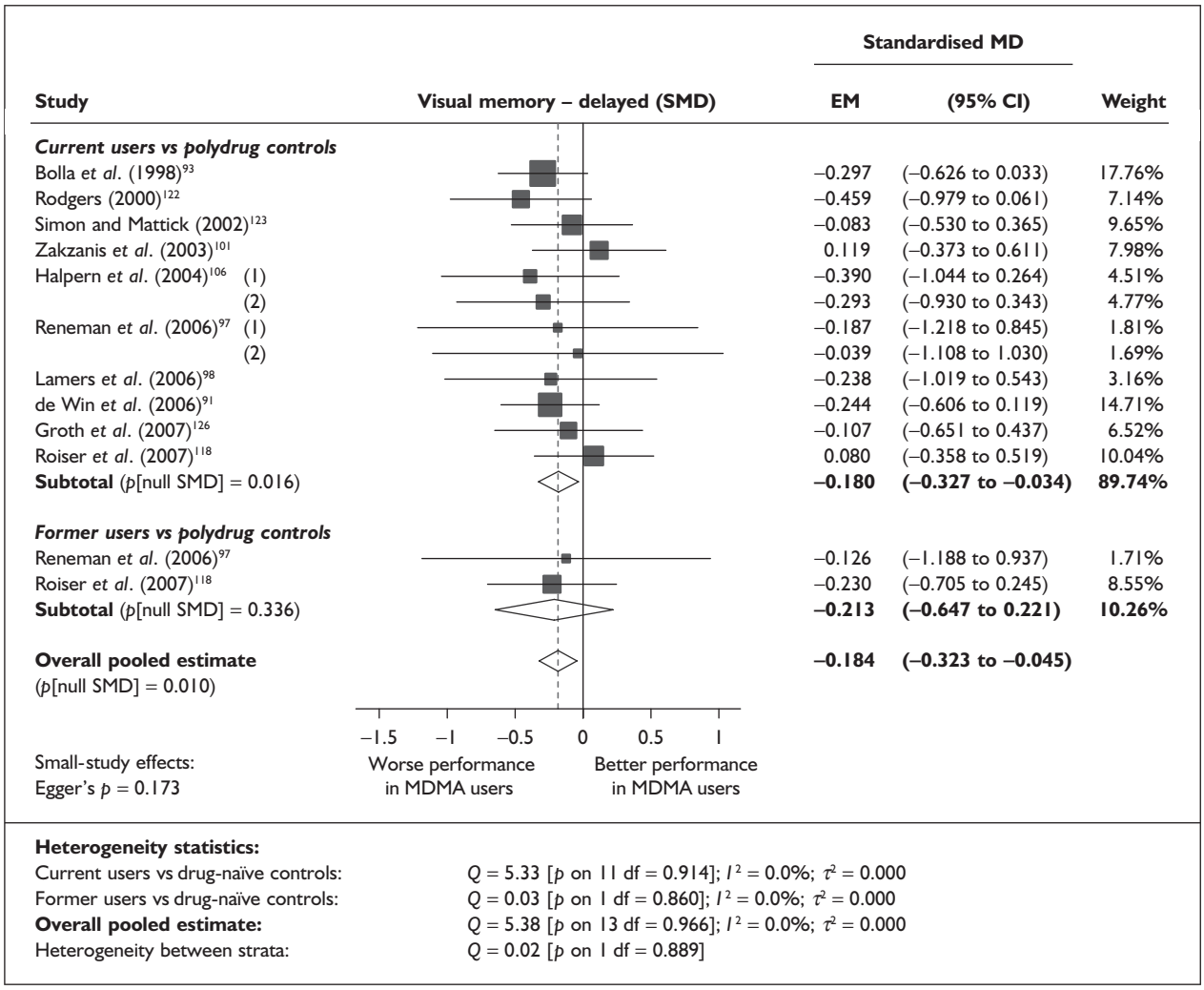

FIGURE 38 *Visual memory – delayed (composite measure) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

bias, though it reinforces the outlying nature of Yip and Lee's effect estimate.

Sufficient data were available to attempt metaregression analyses for seven covariates; details are shown in *Table 22*. None of the analyses were able to provide a statistically convincing explanation of the heterogeneity seen amongst base-case effect estimates, and there was no evidence of a dose–response effect (see *Figure 103* in Appendix 7).

Working memory – MDMA users versus polydrug controls

The dataset assembled for this measure comprises 47 datapoints, representing a total of 23 pairwise comparisons, drawn from 15 different studies (20 comparisons from 15 studies providing data for current ecstasy users and three comparisons from three studies providing data for former ecstasy users). Twenty-nine different outcome measures are included, the most common being computation span (three datapoints), spatial recall (three datapoints) and reading span (two datapoints). The complete dataset is detailed in *Table 59* in Appendix 6.

When meta-analysed (*Figure 41*), these data reflect an inter-population difference of approximately 0.4 SD. This effect size approaches a 'medium'-sized difference, according to Cohen's rule of thumb. Sensitivity analysis with data pooled at study level produced a closely comparable result [SMD –0.406; 95% CI –0.587 to –0.225; p(null SMD) < 0.001]. There is evidence of interstratum heterogeneity: former users performed less well, in comparison to controls, than current users. For current users, the average inter-arm difference was of the order of one-third of an SD, while ex-users' scores showed an effect size approaching two-thirds of an SD.

A representative datapoint from the underlying dataset is found in the 2002 study by Morgan *et*

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TABLE 21 *Visual memory – delayed (composite measure) – ecstasy users versus polydrug controls: univariate metaregression results*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	12	−0.032	(−0.084 to 0.020)	0.223			
Sex (% male)	12	0.351	(−0.886 to 1.588)	0.578			
IQ	6	0.025	(−0.068 to 0.118)	0.599			
Education (years)	5	−0.180	(−0.574 to 0.215)	0.372			
Characteristics of ecstasy exposure							
ETLD (tablets)	8	0.000	(−0.001 to 0.001)	0.952			
ETLE (occasions)	< 5						
Period since last consumption (days)	6	0.000	(−0.001 to 0.000)	0.749			
duration of ecstasy use (days)	8	0.000	(0.000–0.000)	0.799			
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	12	−0.035	(−0.101 to 0.031)	0.302	−0.144	(−0.297 to 0.009)	0.065
Sex (% male)	12	0.371	(−1.191 to 1.934)	0.641	−0.157	(−0.310 to −0.003)	0.045
Baseline intelligence measures (SMD)	12	−0.030	(−0.321 to 0.260)	0.838	−0.156	(−0.332 to 0.021)	0.084
Education (years)	5	0.047	(−0.191 to 0.284)	0.700	−0.134	(−0.465 to 0.196)	0.426
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	9	−0.025	(−0.415 to 0.365)	0.901	−0.126	(−0.329 to 0.077)	0.224
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	9	−0.146	(−0.533 to 0.242)	0.461	−0.088	(−0.305 to 0.129)	0.428
Exposure to cocaine (ETLD)	< 5						
Exposure to cocaine (SMD)	8	−0.033	(−0.748 to 0.682)	0.928	−0.124	(−0.560 to 0.312)	0.578
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	9	0.094	(−0.283 to 0.471)	0.626	−0.158	(−0.370 to 0.053)	0.143

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

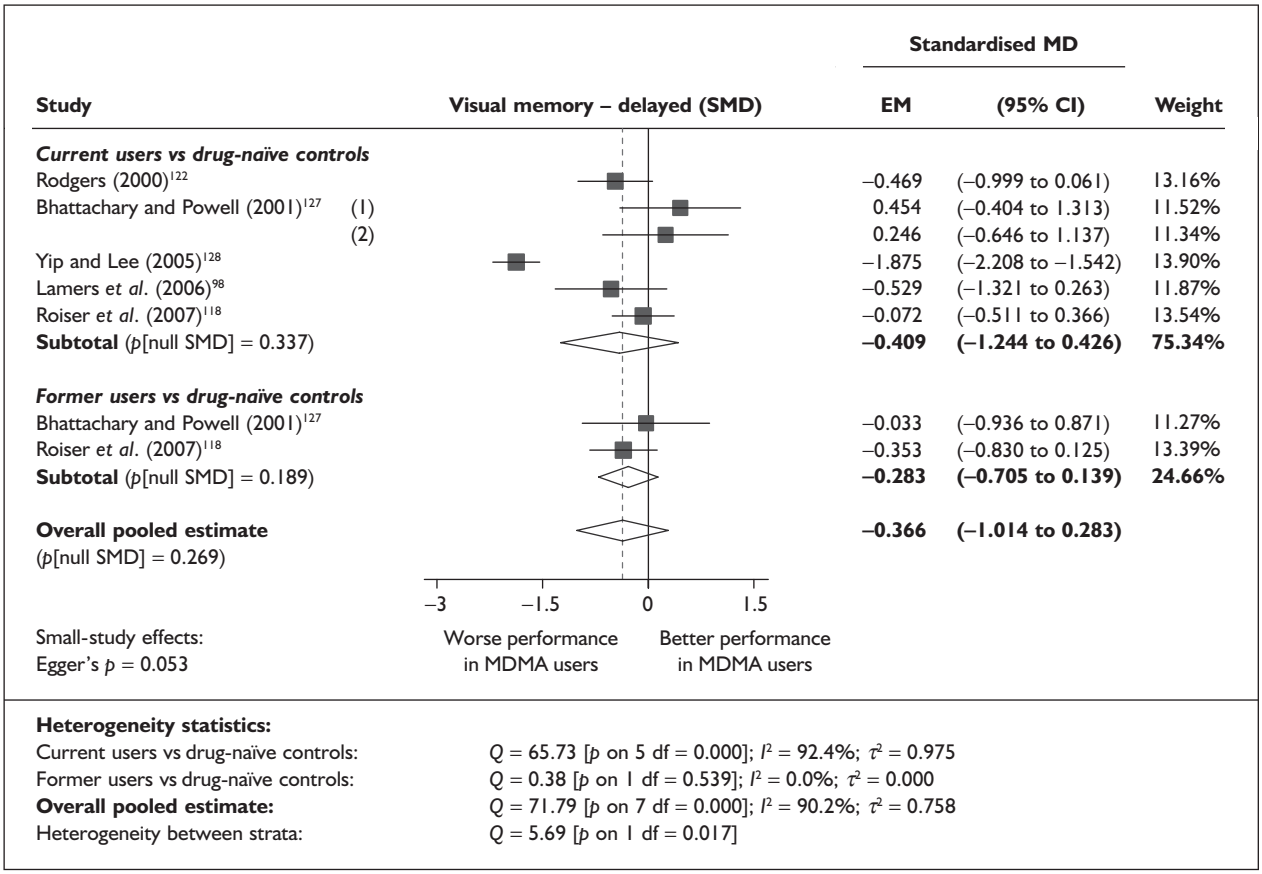

FIGURE 39 *Visual memory – delayed (composite measure) – ecstasy users versus drug-naïve controls: random-effects meta-analysis.*

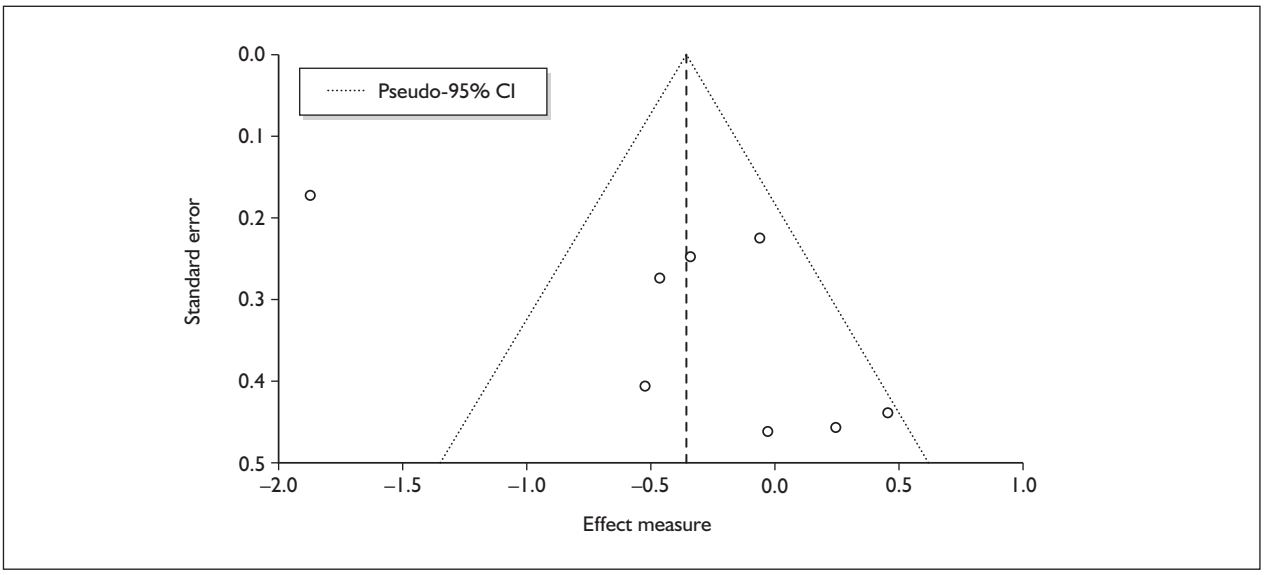

FIGURE 40 *Visual memory – delayed (composite measure) – ecstasy users versus drug-naïve controls: funnel plot.*

al.,[103] in which the ecstasy-using cohort made an average of 0.675 more errors than controls in the serial sevens subtraction task (1.725 versus 1.05; SMD –0.439).

There is no evidence of small-study bias (Egger's $p = 0.238$), and the funnel plot for this dataset (not shown) showed no pronounced trend, although there was a cluster of more powerful studies around the null effect point.

Sufficient data were available to attempt metaregression analyses for 15 covariates, shown in

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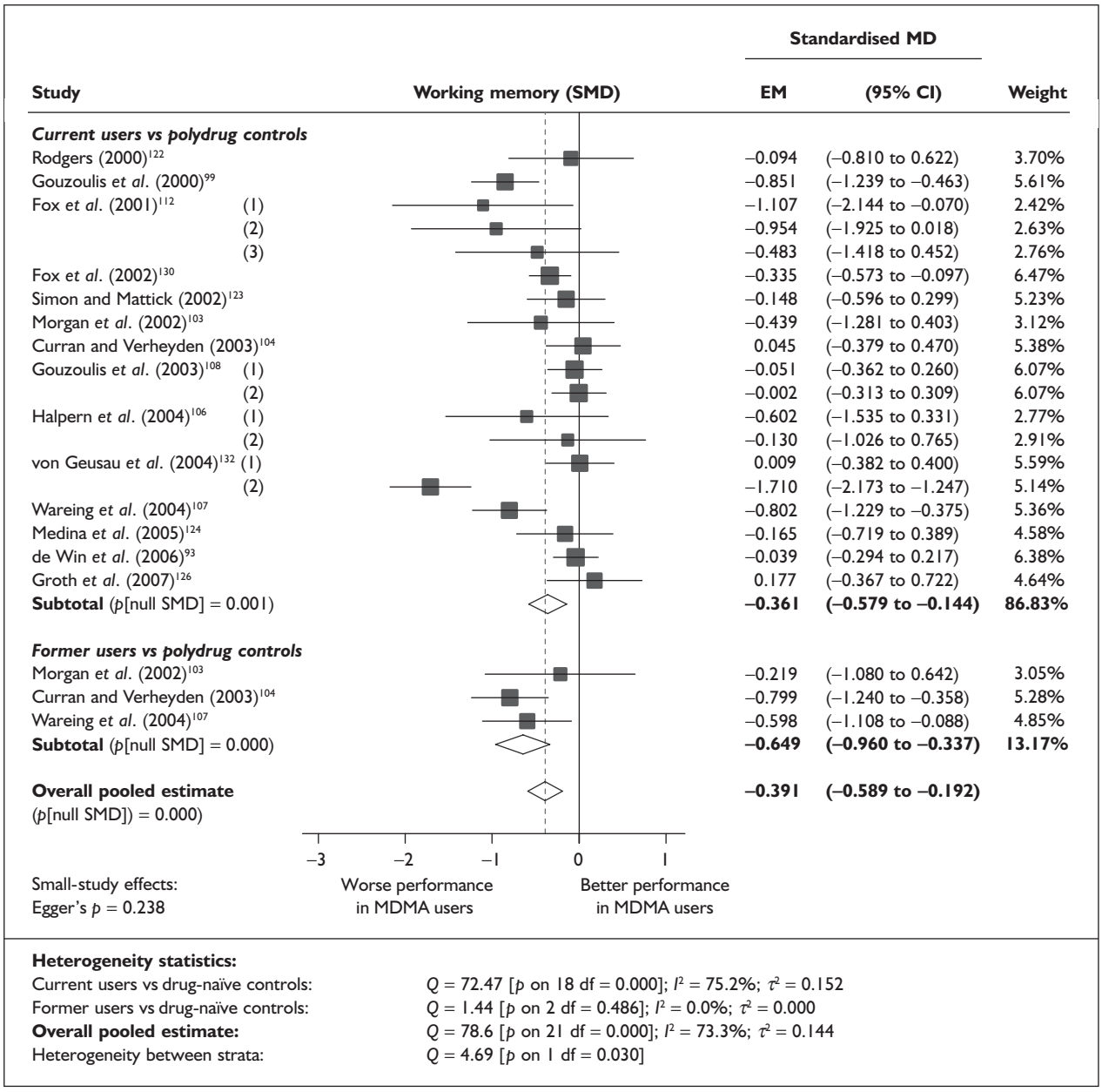
TABLE 22 *Visual memory – delayed (composite measure) – ecstasy users versus drug-naïve controls: univariate metaregression results*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	8	−0.133	(−0.312 to 0.046)	0.145			
Sex (% male)	7	2.027	(−2.256 to 6.310)	0.354			
IQ	6	−0.022	(−0.058 to 0.013)	0.213			
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	< 5						
ETLE (occasions)	< 5						
Period since last consumption (days)	< 5						
Duration of ecstasy use (days)	< 5						
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	8	0.133	(−0.265 to 0.531)	0.512	−0.447	(−1.188 to 0.294)	0.237
Sex (% male)	7	−1.630	(−8.268 to 5.008)	0.630	−0.150	(−0.438 to 0.138)	0.308
Baseline intelligence measures (SMD)	7	0.535	(−1.958 to 3.028)	0.674	−0.250	(−1.159 to 0.659)	0.590
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to amphetamines (ETLD)	< 5						
Exposure to cocaine (ETLD)	< 5						
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	6	−0.206	(−0.866 to 0.455)	0.541	−0.006	(−0.468 to 0.457)	0.981

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.



Heterogeneity statistics:

Current users vs drug-naïve controls:	Q = 72.47 [p on 18 df = 0.000]; I^2 = 75.2%; τ^2 = 0.152
Former users vs drug-naïve controls:	Q = 1.44 [p on 2 df = 0.486]; I^2 = 0.0%; τ^2 = 0.000
Overall pooled estimate:	Q = 78.6 [p on 21 df = 0.000]; I^2 = 73.3%; τ^2 = 0.144
Heterogeneity between strata:	Q = 4.69 [p on 1 df = 0.030]

FIGURE 41 *Working memory (composite measure) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

Table 23. There was no evidence of a dose–response effect (see *Figure 104* in Appendix 7).

Figure 42 plots working memory performance against inter-arm asymmetry in gender. The most immediately noticeable feature of the graph is the dense cluster of datapoints around the origin; this suggests that those studies that were well matched for gender tended to show no difference in working memory between arms. Otherwise, the preponderance of data appears in the 'south-east' quadrant of the graph, showing that, where ecstasy-using participants were more likely to be men than controls, they tended to record worse test scores.

The relationship between inter-arm asymmetry in education and the response variable is visualised in *Figure 43*. The positive coefficient suggests that, in the various tasks synthesised here, worse performance tends to be seen amongst those ecstasy-exposed cohorts who had also received less education, on average, than their respective controls. There was limited availability of covariate data so this analysis is based on a fairly small subset of the full dataset; however, if the model were to be accepted, it would entirely explain the inter-population difference that might otherwise be ascribed to exposure to ecstasy.

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TABLE 23 *Working memory (composite measure) – ecstasy users versus polydrug controls: univariate metaregression results*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	20	0.036	(−0.066 to 0.139)	0.490			
Sex (% male)	18	0.244	(−0.975 to 1.464)	0.695			
IQ	7	0.074	(−0.069 to 0.217)	0.312			
Education (years)	8	−0.088	(−0.524 to 0.348)	0.692			
Characteristics of ecstasy exposure							
ETLD (tablets)	14	0.000	(−0.001 to 0.001)	0.908			
ETLE (occasions)	< 5						
Period since last consumption (days)	10	0.000	(−0.001 to 0.001)	0.790			
Duration of ecstasy use (days)	17	0.000	(−0.001 to 0.000)	0.526			
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	20	−0.053	(−0.185 to 0.078)	0.426	−0.342	(−0.588 to −0.096)	0.006
Sex (% male)	18	−1.922	(−3.550 to −0.294)	0.021	−0.239	(−0.465 to −0.013)	0.038
Baseline intelligence measures (SMD)	16	0.356	(−0.319 to 1.032)	0.301	−0.292	(−0.561 to −0.024)	0.033
Education (years)	8	0.365	(0.036–0.694)	0.030	−0.101	(−0.471 to 0.269)	0.592
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	14	0.014	(−0.518 to 0.546)	0.959	−0.324	(−0.671 to 0.024)	0.068
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	13	−0.082	(−1.233 to 1.069)	0.889	−0.220	(−1.010 to 0.571)	0.586
Exposure to cocaine (ETLD)	< 5						
Exposure to cocaine (SMD)	8	−0.461	(−1.533 to 0.612)	0.400	0.041	(−0.948 to 1.030)	0.935
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	9	0.383	(0.089–0.677)	0.011	−0.224	(−0.355 to −0.092)	0.001

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

Figure 44 plots inter-arm asymmetry in exposure to alcohol against working memory performance. It shows that, once more, greater exposure to alcohol appears to be associated with better relative performance in the ecstasy-exposed cohort. The adjusted effect estimate from this analysis is, at –0.224, a fair amount lower than that calculated in the primary analysis; however, because the regression gradient is relatively shallow, the overall exposure effect remains significant ($p = 0.001$).

Working memory – MDMA users versus drug-naïve controls

The dataset assembled for this measure comprises 12 datapoints, representing a total of seven pairwise comparisons, drawn from five different studies (six comparisons from five studies providing data for current ecstasy users and one comparison from one study providing data for former ecstasy users). Ten different outcome measures are included, none of which is adopted in more than one study. The complete dataset is detailed in *Table 62* in Appendix 6.

When meta-analysed (*Figure 45*), this dataset suggests an exposure effect in the order of 0.5 SD, which slightly exceeds that seen in the comparison with polydrug controls and would be classified as a 'medium'-sized effect in Cohen's schema.

There is no evidence of small-study bias in this dataset (Egger's $p = 0.879$), and the funnel plot (not shown) had an unremarkable appearance.

Because of the very small size of this dataset, it was only possible to perform metaregressions on four covariates; none was significant (*Table 24*), and there was no evidence of a dose–response effect (see *Figure 105* in Appendix 7).

Attention (focus–execute) – MDMA users versus polydrug controls

The dataset assembled for this measure is the largest in this review. It comprises 119 datapoints, representing a total of 30 pairwise comparisons, drawn from 19 different studies (26 comparisons from 19 studies providing data for current ecstasy users and four comparisons from four studies providing data for former ecstasy users). In total, 49 different outcome measures are included, the most common being TMT: Part A – time (seven datapoints), TMT: Part B – time (seven datapoints) and Stroop: colour reading – time (six datapoints). The complete dataset is detailed in *Table 61* in Appendix 6.

When synthesised in a random-effects meta-analysis (*Figure 46*), these data suggest that ecstasy-exposed populations tend to perform worse than polydrug controls by a little over 0.2 SD. This would be considered a 'small' inter-population difference, according to Cohen's schema. There is no evidence of interstratum heterogeneity. Sensitivity analysis using study-level aggregated data produced similar results [SMD –0.256; 95% CI –0.360 to –0.153; p(null SMD) < 0.001].

To compare the pooled estimate with a typical datapoint from a well-known instrument from the underlying dataset, a good example would be the WAIS digit–symbol test reported by McCardle *et al.*,[100] in which current ecstasy users scored 2.01 points less than controls (64.06 versus 66.07; SMD –0.205).

There is no evidence of small-study bias in this dataset (Egger's $p = 0.768$), and the funnel plot (not shown) had an unremarkable appearance.

Sufficient data were available to attempt metaregression analyses for 17 covariates; details are shown in *Table 25*. There was no evidence of a dose–response effect (see *Figure 106* in Appendix 7).

Figure 47 depicts the influence of inter-arm asymmetry in age on the outcome of interest. It shows that, in studies in which ecstasy users were younger than controls, inter-population differences tended to be relatively slight but, where they were older, the exposure effect had a tendency to be larger. However, because this dataset is relatively well balanced on this variable, this gradient has no notable effect on the overall pooled effect estimate (the adjusted value is only 0.01 SD lower than the base-case estimate).

Attention (focus–execute) – MDMA users versus drug-naïve controls

The dataset assembled for this measure comprises 36 datapoints, representing a total of 16 pairwise comparisons, drawn from 12 different studies (14 comparisons from 12 studies providing data for current ecstasy users and two comparisons from two studies providing data for former ecstasy users). A total of 21 different outcome measures are included, the most common being MFFT-20: total errors (six datapoints), MFFT-20: latency to first response (six datapoints) and TMT: Part B – errors (two datapoints). The complete dataset is detailed in *Table 62* in Appendix 6.

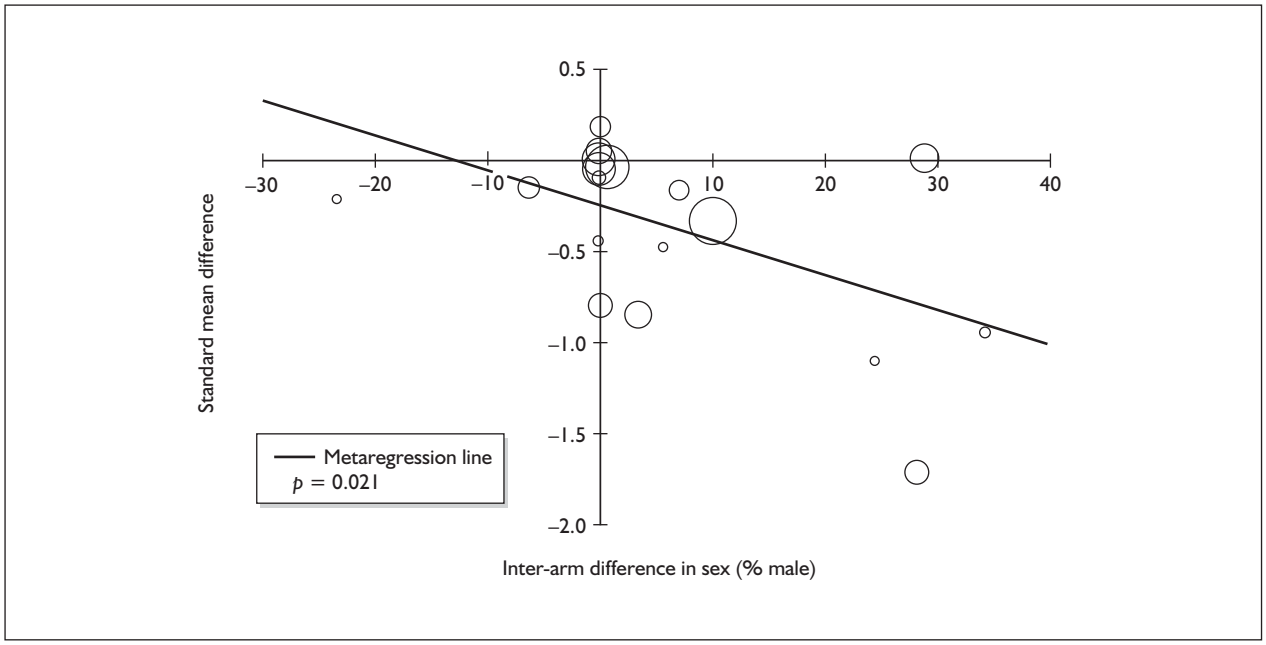

FIGURE 42 *Working memory (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against inter-arm asymmetry in gender.*

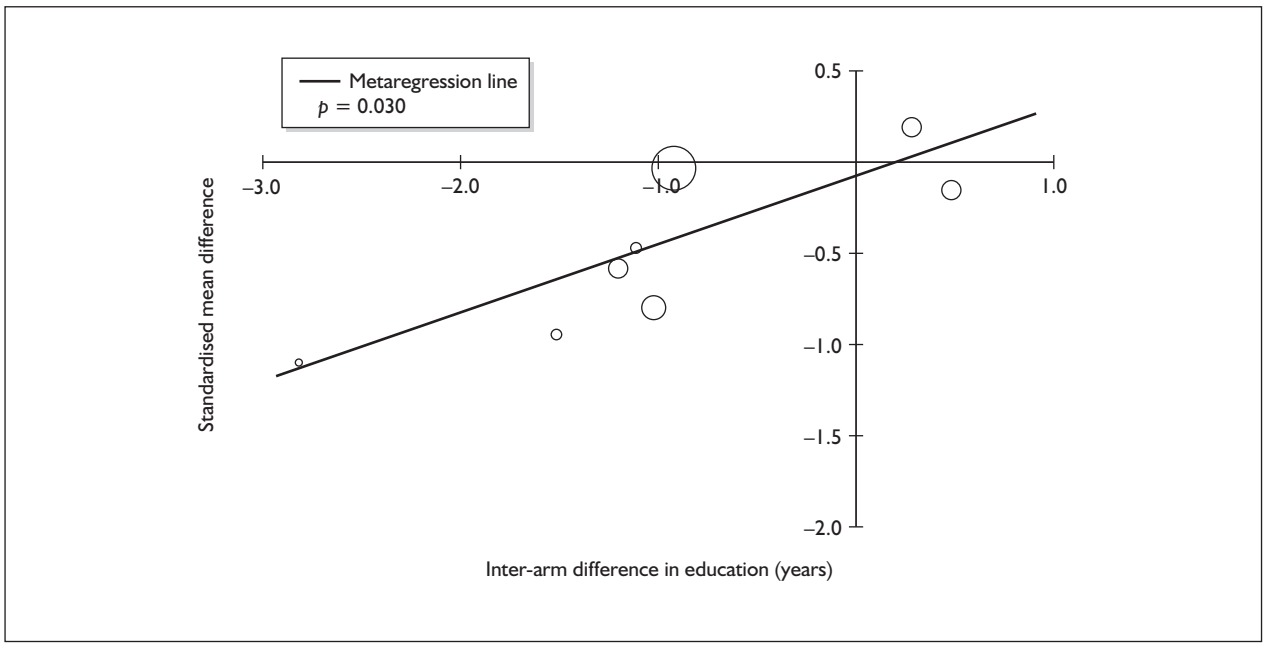

FIGURE 43 *Working memory (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against inter-arm asymmetry in education.*

Our random-effect meta-analysis of these data (*Figure 48*) suggests that ecstasy users tended to perform worse than controls by a little over one-quarter of an SD. This result is comparable to that seen in the comparison between ecstasy users and polydrug controls (see *Figure 46*). Sensitivity analysis using the aggregated data approach generated similar – though slightly more uncertain – results [SMD –0.295; 95% CI –0.538 to –0.052; p(null SMD) = 0.017]. In the dataset on which this meta-analysis is based, the most typical datapoint is the nine-letter comparison speed task reported by Wareing *et al.*,[136] in which former ecstasy users achieved 0.8 fewer correct items than controls (11.7 versus 12.5; SMD –0.288).

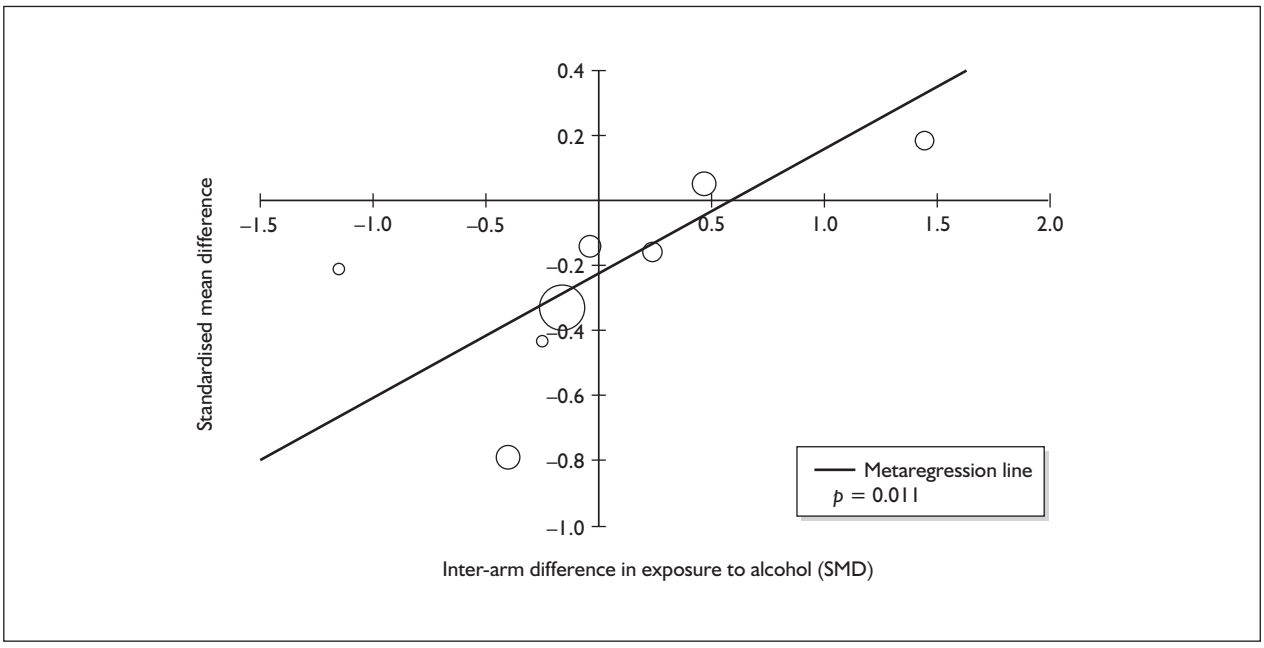

FIGURE 44 *Working memory (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against inter-arm asymmetry in exposure to alcohol (standardised mean difference).*

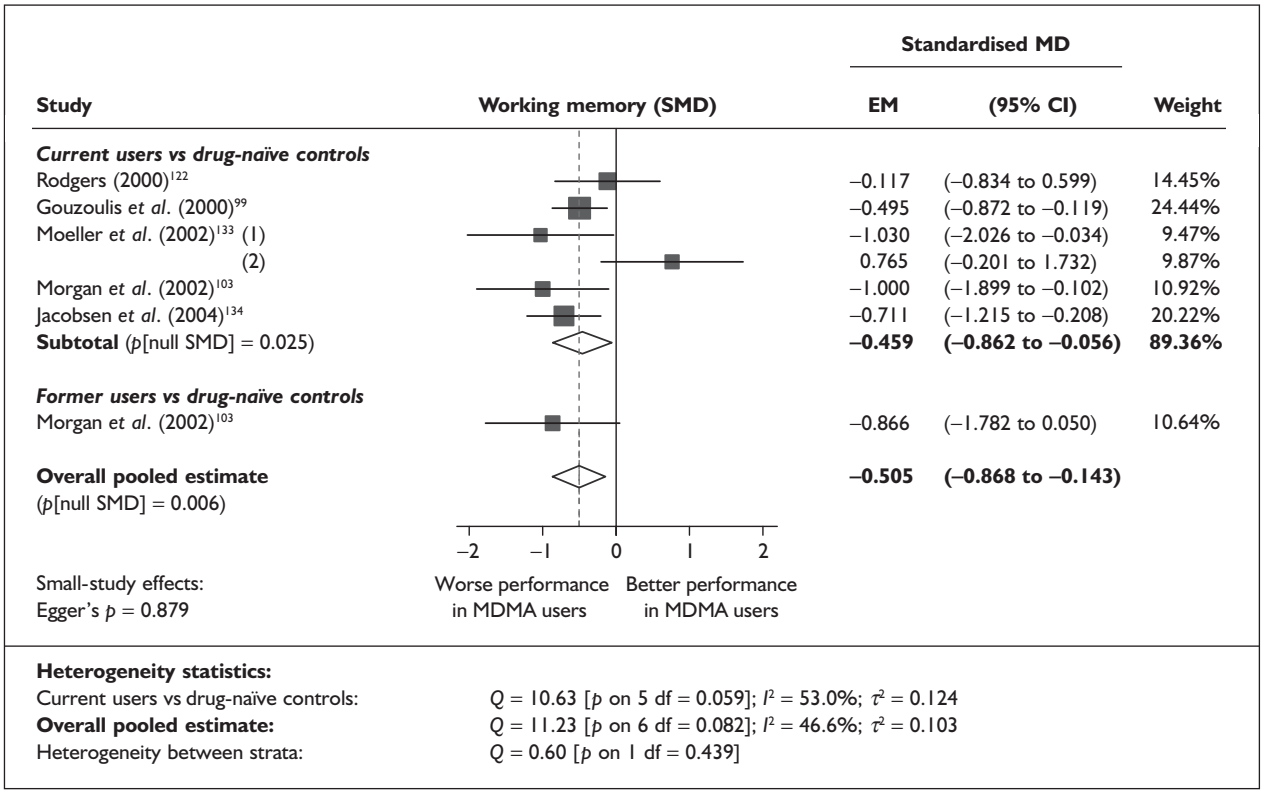

FIGURE 45 *Working memory (composite measure) – ecstasy users versus drug-naïve controls: random-effects meta-analysis.*

There is no evidence of small-study bias in this dataset (Egger's $p = 0.562$); the funnel plot (not shown) suggests a slight trend towards lower exposure effects in higher-precision studies, but all datapoints appear within the expected range.

Sufficient data were available to attempt metaregression analyses for 13 covariates; details are shown in *Table 26*. None of the analyses were able to provide a statistically convincing explanation of the heterogeneity seen amongst base-case effect estimates, and there was no

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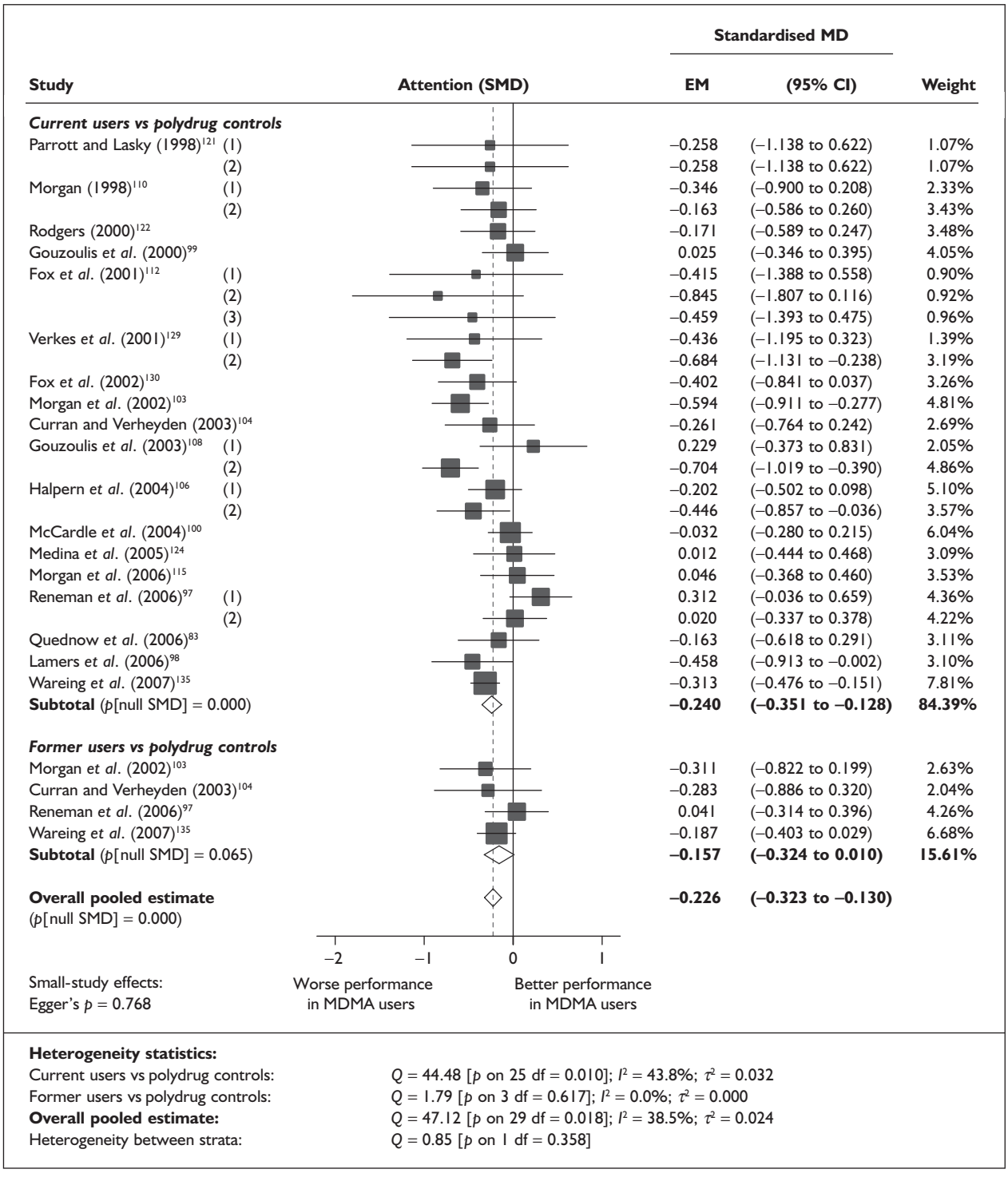
TABLE 24 *Working memory (composite measure) – ecstasy users versus drug-naïve controls: univariate metaregression results.*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	7	0.049	(−0.034 to 0.132)	0.248			
Sex (% male)	5	0.819	(−1.421 to 3.060)	0.474			
IQ	< 5						
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	5	−0.002	(−0.005 to 0.001)	0.150			
ETLE (occasions)	< 5						
Period since last consumption (days)	< 5						
Duration of ecstasy use (days)	< 5						
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	7	−0.195	(−0.434 to 0.044)	0.109	−0.557	(−0.884 to −0.230)	0.001
Sex (% male)	5	0.699	(−3.873 to 5.272)	0.764	−0.569	(−0.839 to −0.298)	0.000
Baseline intelligence measures (SMD)	< 5						
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to amphetamines (ETLD)	< 5						
Exposure to cocaine (ETLD)	< 5						
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	< 5						

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.



Heterogeneity statistics:

Current users vs polydrug controls:	Q = 44.48 [p on 25 df = 0.010]; I^2 = 43.8%; τ^2 = 0.032
Former users vs polydrug controls:	Q = 1.79 [p on 3 df = 0.617]; I^2 = 0.0%; τ^2 = 0.000
Overall pooled estimate:	Q = 47.12 [p on 29 df = 0.018]; I^2 = 38.5%; τ^2 = 0.024
Heterogeneity between strata:	Q = 0.85 [p on 1 df = 0.358]

FIGURE 46 *Attention – focus–execute (composite measure) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

evidence of a dose–response effect (see *Figure 107* in Appendix 7).

Attention (sustain) – MDMA users versus polydrug controls

The dataset assembled for this measure comprises 27 datapoints, representing a total of 11 pairwise comparisons, drawn from seven different studies (eight comparisons from seven studies providing data for current ecstasy users and three comparisons from three studies providing data for former ecstasy users). Sixteen different outcome measures are included, the most common being G/N-G: correct responses (four datapoints),

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TABLE 25 *Attention – focus–execute (composite measure) – ecstasy users versus polydrug controls: univariate metaregression results.*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	28	0.024	(−0.016 to 0.065)	0.235			
Sex (% male)	26	−0.091	(−0.650 to 0.468)	0.750			
IQ	14	−0.028	(−0.063 to 0.006)	0.105			
Education (years)	8	−0.075	(−0.162 to 0.013)	0.094			
Characteristics of ecstasy exposure							
ETLD (tablets)	18	0.000	(−0.001 to 0.000)	0.642			
ETLE (occasions)	< 5						
Period since last consumption (days)	16	0.000	(0.000–0.000)	0.416			
Duration of ecstasy use (days)	18	0.000	(0.000–0.000)	0.698			
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	28	−0.049	(−0.092 to −0.006)	0.025	−0.211	(−0.300 to −0.122)	0.000
Sex (% male)	26	0.655	(−0.102 to 1.411)	0.090	−0.206	(−0.312 to −0.100)	0.000
Baseline intelligence measures (SMD)	19	0.146	(−0.155 to 0.446)	0.341	−0.151	(−0.297 to −0.004)	0.044
Education (years)	8	0.025	(−0.103 to 0.153)	0.703	−0.223	(−0.365 to −0.081)	0.002
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	16	−0.227	(−0.458 to 0.004)	0.054	−0.183	(−0.319 to −0.047)	0.008
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	15	−0.068	(−0.475 to 0.340)	0.745	−0.124	(−0.387 to 0.138)	0.353
Exposure to cocaine (ETLD)	< 5						
Exposure to cocaine (SMD)	13	0.094	(−0.125 to 0.313)	0.399	−0.204	(−0.454 to 0.046)	0.110
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	18	0.019	(−0.277 to 0.316)	0.898	−0.192	(−0.337 to −0.048)	0.009

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

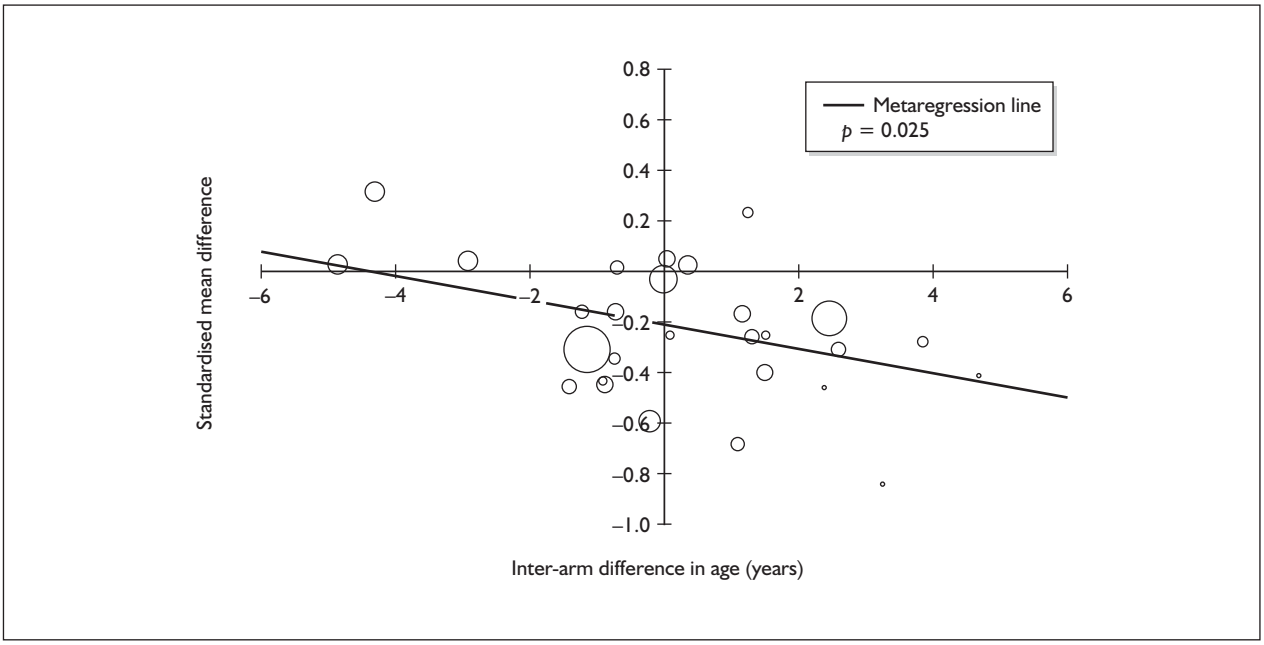

FIGURE 47 *Attention – focus-execute (composite measure) – ecstasy users versus polydrug controls: mean difference in score against inter-arm asymmetry in age.*

visual scanning: non-critical trials – time (three datapoints) and visual scanning: critical trials – time (three datapoints). The complete dataset is detailed in *Table 63* in Appendix 6.

Our random-effects meta-analysis of these data (*Figure 49*) suggests that there is essentially no difference between populations, with no evidence of interstratum heterogeneity. However, for the only occasion in this review, our sensitivity analysis with data aggregated at study level generated markedly different results from our primary analysis, with a significant negative exposure effect estimated [SMD –0.157; 95% CI –0.304 to –0.009; p(null SMD) = 0.037]. This borderline-significant estimate of an exposure effect may represent a more accurate synthesis of the available data, although, even if it is preferred, it remains a very small difference.

Although Egger's test did achieve conventional levels of significance ($p = 0.024$), a positive coefficient is estimated by the test, which suggests that a greater negative exposure effect is associated with *high* precision estimates. This trend is clearly seen in the funnel plot for this dataset (*Figure 50*).

Sufficient data were available to attempt metaregression analyses for 17 covariates; details are shown in *Table 27*. There was no evidence of a dose–response effect (see *Figure 108* in Appendix 7). A significant coefficient was estimated for one covariate: inter-arm asymmetry in exposure to amphetamines other than MDMA. This analysis is plotted in *Figure 51*. A relatively polarised picture can be seen: where ecstasy users had taken fewer amphetamines than controls, their performance was superior, and the opposite is the case where amphetamine consumption was greater in the ecstasy-exposed arms. The adjusted estimate of effect size remains consistent with a null hypothesis of no exposure effect.

Although neither achieves a conventional level of statistical significance, two further metaregressions are worthy of note. First, the relationship between asymmetry in alcohol consumption and test performance appears to show quite a strong trend (*Figure 52*). As has been seen in other analyses, increased alcohol exposure appears to result in a lesser degree of underperformance in the ecstasy-exposed arms.

Second, *Figure 53* shows the relationship between exposure effect and inter-arm imbalance in participant age. Although this metaregression did not reveal a statistically significant relationship, it is worth emphasising the strong similarity between this graph and the analogous analysis for attention focus–execute (see *Figure 47*). The coefficient estimated in that case suggests that, for every year by which ecstasy users were older than controls, the exposure effect can be expected to grow by 0.049 SD. For sustained attention, a coefficient of –0.098 SD is estimated.

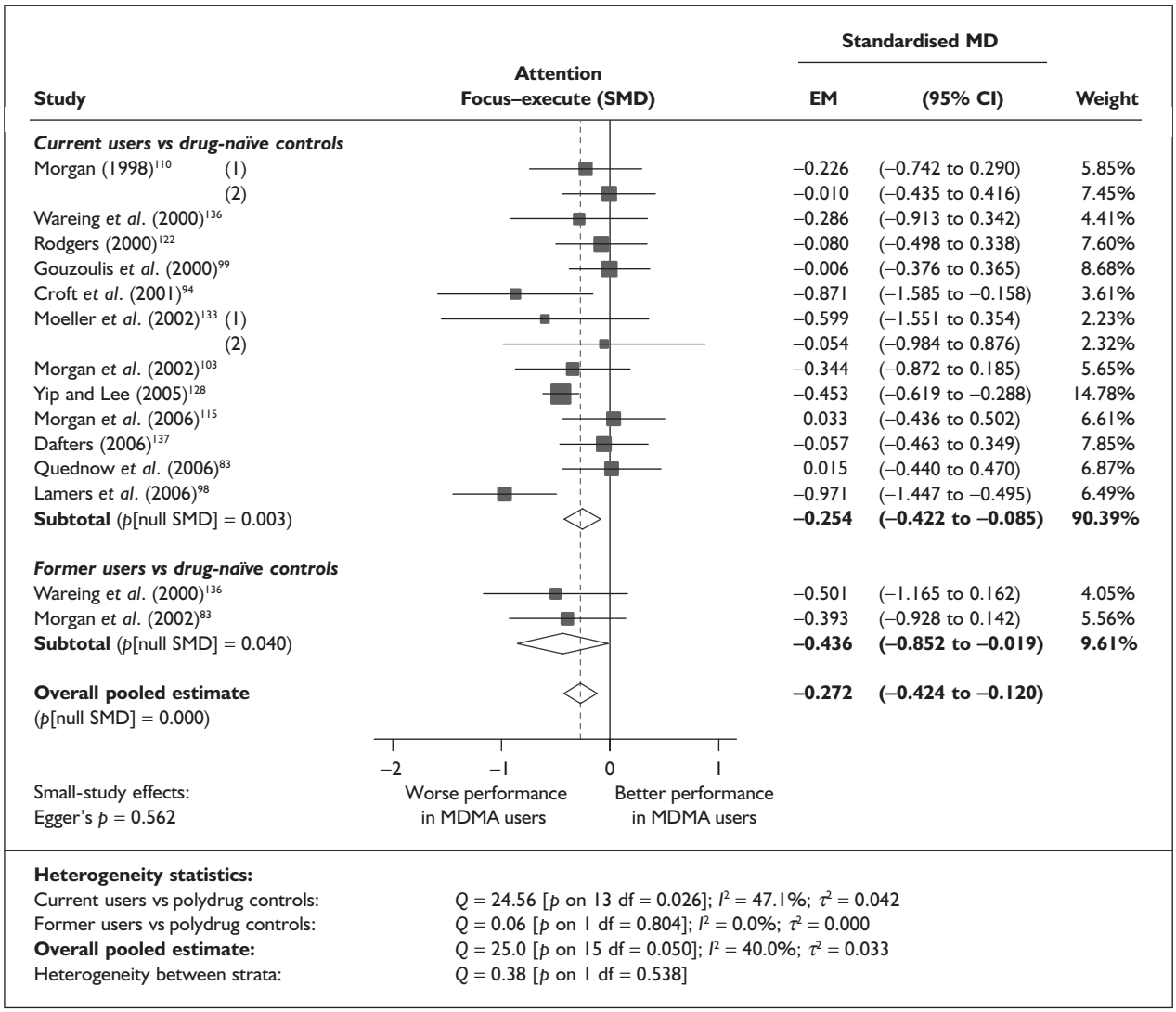

FIGURE 48 *Attention – focus–execute (composite measure) – ecstasy users versus drug-naïve controls: random-effects meta-analysis.*

Attention (sustain) – MDMA users versus drug-naïve controls

Only four studies in the evidence-base reported measures of sustained attention in comparisons between ecstasy users and drug-naïve controls,[61,83,99,125] so we did not pursue extensive analysis of this dataset. When meta-analysed according to the model used in other analyses, these data generate a non-significant SMD of 0.159 [95% CI −0.180 to 0.498; p(null SMD) = 0.358].

Executive function (planning) – MDMA users versus polydrug controls

The dataset assembled for this measure comprises 40 datapoints, representing a total of 11 pairwise comparisons, drawn from five different studies (10 comparisons from five studies providing data for current ecstasy users and one comparison from one study providing data for former ecstasy users). Fourteen different outcome measures are included, the most common being ToL: Planning time (five datapoints). The complete dataset is detailed in *Table 64* in Appendix 6.

Random-effects meta-analysis (*Figure 54*) estimates a pooled effect size of under 0.2 SD, i.e. less than a 'small' difference, in Cohen's schema. The dataset appears to be relatively homogeneous. Sensitivity analysis with data aggregated at study level generated a very similar result [SMD −0.179; 95% CI −0.497 to 0.140; p(null SMD) = 0.271].

TABLE 26 *Attention – focus–execute (composite measure) – ecstasy users versus polydrug controls: univariate metaregression results.*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	16	−0.010	(−0.063 to 0.042)	0.699			
Sex (% male)	13	0.413	(−0.690 to 1.515)	0.463			
IQ	6	0.077	(−0.013 to 0.167)	0.093			
Education (years)	5	−0.103	(−0.271 to 0.064)	0.227			
Characteristics of ecstasy exposure							
ETLD (tablets)	12	0.000	(0.000–0.001)	0.405			
ETLE (occasions)	< 5						
Period since last consumption (days)	9	0.000	(−0.001 to 0.001)	0.395			
Duration of ecstasy use (days)	8	0.000	(0.000–0.000)	0.109			
Frequency of ecstasy use (occasions/month)	5	−0.055	(−0.151 to 0.041)	0.260			
Inter-arm differences							
Age (years)	16	0.017	(−0.132 to 0.167)	0.819	−0.274	(−0.430 to −0.118)	0.001
Sex (% male)	13	0.493	(−1.970 to 2.955)	0.695	−0.257	(−0.454 to −0.060)	0.011
Baseline intelligence measures (SMD)	8	0.107	(−0.491 to 0.704)	0.727	−0.270	(−0.548 to 0.007)	0.056
Education (years)	5	0.580	(−0.140 to 1.300)	0.114	−0.316	(−0.607 to −0.025)	0.033
Exposure to cannabis (ETLD)	< 5						
Exposure to amphetamines (ETLD)	< 5						
Exposure to cocaine (ETLD)	< 5						
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	6	−0.184	(−0.475 to 0.108)	0.217	−0.451	(−0.778 to −0.124)	0.007

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

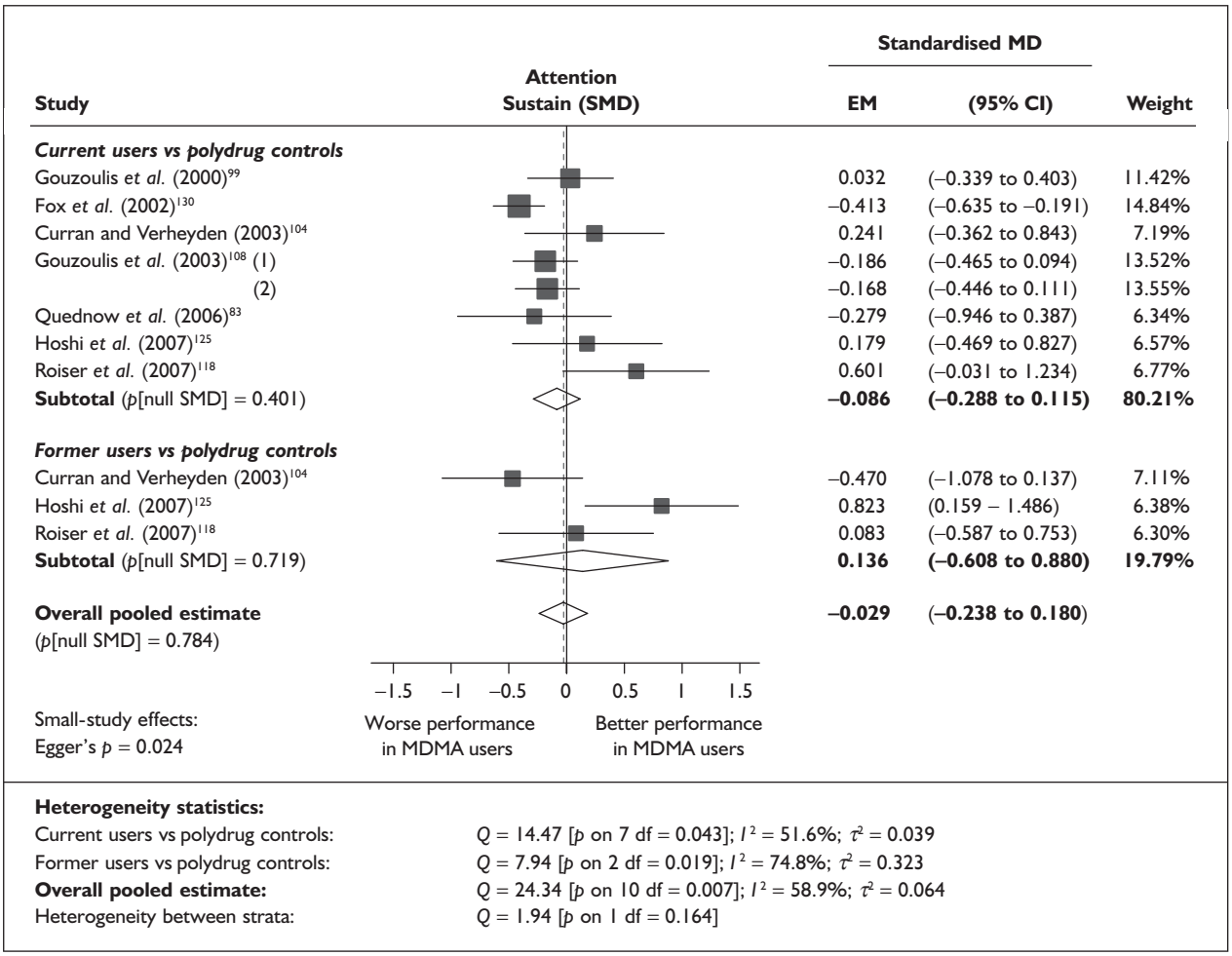

FIGURE 49 *Attention – sustain (composite measure) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

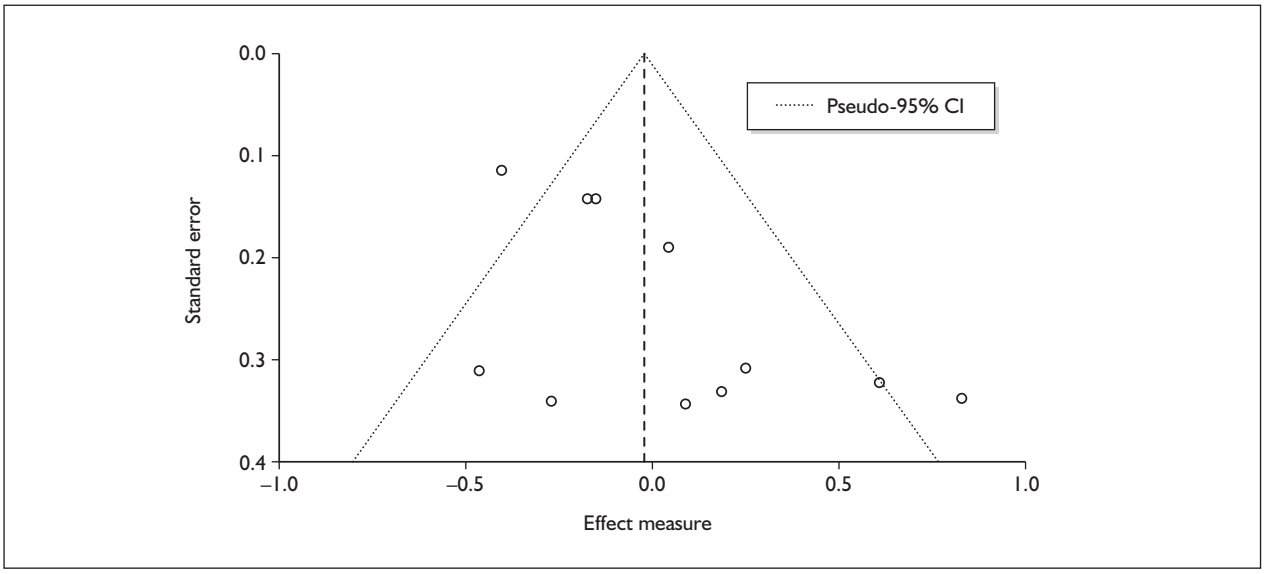

FIGURE 50 *Attention – sustain (composite measure) – ecstasy users versus polydrug controls: funnel plot.*

TABLE 27 *Attention – sustain (composite measure) – ecstasy users versus polydrug controls: univariate metaregression results.*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	11	0.038	(−0.062 to 0.139)	0.455			
Sex (% male)	11	0.333	(−0.623 to 1.288)	0.495			
IQ	< 5						
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	7	0.000	(−0.001 to 0.001)	0.774			
ETLE (occasions)	< 5						
Period since last consumption (days)	6	0.000	(0.000–0.001)	0.421			
Duration of ecstasy use (days)	7	0.000	(0.000–0.001)	0.547			
Frequency of ecstasy use (occasions/months)	8	0.043	(−0.066 to 0.151)	0.443			
Inter-arm differences							
Age (years)	11	−0.098	(−0.207 to 0.010)	0.076	−0.078	(−0.280 to 0.124)	0.450
Sex (% male)	11	−4.220	(−9.602 to 1.162)	0.124	0.045	(−0.178 to 0.269)	0.691
Baseline intelligence measures (SMD)	7	0.364	(−0.395 to 1.124)	0.347	0.107	(−0.227 to 0.441)	0.529
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	10	−0.327	(−0.710 to 0.057)	0.095	0.099	(−0.153 to 0.350)	0.441
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	9	−0.560	(−0.936 to −0.184)	0.004	0.168	(−0.074 to 0.410)	0.174
Exposure to cocaine (ETLD)	< 5						
Exposure to cocaine (SMD)	7	−0.624	(−1.440 to 0.192)	0.134	0.414	(−0.122 to 0.950)	0.130
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	7	0.881	(−0.038 to 1.800)	0.060	0.000	(−0.314 to 0.314)	0.999

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

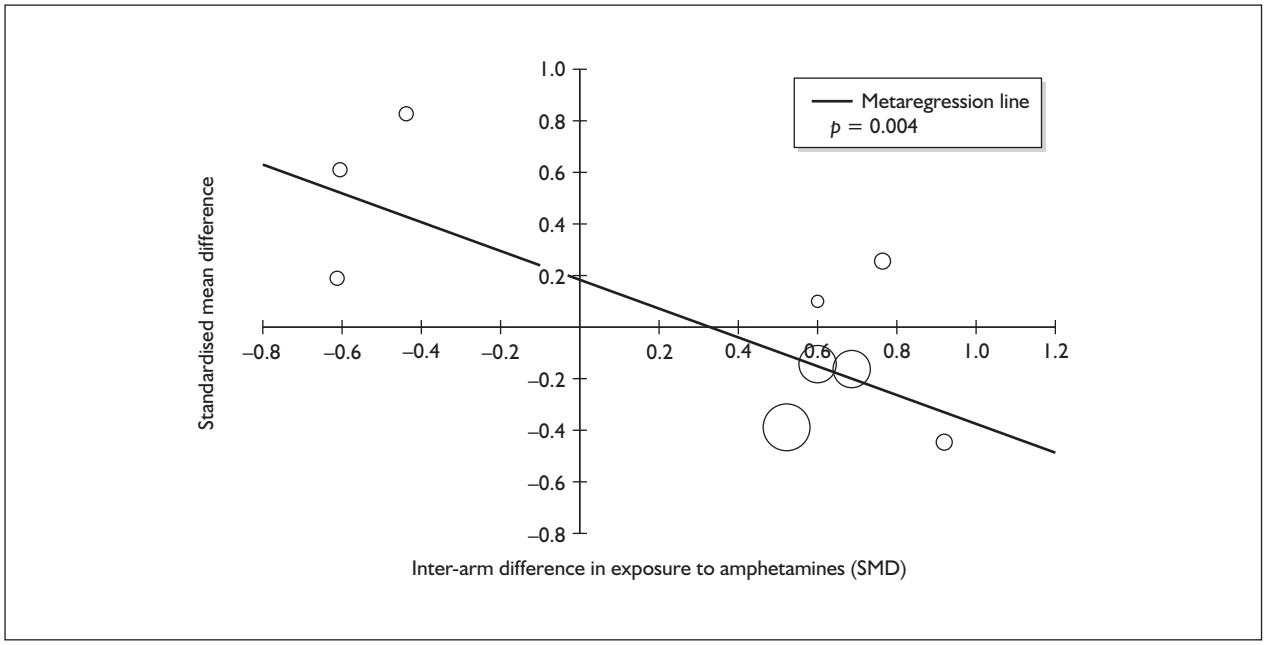

FIGURE 51 *Attention – sustain (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against inter-arm asymmetry in exposure to amphetamines other than MDMA.*

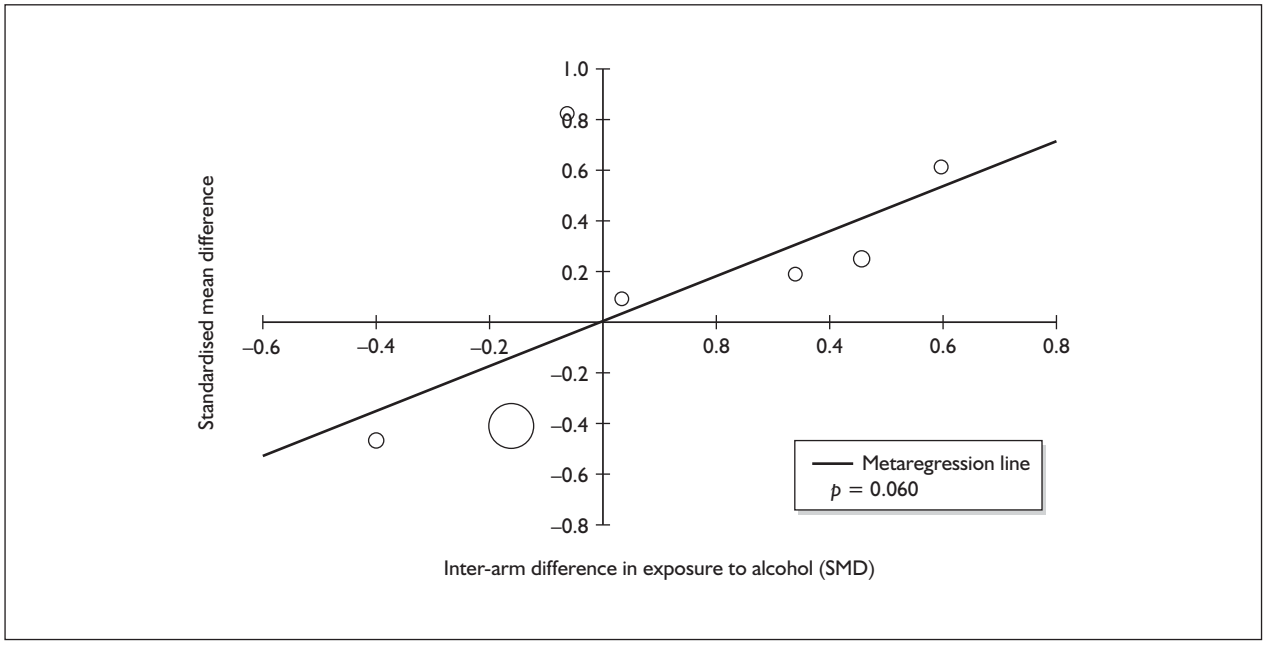

FIGURE 52 *Attention – sustain (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against inter-arm asymmetry in exposure to alcohol (standardised mean difference).*

There is no evidence of small-study bias in this dataset (Egger's $p = 0.525$), and the funnel plot (not shown) had an unremarkable appearance.

Sufficient data were available to attempt metaregression analyses for 13 covariates; details are shown in *Table 28*. There was no evidence of a dose–response effect (see *Figure 109* in Appendix 7).

Significant coefficients were estimated for two covariates: study-level average IQ (classical metaregression, *Figure 55*) and duration of abstinence from ecstasy (*Figure 56*). For the former, a clear shape is seen amongst the five datapoints, with lower average IQ associated with a larger disadvantage for ecstasy users in the outcomes of interest. However, it is easy to conclude that the neatness of the correlation is dependent on

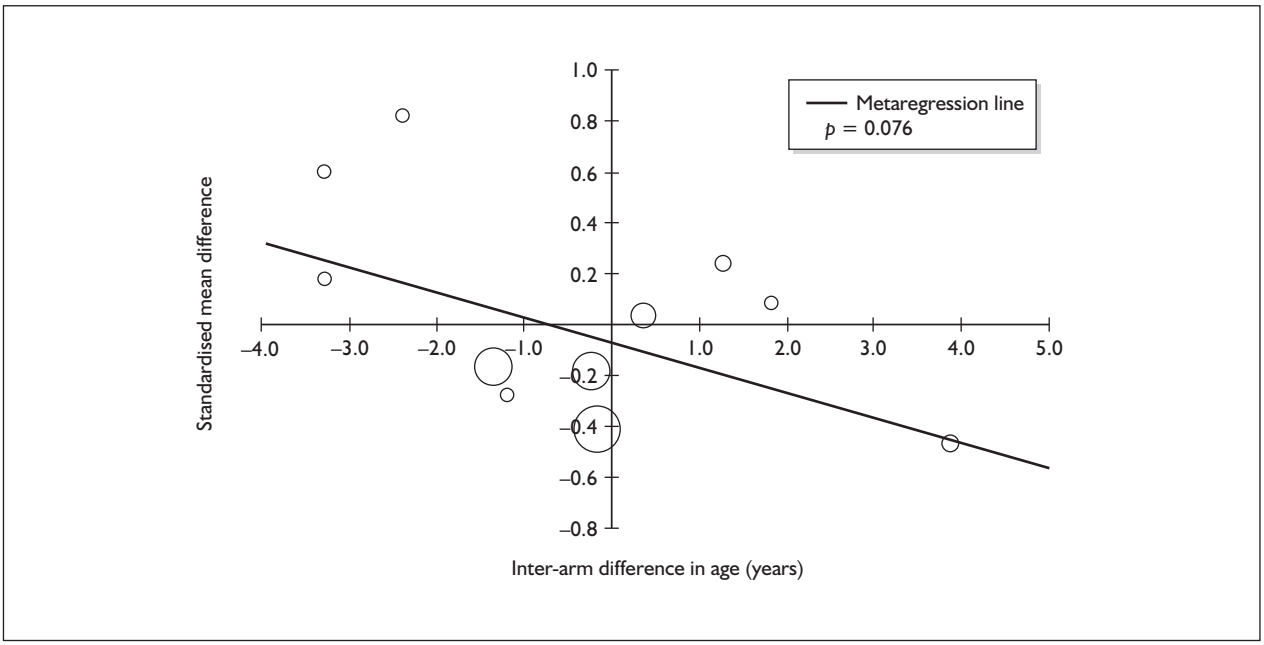

FIGURE 53 *Attention – sustain (composite measure) – ecstasy users versus polydrug controls: mean difference in score against inter-arm asymmetry in age.*

the small number of contributing datapoints. For the latter, a less visually arresting significant association is seen. It may be that, as this picture suggests, the ecstasy users that have been abstinent for the longest are those that perform least well in comparison to controls but, given the small sample and less-than-unequivocal *p*-value, a Type I error is a real danger, so a degree of scepticism is probably appropriate.

Executive function (planning) – MDMA users versus drug-naïve controls

We were only able to identify two studies reporting the appropriate comparison for this outcome.[110,125] When meta-analysed according to the model used elsewhere in this review, a small, non-significant SMD of –0.170 (95% CI –0.484 to 0.144) was estimated.

Executive function (response inhibition) – MDMA users versus polydrug controls

The dataset assembled for this measure comprises 34 datapoints, representing a total of 21 pairwise comparisons, drawn from 13 different studies (18 comparisons from 13 studies providing data for current ecstasy users and three comparisons from three studies providing data for former ecstasy users). Eighteen different outcome measures are included, the most common being Stroop: interference – time (seven datapoints) and G/N-G: reaction time (four datapoints). The complete dataset is detailed in *Table 65* in Appendix 6.

When synthesised in a random-effects meta-analysis (*Figure 57*), these data suggest that there is no difference between ecstasy users and polydrug controls in this domain. The estimated SMD of approximately 0.1 SD would be considered very small, even if the difference was certain enough to meet conventional levels of significance. Sensitivity analysis with study-level aggregate data reveals a similar picture [SMD –0.090; 95% CI –0.338 to 0.159; p(null SMD) = 0.480]. We note that one datapoint in the forest plot appears atypical: the comparison between female ecstasy users and controls in von Geusau *et al*.[132] Above all, this extreme value is driven by performance in the HvdM Eriksen–Flankers test, in which ecstasy users outperformed controls by 3.7 SD (99.3% correct versus 96.7% correct; it should be noted that although this may seem to be a relatively small discrepancy, both estimates are subject to very small variance, so the difference between them is strongly significant and, when standardised, it becomes substantial). If the entire comparison for the female subgroup in this investigation is removed from analysis, then the estimated overall difference between populations does become borderline-significant, although the effect size remains small [SMD –0.172; 95% CI –0.336 to –0.008; p(effect=0) = 0.040].

There is no evidence of small-study bias in this dataset (Egger's $p = 0.381$), and the funnel plot (not shown) had an unremarkable appearance.

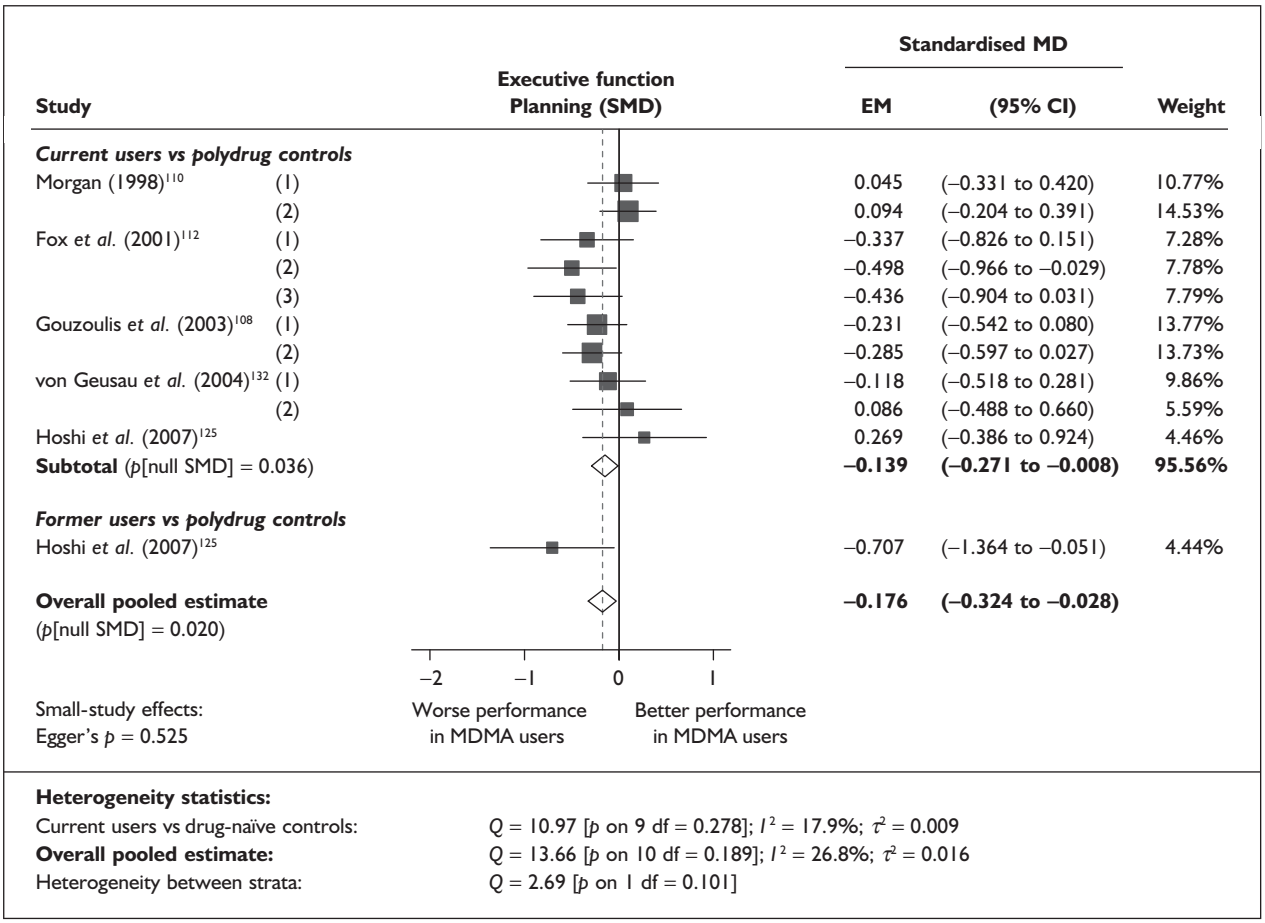

FIGURE 54 *Executive function – planning (composite measure) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

Sufficient data were available to attempt metaregression analyses for 14 covariates, shown in *Table 29*. There was no evidence of a dose–response effect (see *Figure 110* in Appendix 7).

Only one covariate generated a significant coefficient: inter-arm asymmetry in baseline intelligence. *Figure 58* plots this variable against the outcome of interest. The preponderance of datapoints in the 'south-west' quadrant of the graph indicates that, in the majority of cases, ecstasy-exposed cohorts scored lower than controls on both the explanatory and response variables (i.e. they had lower baseline measures of intelligence and also performed worse on tests of response inhibition). The fact that the regression line passes through the graph's origin suggests that, when one corrects for this imbalance, no inter-population difference would be expected at all.

Executive function (response inhibition) – MDMA users versus drug-naïve controls

The dataset assembled for this measure comprises 15 datapoints, representing a total of 10 pairwise comparisons, drawn from eight different studies (eight comparisons from eight studies providing data for current ecstasy users and two comparisons from two studies providing data for former ecstasy users). Ten different outcome measures are included, the most common being Stroop: interference – time difference (three datapoints) and G/N-G (two datapoints). The complete dataset is detailed in *Table 66* in Appendix 6.

When meta-analysed (*Figure 59*), this dataset is closely analogous to the results seen when comparing ecstasy users with polydrug-using controls (see *Figure 57*). As in that analysis, a small, non-significant difference is seen between cohorts, and inter-study heterogeneity is not especially pronounced. Sensitivity analysis with data aggregated at study level is comparable [SMD –0.107; 95% CI –0.364 to 0.151; p(null SMD) = 0.416].

Although Egger's test did achieve conventional levels of significance ($p = 0.048$), it seems unlikely that this analysis is biased by small-study effects. A positive coefficient is estimated by the test, which suggests that a greater exposure effect is associated with *high* precision estimates. This trend is clearly seen in the funnel plot for this dataset (*Figure 60*).

TABLE 28 *Executive function – planning (composite measure) – ecstasy users versus polydrug controls: univariate metaregression results*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	11	−0.042	(−0.102 to 0.018)	0.175			
Sex (% male)	11	0.075	(−0.801 to 0.950)	0.867			
IQ	5	0.097	(0.027–0.167)	0.006			
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	6	0.000	(−0.001 to 0.000)	0.337			
ETLE (occasions)	< 5						
Period since last consumption (days)	7	−0.001	(−0.002 to 0.000)	0.043			
Duration of ecstasy use (days)	11	0.000	(0.000–0.000)	0.694			
Frequency of ecstasy use (occasions/month)	6	−0.047	(−0.255 to 0.161)	0.656			
Inter-arm differences							
Age (years)	11	−0.053	(−0.123 to 0.017)	0.141	−0.166	(−0.305 to −0.026)	0.020
Sex (% male)	11	−0.519	(−1.475 to 0.438)	0.288	−0.138	(−0.299 to 0.023)	0.093
Baseline intelligence measures (SMD)	9	−0.232	(−0.638 to 0.173)	0.261	−0.224	(−0.401 to −0.048)	0.013
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	8	−0.156	(−0.487 to 0.176)	0.357	0.003	(−0.272 to 0.278)	0.983
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	8	−0.098	(−0.463 to 0.268)	0.600	−0.066	(−0.283 to 0.151)	0.553
Exposure to cocaine (ETLD)	< 5						
Exposure to cocaine (SMD)	5	−0.035	(−0.510 to 0.440)	0.885	−0.023	(−0.478 to 0.431)	0.920
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	< 5						

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

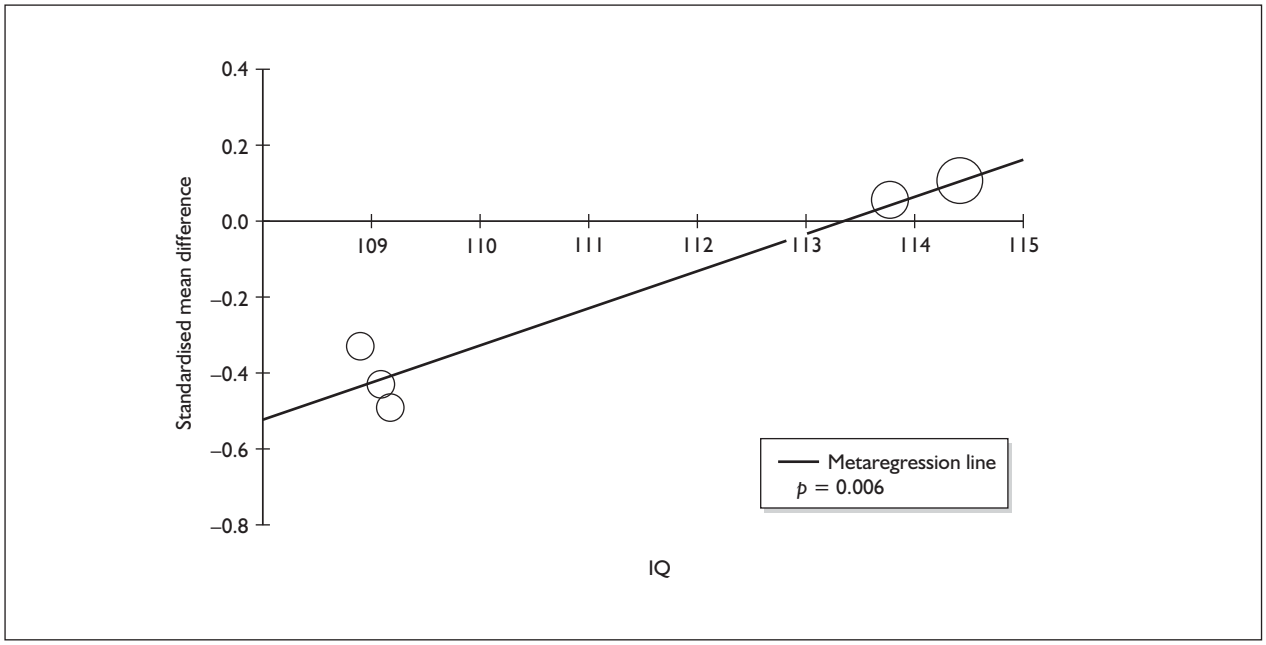

FIGURE 55 *Executive function – planning (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against IQ (across all participants).*

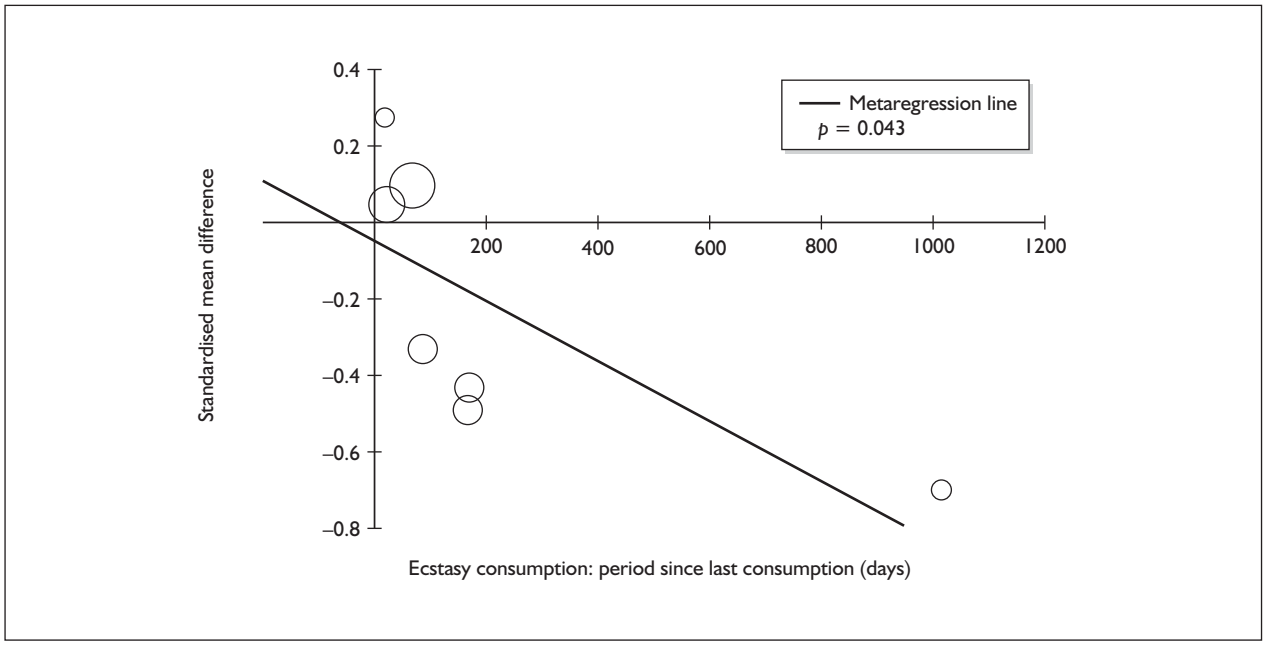

FIGURE 56 *Executive function – planning (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against duration of abstinence in ecstasy users.*

Sufficient data were available to attempt metaregression analyses for eight covariates; details are shown in *Table 30*. There was fairly good evidence of a dose–response effect (see *Figure 111* in Appendix 7). It should be noted, however, that a positive coefficient is estimated, implying that those ecstasy-exposed cohorts that had taken most ecstasy were those that performed best in comparison to their respective controls.

Executive function (shifting) – MDMA users versus polydrug controls

The dataset assembled for this measure comprises 41 datapoints, representing a total of 13 pairwise comparisons, drawn from seven different studies (12 comparisons from seven studies providing data for current ecstasy users and one comparison from one study providing data for former ecstasy users). Fifteen different outcome measures are included, the most common being WCST: categories

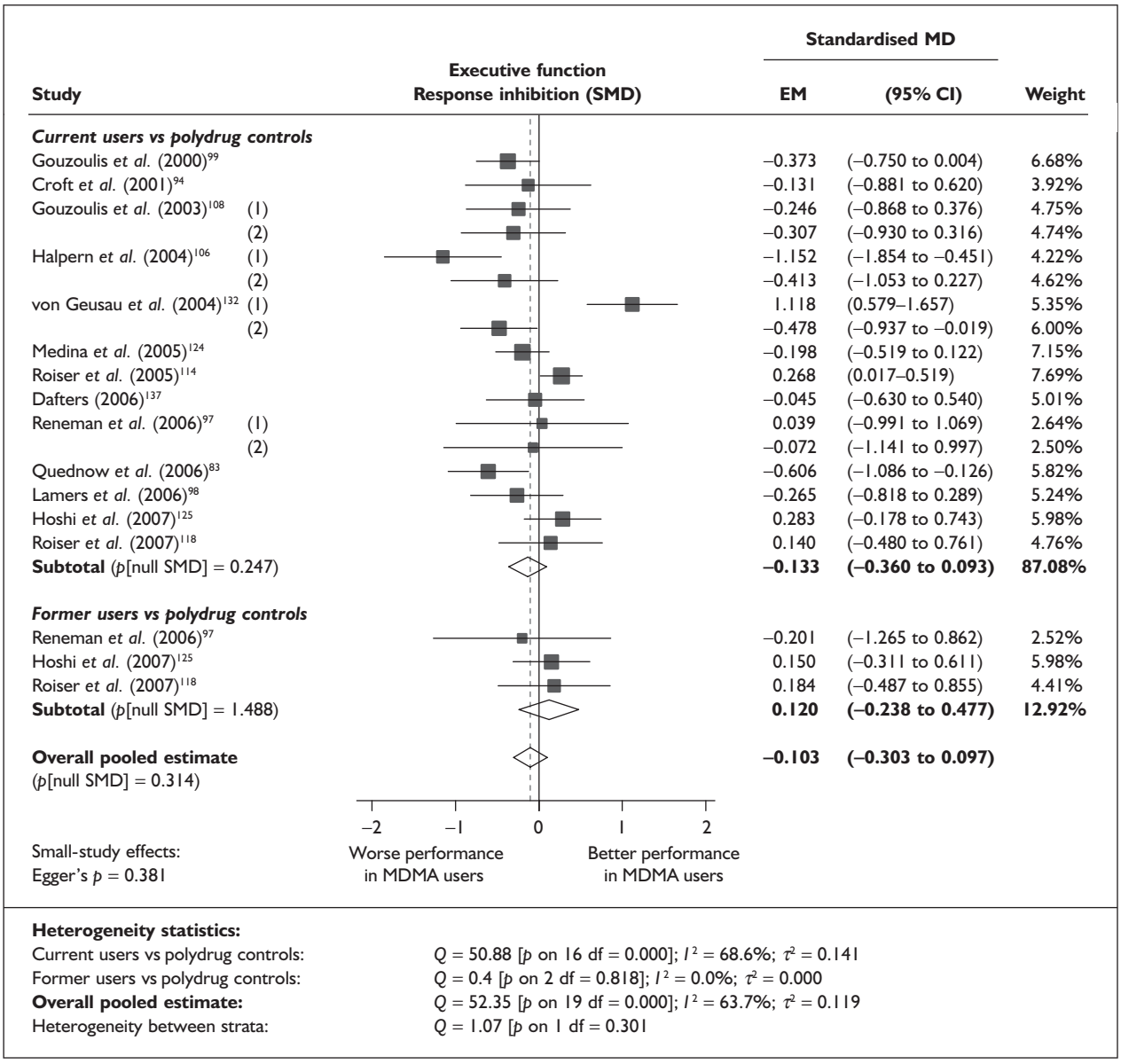

FIGURE 57 *Executive function – response inhibition (composite measure) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

(eight datapoints), WCST: Total no. errors (four datapoints) and WCST: perseverative errors (four datapoints). The complete dataset is detailed in *Table 67*, in Appendix 6.

The meta-analysis for this data-set (*Figure 61*) is reminiscent of the two analyses seen for response inhibition (see *Figures 57* and *59* respectively). Although a small exposure effect (with ecstasy users performing worse than polydrug controls) is estimated, the dataset is also entirely consistent with a null result. Sensitivity analysis with study-level aggregated data generates a similar result [SMD –0.158; 95% CI –0.635 to 0.319; p(null SMD) = 0.516]. Much as in the response inhibition analysis (see *Figure 57*), the good performance of the ecstasy-exposed participants in the female subgroup of von Geusau *et al.*[132] makes the datapoint appear to be somewhat of an outlier in the forest plot. If this comparison is excluded from the overall analysis, a significant exposure effect is estimated [SMD –0.281; 95% CI –0.509 to –0.054; p(null SMD) = 0.015].

There is no evidence of small-study bias in this dataset (Egger's $p = 0.302$), and the funnel plot (not shown) had an unremarkable appearance.

Sufficient data were available to attempt metaregression analyses for 15 covariates; details

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TABLE 29 *Executive function – response inhibition (composite measure) – ecstasy users versus polydrug controls: univariate metaregression results.*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
age (years)	18	0.019	(−0.056 to 0.093)	0.626			
Sex (% male)	18	−0.219	(−1.334 to 0.897)	0.701			
IQ	5	0.073	(−0.008 to 0.153)	0.077			
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	11	0.000	(−0.002 to 0.001)	0.773			
ETLE (occasions)	< 5						
Period since last consumption (days)	< 5						
Duration of ecstasy use (days)	10	0.000	(0.000–0.001)	0.570			
Frequency of ecstasy use (occasions/month)	5	0.098	(−0.122 to 0.317)	0.383			
Inter-arm differences							
Age (years)	18	−0.013	(−0.140 to 0.114)	0.838	−0.052	(−0.292 to 0.188)	0.668
Ssex (% male)	18	0.815	(−0.488 to 2.117)	0.220	−0.087	(−0.291 to 0.117)	0.404
Baseline intelligence measures (SMD)	12	0.540	(0.020 to 1.060)	0.042	0.018	(−0.227 to 0.263)	0.887
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	14	−0.010	(−0.370 to 0.349)	0.955	−0.048	(−0.324 to 0.228)	0.734
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	13	−0.042	(−0.568 to 0.484)	0.876	−0.001	(−0.322 to 0.320)	0.994
Exposure to cocaine (ETLD)	5	0.000	(−0.005 to 0.004)	0.830	−0.041	(−0.458 to 0.376)	0.848
Exposure to cocaine (SMD)	11	0.150	(−0.337 to 0.638)	0.545	−0.063	(−0.484 to 0.357)	0.767
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	9	0.053	(−0.773 to 0.880)	0.899	−0.050	(−0.251 to 0.152)	0.628

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

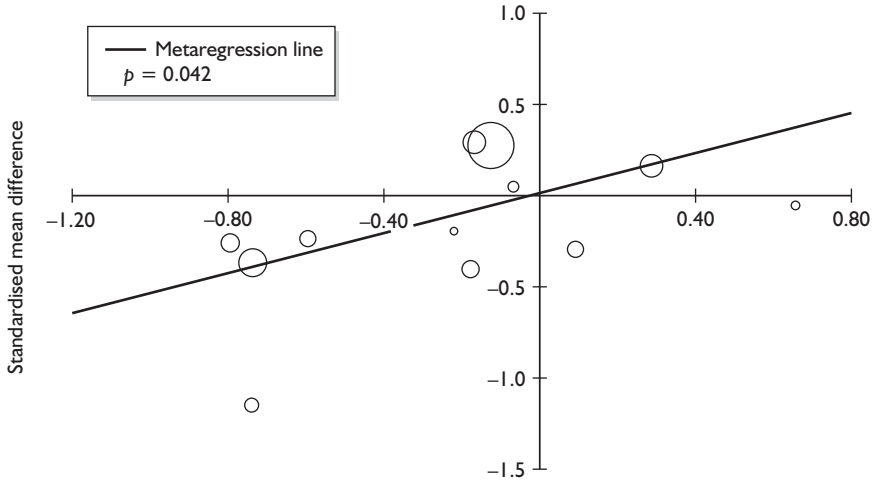


FIGURE 58 *Executive function – response inhibition (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against inter-arm asymmetry in baseline intelligence measures.*

Study	Executive function Response inhibition (SMD)	Standardised MD EM	(95% CI)	Weight
Current users vs polydrug controls				
Gouzoulis *et al.* (2000)[99]		–0.366	(–0.746 to 0.014)	13.84%
Croft *et al.* (2001)[94]		–0.620	(–1.321 to 0.081)	6.06%
Yip and Lee (2005)[128]		–0.374	(–0.654 to –0.095)	18.36%
Dafters (2006)[137]		0.034	(–0.540 to 0.608)	8.21%
Quednow *et al.* (2006)[83]		–0.129	(–0.614 to 0.356)	10.36%
Lamers *et al.* (2006)[98]		0.149	(–0.417 to 0.714)	8.39%
Hoshi *et al.* (2007)[125]		0.158	(–0.331 to 0.647)	10.26%
Roiser *et al.* (2007)[118]		0.360	(–0.265 to 0.984)	7.25%
Subtotal (*p*[null SMD] = 0.204)		**–0.145**	**(–0.354 to 0.063)**	**82.74%**
Former users vs polydrug controls				
Hoshi *et al.* (2007)[125]		–0.015	(–0.483 to 0.454)	
Roiser *et al.* (2007)[118]		0.408	(–0.269 to 1.085)	10.85%
Subtotal (*p*[null SMD] = 0.534)		**0.123**	**(–0.265 to 0.511)**	**6.41%**
Overall pooled estimate (*p*[null SMD] = 0.371)		**–0.088**	**(–0.282 to 0.105)**	
	–2 –1.5 –1 –.5 0 .5 1			
Small-study effects: Egger's *p* = 0.048	Worse performance in MDMA users / Better performance in MDMA users			

Heterogeneity statistics:

Current users vs polydrug controls:	Q = 10.87 [p on 7 df = 0.145]; I^2 = 35.6%; τ^2 = 0.032
Former users vs polydrug controls:	Q = 1.01 [p on 1 df = 0.314]; I^2 = 1.3%; τ^2 = 0.001
Overall pooled estimate:	Q = 13.89 [p on 9 df = 0.126]; I^2 = 35.2%; τ^2 = 0.033
Heterogeneity between strata:	Q = 2.01 [p on 1 df = 0.156]

FIGURE 59 *Executive function – response inhibition (composite measure) – ecstasy users versus drug-naïve controls: random-effects meta-analysis.*

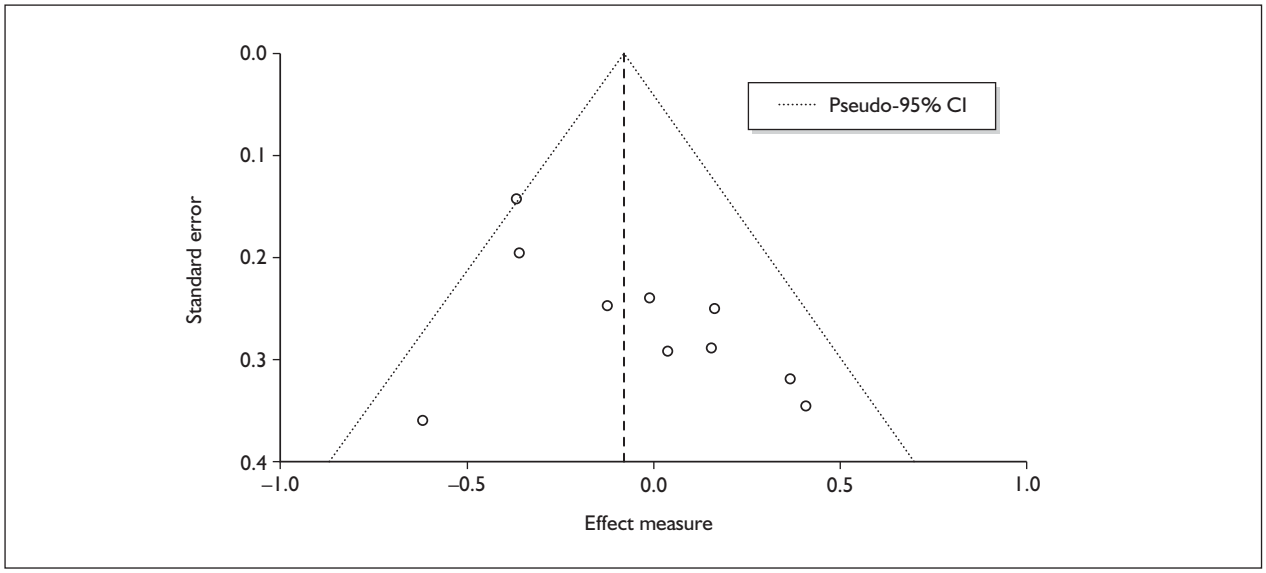


FIGURE 60 *Executive function – response inhibition (composite measure) – ecstasy users versus drug-naïve controls: funnel plot.*

are shown in *Table 31*. None of these analyses generated results that achieved conventional levels of significance, and there was no evidence of a dose–response effect (see *Figure 112* in Appendix 7).

Executive function (shifting) – MDMA users versus drug-naïve controls

Only one datapoint was found comparing ecstasy-exposed individuals with drug-naïve controls for this outcome.[98] The data reported in this study equate to a SMD of –0.03 (95% CI –0.81 to 0.75).

Perceptual organisation – MDMA users versus polydrug controls

The dataset assembled for this measure comprises 31 datapoints, representing a total of six pairwise comparisons, drawn from four different studies (five comparisons from four studies providing data for current ecstasy users and one comparisons from one studies providing data for former ecstasy users). Sixteen different outcome measures are included, the most common being WAIS-R: Block design (three datapoints). The complete dataset is detailed in *Table 68*, in Appendix 6.

When meta-analysed (*Figure 62*), these data provide little evidence of an exposure effect in this area, with a non-significant SMD of only 0.05 SD.

There is no evidence of small-study bias in this dataset (Egger's $p = 0.105$), and the funnel plot (not shown) was not especially illuminating, because of the very small sample under analysis, although it did highlight that the three datapoints suggesting a negative exposure effect are those that are subject to the greatest uncertainty.

Sensitivity analysis with aggregated comparisons for each study provided a rather different effect estimate, with ecstasy-exposed individuals estimated to perform better than controls (SMD 0.114; 95% CI –0.010 to 0.238). However, this reanalysis remained consistent with a null effect ($p = 0.072$). The discrepancy between primary and secondary analysis is explained by the very large number of datapoints contributing to the omnibus outcome in Roiser *et al.*[118]

Because of the small size of this dataset, it was possible to perform metaregression on a single covariate – standardised mean difference in intelligence measures – only (*Table 32*). Nevertheless, this analysis generated significant results, suggesting that any difference between populations in the studies under analysis may be ascribable entirely to baseline imbalances in intelligence (see *Figure 63*). There was no evidence of a dose–response effect (see *Figure 113* in Appendix 7).

Perceptual organisation – MDMA users versus drug-naïve controls

Only two studies in our evidence-base provided data relevant to this comparison.[99,118] When meta-analysed according to the model used elsewhere in this review, a non-significant SMD of –0.204 (95% CI –0.501 to 0.093) is estimated.

TABLE 30 *Executive function – response inhibition (composite measure) – ecstasy users versus drug-naïve controls: univariate metaregression results.*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	10	0.000	(−0.068 to 0.068)	0.992			
Sex (% male)	9	0.105	(−0.851 to 1.060)	0.830			
IQ	< 5						
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	7	0.001	(0.000–0.002)	0.008			
ETLE (occasions)	< 5						
Period since last consumption (days)	7	0.000	(0.000–0.001)	0.473			
Duration of ecstasy use (days)	< 5						
Frequency of ecstasy use (occasons/months)	5	0.084	(−0.019 to 0.188)	0.111			
Inter-arm differences							
Age (years)	10	−0.033	(−0.144 to 0.078)	0.557	−0.099	(−0.304 to 0.106)	0.342
Sex (% male)	9	2.262	(−2.848 to 7.373)	0.386	−0.048	(−0.250 to 0.155)	0.645
Baseline intelligence measures (SMD)	5	−0.115	(−0.879 to 0.649)	0.768	−0.183	(−0.581 to 0.215)	0.368
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to amphetamines (ETLD)	< 5						
Exposure to cocaine (ETLD)	< 5						
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	< 5						

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

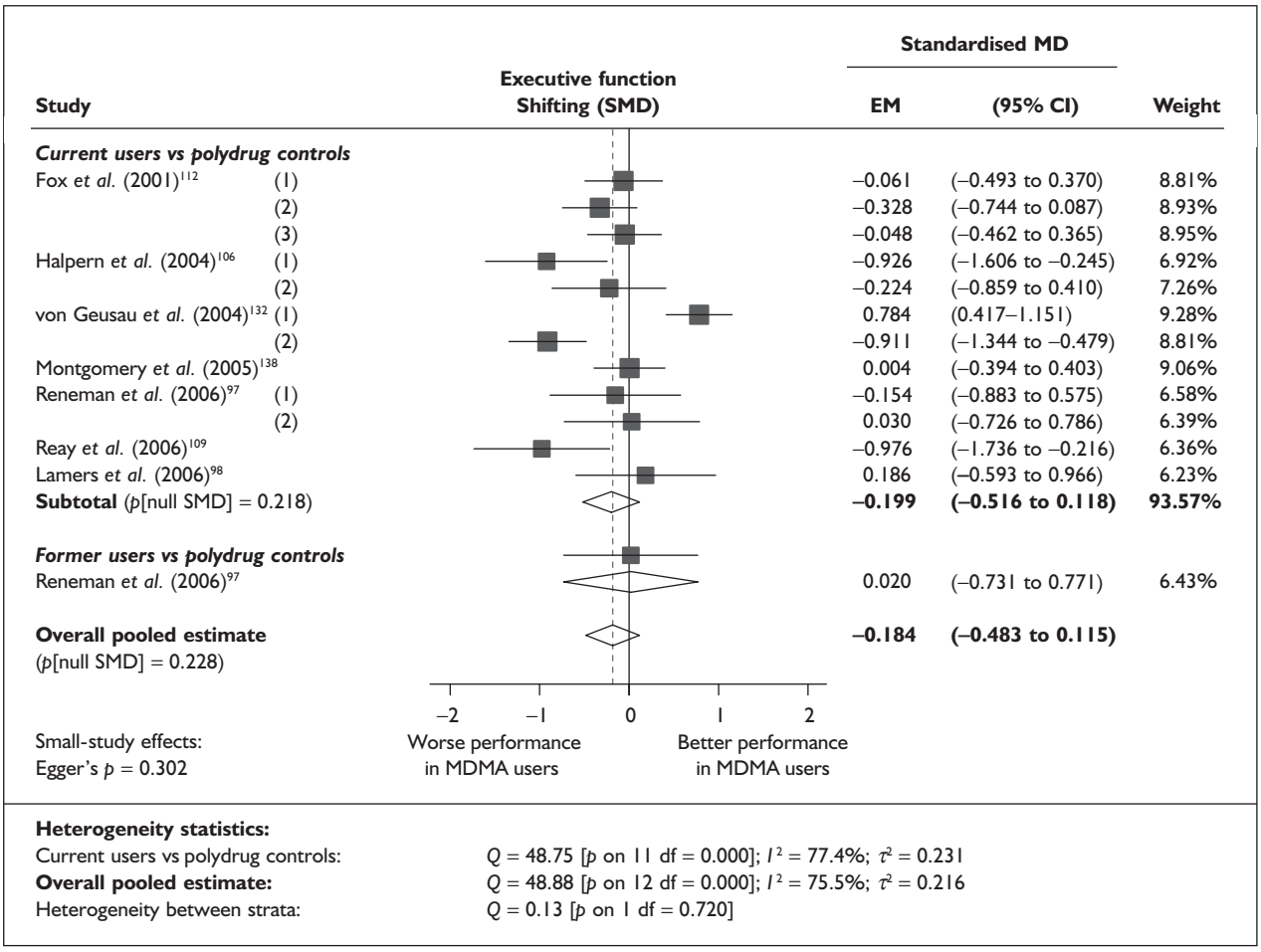


FIGURE 61 *Executive function – shifting (composite measure) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

Depression (self-rated) – MDMA users versus polydrug controls

The dataset assembled for this measure comprises 38 datapoints, representing a total of 38 pairwise comparisons, drawn from 20 different studies (33 comparisons from 20 studies providing data for current ecstasy users and five comparisons from five studies providing data for former ecstasy users). Five different outcome measures are included, the most common being SCL-90: depression score (15 datapoints), BDI: overall score (nine datapoints) and BDI-II: overall score (six datapoints). The complete dataset is detailed in *Table 69*, in Appendix 6.

The meta-analysis, shown in *Figure 64*, suggests that ecstasy-exposed individuals tend to exhibit more depression than polydrug controls by a little over one-quarter of an SD. According to Cohen's guidelines, this would probably be thought of as a 'small' difference. The effect might appear to be greater in former ecstasy users, whom controls outperformed by 0.5 SD (a 'medium' difference, according to Cohen), but the hypothesis test for interstratum heterogeneity provides no statistical justification for supposing the participants belong to different distributions.

Sensitivity analysis with single, pooled comparisons for each study provides a SMD estimated at –0.340 [95% CI –0.478 to –0.202; p(null SMD) < 0.001], which is close to the primary analysis. There is no evidence of small-study bias in this dataset (Egger's $p = 0.591$), and the funnel plot (not shown) had an unremarkable appearance.

For the comparison between current users and controls, a relatively typical datapoint is the SCL-90 depression score reported by Dughiero *et al.*[140] Ecstasy-exposed participants rated 0.15 points higher on the subscale, although both cohorts averaged well below 1.0, which is considered the upper threshold for normality in this test (0.78 versus 0.63; SMD –0.247). Where former users were compared to controls, the most representative datapoint was that from Curran and Verheyden's 2003 study,[104] in which ecstasy users scored a little less than three points more on the BDI (overall score: 8.48 versus 5.59; SMD –0.493).

TABLE 31 *Executive function – shifting (composite measure) – ecstasy users versus polydrug controls: univariate metaregression results.*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	11	0.030	(−0.181 to 0.241)	0.755			
Sex (% male)	11	−0.109	(−4.049 to 3.830)	0.951			
IQ	< 5						
Education (years)	5	0.193	(−0.713 to 1.098)	0.546			
Characteristics of ecstasy exposure							
ETLD (tablets)	6	0.000	(−0.005 to 0.005)	0.914			
ETLE (occasions)	< 5						
Period since last consumption (days)	5	0.000	(−0.008 to 0.009)	0.931			
Duration of ecstasy use (days)	8	0.000	(0.000–0.001)	0.282			
Frequency of ecstasy use (occasions/months)	< 5						
Inter-arm differences							
Age (years)	11	−0.031	(−0.132 to 0.071)	0.514	−0.139	(−0.532 to 0.254)	0.446
Sex (% male)	11	−0.261	(−1.966 to 1.444)	0.737	−0.098	(−0.522 to 0.327)	0.615
Baseline intelligence measures (SMD)	7	0.368	(−0.450 to 1.187)	0.299	−0.079	(−0.426 to 0.267)	0.582
Education (years)	5	0.052	(−0.216 to 0.320)	0.582	−0.033	(−0.463 to 0.397)	0.823
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	8	−0.099	(−1.060 to 0.862)	0.809	−0.034	(−1.055 to 0.987)	0.937
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	6	0.445	(−2.564 to 3.453)	0.702	−0.260	(−2.193 to 1.673)	0.728
Exposure to cocaine (ETLD)	< 5						
Exposure to cocaine (SMD)	7	0.304	(−0.921 to 1.529)	0.551	−0.414	(−1.774 to 0.946)	0.469
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	5	−0.232	(−2.982 to 2.517)	0.805	−0.195	(−0.957 to 0.567)	0.476

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

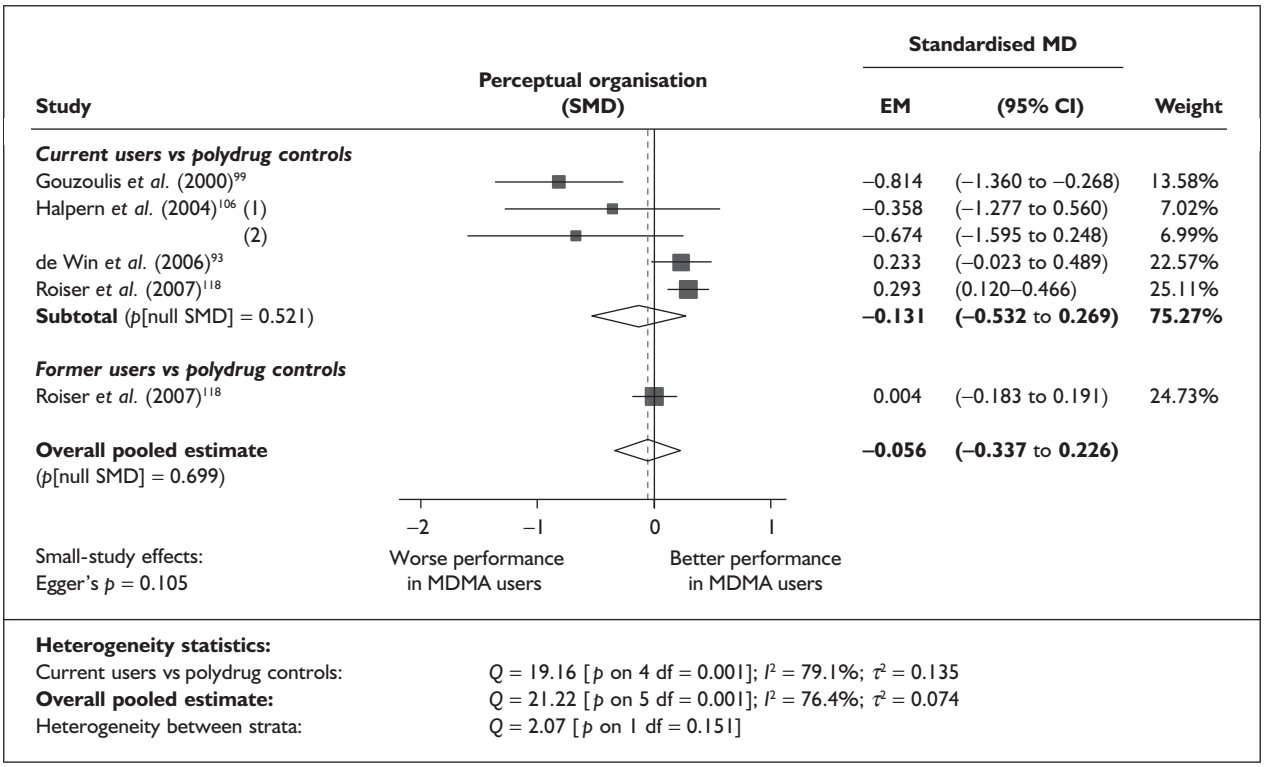


FIGURE 62 *Perceptual organisation (composite measure) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

Sufficient data were available to attempt metaregression analyses for 15 covariates; details are shown in *Table 33*. There was no evidence of a dose–response effect (see *Figure 114* in Appendix 7).

The only apparently strong explanatory variable is inter-arm difference in age, which is plotted against the outcome of interest in *Figure 65*. This dataset looks surprisingly heterogeneous, given the strongly significant *p*-value, and further analysis shows that disproportionate leverage is being exerted by the single datapoint provided by Fingeret *et al.*[145] (appearing in the bottom-left of the graph). When this study is excluded from analysis, the association between variables becomes substantially weaker ($\beta = 0.031$; $p = 0.288$).

Depression (self-rated) – MDMA users versus drug-naïve controls

The dataset assembled for this measure comprises 35 datapoints, representing a total of 31 pairwise comparisons, drawn from 13 different studies (27 comparisons from 13 studies providing data for current ecstasy users and four comparisons from four studies providing data for former ecstasy users). Eight different outcome measures are included, the most common being SCL-90: depression score (12 datapoints), SCL-BSI: depression score (five datapoints) and SCL-90-R: depression score (four datapoints). The complete dataset is detailed in *Table 70* in Appendix 6.

A random-effects meta-analysis of these data is shown in *Figure 66*. It suggests that ecstasy-exposed cohorts tend to exhibit more depression than drug-naïve controls; in current users, the size of effect is approximately 0.5 SD (a 'medium' difference, according to Cohen) while, in former users, the difference is a little over 0.8 SD (which would be considered 'large').

The most notable feature of the forest plot is the outlying status of four datapoints, all of which are drawn from studies published by an Italian research collaboration headed, in each case, by Gilberto Gerra.[63,82,146,147] In comparisons between current users and controls, these are the only datapoints with an estimated effect size greater than 0.8. It is not clear why these studies should have produced such disparate findings, although we note that they rely on an instrument – the Hamilton Depression Rating Scale – that is not used by other investigators.

When these extreme datapoints are excluded from analysis, a clearer picture emerges. There is strong evidence of within-stratum homogeneity in both current users ($Q = 19.72$; p on 22 df = 0.600; $I^2 = 0.0\%$) and former users (unchanged from primary analysis), but there is equally forceful

TABLE 32 *Perceptual organisation (composite measure) – ecstasy users versus polydrug controls: univariate metaregression results.*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	< 5						
Sex (% male)	< 5						
IQ	< 5						
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	< 5						
ETLE (occasions)	< 5						
Period since last consumption (days)	< 5						
Duration of ecstasy use (days)	< 5						
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	< 5						
Sex (% male)	< 5						
Baseline intelligence measures (SMD)	5	0.985	(0.255–1.715)	0.023	−0.019	(−0.231 to 0.194)	0.795
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	< 5						
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	< 5						
Exposure to cocaine (ETLD)	< 5						
Exposure to cocaine (SMD)	< 5						
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	< 5						

ETLD, estimated total lifetime dose; ETLE to estimated total lifetime exposure; SMD, standardised mean difference.

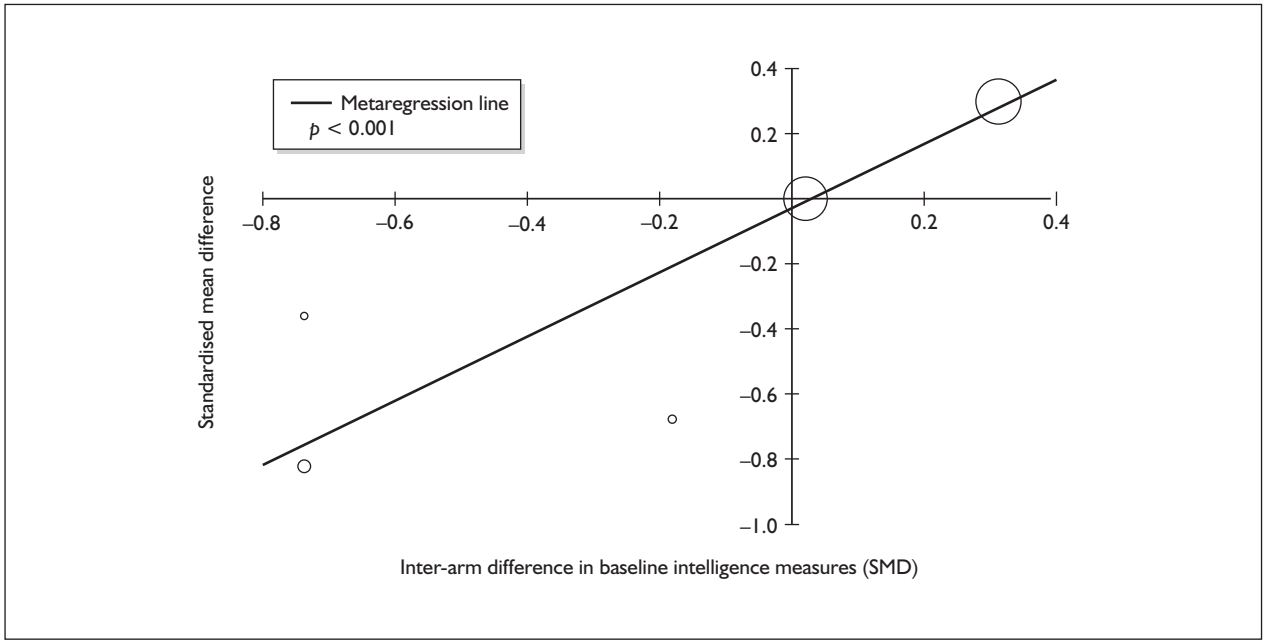


FIGURE 63 *Perceptual organisation (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against inter-arm asymmetry in baseline intelligence measures.*

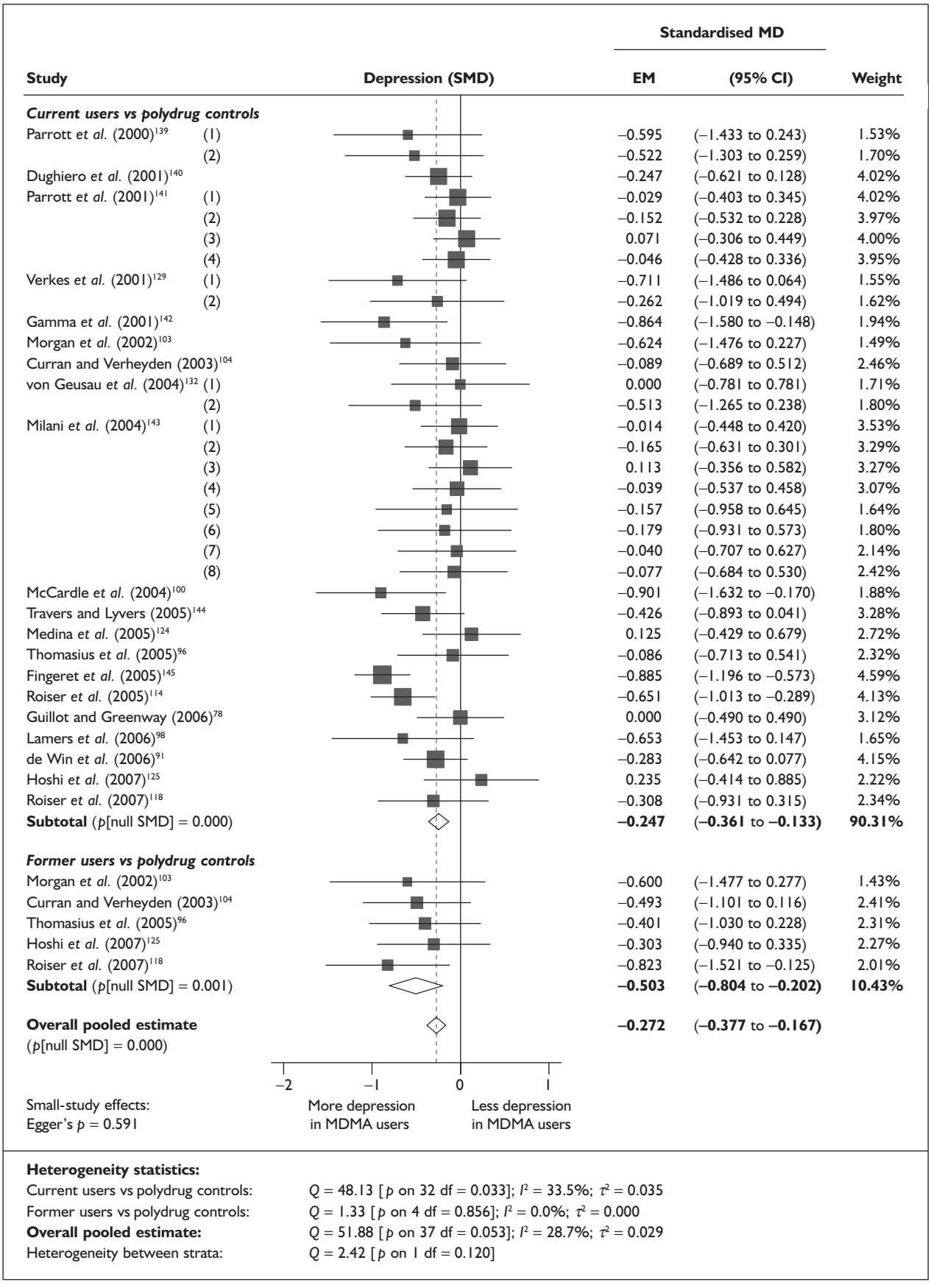
evidence of between-stratum heterogeneity ($Q = 13.14$; $p < 0.001$). Current users are seen to display additional depressive symptoms to a small but significant degree [SMD –0.167; 95% CI –0.261 to –0.072; p(null SMD) = 0.001], whereas the difference between former users and drug-naïve controls is much more pronounced [SMD –0.853; 95% CI –1.211 to –0.494; p(null SMD) < 0.001]. The revised overall effect size is estimated at –0.245 [95% CI –0.356 to –0.134; p(null SMD) < 0.001].

Initial sensitivity analysis with single, pooled comparisons for each study provided an SMD of –1.173 (95% CI –1.524 to –0.822). The fairly large size of the discrepancy between this estimate and that from the primary analysis arises because the aggregated approach is affected to an even greater extent by Gerra's team's outlying estimates (these studies comprise 34.3% of total weight in the sensitivity analysis, compared to 10.8% in primary analysis). Without the anomalous datapoints, the aggregate approach estimates an effect size of –0.330 (95% CI –0.520 to –0.139), which is comparable to that generated in our primary reanalysis.

Returning to the raw data on which the analysis was based, several individual datapoints could be cited as providing a reasonable example of the calculated average effect sizes:

- For the comparison between current users and controls in the restricted dataset excluding Gerra's team's publications, the most typical datapoint is the SCL-90 depression score reported for the comparison of heavy ecstasy users and drug-free controls by Milani *et al.*[143] where users scored an average of 0.17 points higher than controls (0.91 versus 0.74; SMD –0.154).
- For the comparison between former users and controls, no individual datapoint provides an especially good approximation of the estimated pooled effect. It falls somewhere between two estimates using the SCL-90-R depression score: those from the studies of Morgan *et al.*[103] [in which ecstasy users scored 0.57 points higher than controls (0.92 versus 0.35); SMD –0.696] and Thomasius *et al.*[96,105] [in which ecstasy users scored 0.56 points higher than controls (0.98 versus 0.42)]; SMD –1.040]. It will be noted that the absolute differences are very similar in these two studies; however the greater variability in the paper by Morgan *et al.*[103] leads to a lower SMD.

There is strong evidence of small-study bias in this dataset (Egger's $p < 0.001$). The funnel plot (*Figure 67*) shows a clear trend for the effect estimate to decrease as the precision of the study increases, and emphasises the outlying nature of the datapoints discussed above. However, excluding all four of the studies by Gerra *et al.* did nothing to diminish



Heterogeneity statistics:

Current users vs polydrug controls:	$Q = 48.13$ [p on 32 df = 0.033]; $I^2 = 33.5\%$; $\tau^2 = 0.035$
Former users vs polydrug controls:	$Q = 1.33$ [p on 4 df = 0.856]; $I^2 = 0.0\%$; $\tau^2 = 0.000$
Overall pooled estimate:	$Q = 51.88$ [p on 37 df = 0.053]; $I^2 = 28.7\%$; $\tau^2 = 0.029$
Heterogeneity between strata:	$Q = 2.42$ [p on 1 df = 0.120]

FIGURE 64 *Depression – self-rated (composite measure) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

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TABLE 33 *Depression – self-rated (composite measure) – ecstasy users versus polydrug controls: univariate metaregression results*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	38	−0.030	(−0.075 to 0.016)	0.201			
Sex (% male)	30	0.273	(−0.418 to 0.965)	0.438			
IQ	8	−0.028	(−0.082 to 0.026)	0.307			
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	23	0.000	(−0.001 to 0.000)	0.699			
ETLE (occasions)	6	0.002	(0.000–0.005)	0.079			
Period since last consumption (days)	12	0.000	(−0.001 to 0.001)	0.882			
Duration of ecstasy use (days)	12	0.000	(0.000–0.000)	0.393			
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	38	0.068	(0.030–0.105)	0.000	−0.284	(−0.372 to −0.195)	0.000
Sex (% male)	30	0.011	(−0.936 to 0.958)	0.982	−0.332	(−0.475 to −0.189)	0.000
Baseline intelligence measures (SMD)	11	0.372	(−0.317 to 1.061)	0.290	−0.303	(−0.496 to −0.110)	0.002
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	17	−0.178	(−0.445 to 0.089)	0.191	−0.266	(−0.445 to −0.088)	0.003
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	17	−0.244	(−0.553 to 0.065)	0.121	−0.097	(−0.310 to 0.116)	0.370
Exposure to cocaine (ETLD)	7	0.000	(−0.002 to 0.002)	0.749	−0.303	(−0.612 to 0.005)	0.054
Exposure to cocaine (SMD)	15	−0.214	(−0.556 to 0.128)	0.220	−0.131	(−0.328 to 0.065)	0.190
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	26	0.092	(−0.228 to 0.411)	0.574	−0.158	(−0.268 to −0.048)	0.005

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

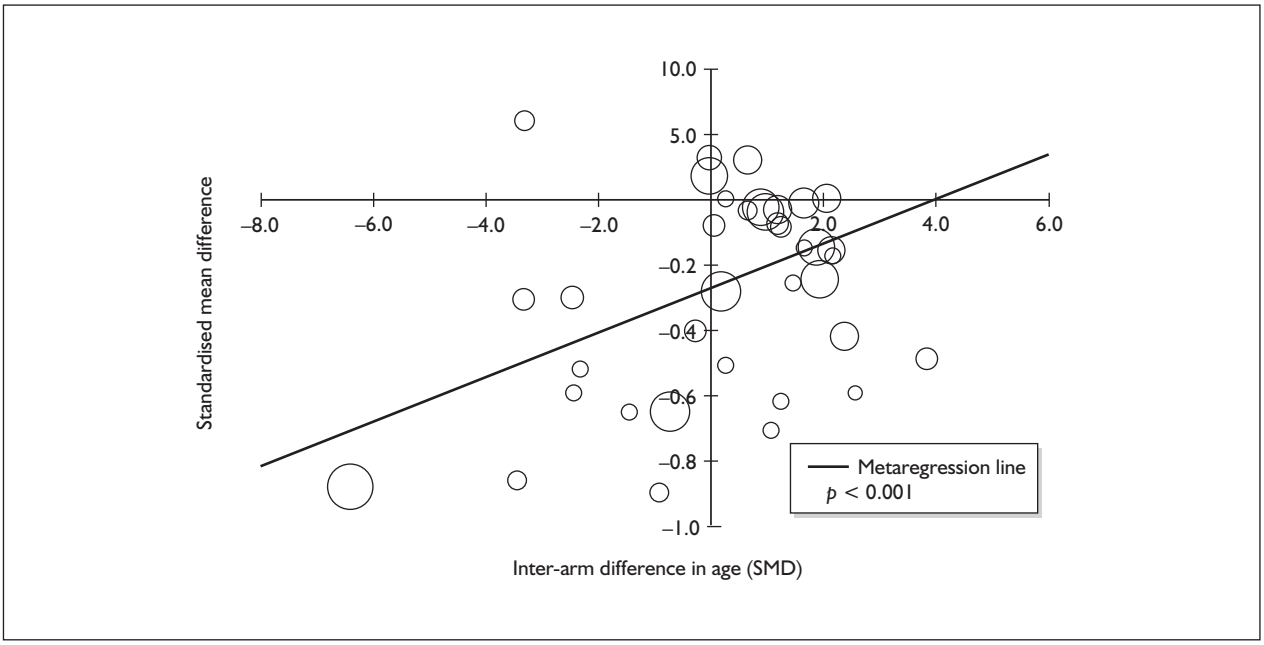

FIGURE 65 *Depression – self-rated (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against inter-arm asymmetry in age.*

the suggestion of bias, with Egger's p remaining less than 0.001. Similarly, even if one overlooks extreme observations, the funnel plot has the typical appearance of a dataset with substantial small-study bias. In particular, we note that all of the studies with the highest precision cluster on or around the point of null effect.

Sufficient data were available to attempt metaregression analyses for 12 covariates, shown in *Table 34*. There was some evidence of a dose–response effect, with studies in which the participants had a higher average ETLD more likely to report increased depression amongst users (see *Figure 115*, in Appendix 7). In view of this finding, it might be seen as paradoxical that the metaregression in which duration of ecstasy use is the covariate (*Figure 68*) produces a significant positive coefficient, suggesting that the largest depression effects are seen in those who have been using ecstasy for the shortest time.

A significant regression coefficient was also calculated for the association between depression and study-level gender distribution (*Figure 69*). This suggests that the greater the extent to which men outnumbered women in studies, the higher the relative level of depression that could be expected to be seen amongst ecstasy-exposed arms.

Memory (self-rated) – MDMA users versus polydrug controls

The dataset assembled for this measure comprises 20 datapoints, representing a total of eight pairwise comparisons, drawn from five different studies (all providing data for current ecstasy users only). Eleven different outcome measures are included, the most common relating to the PMQ and CFQ. The complete dataset is detailed in *Table 71* in Appendix 6.

When synthesised in a random-effects meta-analysis (*Figure 70*), this dataset suggests that ecstasy users report significantly more memory problems than controls, with an average effect size of around 0.5 SD (a 'medium' difference). Sensitivity analysis with single, aggregated comparisons for each study provides an SMD estimated at –0.549 [95% CI –0.756 to –0.343; p(null SMD) < 0.001], which is closely comparable to the primary analysis.

There is no evidence of small-study bias in this dataset (Egger's $p = 0.341$), and the funnel plot (not shown) had an unremarkable appearance.

Sufficient data were available to attempt metaregression analyses for four covariates, shown in *Table 35*. There was no evidence of a dose–response effect (see *Figure 116* in Appendix 7). The bubble-plot comparing study-level gender distribution with the outcome of interest (*Figure 71*) shows an apparently convincing association between these variables, with those studies in which men were outnumbered by women being more likely to report a sizeable deficit for ecstasy users. However, with very few datapoints contributing to the analysis, it is easy to imagine such an appearance occurring by chance.

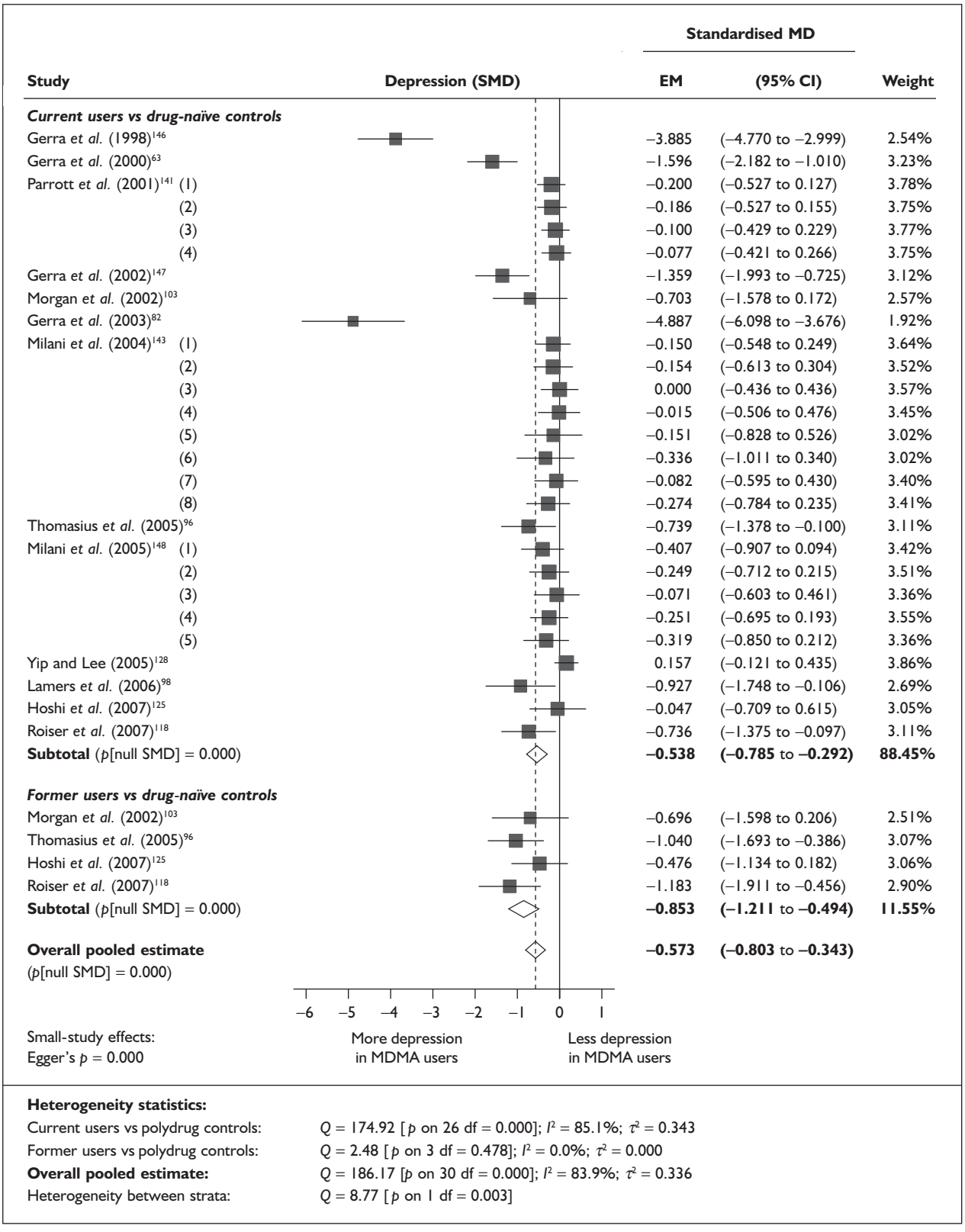

FIGURE 66 *Depression – self-rated (composite measure) – ecstasy users versus drug-naïve controls: random-effects meta-analysis.*

Memory (self-rated) – MDMA users versus drug-naïve controls

Only three studies in the evidence-base reported measures of self-rated memory in comparisons between ecstasy users and drug-naïve controls,[76,99,122] so we did not pursue extensive analysis of this dataset. When meta-analysed according to the model used in other analyses, these data generate a non-significant SMD of 0.156 (95% CI −0.210 to 0.521).

Anxiety (self-rated) – MDMA users versus polydrug controls

The dataset assembled for this measure comprises 32 datapoints, representing a total of 32 pairwise comparisons, drawn from 14 different studies (27 comparisons from 14 studies providing data for current ecstasy users and five comparisons from five studies providing data for former ecstasy users). Six different outcome measures are included, the most common being SCL-90: anxiety score (14 datapoints), SCL-90-R: anxiety score (seven datapoints) and STAI: trait anxiety (five datapoints). Measures of in-test state anxiety (e.g. those reported by Medina *et al.*[124]) were excluded. The complete dataset is detailed in *Table 72* in Appendix 6.

When analysed in a random-effects meta-analysis (*Figure 72*), these data suggest that ecstasy users display significantly greater symptoms of anxiety than controls, with the magnitude of difference in the order of one-quarter of an SD (which Cohen would label a 'small' difference). No substantial differences were seen between strata, although, on face value, former users showed a larger effect size.

Sensitivity analysis with aggregated comparisons for each study suggests that our primary analysis is relatively robust, but may slightly underestimate the inter-population difference, with the alternative estimate equating to exactly one-third of an SD [SMD −0.333; 95% CI −0.514 to −0.152; p(null SMD) < 0.001].

Using the calculated pooled value to identify a typical datapoint in the raw data on which the analysis was based, the most representative appears to be the BAI overall score from Ward *et al.*,[116] in which ecstasy-exposed participants scored 2.07 points higher than controls (10.1 versus 8.03; SMD −0.238).

There is no evidence of small-study bias in this dataset (Egger's $p = 0.322$), and the funnel plot (not shown) had an unremarkable appearance.

Sufficient data were available to attempt metaregression analyses for 14 covariates; details are shown in *Table 36*. There was no evidence of a dose–response effect (see *Figure 117* in Appendix 7).

The only covariate for which a significant regression coefficient was estimated was inter-arm asymmetry in age. The positive coefficient suggests that the extent to which ecstasy-exposed cohorts were younger than controls was associated with the extent to which they exhibited more anxiety. This is a very similar picture to that seen for self-rated measures of depression (see *Figure 65*). In common with that analysis, disproportionate leverage is being exerted by the single datapoint provided by Fingeret *et al.*[145] (appearing in the bottom-left of *Figure 73*). When this study is excluded from the analysis, the association between variables disappears entirely ($\beta = 0.005$; $p = 0.897$).

Anxiety (self-rated) – MDMA users versus drug-naïve controls

The dataset assembled for this measure comprises 25 datapoints, representing a total of 25 pairwise comparisons, drawn from eight different studies

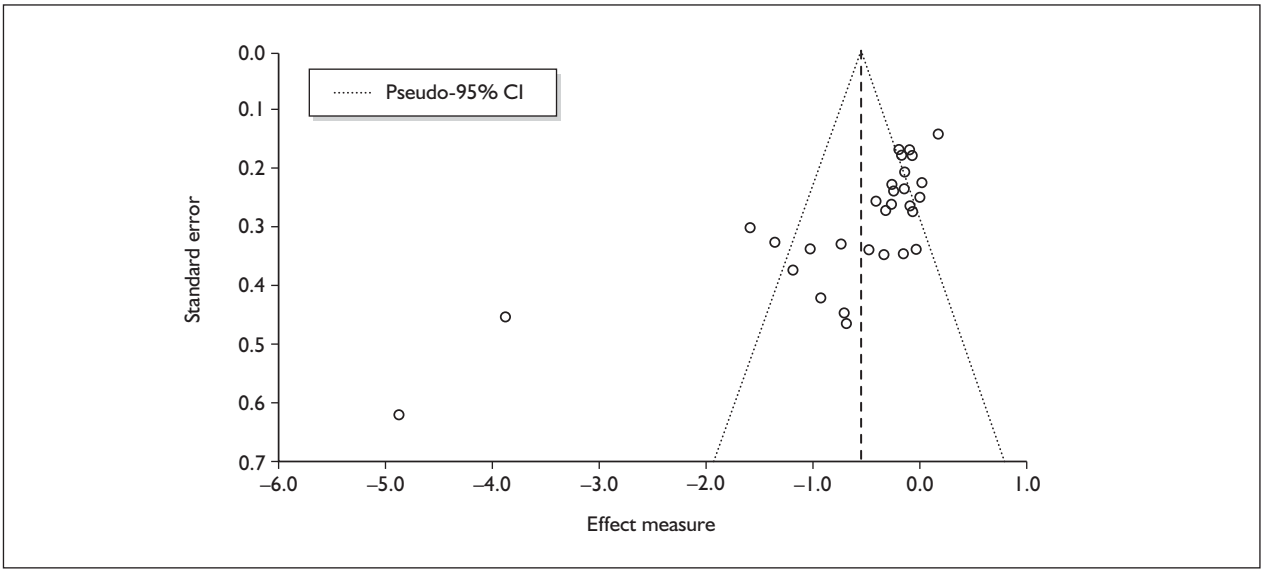

FIGURE 67 *Depression – self-rated (composite measure) – ecstasy users versus drug-naïve controls: funnel plot.*

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TABLE 34 *Depression – self-rated (composite measure) – ecstasy users versus drug-naïve controls: univariate metaregression results.*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	26	0.027	(−0.077 to 0.131)	0.612			
Sex (% male)	15	−2.671	(−4.647 to −0.696)	0.008			
IQ	5	0.014	(−0.060 to 0.088)	0.706			
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	19	−0.001	(−0.002 to 0.000)	0.004			
ETLE (occasions)	5	0.012	(0.000–0.025)	0.057			
Period since last consumption (days)	11	−0.001	(−0.001 to 0.000)	0.075			
Duration of ecstasy use (days)	13	0.001	(0.000–0.002)	0.043			
Frequency of ecstasy use (occasions/month)	5	−0.744	(−1.517 to 0.030)	0.060			
Inter-arm differences							
Age (years)	26	0.108	(−0.013 to 0.229)	0.079	−0.808	(−1.134 to −0.482)	0.000
Sex (% male)	15	3.063	(−0.232 to 6.359)	0.068	−1.163	(−1.661 to −0.665)	0.000
Baseline intelligence measures (SMD)	8	−0.018	(−1.294 to 1.258)	0.978	−0.514	(−0.965 to −0.063)	0.025
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to amphetamines (ETLD)	< 5						
Exposure to cocaine (ETLD)	< 5						
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	17	0.093	(−0.162 to 0.349)	0.474	−0.316	(−0.540 to −0.093)	0.005

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

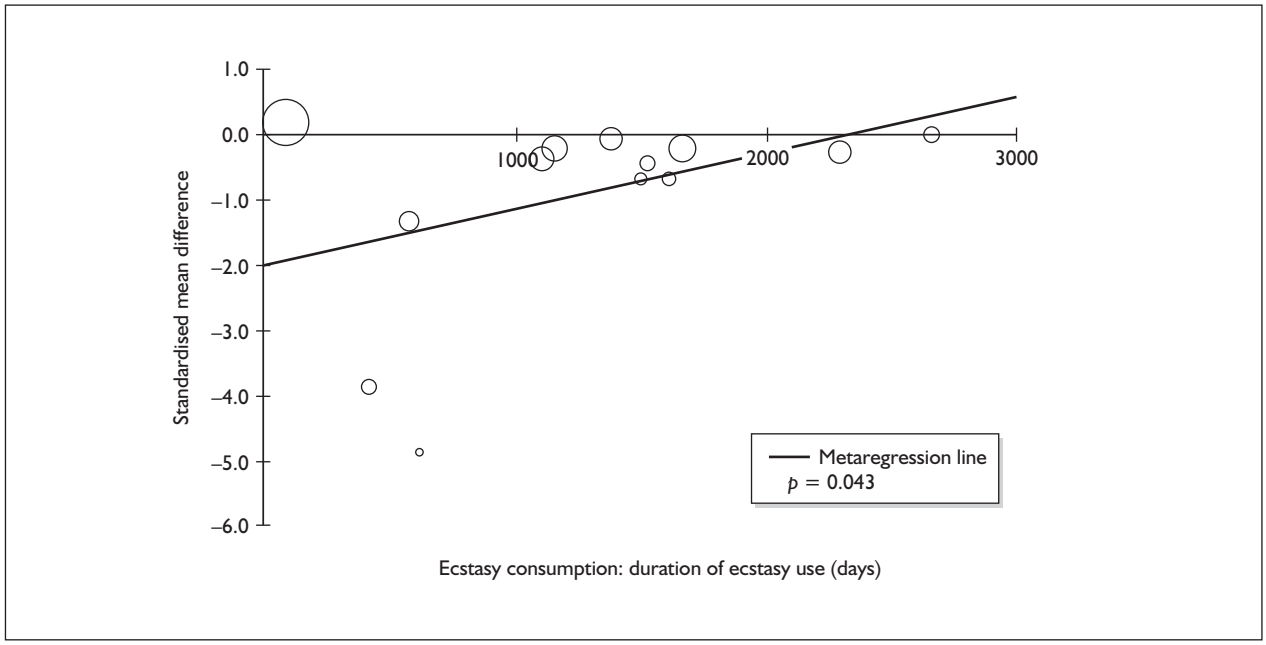


FIGURE 68 *Depression – self-rated (composite measure) – ecstasy users versus drug-naïve controls: standardised mean difference against duration of ecstasy use.*

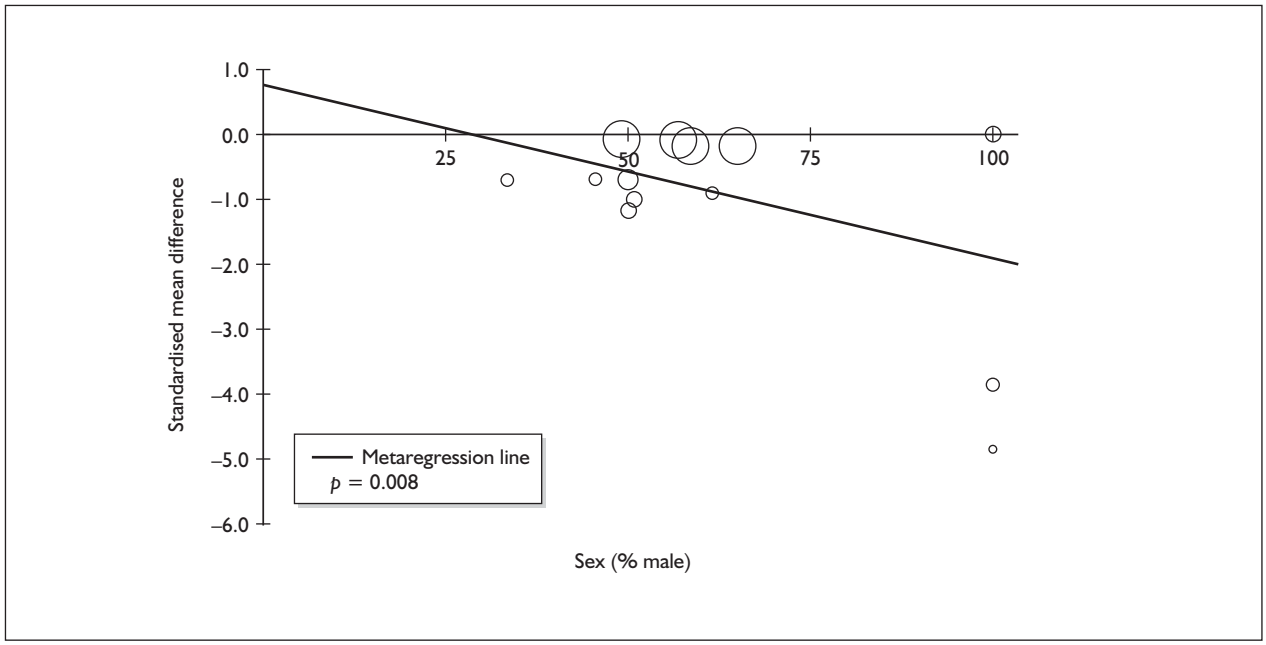


FIGURE 69 *Depression – self-rated (composite measure) – ecstasy users versus drug-naïve controls: standardised mean difference against gender (across all participants.*

(22 comparisons from eight studies providing data for current ecstasy users and three comparisons from three studies providing data for former ecstasy users). Six different outcome measures are included, the most common being SCL-90: anxiety score (12 datapoints), SCL-BSI: anxiety score (five datapoints) and SCL-90-R: anxiety score (four datapoints). As before, measures of in-test state anxiety (e.g. those reported by Wareing *et al.*[136]) were excluded. The complete dataset is detailed in *Table 73* in Appendix 6.

The random-effects meta-analysis (*Figure 74*) is similar to that seen in the comparison with polydrug controls (*Figure 72*), with a slightly larger effect size estimated at all levels of the analysis. The overall difference between populations is approximately one-third of an SD (this would

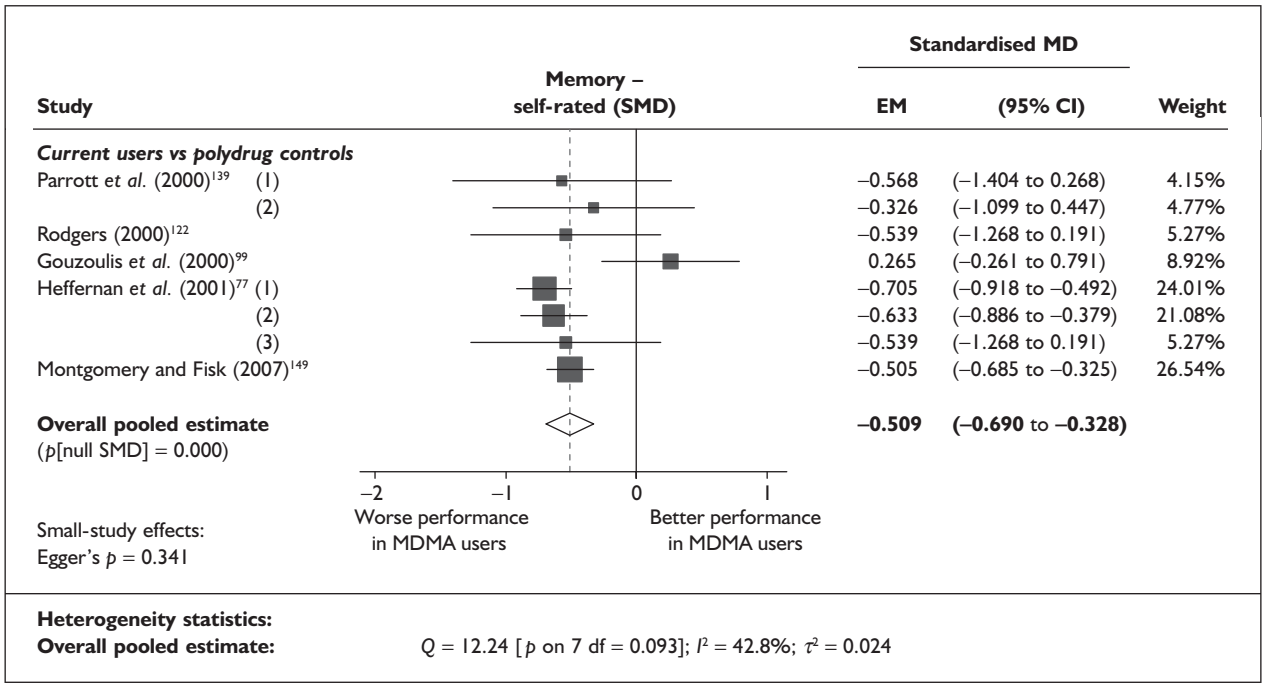


FIGURE 70 *Memory – self-rated (composite measure) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

probably fall into the category of a 'small' effect size), a similar effect was seen in the current users stratum, while a 'medium' difference a little over one-half of an SD was estimated amongst former users. Sensitivity analysis with single, pooled comparisons for each study provides a mean difference estimated at –0.340 [95% CI –0.438 to –0.242; p(null SMD) ≤ 0.001], which is extremely close to the primary analysis.

In the raw data underpinning this analysis, the datapoint that most closely reflects the meta-analysed effect size is the comparison by Parrott *et al.*[141] between heavy ecstasy users and alcohol–tobacco controls, in which users scored 0.19 points higher on the SCL-90 anxiety score (0.88 versus 0.69; SMD –0.351).

Statistical testing provided no evidence of small-study bias (Egger's $p = 0.228$), although the funnel plot for this dataset (*Figure 75*) appears to show a trend towards larger effect sizes in the least precise comparisons.

Sufficient data were available to attempt metaregression analyses for 11 covariates; details are shown in *Table 37*. None of these analyses generated results that achieved conventional levels of significance, and there was no evidence of a dose–response effect (see *Figure 118* in Appendix 7).

Impulsivity (objective measures) – MDMA users versus polydrug controls

The dataset assembled for this measure comprises 20 datapoints, representing a total of 10 pairwise comparisons, drawn from five different studies (nine comparisons from five studies providing data for current ecstasy users and one comparison from one study providing data for former ecstasy users). Seven different outcome measures are included, the most common relating to the RGT and MFFT. The complete dataset is detailed in *Table 74* in Appendix 6.

The meta-analysis of these data (*Figure 76*) generates a pooled estimate which, at 0.2 SD (precisely matching Cohen's definition of a 'small' effect size), falls just short of conventional statistical significance. Sensitivity analysis with single, pooled comparisons for each study provides a very similar effect estimate [SMD –0.181; 95% CI –0.367 to 0.006; p(null SMD) = 0.058].

There is no evidence of small-study bias in this dataset (Egger's $p = 0.249$), and the funnel plot (not shown) had an unremarkable appearance.

Sufficient data were available to attempt metaregression analyses for nine covariates; details are shown in *Table 38*. There was no evidence of a dose–response effect (see *Figure 119* in Appendix 7).

TABLE 35 *Memory – self-rated (composite measure) – ecstasy users versus polydrug controls: univariate metaregression results.*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	8	−0.034	(−0.117 to 0.049)	0.420			
Sex (% male)	8	4.439	(1.598–7.280)	0.002			
IQ	< 5						
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	< 5						
ETLE (occasions)	< 5						
Period since last consumption (days)	< 5						
Duration of ecstasy use (days)	< 5						
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	8	0.063	(−0.043 to 0.169)	0.243	−0.422	(−0.654 to −0.189)	0.000
Sex (% male)	8	−0.797	(−3.099 to 1.506)	0.498	−0.418	(−0.721 to −0.115)	0.007
Baseline intelligence measures (SMD)	< 5						
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	< 5						
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	< 5						
Exposure to cocaine (ETLD)	< 5						
Exposure to cocaine (SMD)	< 5						
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	< 5						

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

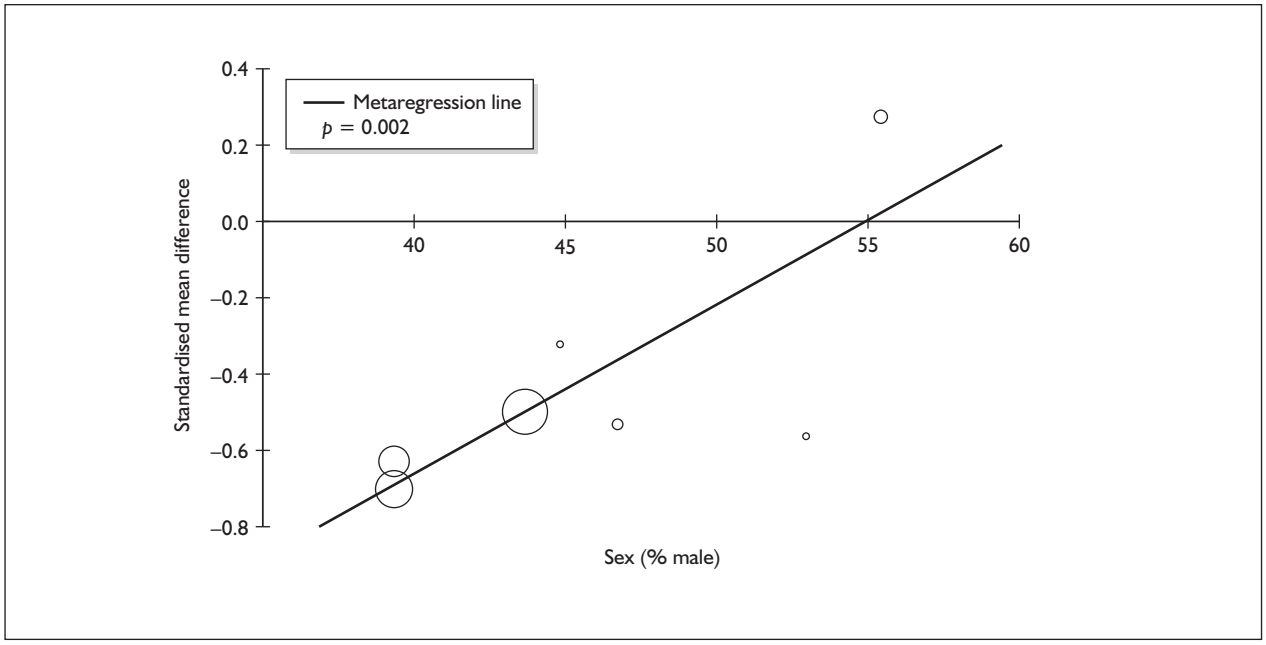


FIGURE 71 *Memory – self-rated (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against gender (across all participants).*

Significant coefficients were estimated for two covariates: inter-arm asymmetry in gender distribution and inter-arm asymmetry in exposure to alcohol. The impact of imbalances in gender is visualised in *Figure 77*. It appears that greater impulsivity is seen amongst ecstasy users in those studies in which the proportion of men is smaller in the exposed arm than in controls. A positive coefficient was also estimated for confounding by alcohol (*Figure 78*), suggesting that greatest additional impulsivity was found in those studies where ecstasy users drank more than polydrug controls. Because this model runs in a counterintuitive direction, it suggests that imbalances in alcohol exposure are masking a greater effect than is seen in the primary analysis (the adjusted effect estimate provides reasonably strong evidence against the null hypothesis of no effect). Both these analyses are based on very restricted datasets.

Impulsivity (objective measures) – MDMA users versus drug-naïve controls

The dataset assembled for this measure comprises 23 datapoints, representing a total of 10 pairwise comparisons, drawn from six different studies (nine comparisons from six studies providing data for current ecstasy users and one comparison from one study providing data for former ecstasy users). Ten different outcome measures are included, the most common relating to the RGT and MFFT. The complete dataset is detailed in *Table 75* in Appendix 6.

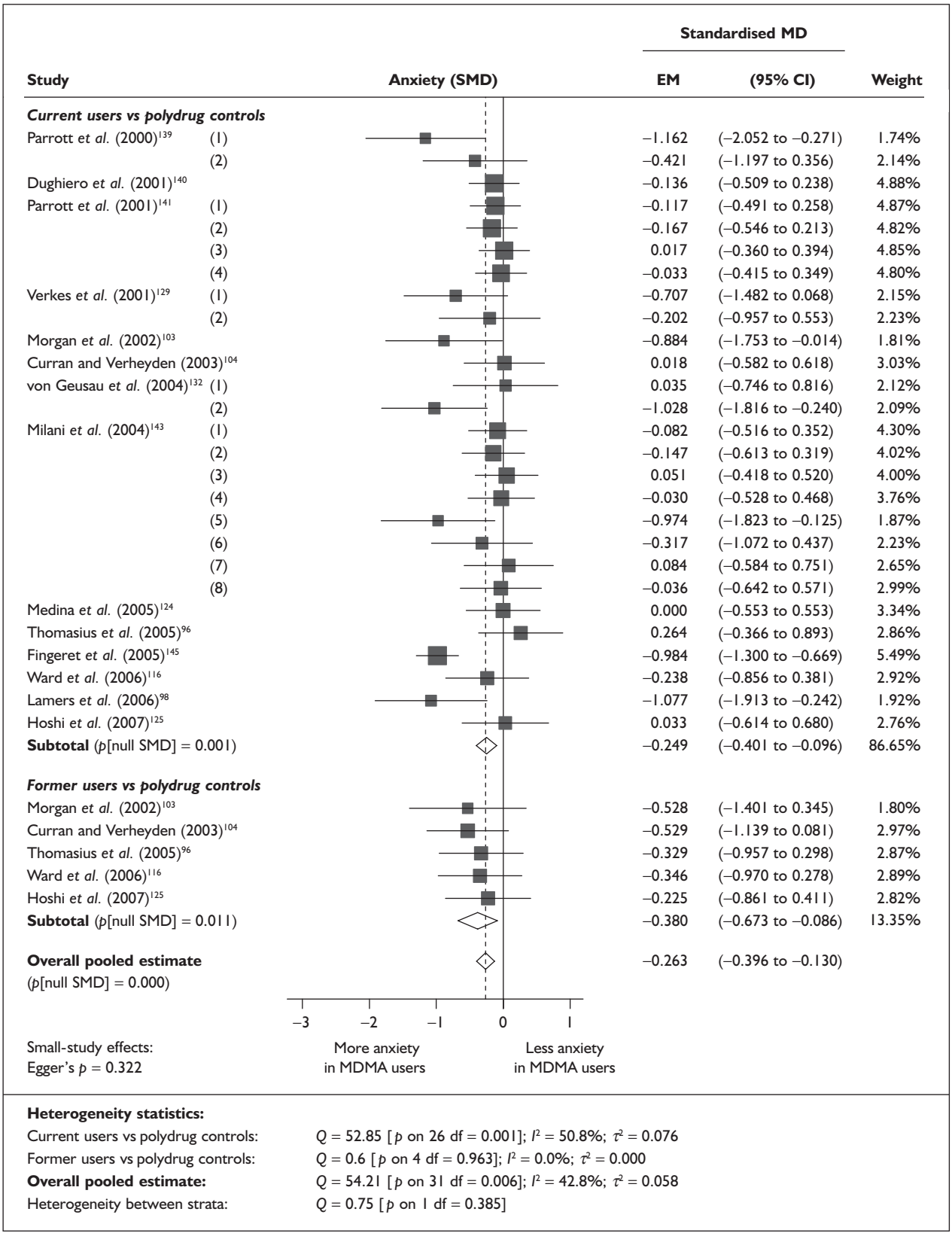
Figure 79 shows a random-effects meta-analysis of these data. The estimated effect size is exactly one-third of an SD (which would probably be a 'small' difference, in Cohen's schema). The evidence against the null hypothesis of no inter-population difference is sufficiently weak to meet conventional definitions of statistical significance.

Sensitivity analysis with aggregated, study-level estimates of effect generated a slightly lower effect estimate than that seen in the primary analysis, but shared the key feature of a small but significant difference [SMD –0.264; 95% CI –0.460 to –0.068; p(null SMD) = 0.008].

A representative datapoint from the underlying dataset is found in the 2006 study by Morgan *et al.*,[115] in which the ecstasy-using cohort responded more swiftly than controls by 677 milliseconds in the gains-only trial of the RGT (3589 milliseconds versus 4266 milliseconds; SMD –0.337).

There may be a tendency towards small-study bias in this dataset (Egger's $p = 0.075$). This suspicion is strengthened by scrutiny of the funnel plot (*Figure 80*), in which a trend with a negative coefficient – suggesting high study precision is associated with lower exposure effects – is discernible.

Sufficient data were available to attempt metaregression analyses for seven covariates; details are shown in *Table 39*. None of the analyses were able to provide a statistically convincing explanation of the heterogeneity seen amongst



Heterogeneity statistics:

Current users vs polydrug controls: $Q = 52.85$ [p on 26 df = 0.001]; $I^2 = 50.8\%$; $\tau^2 = 0.076$

Former users vs polydrug controls: $Q = 0.6$ [p on 4 df = 0.963]; $I^2 = 0.0\%$; $\tau^2 = 0.000$

Overall pooled estimate: $Q = 54.21$ [p on 31 df = 0.006]; $I^2 = 42.8\%$; $\tau^2 = 0.058$

Heterogeneity between strata: $Q = 0.75$ [p on 1 df = 0.385]

FIGURE 72 *Anxiety – self-rated (composite measure) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

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TABLE 36 *Anxiety – self-rated (composite measure) – ecstasy users versus polydrug controls: univariate metaregression results*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	32	−0.021	(−0.075 to 0.034)	0.460			
Sex (% male)	24	0.309	(−0.504 to 1.121)	0.457			
IQ	9	−0.031	(−0.085 to 0.023)	0.264			
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	20	0.000	(−0.001 to 0.000)	0.557			
ETLE (occasions)	6	0.001	(−0.002 to 0.004)	0.352			
Period since last consumption (days)	8	0.000	(−0.001 to 0.001)	0.985			
Duration of ecstasy use (days)	10	0.000	(0.000–0.001)	0.318			
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	32	0.073	(0.024–0.121)	0.004	−0.278	(−0.390 to −0.166)	0.000
Sex (% male)	24	−0.216	(−1.371 to 0.940)	0.714	−0.299	(−0.488 to −0.111)	0.002
Baseline intelligence measures (SMD)	11	0.284	(−0.406 to 0.973)	0.420	−0.222	(−0.493 to 0.049)	0.108
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	13	−0.221	(−0.660 to 0.219)	0.325	−0.315	(−0.549 to −0.082)	0.008
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	13	−0.115	(−0.554 to 0.325)	0.609	−0.201	(−0.497 to 0.094)	0.181
Exposure to cocaine (ETLD)	< 5						
Exposure to cocaine (SMD)	11	−0.290	(−0.667 to 0.088)	0.133	−0.098	(−0.335 to 0.138)	0.414
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	23	0.233	(−0.144 to 0.610)	0.225	−0.169	(−0.286 to −0.053)	0.004

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

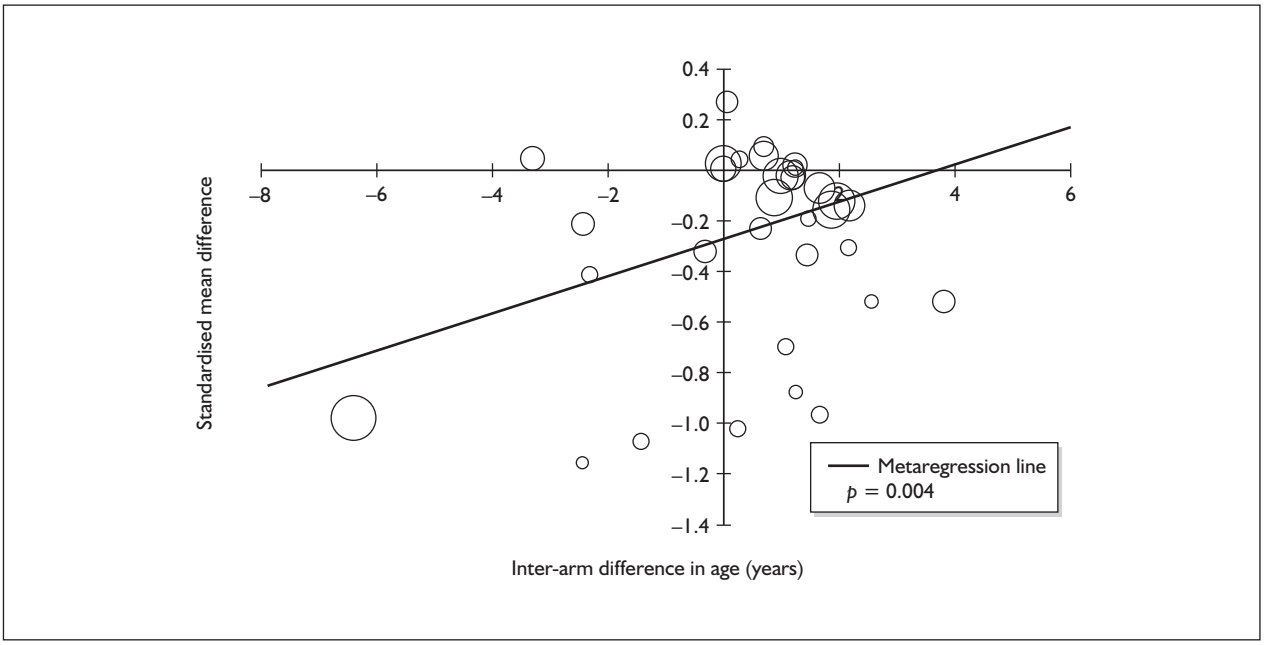

FIGURE 73 *Anxiety – self-rated (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against inter-arm asymmetry in age.*

base-case effect estimates, and there was no evidence of a dose–response effect (see *Figure 120* in Appendix 7).

Impulsivity (subjective measures) – MDMA users versus polydrug controls

The dataset assembled for this measure comprises 14 datapoints, representing a total of 14 pairwise comparisons, drawn from eight different studies (12 comparisons from eight studies providing data for current ecstasy users and two comparisons from two studies providing data for former ecstasy users). Only two different outcome measures are included: IVE: overall score (10 datapoints) and BIS-II: total (four datapoints). The complete dataset is detailed in *Table 76* in Appendix 6.

When synthesised in a random-effects meta-analysis (*Figure 81*), these data suggest that ecstasy users report significantly more impulsive behaviour than controls, with the size of the difference estimated at approximately 0.4 SD. There is no evidence of differential effects among current and former users of ecstasy. Sensitivity analysis with data aggregated at study level generates results that are very close to the primary analysis [(SMD –0.387; 95% CI –0.660 to –0.115; p(null SMD) = 0.005].

Of all the observations in the raw dataset on which the meta-analysis is based, the IVE impulsivity score from Butler and Montgomery's 2004 study[78] – in which light ecstasy users scored 1.6 points higher than cannabis-using controls (10.3 versus 8.7; SMD –0.406) – is closest to the estimated pooled overall effect size.

There is no evidence of small-study bias in this dataset (Egger's $p = 0.502$), and the funnel plot (not shown) had an unremarkable appearance.

Sufficient data were available to attempt metaregression analyses for 12 covariates; details are shown in *Table 40*. There was no evidence of a dose–response effect (see *Figure 121* in Appendix 7).

The only apparently strong explanatory variable is inter-arm difference in age, which is plotted against the outcome of interest in *Figure 82*. This graph shows a very similar picture to that seen for previous self-rated measures of depression (*Figure 65*) and anxiety (*Figure 73*). In common with those analyses, disproportionate leverage is being exerted by the single datapoint provided by Fingeret *et al.*[145] (appearing in the bottom-left of the graph) and, when this study is excluded from analysis, the association between variables disappears entirely ($\beta = 0.010$; $p = 0.819$).

Impulsivity (subjective measures) – MDMA users versus drug-naïve controls

The dataset assembled for this measure comprises 11 datapoints, representing a total of nine pairwise comparisons, drawn from five different studies (eight comparisons from five studies providing data for current ecstasy users and one comparison from one study providing data for former ecstasy users).

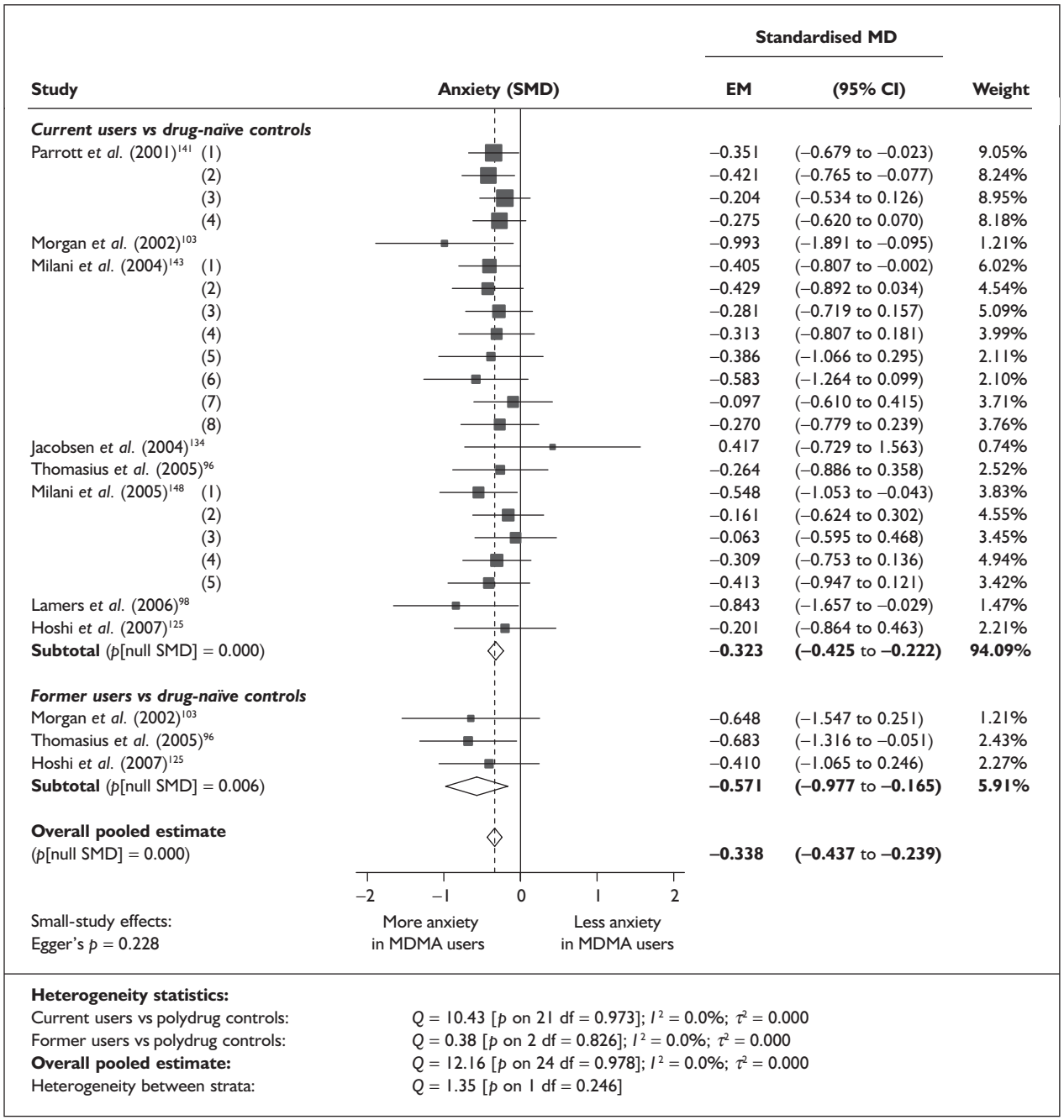

FIGURE 74 *Anxiety – self-rated (composite measure) – ecstasy users versus drug-naïve controls: random-effects meta-analysis.*

Only two different outcome measures are included: IVE: overall score (seven datapoints) and BIS-II: total (four datapoints). The complete dataset is detailed in *Table 77*, in Appendix 6.

A random-effects meta-analysis of these data (*Figure 83*) suggests that there is a 'large' difference of just under 0.8 SD between cohorts, with ecstasy users reporting significantly more impulsive behaviour than controls. Sensitivity analysis with study-level aggregated data generated results that were extremely close to the primary analysis [SMD –0.784; 95% CI –1.041 to –0.528; p(null SMD) < 0.001].

The most typical datapoint in the raw dataset underlying the meta-analysis is the IVE impulsivity score from Morgan's study,[110] in which the ecstasy-exposed arm averaged 3.53 points higher than drug-naïve controls (12.00 versus 8.47; SMD –0.760).

There is no evidence of small-study bias in this dataset (Egger's $p = 0.718$), and the funnel plot (not shown) had an unremarkable appearance.

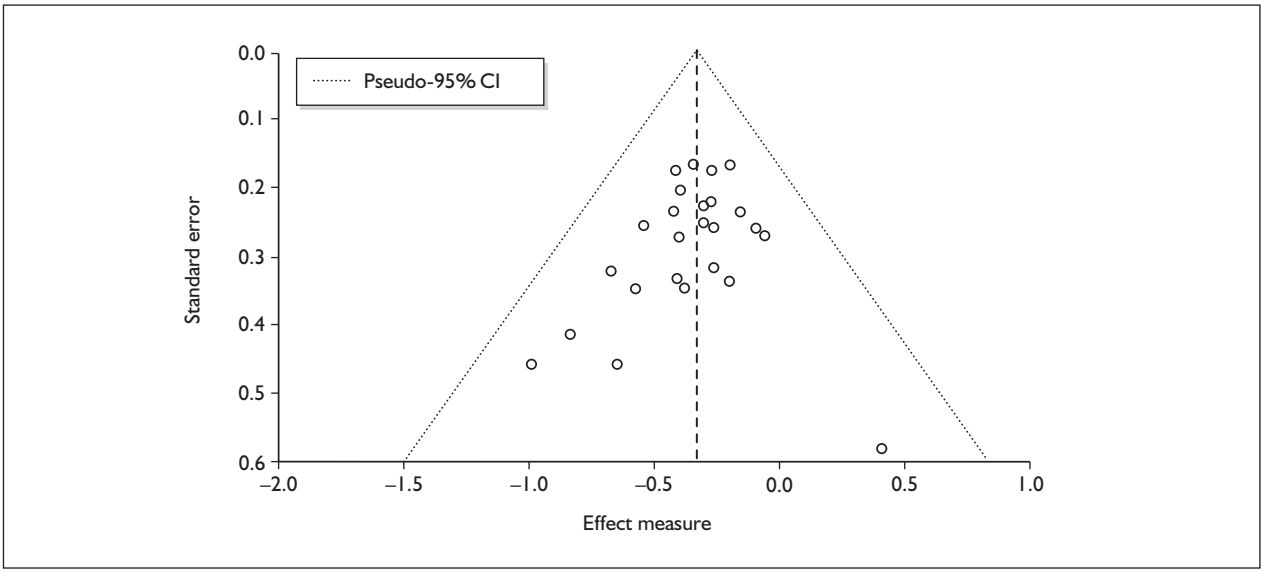

FIGURE 75 *Anxiety – self-rated (composite measure) – ecstasy users versus drug-naïve controls: funnel plot.*

Sufficient data were available to attempt metaregression analyses for 17 covariates; details are shown in *Table 41*. None of the analyses could provide a statistically meaningful explanation of the intercomparison heterogeneity seen in the meta-analysis, and there was no evidence of a dose–response effect (see *Figure 122* in Appendix 7).

Summary of quantitative syntheses of Level II evidence

The key findings of our quantitative syntheses are shown in *Table 42*. These results may be further summarised as follows:

- *Ecstasy-using populations performed worse than their controls* in all except one of our meta-analyses, and the effect was strong enough to meet conventional definitions of statistical significance in six out of eight individual measures and 20 out of 28 composite meta-outcomes.
- The *magnitude of difference* between ecstasy users and polydrug controls tended to be no more than 0.5 SD, with many falling in the range 0.15–0.4 SD. When drug-naïve control groups are considered, evidence becomes slightly more heterogeneous, with effect sizes ranging from very small to relatively large (the greatest SMD was a little over 1 SD).
- The *largest, most consistent exposure effects* were seen in meta-analyses of memory domains. Deficits appear to be greatest in verbal and working memory, with less marked effects seen in visual memory. The focus–execute component of attention also appears to be affected, though sustained attention may not be. A significant exposure effect was seen in the planning but not in the response-inhibition or shifting components of executive function.
- There was a fair degree of *inter-study heterogeneity* in most of the meta-analyses we performed. In some cases, the heterogeneity was substantially ascribable to single studies (or groups of studies from the same research centres), with a much more homogeneous picture emerging when outlying estimates were excluded from analysis [for examples, see sections on Verbal memory (delayed) – MDMA users versus drug-naïve controls, Visual memory (delayed) – MDMA users versus drug-naïve controls, and Depression (self-rated) – MDMA users versus drug-naïve controls].
- In our *stratified meta-analyses*, former ecstasy users frequently showed deficits that matched or exceeded those seen among current users. A significant difference between strata, with a greater exposure effect seen in ex-users, was found in three instances (with a further case very close to conventional levels of significance). In contrast, none of the analyses showed a significant advantage for former over current users, when compared to controls. Most of the analyses showed no difference between strata.
- Significant evidence of *small-study bias* was found in a few analyses, but only in comparisons between ecstasy users and drug-naïve controls. There is strong evidence that the meta-analysis of depression in ecstasy users versus drug-naïve controls may be distorted by this bias [see Depression (self-rated) – MDMA users versus drug-naïve controls].

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TABLE 37 *Anxiety – self-rated (composite measure) – ecstasy users versus drug-naïve controls: univariate metaregression results.*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	20	−0.013	(−0.062 to 0.036)	0.602			
Sex (% male)	12	0.070	(−0.890 to 1.029)	0.887			
IQ	5	−0.038	(−0.112 to 0.036)	0.310			
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	17	0.000	(−0.001 to 0.000)	0.230			
ETLE (occasions)	< 5						
Period since last consumption (days)	10	0.000	(−0.001 to 0.001)	0.924			
Duration of ecstasy use (days)	9	0.000	(0.000–0.000)	0.985			
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	20	−0.010	(−0.065 to 0.045)	0.721	−0.325	(−0.493 to −0.158)	0.000
Sex (% male)	12	−0.053	(−0.997 to 0.892)	0.913	−0.349	(−0.558 to −0.140)	0.001
Baseline intelligence measures (SMD)	8	−0.102	(−0.911 to 0.707)	0.805	−0.486	(−0.775 to −0.196)	0.001
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to amphetamines (ETLD)	5	−0.392	(−1.270 to 0.487)	0.382	−0.211	(−1.203 to 0.781)	0.676
Exposure to cocaine (ETLD)	< 5						
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	17	0.008	(−0.240 to 0.257)	0.947	−0.363	(−0.576 to −0.151)	0.001

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

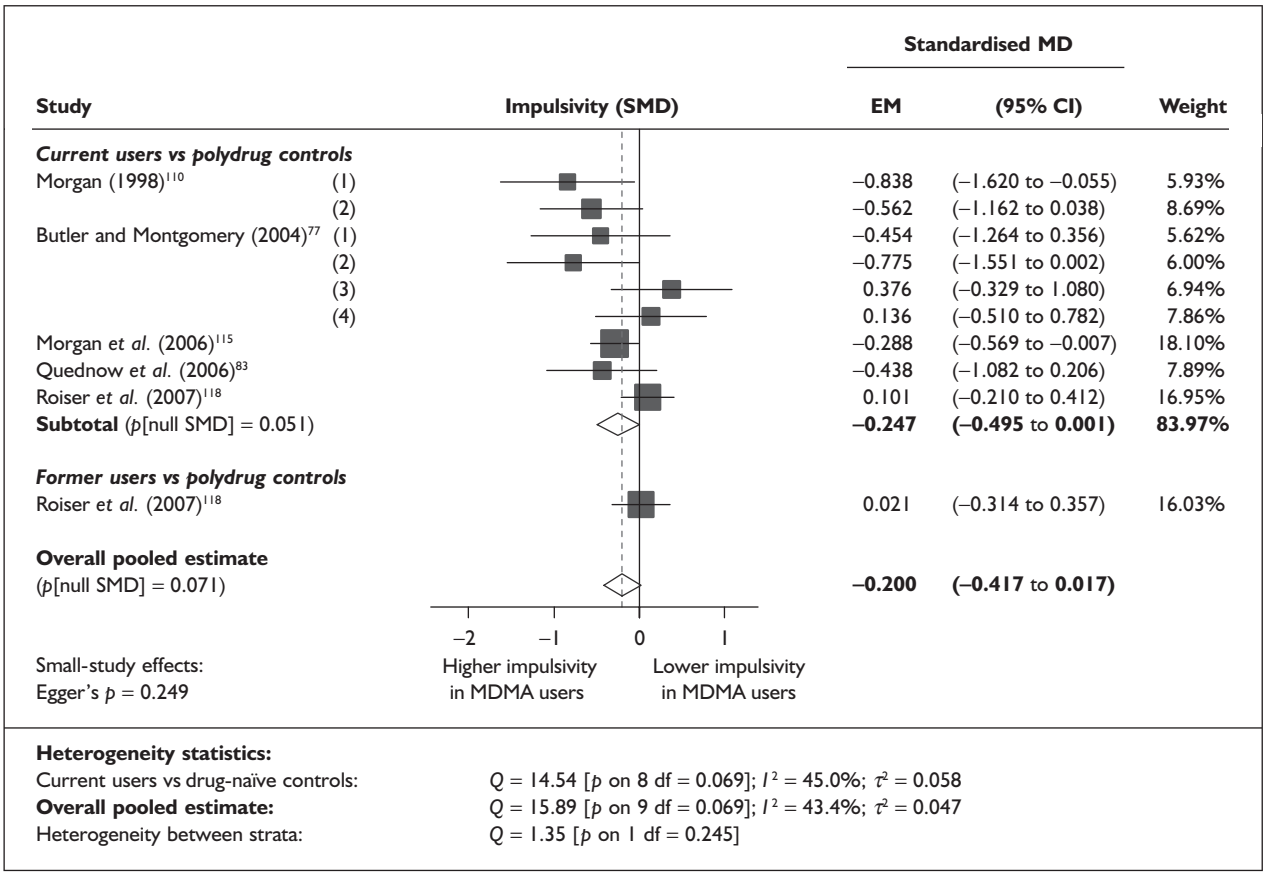

FIGURE 76 *Impulsivity – objective measures (composite measure) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

- Our *metaregression analyses* sought to explain heterogeneity in estimated exposure effects with reference to study-level and arm-level characteristics, as well as inter-arm differences. Most results were inconsistent and, in the context of multiple testing, should be seen as uncertain. For two covariates, a more uniform pattern emerged:
  - Several meta-analyses appeared to be biased by **asymmetry in the baseline intelligence** of participants in the studies. In these cases, a preponderance of studies in which ecstasy users were less intelligent than their respective controls appeared to have an influence on the estimated inter-population effect.
  - In the 25 separate analyses for which sufficient data were available to perform metaregression analyses with **asymmetry in exposure to alcohol** as the explanatory variable, 19 (76%) estimated a positive coefficient and, in five of these cases, a significant *p*-value (< 0.05) was generated. This suggests that effects were least in studies in which ecstasy users had greater exposure to alcohol than their controls.

Additional description of metaregressions

The results of these analyses (encompassing both individual and composite outcome measures) are discussed in the following section.

Average values across all participants

Our first category of metaregressions was the 'classical' type, in which covariates representing a characteristic of all participants were investigated, to ascertain the extent to which study-level factors may influence outcomes.

Age

Sufficient information about participant age was provided to enable metaregression on this covariate in most cases. The resulting picture was ambiguous: only one of 34 analyses was significant (immediate verbal memory in ecstasy users versus polydrug controls), and there was an even split between positive and negative coefficients (17 : 17).

Gender

Again, most studies reported this variable, so we were able to perform metaregressions in 33 cases. Three analyses generated significant results: immediate visual memory (polydrug), self-rated

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TABLE 38 *Impulsivity – objective measures (composite measure) – ecstasy users versus polydrug controls: univariate metaregression results.*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	10	0.094	(−0.039 to 0.226)	0.165			
Sex (% male)	10	−0.402	(−1.881 to 1.077)	0.594			
IQ	5	−0.153	(−0.451 to 0.146)	0.316			
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	5	0.001	(0.000–0.002)	0.144			
ETLE (occasions)	< 5						
Period since last consumption (days)	< 5						
Duration of ecstasy use (days)	< 5						
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	10	0.014	(−0.122 to 0.151)	0.835	−0.206	(−0.448 to 0.036)	0.096
Sex (% male)	10	4.229	(1.077–7.380)	0.009	−0.094	(−0.257 to 0.069)	0.258
Baseline intelligence measures (SMD)	5	0.285	(−0.483 to 1.054)	0.467	−0.197	(−0.468 to 0.074)	0.154
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	5	−1.004	(−2.447 to 0.438)	0.172	−0.211	(−0.487 to 0.066)	0.135
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	< 5						
Exposure to cocaine (ETLD)	< 5						
Exposure to cocaine (SMD)	< 5						
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	5	0.653	(0.131–1.174)	0.014	−0.223	(−0.402 to −0.044)	0.015

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

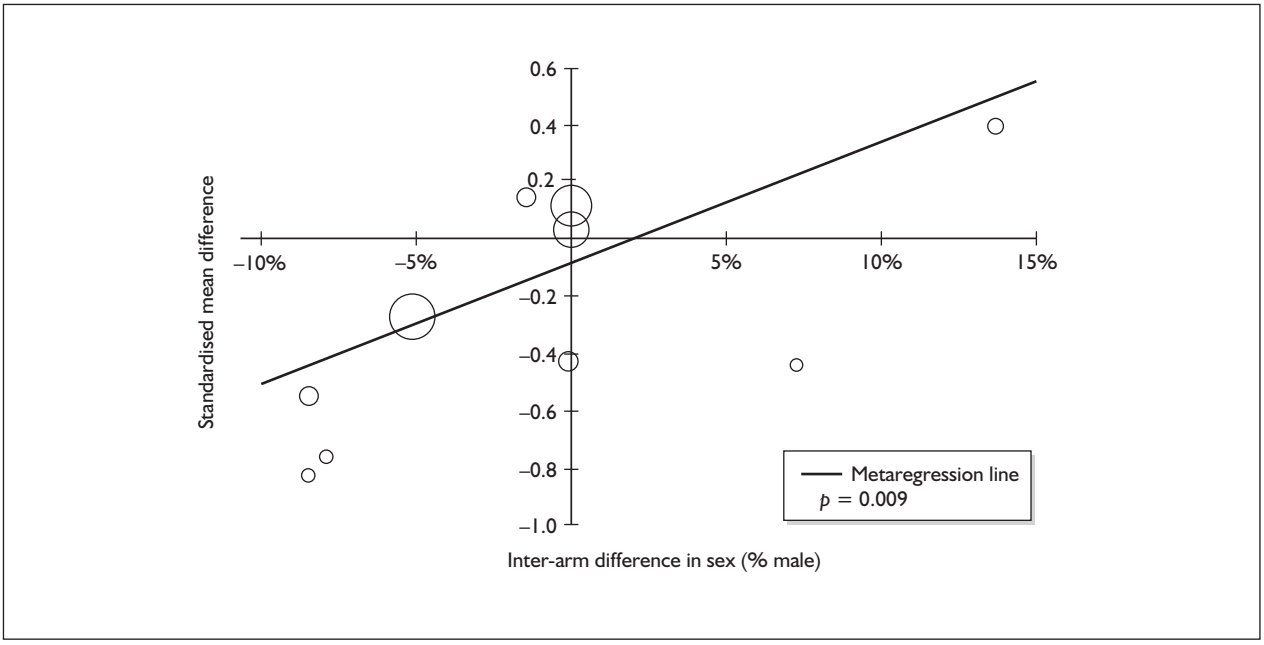

FIGURE 77 *Impulsivity – objective measures (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against inter-arm asymmetry in gender.*

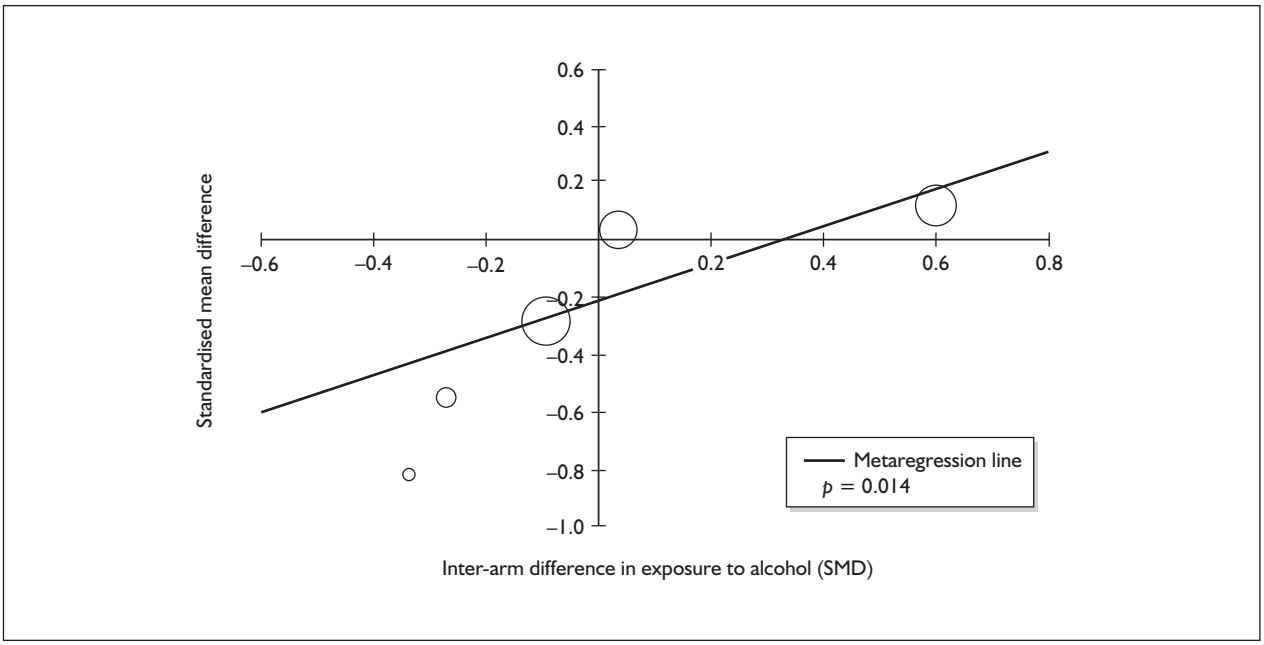

FIGURE 78 *Impulsivity – objective measures (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against inter-arm asymmetry in exposure to alcohol.*

memory (polydrug) and self-rated depression (drug-naïve). The first and last of these had negative coefficients, suggesting that deficits were greatest in ecstasy cohorts when the proportion of males was higher, but there was a positive coefficient for the remaining variable, indicating the opposite relationship. It is hard to draw any conclusions from these ostensibly contradictory findings.

IQ

Baseline IQ was reported with insufficient frequency to enable many metaregressions to be performed; where they were possible, they appear uninformative.

Education

Sufficient study-level covariate data for years of education was available for only 10 meta-analyses. In two cases, a significant, positive coefficient was

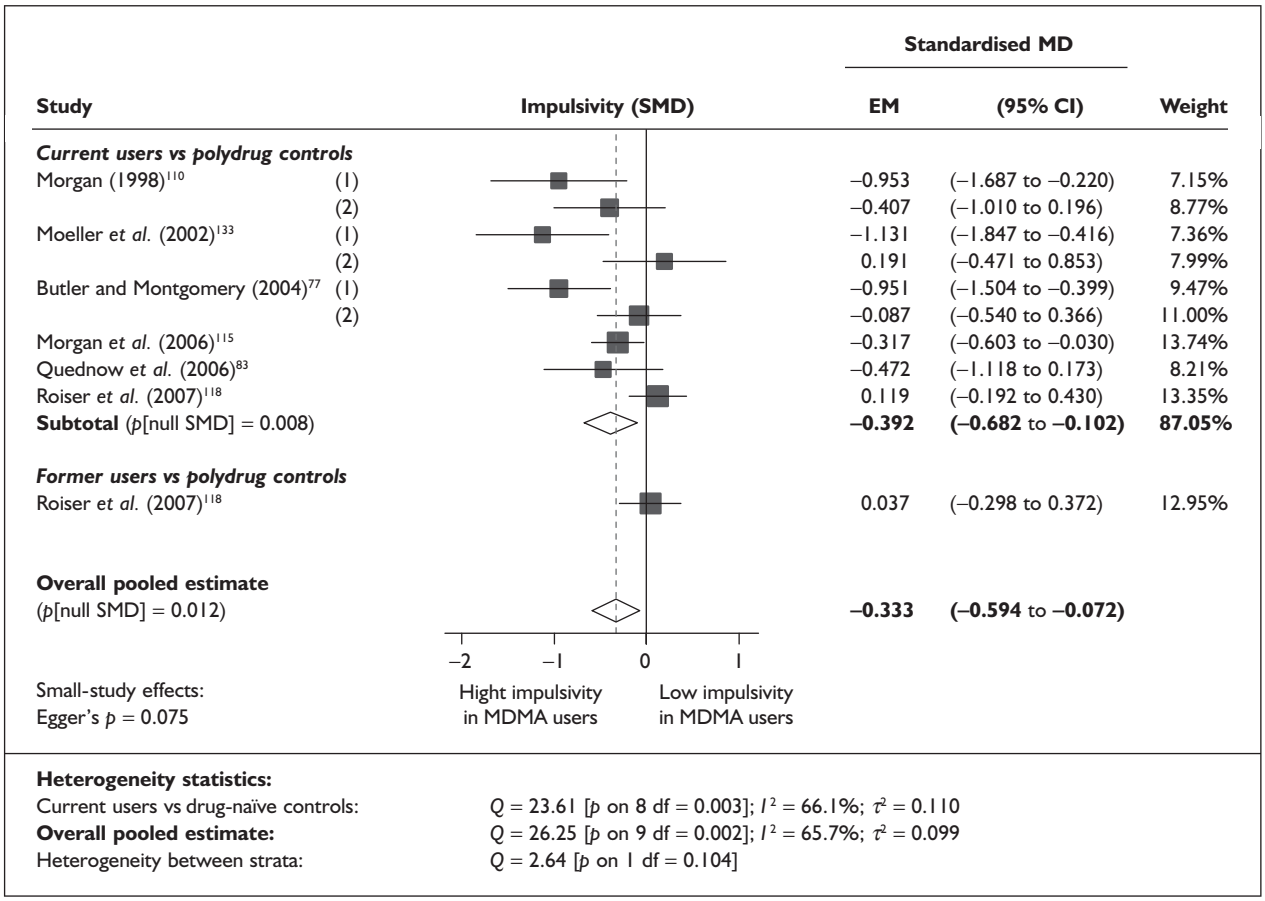

FIGURE 79 *Impulsivity – objective measures (composite measure) – ecstasy users versus drug-naïve controls: random-effects meta-analysis.*

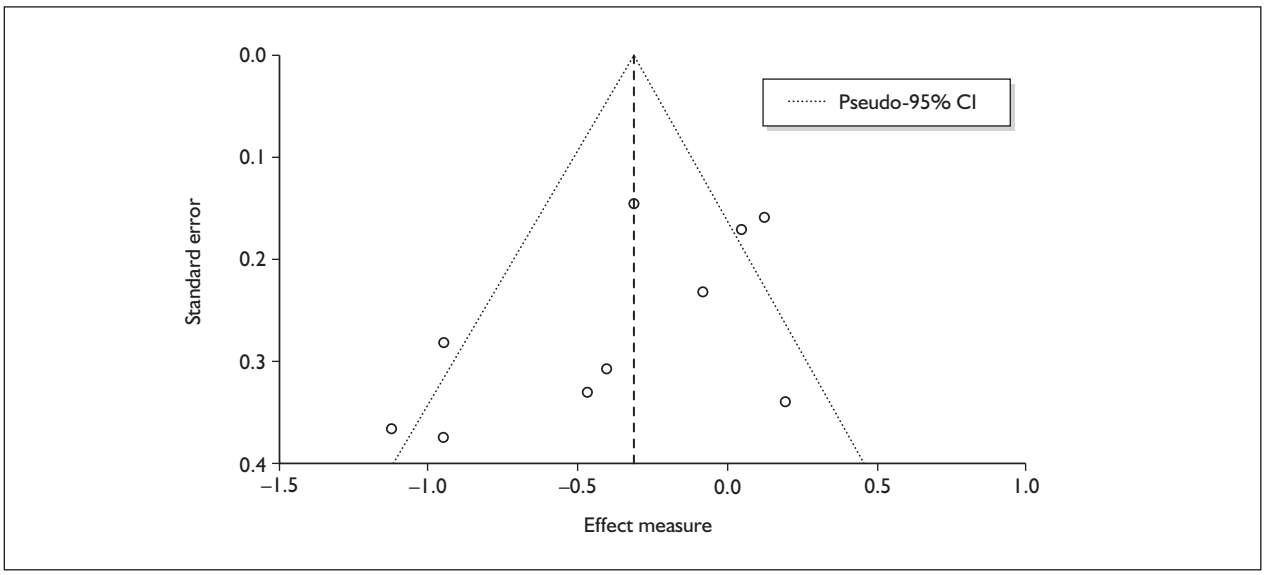

FIGURE 80 *Impulsivity – objective measures (composite measure) – ecstasy users versus drug-naïve controls: funnel plot.*

estimated (immediate and delayed memory in comparisons with polydrug controls), suggesting that reported exposure effects diminished as study-level education values rose. However, this was not a universal finding.

Characteristics of ecstasy exposure

Our metaregressions suggested that very little of the heterogeneity in reported exposure effects could be explained by aggregate measurements

TABLE 39 *Impulsivity – objective measures (composite measure) – ecstasy users versus drug-naïve controls: univariate metaregression results*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	10	0.068	(−0.106 to 0.243)	0.442			
Sex (% male)	8	−0.515	(−1.913 to 0.883)	0.470			
IQ	5	−0.003	(−0.323 to 0.318)	0.988			
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	7	0.001	(−0.001 to 0.002)	0.283			
ETLE (occasions)	< 5						
Period since last consumption (days)	< 5						
Duration of ecstasy use (days)	< 5						
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	10	0.028	(−0.125 to 0.181)	0.717	−0.350	(−0.635 to −0.064)	0.016
Sex (% male)	8	−0.248	(−4.208 to 3.712)	0.902	−0.309	(−0.583 to −0.035)	0.027
Baseline intelligence measures (SMD)	5	−0.317	(−1.799 to 1.165)	0.675	−0.261	(−0.644 to 0.122)	0.181
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to amphetamines (ETLD)	< 5						
Exposure to cocaine (ETLD)	< 5						
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	< 5						

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

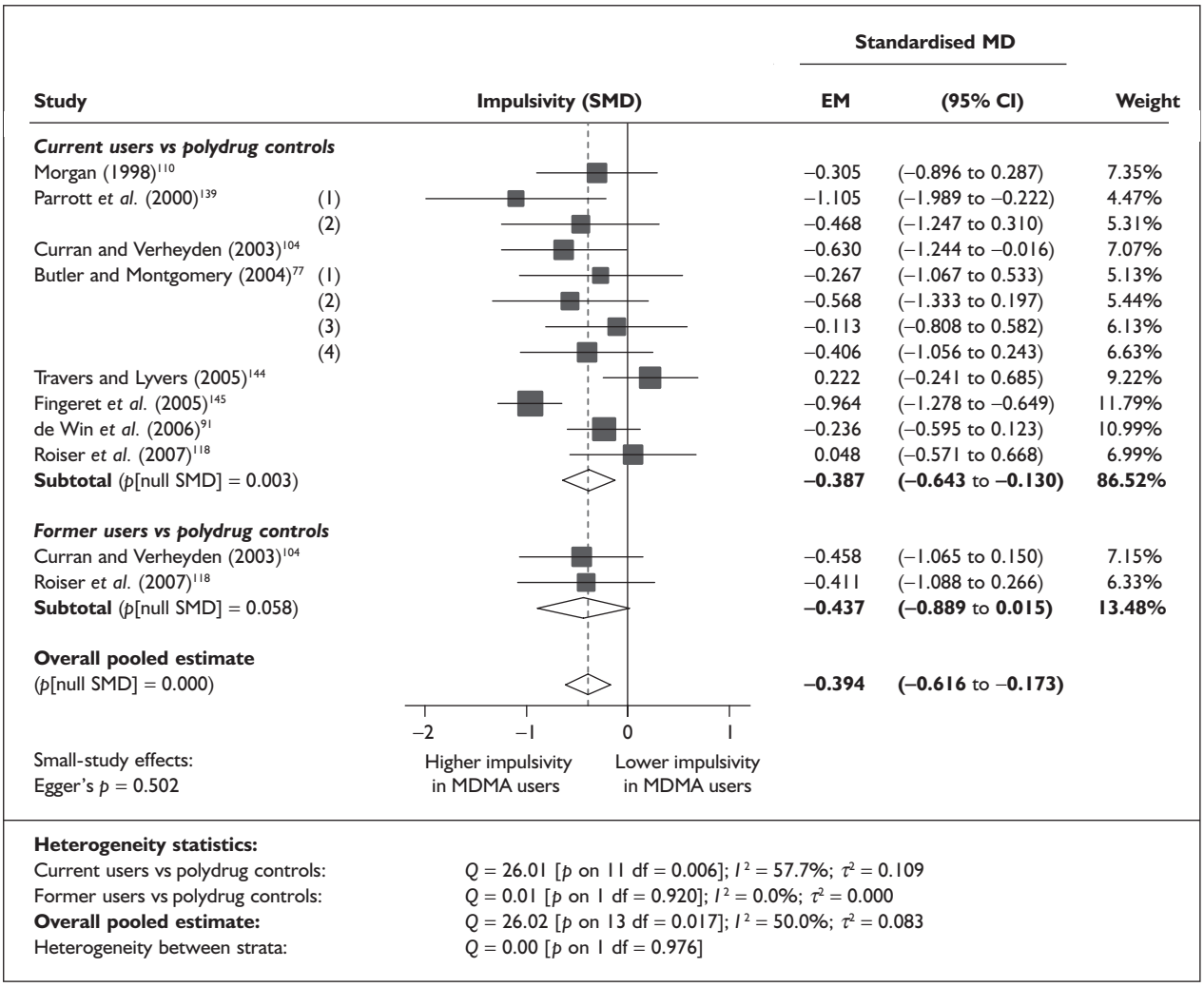

FIGURE 81 *Impulsivity – subjective measures (composite measure) – ecstasy users versus polydrug controls: random-effects meta-analysis.*

of ecstasy exposure. A significant coefficient was estimated for ETLD of ecstasy in two instances – executive function (response inhibition) and self-rated depression (both drug-naïve). However, a positive coefficient was estimated in the former case and a negative one in the latter, which suggests that any apparent differences may well have developed by chance. None of the other ecstasy exposure variables for which we collected and analysed data provided informative results. We conclude that – at aggregated study level, at least – there is no reliable evidence of a dose–response effect between exposure to ecstasy and long-term neurocognitive deficit.

Inter-arm differences

These analyses sought to examine the extent to which heterogeneity in reported effects could be explained by imbalances between the ecstasy-exposed cohort(s) and their controls.

Asymmetry in age

Although this variable appears to be an influential one, with five statistically significant metaregressions, the direction of results is inconsistent. In two cases – immediate visual memory (polydrug) and attention (focus–execute) (polydrug) – a negative coefficient suggests that worse performance is seen in ecstasy-exposed cohorts who are older than their controls. In contrast, the remaining three significant analyses – self-rated depression, self-rated anxiety and subjective measures of impulsivity (all with polydrug controls) – have positive coefficients, which indicates that the studies in which ecstasy users were younger than their controls were

TABLE 40 *Impulsivity – subjective measures (composite measure) – ecstasy users versus polydrug controls: univariate metaregression results.*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	14	−0.095	(−0.193 to 0.003)	0.056			
Sex (% male)	14	−0.193	(−1.449 to 1.062)	0.763			
IQ	6	−0.010	(−0.063 to 0.043)	0.701			
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	7	0.000	(−0.002 to 0.001)	0.420			
ETLE (occasions)	< 5						
Period since last consumption (days)	6	0.000	(−0.001 to 0.001)	0.465			
Duration of ecstasy use (days)	< 5						
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	14	0.068	(0.013–0.123)	0.015	−0.365	(−0.540 to −0.190)	0.000
Sex (% male)	14	0.361	(−1.954 to 2.676)	0.760	−0.408	(−0.657 to −0.158)	0.001
Baseline intelligence measures (SMD)	6	0.287	(−0.505 to 1.078)	0.478	−0.249	(−0.521 to 0.023)	0.073
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to cannabis (SMD)	6	0.231	(−0.731 to 1.193)	0.638	−0.335	(−0.584 to −0.087)	0.008
Exposure to amphetamines (ETLD)	< 5						
Exposure to amphetamines (SMD)	6	−0.384	(−0.889 to 0.121)	0.136	−0.157	(−0.453 to 0.138)	0.297
Exposure to cocaine (ETLD)	< 5						
Exposure to cocaine (SMD)	6	−1.125	(−2.960 to 0.711)	0.230	0.239	(−0.680 to 1.158)	0.610
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	6	0.186	(−0.508 to 0.879)	0.600	−0.326	(−0.556 to −0.096)	0.005

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

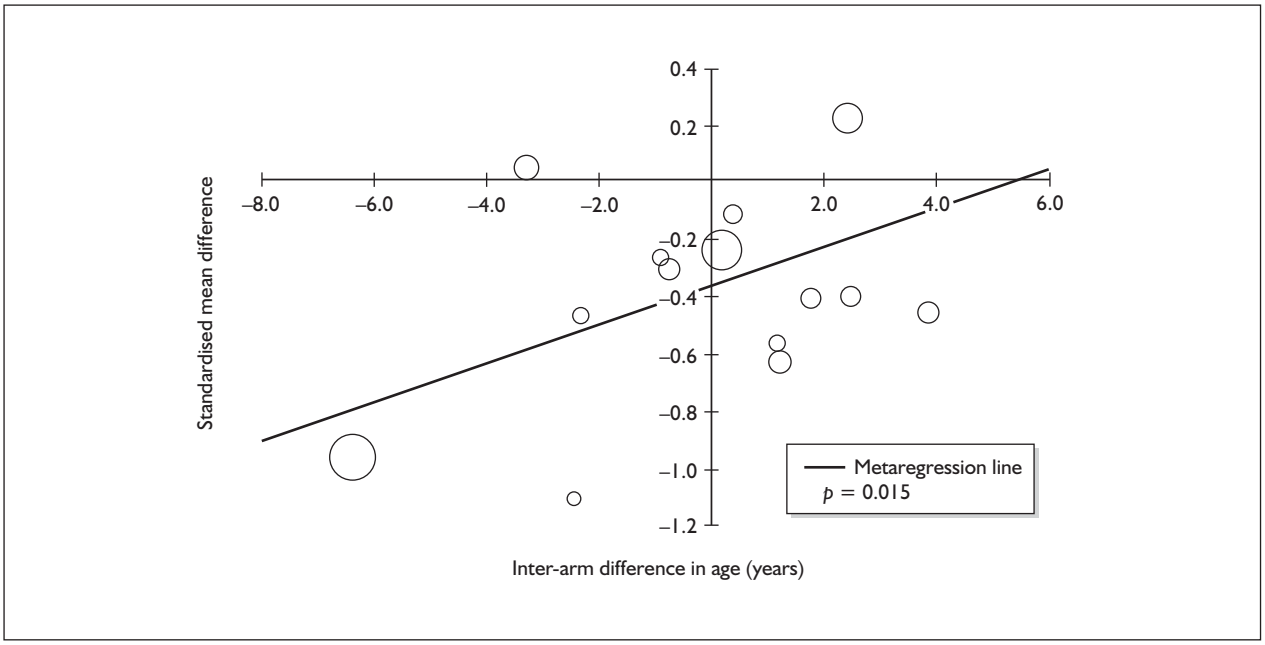

FIGURE 82 *Impulsivity – subjective measures (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against inter-arm asymmetry in age.*

Study		Impulsivity (SMD)	Standardised MD EM	(95% CI)	Weight
Current users vs drug-naïve controls					
Morgan (1998)[110]			–0.760	(–1.379 to –0.142)	11.88%
Moeller *et al.* (2002)[133]	(1)		–1.217	(–2.238 to –0.196)	5.94%
	(2)		0.341	(–0.596 to 1.278)	6.78%
Butler and Montgomery (2004)[77]	(1)		–0.812	(–1.357 to –0.267)	13.65%
	(2)		–0.678	(–1.140 to –0.215)	15.96%
Dafters (2006)[150]	(1)		–1.102	(–1.708 to –0.497)	12.17%
	(2)		–1.443	(–2.076 to –0.809)	11.55%
Roiser *et al.* (2007)[118]			–0.361	(–0.985 to 0.264)	11.74%
Subtotal (*p*[null SMD] = 0.000)			**–0.780**	**(–1.096 to –0.465)**	**89.66%**
Former users vs drug-naïve controls					
Roiser *et al.* (2007)[118]			–0.744	(–1.437 to –0.050)	10.34%
Overall pooled estimate (*p*[null SMD] = 0.000)			**–0.778**	**(–1.058 to –0.499)**	
		–2 –1 0 1 2			
Small study effects: Egger's *p* = 0.718		Higher impulsivity in MDMA users / Lower impulsivity in MDMA users			

Heterogeneity statistics:	
Current users vs polydrug controls:	Q = 13.43 [p on 7 df = 0.062]; I^2 = 47.9%; τ^2 = 0.096
Overall pooled estimate:	Q = 13.44 [p on 8 df = 0.097]; I^2 = 40.5%; τ^2 = 0.072
Heterogeneity between strata:	Q = 0.01 [p on 1 df = 0.903]

FIGURE 83 *Impulsivity – subjective measures (composite measure) – ecstasy users versus drug-naïve controls: random-effects meta-analysis.*

TABLE 41 *Impulsivity – subjective measures (composite measure) – ecstasy users versus drug-naïve controls: univariate metaregression results.*

		Effect modification			Adjusted effect estimate		
Covariate	***n***	**β-coefficient**	**(95% CI)**	***p***	**SMD**	**(95% CI)**	***p***
Average values across all participants							
Age (years)	9	0.080	(−0.132 to 0.293)	0.458			
Sex (% male)	7	−0.156	(−1.931 to 1.620)	0.864			
IQ	< 5						
Education (years)	< 5						
Characteristics of ecstasy exposure							
ETLD (tablets)	7	0.000	(−0.002 to 0.001)	0.551			
ETLE (occasions)	< 5						
Period since last consumption (days)	< 5						
Duration of ecstasy use (days)	< 5						
Frequency of ecstasy use (occasions/month)	< 5						
Inter-arm differences							
Age (years)	9	−0.078	(−0.243 to 0.087)	0.355	−0.746	(−1.039 to −0.452)	0.000
Sex (% male)	7	−1.628	(−3.926 to 0.671)	0.165	−0.792	(−1.020 to −0.563)	0.000
Baseline intelligence measures (SMD)	< 5						
Education (years)	< 5						
Exposure to cannabis (ETLD)	< 5						
Exposure to amphetamines (ETLD)	< 5						
Exposure to cocaine (ETLD)	< 5						
Exposure to alcohol (ETLD)	< 5						
Exposure to alcohol (SMD)	< 5						

ETLD, estimated total lifetime dose; ETLE, estimated total lifetime exposure; SMD, standardised mean difference.

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TABLE 42 *Syntheses of Level II evidence: summary of findings*

Outcome	Result	Inter-study heterogeneity	Interstratum heterogeneity	SS bias	Significant effect-modifiers
Individual outcome measures – polydrug controls					
RAVLT verbal recall (immediate)	Ecstasy users sig. < controls by 4.0 items	High	No	No	+ Inter-arm asymmetry in age – Inter-arm asymmetry in sex (% male) – Inter-arm asymmetry in exposure to cocaine
RAVLT verbal recall (delayed)	Ecstasy users sig. < controls by 1.2 items	Moderate	No	No	– Inter-arm asymmetry in intelligence
RBMT prose recall (immediate)	Ecstasy users sig. < controls by 0.66 items	Low	No	No	+ Inter-arm asymmetry in intelligence + Inter-arm asymmetry in exposure to alcohol
RBMT prose recall (delayed)	Ecstasy users sig.< controls by 0.77 items	Low	Former?< current	No	+ Inter-arm asymmetry in intelligence + Inter-arm asymmetry in exposure to amphetamines + Inter-arm asymmetry in exposure to alcohol
Digit span (forwards)	Ecstasy users sig. < controls by 0.42	None	No	No	None
Digit span (backwards)	Ecstasy users sig. < controls by 0.63	None	NA	No	None
IQ (National Adult Reading Test)	Ecstasy users sig. < controls by 0.32 points	None	Former sig. < current	No	+ Inter-arm asymmetry in exposure to alcohol
Individual outcome measures – drug-naïve controls					
IQ (National Adult Reading Test)	Ecstasy users sig. < controls by 0.47 points	None	No	No	None
Composite outcome measures – polydrug controls					
Verbal memory – immediate	Ecstasy users sig. < controls by 0.33 SD	High	No	No	+ Education + Inter-arm asymmetry in intelligence
Verbal memory – delayed	Ecstasy users sig. < controls by 0.38 SD	Low	No	No	+ Education
Visual memory – immediate	Ecstasy users sig. < controls by 0.15 SD	Moderate	No	No	+ Age – Sex (% male) – Inter-arm asymmetry in age + Inter-arm asymmetry in intelligence – Inter-arm asymmetry in exposure to amphetamines
Visual memory – delayed	Ecstasy users sig. < controls by 0.18 SD	None	No	No	None

continued

TABLE 42 *Syntheses of Level II evidence: summary of findings (continued)*

Outcome	Result	Inter-study heterogeneity	Interstratum heterogeneity	SS bias	Significant effect-modifiers
Working memory	Ecstasy users sig.< controls by 0.39 SD	High	Former sig. < current	No	– Sex (% male) + Inter-arm asymmetry in education + Inter-arm asymmetry in exposure to alcohol
Attention – focus–execute	Ecstasy users sig. < controls by 0.23 SD	Moderate	No	No	– Inter-arm asymmetry in age
Attention – sustain	No significant difference	High	No	Maybe	–Inter-arm asymmetry in exposure to amphetamines
Executive function – planning	Ecstasy users sig. < controls by 0.32 SD	Low	No	No	+ IQ –Period since last consumption of ecstasy
Executive function – response inhibition	No significant difference	High	No	No	+ Inter-arm asymmetry in intelligence
Executive function – shifting	No significant difference	High	No	No	None
Perceptual organisation	No significant difference	High	No	No	+ Inter-arm asymmetry in intelligence
Depression – self-rated	Ecstasy users sig. < controls by 0.27 SD	Moderate	No	No	+ Inter-arm asymmetry in age
Memory – self-rated	Ecstasy users sig. < controls by 0.51 SD	Moderate	NA	No	+ Sex (% male)
Anxiety – self-rated	Ecstasy users sig. < controls by 0.26 SD	Moderate	No	No	+ Inter-arm asymmetry in age
Impulsivity – objective measures	No significant difference	Moderate	No	No	+ Inter-arm asymmetry in sex (% male) + Inter-arm asymmetry in exposure to alcohol
Impulsivity – subjective measures	Ecstasy users sig. < controls by 0.39 SD	Moderate	No	No	+ Inter-arm asymmetry in age
Composite outcome measures – drug-naïve controls					
Verbal memory – immediate	Ecstasy users sig. < controls by 0.84 SD	Moderate	No	Yes	None
Verbal memory – delayed	Ecstasy users sig. < controls by 1.04 SD	High	No	No	None
Visual memory – immediate	No significant difference	High	No	No	None
Visual memory – delayed	No significant difference	High	No	Maybe	None

Outcome	Result	Inter-study heterogeneity	Interstratum heterogeneity	SS bias	Significant effect-modifiers
Working memory	Ecstasy users sig. < controls by 0.50 SD	Moderate	No	No	None
Attention – focus–execute	Ecstasy users sig. < controls by 0.27 SD	Moderate	No	No	None
Attention – sustain	–				
Executive function – planning	–				
Executive function – response inhibition	No significant difference	Moderate	No	Maybe	+ ETLD of ecstasy
Executive function – shifting	–				
Perceptual organisation	–				
Depression – self-rated	Ecstasy users sig. < controls by 0.57 SD	High	Former sig. < current	Yes	– Sex (% male) – ETLD of ecstasy + Duration of ecstasy use
Memory – self-rated	–				
Anxiety – self-rated	Ecstasy users sig. < controls by 0.34 SD	None	No	No	None
Impulsivity – objective measures	No significant difference	Moderate	No	Maybe	None
Impulsivity – subjective measures	Ecstasy users sig. < controls by 0.78 SD	Moderate	No	No	None

ETLD, estimated total lifetime dose; NA, not applicable; RAVLT, Rey Auditory Verbal Learning Test; RBMT, Rivermead Behavioural Memory Test; sig., significantly; SS, small study.

those in which the greatest deficits were seen. As explained in the description of each analysis, there are good statistical reasons to be sceptical about these findings because they are very heavily influenced by a single datapoint. Aside from this, the fact that all three of these meta-outcomes are based on self-reported measures may be significant.

Another speculative explanation is that this variable could, in fact, be expected to act in different directions, with increasing age representing a disadvantage in measures of cognitive function, whereas the opposite applies for measures of mood.

Asymmetry in gender

This is another variable which produced inconsistent results in our metaregressions. Three significant coefficients were estimated – two negative (immediate RAVLT verbal recall and working memory) and one positive (objective measures of impulsivity) – all in comparisons with polydrug controls. The equivocal nature of these analyses, together with a similar lack of consistency in non-significant metaregressions, suggests that this variable does not have any detectable, uniform effect on reported exposure effects.

Asymmetry in baseline intelligence

In 30 separate analyses, sufficient data were available to perform metaregression analyses with asymmetry in baseline intelligence (standardised difference across various measures) as the explanatory variable. Of these analyses, 21 (70%) estimated a positive coefficient and, in six of these cases, a significant p-value (< 0.05) was generated. In contrast, a negative coefficient was estimated in nine instances, of which only one was significant by conventional standards. These results suggest that baseline imbalance in this area could have an adverse influence on the ability of a study to detect and quantify inter-population differences that could be ascribed to the exposure of interest.

Asymmetry in exposure to other drugs (absolute differences in ETLD)

There were very few instances in which sufficient studies reported ETLD of substances of interest in standard units in a way that would permit metaregression analyses. As a result, we were unable to draw any conclusions about the influence of these variables.

Asymmetry in exposure to other drugs (standardised mean differences)

Cannabis No significant coefficients were estimated in metaregressions in which inter-arm asymmetry in exposure to cannabis was the covariate of interest.

Amphetamines No clear pattern appeared in analyses in which the explanatory variable was inter-arm asymmetry in exposure to amphetamines other than ecstasy. In 11 of 18 cases (61%), a negative coefficient was estimated (suggesting that greater exposure effects were estimated in those studies in which the ecstasy-using arms also had greater exposure to amphetamines than their respective controls). In one instance (delayed RAVLT verbal recall), the association was statistically significant. On the other hand, there were seven metaregressions (39%) in which the opposite relationship was suggested.

Cocaine In 13 of the 18 (72%) metaregressions for which there were sufficient covariate data to analyse the potential influence of inter-arm asymmetry in exposure to cocaine, a negative coefficient was estimated, implying that greater exposure effects were estimated in those studies in which the ecstasy-using arms also had greater exposure to cocaine than their respective controls. However, in only one instance (immediate RAVLT verbal recall) was the association statistically significant.

Alcohol In 25 separate analyses, sufficient data were available to perform univariate metaregression analyses with a standardised difference in exposure to alcohol as the explanatory variable. Of these, 19 (76%) estimated a positive coefficient and, in five of these cases, a significant p-value (< 0.05) was generated. In contrast, a negative coefficient was estimated in only six instances, none of them significant by conventional standards. These results are relatively clear, but somewhat counterintuitive, because they suggest that effects were least in studies in which ecstasy users had greater exposure to alcohol than their controls. Nevertheless, these findings may be explicable. Early experimental research suggests that there is a complex pharmacological interaction between MDMA and alcohol, which may include some degree of attenuation of the hyperthermic effect of MDMA,[151] so it is possible that alcohol consumption is, to some degree, neuroprotective to ecstasy users. Alternatively, it is possible that there are differences between ecstasy users who drink alcohol and those who tend not to. One Australian study has found that ecstasy users who do not drink alcohol tend to be more disadvantaged, with greater levels of unemployment, less education, higher rates of drug-user treatment and prison history, as well as being more likely to be drug injectors and to be positive for hepatitis C virus,

in comparison with those who use ecstasy and alcohol together.[152] Whether or not these findings can be generalised to a UK context, they can be interpreted as indicative of radically distinct populations of ecstasy–alcohol and ecstasy-only consumers. A difference such as this – with low alcohol consumption characteristic of high-risk ecstasy users, and heavier drinking associated with a more casual approach to ecstasy – could easily explain the results seen in our analyses.

Other Level II outcome measures

We found a number of reported outcomes in the Level II evidence-base which could not be combined into pools that were amenable to full-scale quantitative synthesis. This evidence is described in the following section.

Psychopathology

A small number of included studies reported measures of long-term psychiatric harm using the SCL-90. This instrument measures self-reported symptom severity on a number of psychological subscales for 90 items using a Likert scale. There are nine primary symptom dimensions (Somatisation, Obsessive–Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation and Psychoticism) and three global indices (the Global Severity Index, The Positive Symptom Distress Index and the Positive Symptom Total). A revised edition also exists (SCL-90-R) which replaces some items on the Anxiety and Obsessive–Compulsive dimensions that were considered psychometrically flawed.

We were able to provide pooled estimates for the global severity index, domains of obsessive–compulsion, somatisation, sensitivity, psychoticism and hostility. For these pooled analyses we have used scores generated from both revised and unrevised checklists and, because scores have been reported differently in different studies, we have used standardised mean differences.

Ecstasy users versus polydrug controls

For most analyses, including the global severity index, pooled data shows no difference between ecstasy users and polydrug using controls. Pooled data for one domain, Obsessive–Compulsive, suggests this is greater in ecstasy users (see *Table 43*). Only one of the studies pooled used the revised SCL-90. Tests for heterogeneity were not significant.

Ecstasy users versus drug-naïve controls

Data from fewer studies were available for comparisons of ecstasy users and drug-naïve comparators, with only two studies reporting on each of the outcomes (one study each using the original and revised scales). For the global severity index, pooled analysis of psychoticism and obsessive–compulsive domains shows higher scores, meaning worse outcome, in ecstasy users (*Table 44*). No significant difference was seen between exposure groups in the measure of sensitivity.

Aggression/anger

We found 14 studies that provided data assessing measures of aggression/anger/hostility. Seven studies assessed subacute effects with measures recorded between 0 and 15 days after an exposure to ecstasy.[62,125,153–158] These were excluded from analysis because the data were not judged to represent either an acute health harm or a long-term, clinically observable health harm. Data recorded after a minimum abstinence period of 21 days were available from the remaining seven studies;[61,82,104,125,147,148,158,159] this time period was judged sufficiently long after exposure that any effects noticed might represent a long-term effect.

Two studies of subjects with a minimum abstinence period of 21 days provided data derived from objective measures; however, they were considered unsuitable to be pooled for further analysis because one experimental design used an interpretative paradigm[158] while the other used a behavioural measure.[159] The study using a behavioural paradigm found aggressive-responding behaviour more frequent among a predominantly ecstasy-using group compared to non-drug users, whereas the interpretive paradigm study found an angry cognitive bias among three groups of substance misusers including current and ex-ecstasy users, but this study lacked a non-drug-using control group.

The remaining studies provided data from subjective measurement tools. One was considered to use control groups (ex-users and polydrug-using controls) that were too dissimilar from the other studies to permit pooling (non-drug-using controls verified by urine screens). Subjective measures were available from five studies (all originating from the same research group)[63,82,147,158,159] which were similar in key aspects of design relevant to this outcome domain. They all assessed the same measure of aggression (BDHI direct subscale) at 3–4 weeks after discontinuing ecstasy and compared the results with those obtained from a control group

of non-drug-using hospital workers and high school students. Two of the papers[63,158] appeared to present data from the same or substantially the same cohort as part of a longitudinal study, so we had data from four studies that were potentially suitable to be pooled for further analysis. Throughout this work we have considered that five or more datapoints would be required for meaningful meta-analysis to be carried out and we therefore decided not to present the results as a table with subsequent analyses. Nevertheless, we subjected these data to some statistical analysis and found a weighted mean difference in BDHI direct hostility score of 16.58 (95% CI 15.08–18.08; $p < 0.001$) with no evidence of heterogeneity in the data ($I^2 = 0\%$). These data from four studies with little heterogeneity suggest that ecstasy users have significantly higher levels of subjectively-rated aggression than non-drug-using controls. This finding is limited by all the comparisons being made between ecstasy users who were seeking treatment or advice regarding their drug use and non-drug-using hospital workers and high school students. We note that this research group produced results that were markedly divergent from those reported in other centres for self-rated depression [see Depression (self-rated) – MDMA users versus drug-naïve controls, above]. The wider generalisability of these findings, therefore, is not clear.

Motor function

We found three studies reporting data for the outcome domain of motor function. These studies did not provide sufficient datapoints considered suitable for meta-analysis but brief summaries of findings are presented here. Two outcome measures were used to assess motor function – finger tap and pegboard – which were assessed in dominant and non-dominant hands in one study,[47] the non-dominant hand only in one study,[160] and left and right without defining dominance in the third study.[94] Unsurprising findings were that motor function speed and fine dexterity were greater in dominant hands. Finger tap speed was found to be faster in the dominant hand only in drug-naïve controls compared to current ecstasy users in the first study. This contrasts with the second study, which found no differences in non-dominant hands between ex-users, current users and drug-naïve controls. However, this study probably lacked statistical power because this was one measure contributing to a composite 'cognitive battery' assessment. Finger tap scores decreased numerically in the order ex-ecstasy users, drug-naïve controls, and finally current ecstasy users. Pegboard test speed and fine control (number of drops) using either hand did not differ significantly between groups in the second study. The third study found that pegboard speed using the right hand (controlled by the left hemisphere of the brain as reported) was significantly faster in ecstasy users than in polydrug controls.

Given the small number of studies, the unsuitability of the data for pooling and the contrasting results, it is not possible to draw even tentative conclusions on the effects of ecstasy exposure on measures of motor control.

Sleep disturbance

We found 11 papers reporting outcome measures assessing various aspects of sleep. Four of these emanated from the same research group, reporting five studies, and we could not be sure that these were reporting mutually exclusive cohorts. As a result, we decided not to consider these for pooling with others for meta-analysis. The paper including the largest number of participants[120] found no significant difference between ecstasy users and controls (around a quarter of whom used cannabis) on either the Epworth Sleepiness Scale or the average amount of sleep per night. This finding was in accordance with the results reported by the same group in three out of four of their other papers.[138,149,161] Five other papers were found reporting self-reported measures of sleep. In three of these,[132,139,162] no significant difference was found between ecstasy users and controls (polydrug-using and drug-naïve). In two papers[140,163] ecstasy users reported poorer sleep than did polydrug controls.

Two papers reported the results from polysomnographic sleep studies. One of these investigated the effect of pharmacologically induced inhibition of monoamine synthesis and the direct clinical relevance of the differences in sleep architecture observed are not clear.[117] The other study found differences in sleep architecture between ecstasy users and controls with less total sleep time amongst ecstasy users, primarily because of less time in REM sleep.[164]

These studies provided insufficient data that were suitable for meta-analysis. An effect on sleep is suggested from both objective sleep measures in polysomnographic studies and self-reported sleep quality. It is not clear if this results in daytime sleepiness or other clinical sequelae.

Dental damage/oral health

We found two papers assessing aspects of oral health. These provided insufficient data for

TABLE 43 *Results from pooled analyses of psychopathological measures for ecstasy users compared to polydrug users.*

SCL-90 measure	SMD	(95% CI)	*p*(null SMD)	*p* (heterogeneity)	Studies included in analysis
GSI	0.187	(−0.039 to 0.413)	0.106	0.41	Thomasius *et al*. 2005;[92] Morgan *et al*. 2002;[99] Dughiero *et al*. 2001[136]
Somatisation	0.194	(−0.048 to 0.255)	0.181	0.78	Thomasius *et al*. 2006;[58] von Geusau *et al*. 2004;[128] Parrott *et al*. 2000;[135] Parrott *et al*. 2001[137]
Sensitivity	0.132	(−0.061 to 0.325)	0.181	0.21	Thomasius *et al*. 2005;[92] von Geusau *et al*. 2004;[128] Parrott *et al*. 2000;[135] Parrott *et al*. 2001[137]
Hostility	0.079	(−0.076 to 0.234)	0.318	0.47	von Geusau *et al*. 2004;[128] Parrott *et al*. 2000;[135] Parrott *et al*. 2001[137]
Psychoticism	0.233	(−0.012 to 0.478)	0.063	0.04	Thomasius *et al*. 2006;[58] Parrott *et al*. 2000;[135] Parrott *et al*. 2001[137]
Obsessive–compulsive	0.264	(0.092–0.435)	0.003	0.29	Thomasius *et al*. 2005;[92] Parrott *et al*. 2000;[135] Parrott *et al*. 2001[137]

GSI, Global Severity Index.

TABLE 44 *Results from pooled analyses of psychopathological measures for ecstasy users compared to drug-naïve controls.*

SCL-90 measure	SMD	(95% CI)	*p* (null SMD)	*p* (heterogeneity)	Studies included in analysis
GSI	0.908	(0.538–1.281)	< 0.001	0.90	Thomasius *et al*. 2005;[92] Morgan *et al*. 2002[99]
Sensitivity	0.164	(−0.080 to 0.407)	0.19	0.05	Thomasius *et al*. 2005;[92] Parrott *et al*. 2001[137]
Psychoticism	0.367	(0.204–0.531)	< 0.001	0.85	Thomasius *et al*. 2006;[58] Parrott *et al*. 2001[137]
Obsessive–compulsive	0.670	(0.420–0.921)	< 0.001	0.05	Thomasius *et al*. 2005;[92] Parrott *et al*. 2001[137]

GSI, Global Severity Index.

meta-analysis. One study[165] reports significantly increased wear of molar teeth in a group of 30 ecstasy users compared to 28 polydrug controls. There was no difference in wear of front teeth. The authors attribute these findings to reports of teeth clenching by the ecstasy users. The second study[166] compared responses to an oral sensation questionnaire amongst 119 polydrug users. Those who used ecstasy reported grinding of teeth, the desire to chew something and temporomandibular joint tenderness significantly more frequently than non-ecstasy drug users.

Loneliness

A single researcher has published two studies comparing the experience of ecstasy-exposed individuals with controls measured according to a self-created 'Loneliness Questionnaire'.[167,168] Results suggest that ecstasy users may experience more loneliness (including 'Unfulfilling Intimate Relationships' and 'Social Marginality') than non-users. The relevance and robustness of these findings is unclear.

Uncontrolled (Level III) evidence (acute harms)

The Level II evidence we identified covered most chronic harms of interest, so our review of Level III evidence is dominated by the acute harms of ecstasy.

There are a number of fatal and non-fatal acute harms that may result from the use of ecstasy. These harms may be direct (for example as the result of toxicity) or indirect (relating to accidents while under the influence of a drug, for example.)

We are primarily concerned with direct harms. Information about acute harms may be gleaned from a number of sources – registry data records, and case series or case reports in the medical literature, none of which is without problems. We have focused on datasets that are drawn from coherent sampling frames, for example registry data relating to death certificates and coroners' reports for fatalities related to ecstasy (see Deaths related to ecstasy use) and audits of consecutive cases presenting at emergency rooms for non-fatal harms (see Acute harms reported in retrospective case series from hospital emergency departments). While these registries give an indication of the scale of fatalities associated with ecstasy use, clinical causes of death are not well described, so data available from other case series in the literature are also surveyed (see Acute harms of ecstasy reported in case series and case reports).

Given the large number of papers identified and their study design, we did not assess the quality of individual study reports as originally planned. Case reports and case series of acute harms suffer from a number of well-recognised problems. They are unlikely to be representative of the population under study, and there is no comparison group from which to draw inferences. Further, publication bias is a problem, as case reports on any particular condition are more likely when these are first reported, or are reported in novel circumstances. Later, as effects become recognised by clinicians and therefore become well described and researched, they are less likely to be reported in the literature as worthy of note. This means that the information found in such reports cannot be used to indicate the prevalence of any particular adverse effect, or cause of death, but is restricted to providing a catalogue of events as reported in the literature. Even in this there were limitations. We found acute outcomes difficult to catalogue accurately because there are overlapping outcomes in many cases that are the result of an initiating event such as hyperthermia. We found that there was poor and inconsistent reporting and indexing of outcomes, with symptomatic and clinical sequelae not always clear and missing data about the nature of drug-taking history and co-used substances common. Our reporting of these data sources remains necessarily brief and impressionistic.

Audit data based on all those presenting at emergency rooms having taken ecstasy are generally of too short a duration to provide enough cases to enable an accurate picture of the frequency with which different adverse effects are experienced. Only one such study comes from the UK, and presents a series of 48 cases, none of which were fatal. However, these studies suggest that, even among those experiencing adverse effects serious enough to present at Accident and Emergency (A&E), fatal instances are rare.

It is difficult to assess what might be a fatal dose of ecstasy. Fatalities have occurred from doses that are the same as a normally active dose which others tolerate. It is difficult to know how much MDMA has been ingested because self-reports may be unreliable, and the composition of any taken substance may vary. Most studies use (femoral) blood following a postmortem to assess the levels of MDMA concentration; however, levels of MDMA in the blood are known to rise following death because MDMA is released from body tissues.[169] Conversely, in a few studies, the levels of MDMA in blood were from the time of admission to A&E, leading to an underestimation of levels in a comparison.

The case series of non-fatal acute harms were heterogeneous, selective in their reporting of outcomes and unlikely to be generalisable to the whole population of recreational ecstasy users. We have made no attempt to report or calculate frequencies of individual health harms and have confined ourselves to simply listing the main effects documented.

Deaths related to ecstasy use

Deaths associated with ecstasy use are recorded in national and regional database studies (retrospective case series), as well as in case series or in individual case reports in the literature. In this section we report registry data which give an indication of the incidence of death in England and Wales, information about whether ecstasy was the sole drug involved or whether other drugs were co-used and some demographic information. There are two main national sources for information on number of drug-related deaths (DRDs) for England and Wales from which those involving ecstasy can be identified:[23]

- General Mortality Register (GMR), collated by the Office of National Statistics
- Special Mortality Register collated by the National Programme on Substance Abuse Deaths (np-SAD) St George's Hospital, London.

This section will describe the number of deaths related to ecstasy use (alone or in combination with

other substances) from available registry data. Data will be presented to allow an overview of trends and comparison with deaths related to other illicit drugs.

General Mortality Register data

The GMR is a database maintained by the Office for National Statistics based on information from death certificates and coroner's reports.[170,171] For registry data, accuracy relies on the information recorded on the death certificate by the coroner. About 10% of deaths on the GMR relate to a general description only (such as 'drug overdose'), limiting its use in the data, while in others it is not always possible to determine which is the primary drug involved where more than one is identified.[170]

Included on the GMR are deaths as a result of illegal drugs, prescription drugs (such as antidepressants) and over-the-counter medications (such as paracetamol). Deaths from accidents and suicides, as well as poisoning as the result of abuse and drug dependence, are reported. As no detailed information is recorded on toxicology,[23] a death may be categorised as ecstasy related without MDMA (or its metabolites) being reported on postmortem forms.[172] The GMR therefore combines deaths related to substances known to be MDMA and those related to reported ingestion of a substance believed to be ecstasy. In the case of multiple substances (co-drug use) being present, the GMR records all those mentioned on the death certificate. This was the case in 31% of DRDs recorded in 2006.

Between 1993 and 2006, the average annual number of DRDs in England and Wales according to the GMR was 2727, about two-thirds of which were in men. Trends are shown in *Figure 84*. In men, 30% of deaths were accidental, while this was the case in 24% of deaths in women. (Other drug-related deaths are recorded as intentional, undetermined, mental and behavioural disorders due to drug use or due to assault.) There were 1102 records annually of illicit (and related prescription) drugs over the same time period. These include heroin, morphine, methadone, cocaine, amphetamines (including MDMA/ecstasy), cannabis and GHB. Because the GMR records all co-use drugs mentioned, this figure will be higher than the number of people dying from these drugs.

Table 45 shows the average annual number of deaths where illicit drugs were recorded by the GMR either as the sole drug or as one of the drugs involved. The category 'all amphetamines' includes those related to ecstasy/MDMA. For 1993 to 2006, an annual average of 681 deaths related to a single illicit drug is recorded, of which heroin and morphine account for two-thirds, and methadone a further 22%. Similar numbers are attributable solely to cocaine or amphetamines (4.6%, 4.9%) and half of all amphetamine deaths are attributed to ecstasy ($n = 17$; 2.5% of the annual average of sole illicit DRDs).

Figure 85 shows trends in deaths related to illicit drug use (and methadone) for 1993–2006. Cocaine deaths appear to be increasing year on year, while amphetamine deaths generally, and ecstasy specifically, appear to have increased to 2001 but stabilised thereafter.

The much higher fatal impact of heroin, morphine and methadone masks the detail of stimulant trends. We therefore excluded these substances from *Figure 86*. In addition, we separated out amphetamine deaths that were related to MDMA/ecstasy and other amphetamine deaths. Given that the absolute number of deaths due to sole drugs is small, there may be natural variations in deaths which appear as large fluctuations when presented graphically. To ameliorate the impact of these fluctuations, 3-year rolling averages were calculated. *Figure 86* shows 3-year rolling averages in relation to deaths which are attributable to a sole drug only. Amphetamines data in *Figure 86* have been calculated by the reviewers based on all amphetamine deaths less those recorded as MDMA/ecstasy. These are not cleanly distinct categories so some misclassification is likely. There was a relatively rapid rise in ecstasy deaths between 1999–2001, where it overtook deaths from other amphetamines which were falling at the same time. Thereafter, the number of ecstasy deaths plateau while other amphetamine deaths rise, so that these two appear to be converging. Deaths from cocaine continue to rise steeply.

National Programme on Substance Abuse Deaths (np-SAD) data

The National Programme on Substance Abuse Deaths (np-SAD) maintains the Special Mortality Register (SMR) at St George's Hospital, London. This records voluntary submissions of coroners' reports for England and Wales, including post mortem and toxicological reports.[173] Records implicating ecstasy will rely on evidence and reports from the scene as well as toxicology reports. As this database relies on coroners voluntarily returning their reports, it is unlikely to be a complete record.[173,174] Comprehensiveness is also limited by differences in the way coroners, or their

pathologists, incorporate findings.[174] Despite this, it also has advantages over the GMR data in that it relates to greater detail recorded on the coroners' reports, including toxicology, which may not have been available at the time of the death certificates being filed. While returns from coroners' reports were low initially (13% in 1997), they rose to over 90% by 1999. In addition, the np-SAD database records greater contextual and social demographic information than the GMR.[23]

For the np-SAD, MDMA, MDA, MDEA, PMA and methylthioamphetamine (MTA) are classed as ecstasy. It should be noted that this definition is broader than that adopted elsewhere in this review. To emphasise this distinction, the term *ecstasy-related substances* (ERS) has been used in the following discussion. The amphetamine category includes amphetamine sulphate and methamphetamine.

In 2006, there were 1366 drug-related deaths recorded by the np-SAD database, of which 69 (5.0%) mentioned ERS as present. In the same year, 78 (5.7%) mentioned amphetamines.

Figure 87 shows deaths recorded by GMR and np-SAD over the same time period, 1997–2006. These are deaths in which ERS were mentioned (GMR) or implicated (np-SAD), meaning that other substances may be co-implicated or causal in the fatality. After an initial lower count (when fewer coroners returned their reports), the np-SAD has consistently shown more deaths in which ERS were involved. For 1997 to 2005, over which period data are available from both databases, the np-SAD recorded 426 deaths in which ERS were implicated, compared to 343 in the GMR. Both sources show similar trends.

Between 1997 and 2006, 495 deaths were recorded by np-SAD in which ERS were implicated. This compares to 689 in which other amphetamines were implicated, 1917 in which cocaine was implicated and 6643 in which heroin/morphine was implicated. *Table 46* shows whether these drugs were considered to be the sole drug implicated, to have contributed to the death together with another substance or, although present, were not considered to have contributed to the death according to the np-SAD. In 14% of cases ERS were not believed to have contributed to the death although it was present, while they were the sole drug implicated in 20% of cases. ERS were considered to have contributed, together with another substance, in 67% of cases. Where other drugs were also implicated, these results are broken down in *Table 46*. In 62% of cases relating to ERS, three or more drugs were identified at post mortem and all the drugs implicated are recorded, meaning that the percentages presented in the table cannot be summed.

Data about amphetamines are also shown in *Table 46*. Amphetamine was thought to be the sole drug or was not implicated in the death in proportions similar to those in ERS-related deaths. Again, in more than two-thirds of cases, co-use of drugs was implicated. Amphetamine fatalities are less likely than ecstasy fatalities to have co-used cocaine or alcohol.

Table 47 shows the characteristics of people with ERS-related deaths from 1997 to 2006. Similar data are presented for other amphetamines, cocaine and heroin/morphine. This updated analysis of data kept by np-SAD was undertaken for this review. The cohorts are similar, although fewer ERS users are known drug addicts and more are employed. A picture of the usual ERS-related fatality emerges as an employed white male in his twenties, who is a registered drug addict and who has co-used a number of other substances.

Nearly half of the ERS-related deaths (49%) occurred on Saturday or Sunday night, whereas this was the case for about a third (36%) of amphetamine fatalities. This could indicate different patterns of use.

Identified studies reporting database and registry data

Our searches identified 16 studies which were based on national and regional registries and databases (retrospective case series). Seven studies are not related to the UK and were not considered in detail (two from the USA,[175,176] and one each from Belgium,[177] Spain,[178] Greece,[179] Slovenia[180] and the Netherlands.[181])

Nine UK studies were reviewed in detail and these are summarised in *Table 48*. Three of these relate to data from the np-SAD over different time periods up to 2002,[182–184] and one to GMR for the UK 1994–2003.[23] A further two studies audited death certificates in Scotland in the 1990s (using Registrar General data)[39] or in Scotland 1995–7 (using Registrar General data) and England in 1995–6 (using death certificates).[29] Three studies audited regional data, one in Sheffield 1997–9,[185] one in London 2003[186] and one in Strathclyde 1995–8.[187]

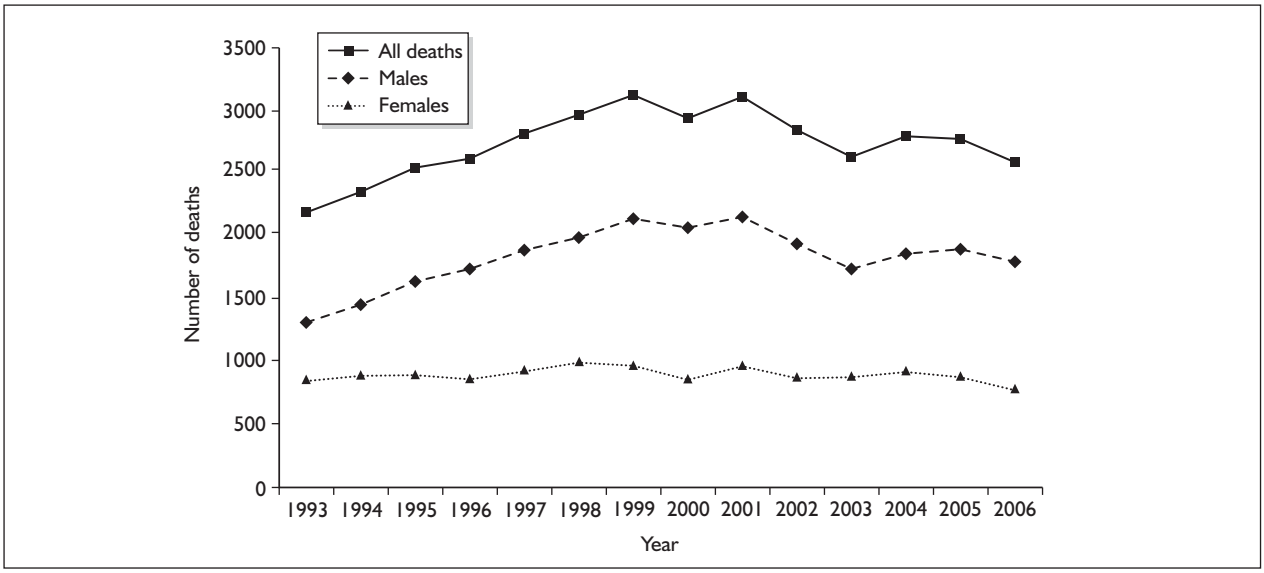

FIGURE 84 *General Mortality Register all drug-related deaths 1993–2006.*

Given the lack of solid information about the number of people taking ecstasy, the amount they take (in terms of the number of tablets taken, the composition of those tablets and their purity), it is very difficult to make sensible estimates about the risk to any individual taking any particular pill. In the literature, estimates of the death rates from ecstasy are few. Gore estimates that the ecstasy-related death rate in those aged 15–24 years in 1995–6 in England was between 0.2 and 5.3 per 10,000 (all users), i.e. between 1 in 2000 to 1 in 50,000.[29] She compares this with a death rate of 1.0 per 10,000 from road traffic accidents. More specifically, the death rate for first-time users was estimated to be approximately two to four times (1.29/0.38 and 0.70/0.38) that of sporadic users – defined as having used ecstasy in the past year for more than 1 year – depending on the method of calculation.[29] (Gore argues that use in the previous month is assumed to reflect regular user, and use in the previous year, but not in the previous month, reflects sporadic use. So some sporadic users will be first-time users.[29]) However, this calculation does not take into consideration the number of exposures (or dose and purity) within the previous year (excluding the previous month). Three death rates were estimated for Slovenia,[180] the Netherlands[181] and USA,[175] where population size was provided. Rates were 0.15, 0.73 and 0.88 per million population per year respectively. However, these estimates did not take into consideration the number of users, dose or purity, while the Dutch study also included deaths in the presence of amphetamine and other phenethylamines.

Cause of death data from registries

It is not possible to identify causes of death in the np-SAD registry data. The data are presented for all ERS-related deaths, whether the drug was present or causal, or a single or co-used substance.

TABLE 45 *Annual number of deaths recording illicit drugs (General Mortality Register 1993–2006).*

	Mean annual deaths (%) – sole drug	Mean annual deaths – co-use drug mentions
Heroin and morphine	447 (65.6)	622
Methadone	150 (22.0)	276
Cocaine	31 (4.6)	86
All amphetamines	34 (4.9)	70
MDMA/ecstasy	17 (2.5)	33[a]
Cannabis	1 (0.2)	14
Gamma-hydroxybutyrate (GHB)	1 (0.2)	2

a Alcohol was also recorded in an annual average of six co-drug-use deaths involving ecstasy.
Source: Office for National Statistics.

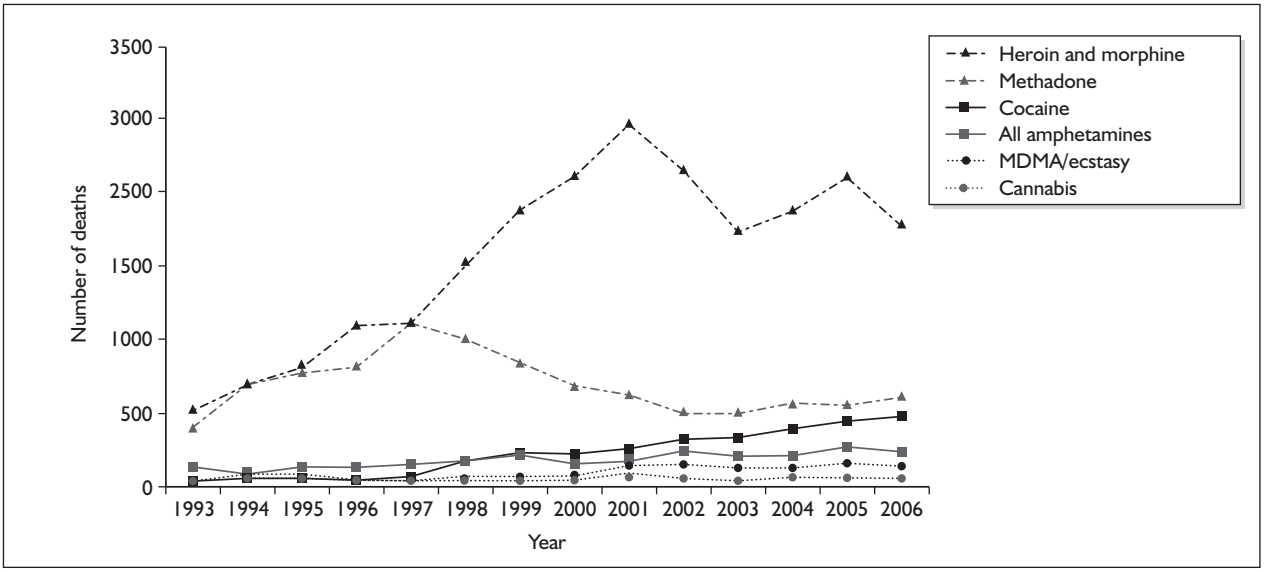

FIGURE 85 *General Mortality Register drug-related deaths 1993–2006 (including co-drug mentions).*

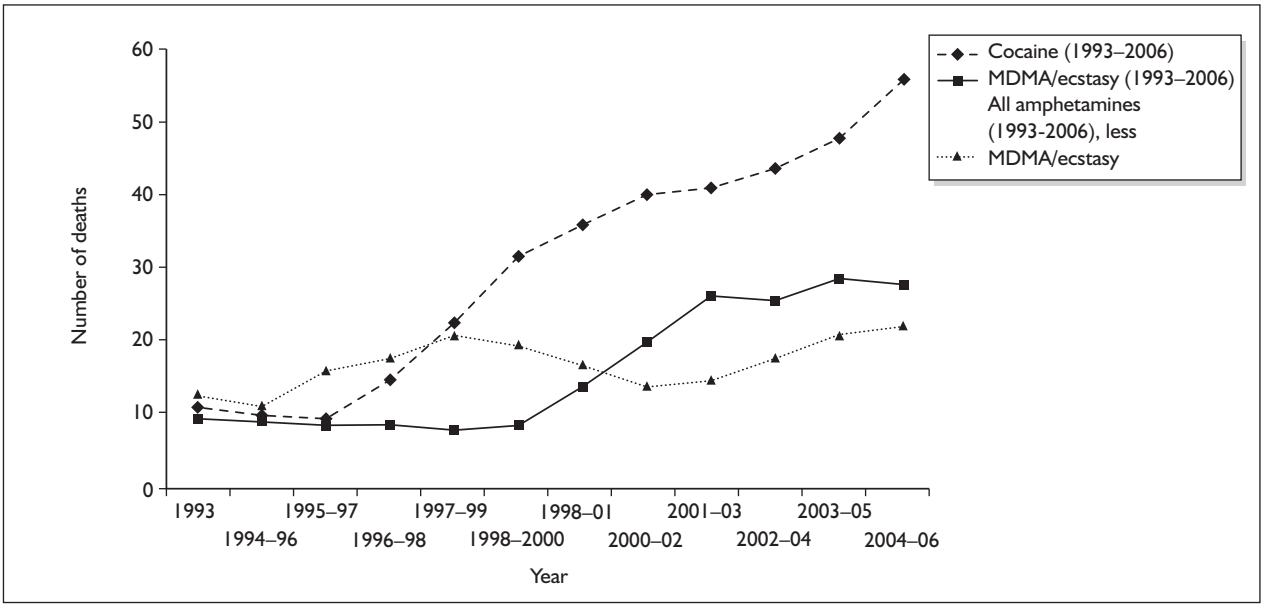

FIGURE 86 *General Mortality Register drug related deaths 1993–2006 (sole drug mentioned): three-year rolling averages for cocaine, MDMA/ecstasy and amphetamines (excluding MDMA/ecstasy).*

In addition, the majority of cases are recorded as accidental poisonings – which do not give an indication of the clinical picture. For example, 69% of ecstasy deaths are categorised as ICD code X42 (accidental poisoning by and exposure to narcotics and psychodysleptics) or X41 (accidental poisoning by and exposure to antiepileptic, sedative–hypnotic, antiparkinsonism and psychotropic drugs). Suicide was recorded as the cause of death in 7% of cases and traumatic injury (such as that due to a traffic accident or to drowning) accounted for another 7%.

As the information about cause of death was limited, we turned to case series and case reports in the literature. The following sections report first on retrospective case series which are based on consecutive data about people presenting with ecstasy-related harms at hospital emergency rooms, both fatal and non-fatal, and second on other case series and case reports in the literature.

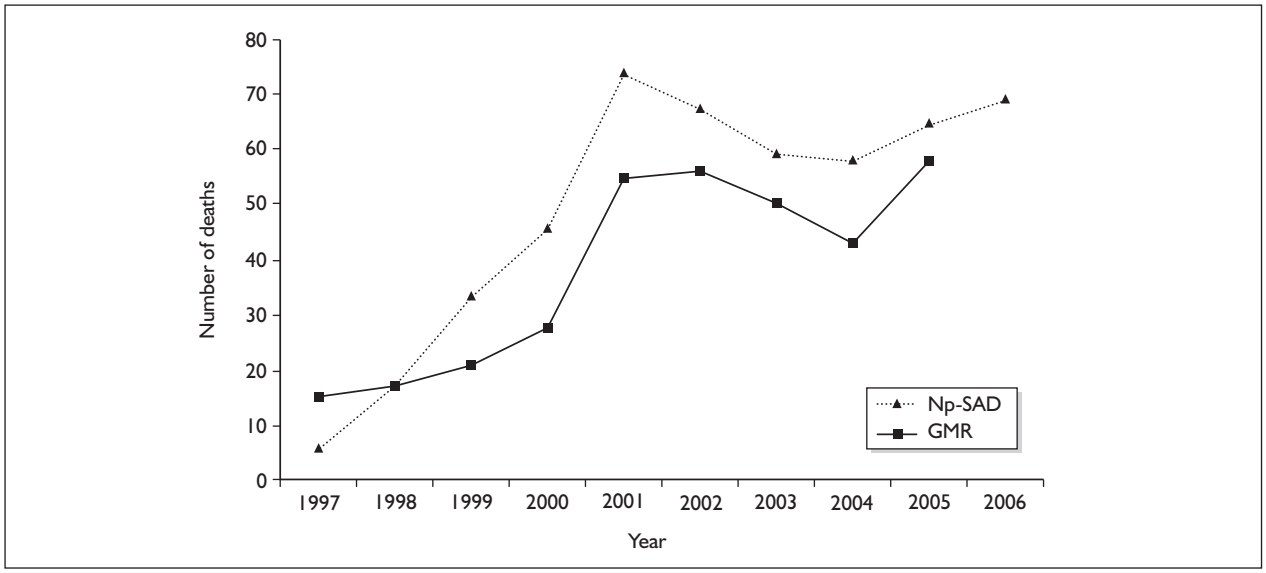

FIGURE 87 *Comparison of deaths in which ecstasy was present for General Mortality Register (GMR) and the National Programme on Substance Abuse Deaths (np-SAD) 1997–2006.*

Acute harms reported in retrospective case series from hospital emergency departments

We identified three retrospective case series that were based on audits of hospital emergency department databases of admissions due to ecstasy use. These are based on self-reported use, clinical signs and toxicologically confirmed cases (*Table 49*). These papers record a death rate between 0 and 2%, suggesting that most acute adverse effects resolve either spontaneously or with treatment, even among those serious enough to present at hospital.[188–192]

Only one such audit was identified from the UK. This report, by Williams *et al.*,[192] uses all cases treated over a 15-month period at one London A&E department where case notes recorded MDMA involvement ($n = 48$). (This involved triage notes on arrival relating to ecstasy, substance misuse/ingestion, intoxication, overdose or a number of other key clinical symptoms.) Cases were aged 16–30 years (mean 23 years) and 67% were men. One-third had taken solely ecstasy, with the remainder co-using alcohol and/or other illicit drugs. Differences in symptoms and clinical signs at presentation between those solely using ecstasy and those co-using additional substances are reproduced in *Table 50*. Numbers are too small to permit meaningful statistical comparisons; however, some possible differences between those who have only taken ecstasy and those who have co-used other drugs are collapse/loss of consciousness (6% versus 31%), hyperventilation (18% versus 13%) and hyperthermia (32% versus 13%). Other emergency room studies have also noted that coma was only present in those who co-used other substances (specifically GHB and opiates[188]).

All three emergency room audits showed very high proportions of presentation at the weekend (67–75%). In the UK, 40% of cases reported previous ecstasy use whereas the Swiss study reported 87% had a previous history of drug use.[188]

Acute harms of ecstasy reported in case series and case reports

We identified a total of 57 case series or case study papers reporting on fatalities related to the use of ecstasy. Six of these did not report causes of death or preceding symptoms, leaving 51 papers that reported a number of adverse effects of ecstasy that were associated with fatalities:

- hyperthermia
- cardiovascular dysfunction
- disseminated intravascular coagulopathy (DIC) and other haematological disorders
- seizures
- rhabdomyolysis (and other muscular dysfunction)
- kidney failure
- brain haemorrhage/other organic brain damage
- hyponatraemia
- liver failure
- suicide/attempted suicide
- neurological dysfunction

TABLE 46 *Drugs implicated in ecstasy, amphetamine, cocaine and heroin/morphine deaths recorded in the np-SAD 1997–2006*

	Ecstasy-related substances (*n* = 495)		**Other amphetamines (*n* = 689)**		**Cocaine (*n* = 1917)**		**Heroin/morphine (*n* = 6643)**	
Drug implicated in deaths	***n* (%)**	**Annual mean = 49.5**	***n* (%)**	**Annual mean = 68.9**	***n* (%)**	**Annual mean = 191.7**	***n* (%)**	**Ann. mean = 664.3**
Sole drug	97 (20)	9.7	103 (15)	10.3	218 (11)	21.8	1866 (28)	186.6
Other drug implicated (drug of interest present)	67 (14)	6.7	113 (16)	11.3	396 (21)	39.6	195 (3)	19.5
Drug of interest and another drug implicated	331 (67)	33.1	473 (69)	47.3	1303 (68)	13.03	4582 (69)	458.2
Other drugs co-implicated in death	(*n* = 331)		(*n* = 473)		(*n* = 1303)		(*n* = 4582)	
Alcohol	145 (44)		137 (20)		558 (29)		2389 (36)	
Heroin/morphine	110 (33)		260 (38)		1002 (52)			
Other opiates	44 (13)		94 (14)		299 (16)		1193 (18)	
Methadone	41 (12)		110 (16)		320 (17)		790 (12)	
Cannabis	60 (18)		101 (15)		188 (10)		432 (6)	
Cocaine	95 (29)		76 (11)				935 (14)	
Ecstasy-related substances			85 (12)		96 (5)		113 (2)	
Amphetamines	78 (24)				69 (4)		237 (4)	
Gamma-hydroxybutyrate (GHB)	9 (3)		5 (1)		8 (<1)		2 (<1)	
Hypnotics/sedatives	74 (22)		116 (24)		409 (21)		1603 (24)	
Antidepressants	31 (9)		63 (9)		124 (7)		435 (7)	
Antiepileptics	3 (1)		6 (1)		16 (1)		46 (1)	
Antipsychotics	5 (2)		15 (2)		20 (1)		81 (1)	
Antiparkinsonism drugs	1 (<1)		6 (1)		6 (<1)		23 (<1)	

TABLE 47 *Summary of characteristics of MDMA/ecstasy and other amphetamine deaths (less MDMA/ecstasy) in England and Wales 1997–2006*

Characteristic		Ecstasy-related substances (*n* = 495)	Amphetamines (*n* = 689)	Cocaine (*n* = 1917)	Heroin (*n* = 6643)
Sex	Male (%)	83	80	84	86
Age (years)	Mean	29	32	33	34
	Mode	24	27	31	29
	Range	14–71	15–62	16–83	1–95
Employment status	Employed (%)	52	32	38	26
	Unemployed (%)	34	55	52	64
	Student/pupil (%)	6	3	2	1
	Other (%)	9	5	8	9
Ethnicity	White (%)	84	84	79	84
	Not known (%)	11	14	13	13
	Other (%)	5	2	8	3
Known drug addicts (%)		76[a]	86[a]	87[a]	89[a]
Place of death	Private residence (%)	50	59	63	66
	Hospital (%)	40	32	28	25
	Other (%)	10	9	9	9
No. of drugs found at postmortem	0 (%)	7	4	<1	4
	1 (%)	11	11	9	17
	2 (%)	20	22	22	28
	3 (%)	24	26	29	26
	4+ (%)	38	36	39	25

Source: National Programme on Substance Abuse Deaths. Some characteristics may not sum to 100 as a result of rounding.
a Drug addict status unknown in a further 11%, 8%, 8% and 5%, respectively.

- respiratory dysfunction
- psychotic episodes
- hypoglycaemia
- immunological dysfunction (aplastic anaemia, etc.)
- movement disorder (dystonia)
- diabetic complications
- vascular abnormalities.

For an evidence map showing the number of and references for case series which reported these outcomes, please see Appendix 8. Note that this list includes symptoms that were reported in the same case (for example, hyperthermia-related DIC, rhabdomyolysis and organ failure).

We also identified 236 case series and case reports which reported on non-fatal acute harms of ecstasy. In descending order of the frequency with which they are reported, these harms are (note again that one case may be subject to multiple negative outcomes, particularly where a major syndrome is involved):

- hyperthermia
- seizures
- acute central nervous system abnormalities
- liver failure
- hyponatraemia
- rhabdomyolysis (and other muscular dysfunction)
- pneumomediastinum, pneumothorax and similar
- acute psychotic episodes
- DIC and other haematological disorders
- brain haemorrhage/other organic brain damage
- kidney failure
- acute movement disorders
- acute cardiac events
- sensorineural dysfunction (auditory, optical)
- urogenital dysfunction (including urinary retention)

TABLE 48 *Summary of studies reporting ecstasy-related deaths from registries and databases*

Study	Location	Year of deaths	Total no. of DRDs	No. of ecstasy deaths	Deaths ecstasy sole drug (% all ecstasy deaths)	Age (mean years)	Male (%)	Data source
UK national								
Schifano *et al.* 2003[178]	England and Wales	August 1996–April 2002	NA	202, 36 annual mean 2.9/month	34 (17%), 6 annual average, 0.5/month	<30 years 73%	80	np-SAD database
Schifano *et al.* 2003[179]	England and Wales	July 1997–June 2000	NA	81, 27 annual mean	6 (7%), 2 annual average, 0.2/month	27.2	81	np-SAD database
Webb *et al.* 2003[180]	England and Wales	2000	1037	26 implicated 30, on post mortem	NR	37.7 (all DRD)	80 (all DRD)	np-SAD database
Gore 1999[29]	England and Scotland	1995–6 (England)	NA	18, 9 annual mean	NR	Only those aged 15–24 included	NR	Death certificates (England)
		1995–7 (Scotland)		11, 3.7 annual mean				Audit of Registrar General (Scotland)
Forsyth 2001[39]	Scotland	1990–9	2255	28, 4.0 annual mean[a]	7 (33%)	NR	68	Audit of Registrar General (Scotland)
Schifano *et al.* 2006[23]	UK	1994–2003	NA	394	165 (42%)	NR	NR	GMR for England, Scotland, N. Ireland
UK regional								
Oliver *et al.* 2002[181]	Sheffield	1997–9	82	2 (contributory cause of death)	NR	29.4 (all DRD)	92 (all DRD)	Audit of Sheffield's coroner's reports
Hickman *et al.* 2007[182]	London	2003	148	16 (combined total for all amphetamines)	1 (6%)	35.8	80	Audit of 7/8 London coroners
Seymour *et al.* 2001[183]	Strathclyde	1995–8	443	12, 3.0 annual mean	NR	28 (all DRD)	81 (all DRD)	Audit of toxicological database, University of Glasgow

Ecstasy-related deaths are defined differently in Scotland compared with England and Wales.[37] In Scotland, an ecstasy DRD is defined by ecstasy being found in the body (other illegal drugs may also have been found), whereas in England recording of Ecstasy death on the death certificate may not have been confirmed toxicologically.
a There were no ecstasy deaths recorded in 1990–2, so this annual mean is for 1993–9. For 1990–9 the annual mean is 2.8 deaths.

TABLE 49 *Emergency room audits of ecstasy-related presentations*

Author	Country	Sample	Common presentations (all)	Other substances	Outcomes
Liechti *et al*. 2005[184]	Zurich, Switzerland	All 52 self-reported cases of ecstasy intoxication at emergency department 2001–3; aged 16–44 years (mean 26); 79% men	Collapse/loss of consciousness 36%, palpitations 19%, dizziness/weakness 15%, anxiety 14% Five severe presentations – symptoms included cardiac arrest, hyperthermia, rhabdomyolysis, DIC, renal insufficiency, liver failure, seizures	90% co-used other substances (commonly alcohol, cocaine, GHB, amphetamines, cannabis); 72% had co-used illicit drugs	Most managed in A&E. 11% to ICU; one fatality.
Williams *et al*. 1998[186]	London, UK	All cases treated at one A&E department where case notes recorded MDMA involvement; $n = 48$; aged 16–30 years (mean 23); 67% men	Feeling unwell/dizzy/strange 31%, collapse/loss of consciousness 23%, palpitations 21%, dizziness/weakness 23%, anxiety 23% Six severe presentations – symptoms included delirium, seizure, coma	67% had co-used other substances; 50% had co-used other illicit substances (commonly other amphetamines, cocaine)	Most managed in A&E; 15% admitted (one ecstasy use alone); no fatalities.
Sanuro *et al*. 2004[a]	Barcelona, Spain	All cases of self-reported or toxicologically confirmed amphetamine ingestion 2000–2 no. of ecstasy cases 135; aged 16–47 years (mean 24); 68% men	Anxiety, agitation, cognitive disturbances, loss of consciousness, fits. Three severe presentations	67% co-used other drugs or alcohol	One admitted to ICU; two fatalities

DIC, disseminated intravascular coagulopathy; ER, emergency room; ICU, intensive care unit.
a Note that this paper is written in Spanish, so details used here have been taken from the abstract and those reproduced in Liechti *et al*. 2005.[198]

TABLE 50 *Clinical features associated with A&E presentations for sole ecstasy users and ecstasy users with co-use of alcohol/other illicit drugs*

Complaint	Ecstasy alone ($n = 16$) No. (%)	Ecstasy and other drugs/alcohol ($n = 32$) No. (%)	Clinical findings	Ecstasy alone ($n = 16$) No. (%)	Ecstasy and other drugs/alcohol ($n = 32$) No. (%)
Strange/unwell/dizzy/weak	7 (44)	8 (25)	High pulse rate (> 100 bpm)	13 (81)	19 (59)
Collapse/loss of consciousness	1 (6)	10 (31)	Dilated pupils	6 (38)	12 (38)
Nausea/vomiting	5 (31)	6 (19)	Hyperventilation (> 20 breaths/minute	6 (38)	4 (13)
Panic/anxiety/restlessness	5 (31)	4 (13)	Anxiety/agitation/disturbed behaviour	4 (25)	6 (19)
Palpitations	6 (38)	6 (19)	High temperature (> 37.1°C)	5 (32)	4 (13)
Feeling feverish/shivering	4 (25)	3 (9)	High blood pressure (> 160/95 mmHg)	0	6 (19)
Sweating	3 (19)	3 (9)	Drowsiness	0	3 (9)
Shaking	2 (13)	4 (13)	Dehydration	1 (6)	1 (3)
Headache	2 (13)	4 (13)	Shivering	1 (6)	1 (3)
Chest pain	1 (6)	3 (9)	Seizure	0	2 96)
Difficulty breathing	2 (13)	2 (6)	Nystagmus	2 (13)	0
Abdominal pain	3 (19)	1 (3)	Hallucination	0	1 (3)
Muscle aches/pains	1 (6)	3 (9)	Sweating	1 (6)	0
Visual disturbance	2 (13)	1 (3)	Unconscious	0	1 (3)
Thirst	2 (13)	1 (3)	Tremulousness	0	1 (3)
Seizure	0	3 (9)	No abnormality found	0	3 (9)
Twitching	0	1 (3)	Other	3 (19)	6 (19)
Other	4 (25)	1(3)	Missing data	0	1 (3)

Reproduced from Williams H, Dratcu L, Taylor R, Roberts M, Oyefeso A. Saturday night fever: ecstasy related problems in a London accident and emergency department. *J Accident Emerg Med* 1998;**15:**322–6,[190] with permission from BMJ Publishing Group.
More than one sign/symptom may be recorded for each case. Numbers are too small to permit meaningful statistical comparison.

- dental damage/other oral injury
- dermatological disorders
- stroke
- ocular injury
- vascular abnormalities
- movement disorders (including parkinsonism)
- attention deficit disorder
- dependency
- diabetic complications
- hypoglycaemia
- attempted suicide
- asthma exacerbation/other respiratory distress
- hyperkalaemia
- hypothermia
- immunological dysfunction (aplastic anaemia, etc.).

For an evidence map showing the number of and references for case series which reported these outcomes, please see Appendix 8.

This chapter now outlines what is known about the major syndromes associated with ecstasy use – hyperthermia and hyponatraemia – and their sequelae in fatal and non-fatal cases. It then moves on to consider other major acute harms in cardiovascular dysfunction, neurological dysfunction, respiratory dysfunction, liver failure, kidney failure, suicide and other psychiatric effects.

Major syndromes

The most critical acute complications of ecstasy consumption are, in a majority of cases, related to two well-recognised syndromes, each involving serious derangement of homeostasis leading to multiple organ failure: hyperthermia and hyponatraemia.

Hyperthermia

Derangements of thermoregulation are a widely reported feature of MDMA toxicity,[191] repeatedly demonstrated in experimental settings,[192,193] and commonly observed in humans. The mechanism by which body temperature is increased is still debated; activation of the sympathetic nervous system and the hypothalamic–pituitary–thyroid axis might be involved.[194] The susceptibility of a small minority of ecstasy users to dangerous degrees of hyperthermia is idiosyncratic, and probably multifactorial, involving factors such as co-ingestants, ambient room temperature, physical activity and fluid intake.[194,195] It is also possible that underlying medical or genetic conditions affect either thermoregulation or fatal susceptibility to hyperthermia.[194–196]

The physiological manifestations of MDMA-induced hyperthermia are similar to those seen in severe heatstroke.[197] The most noteworthy effects are:

- **Rhabdomyolysis** Rapid breakdown of skeletal muscle, leading to tissue necrosis, with intracellular constituents (most notably myoglobin) leaking into the circulation.
- **Disseminated intravascular coagulopathy (DIC)** Serious derangement of blood coagulation, which results in both excessive clotting (leading to localised ischaemia and tissue necrosis) and widespread bleeding.
- **Acute renal failure (ARF)** Kidney dysfunction can develop as a consequence of either of the above. ARF secondary to rhabdomyolysis is caused by myoglobinuria (meaning the renal filtration system becomes obstructed by a build-up of the myoglobin that has leaked into the circulation). ARF secondary to DIC occurs when microvascular thrombosis causes renal ischaemia.
- **Acute liver failure** Hepatic necrosis is a primary effect of hyperthermia,[198,199] and it is possible that such injury may be exacerbated in the presence of amphetamines, which may impair the liver's natural thermotolerance.[200] DIC and ARF may both contribute to and be exacerbated by liver failure.

These changes are often accompanied by a variety of symptoms, the most commonly reported being palpitations, anxiety, agitation and confusion (and to a lesser extent tremors, myoclonus and seizures).[188–190,201] In some cases, these result in rapid presentation (i.e. within hours) to A&E departments.[188–190] Collapse or loss of consciousness is reported in a significant proportion of admissions (8.8–36.5%).[188–190]

We found hyperthermia to be the most commonly reported adverse effect of ecstasy use for both fatal and non-fatal cases. There were 41 fatalities relating to hyperthermia reported in the literature between 1991 and 2007.[36,37,169,181,188,194–196,201–216] However, these numbers should be treated with caution given the nature of case series evidence, and because there were also a number of other cases where the cause of death or the precursors of fatal organ failure were not clear. In addition to the fatal cases, we identified 43 case series or case reports giving details of non-fatal hyperthermia and related conditions.

The association between ecstasy use and prolonged dancing may be important for hyperthermia because core temperature also rises during intensive exercise.[217] Furthermore, ambient temperature is believed to influence MDMA-impaired thermoregulation, and ecstasy is commonly consumed in environments that are likely to be crowded, hot and poorly ventilated. In rats, MDMA induces an exaggerated degree of hyperthermia when ambient temperature is high but, conversely, hypothermia is engendered in cold conditions.[218–220] However, recent research suggests that the latter effect may not be reproduced in humans.[11] In the literature, slightly more than half of reported fatal cases occurred after the subject had been at a club, nightclub or rave (22/41).

Peak body temperature varied from 38.5 to 46.1°C. The average of the 31 cases that reported a temperature was 41.5°C, with only five fatal cases reporting a temperature below 40°C.[176,204,211,213] Note, however, that such very high temperatures have also proved non-fatal with medical intervention.[221]

Two studies based on retrospective A&E databases suggest that hyperthermia is more common among those solely ingesting ecstasy, compared to those co-using other drugs.[195,211] Substances such as GHB and opiates when ingested with MDMA are reported to reduce body temperature, sometimes resulting in hypothermia.[198–200] However, co-use of PMA may compound the problem.[211] In 13 of the cases, co-use of other drugs was noted; however, this was not reported in all of the studies. Other drugs noted (some cases had multiple drug use) were alcohol ($n = 4$), PMA ($n = 2$), MDA ($n = 6$, although this is a metabolite of MDMA and may not have been ingested separately), LSD ($n = 1$) and cannabis ($n = 1$).

Four deaths were known to be in first-time or second-time users of MDMA,[36,202,205] although the type of user was not reported in all studies, and deaths for first-time users may also be more 'newsworthy' in terms of publishing case reports. In 14 deaths, the number of MDMA tablets was reported, with an average of 2.9 (range 1–10), and in 26 deaths, the concentration of MDMA in the blood was reported, with an average of 1.1 mg/l (0.02–7.15 mg/l) (although see the note in the earlier section, Cause of death data from registries, about measuring MDMA concentrations).

Hyponatraemia

When the hyperthermogenic properties of MDMA are combined with intense physical activity (such as dancing) substantial amounts of sodium can be lost in perspiration. This problem is significantly compounded by the tendency of ecstasy users to drink large quantities of water, for which there are several reasons: 'dry mouth' is a common subjective response to MDMA;[3] users exposed to publicity regarding the dangers of MDMA-induced hyperthermia may overcompensate by consuming excessive amounts of water;[222] and MDMA may induce compulsive repetitive behaviour such as obsessive drinking of water.[223]

The combination of sodium loss and excessive water consumption may also be exacerbated by excess fluid retention (as the result of inappropriate secretion of antidiuretic hormones and/or impairment of renal function[224]). The resultant hyponatraemic state sees a fall in serum osmolar pressure, allowing intracellular displacement of water, the most hazardous result of which is cerebral oedema.[225]

The early clinical manifestations of hyponatraemic cerebral oedema are headache and nausea, progressing to confusion and seizures,[224–227] although such altered states may be difficult to distinguish from the 'normal' intoxicative effects of MDMA or alcohol.[222] If not corrected, the syndrome will commonly progress to tentorial herniation, respiratory arrest, cerebral hypoxia and death.

Retrospective studies of A&E admissions suggest that hyponatraemia and associated brain oedema is a severe but rare complication of MDMA toxicity.[188] We identified 10 deaths resulting from hyponatraemia reported in the eight case reports and case series.[206,224–233] Most were reported between 1997 and 2002, with one in 2006.[232] Only three were in England and Wales.[206,224] Twenty-four case series or case reports involving non-fatal hyponatraemia were also identified.[234–254]

All fatal cases were women aged between 16 and 21 years (average 18.4 years), which could support suggestions that women (and children) are more prone to hyponatraemia.[230,255] A retrospective study of enquiries to the London Centre of the National Poisons Information Service from December 1993 to March 1996 identified 17 such enquiries regarding hyponatraemia associated with ecstasy use, two of which were fatal, both in women. Seven non-fatal cases were in men.[224]

The clinical pattern reported in the literature was remarkably uniform, with initial vomiting, disturbed behaviour, followed by seizures,

drowsiness, a mute state of disorientation,[224] loss of consciousness,[206,224–230] tentorial herniation,[230] respiratory arrest,[228] pulmonary and cerebral oedema,[224,229,231,232,256] hypoxia,[224,230,232] and finally brain death.[224,228,230] Four cases were identified as hypothermic (i.e. body temperature < 35°C).[224,230,232] Levels of MDMA intoxication were relatively low (0.03–0.4 mg/l, with an average 0.13 mg/l, where reported).

Of the 10 deaths, there were seven cases in which prior dancing or party attendance was reported,[206,224,229,230,232,233] in four of which the consumption of large amounts of water and consumption of alcohol were also recorded.[224,229,232] Although not all reported on co-use of other drugs, three reported that alcohol ($n = 3$), cannabis ($n = 1$) and other amphetamines ($n = 1$) were used.

Isolated acute harms

Cardiovascular dysfunction

Tachycardia is an invariable response to MDMA consumption, and is the most frequently reported clinical symptom in series detailing acute admissions in A&E departments.[188,192] There are reports of MDMA-related myocardial infarction[157–260] and sudden cardiac death.[261] The importance of excluding concomitant use of other drugs (especially cocaine, which is well known to induce critical cardiovascular dysfunction) has been emphasised.[262]

We identified seven deaths due to cardiovascular dysfunction that appeared unrelated to the major syndromes described in the previous section.[35,178,179,201,261–265] All were in men, aged 17–39 years (mean 27 years). Where reported, levels of MDMA intoxication were 0.2–4.56 mg/l (mean 1.65 mg/l). Co-use of other drugs was reported in four cases, for alcohol ($n = 3$) and MDEA ($n = 1$).

One man had a history of Wolff–Parkinson–White syndrome[261] and another was human immunodeficiency virus-positive and his death was thought to be the result of interaction between ecstasy and ritonavir medication.[263] In one case, the victim fell down stairs and hit his head, although it is not clear if this caused, or was the result of, the cardiac arrest.[265]

Fourteen case series and case reports reporting non-fatal cardiac events were also identified.[90,258–260,266–275]

Neurological dysfunction

Seizures are a recognised manifestation of both hyponatraemia and hyperthermia as discussed earlier. Cases have also been reported of MDMA-induced seizures which apparently do not involve either of these underlying causes.[276] We identified three studies that reported seizures without hyperthermia or hyponatraemia. However, it has been emphasised that concomitant administration of other substances may be an important element in such findings, with the conclusion that, for those who have taken MDMA alone, central nervous system (CNS) dysfunction appears rare in the absence of hyponatraemia or hyperthermia.[1]

Most of the CNS problems reported in the literature were non-fatal – we identified 63 case series reporting 88 non-fatal cases and 66 fatal cases, 20 of which were the result of indirect causes such as road traffic accidents.[176,177,179,190,202,222,244,250,254,277–299] In the majority of cases ($n = 58$) other drugs had also been ingested, most commonly other amphetamines ($n = 28$) and cannabis ($n = 14$), but also opiates, cocaine, LSD, benzatropines and ketamine.

Nearly three-quarters of patients were aged under 25 years and 70% were men. Most made a full recovery (63 cases, 72%). However, in 18 cases (12% of patients with brain disorders), a more severe course of CNS disorders led to complications which may be the result of chronic cerebral/cerebellar damage: four papers reported psychological personality disorders,[290,293,300,301] two reported epilepsy,[291,292] three reported chronic movement disorders,[284,285,302] and three reported serious neurological disorders (such as vegetative state).[213,282,295]

Brain haemorrhage/haematoma related to ecstasy use has been reported in 21 cases, six of which were fatal.[176,202,230,276,277,292] Such events are commonly associated with pre-existing cerebrovascular vulnerabilities (e.g. aneurysm[278,288] or arteriovenous malformation[283,292]); however, cases have also been reported in which no such features were identified.[292,303] It has been postulated that long-term MDMA use may expose individuals to a higher risk of cerebrovascular accident, either through vasculitis[292,303,304] or as a consequence of arterial damage sustained through repeated episodes of vasoconstriction and hypertension ('surge').[288] Of the 15 patients who recovered, 12 recovered fully[278–280,283,288,292,305,306] while three experienced ongoing effects such as hemiparesis and seizures.[284,285,292]

We identified two reports in the literature of non-fatal cerebral ischaemic stroke, both of whom recovered fully.[289,307] One study reported a lesion

of the spinal cord C1–C4 causing residual mild hemiparesis.[302]

Respiratory dysfunction

Pneumomediastinum is an abnormal presence of air in the mediastinal tissues. The main symptoms include chest pain, dyspnoea and neck pain.[308] Chest pain secondary to pneumomediastinum may be reported by those presenting for medical attention following MDMA consumption.[309–321] Less frequently, pneumothorax[313,317] and pneumopericardium[316] have also been reported. Pneumomediastinum is believed not to be a direct pharmacological effect of MDMA, but rather the result of physical activity over a prolonged period accompanied by episodes of forced expiratory effort against a closed airway, such as that through screaming, whistle blowing, coughing or vomiting.[322–325] Onset of symptoms is mostly reported within 12 hours of taking ecstasy, and some symptoms, such as shortness of breath or chest pain, may appear even sooner.[316] In most cases, symptoms resolve spontaneously in few days.

We identified 29 cases of pneumomediastinum in 22 studies. In six cases pneumothorax was also present.[269,308,319–322] Most (24/25) were under 25 years old and two-thirds were men. Only five were known to be smokers and one was asthmatic, both of which are known risk factors for pneumomediastinum. In one case, symptoms were experienced after taking only half a tablet of ecstasy.[312] Most studies (23/29) do not report whether other substances were co-used.

Other types of isolated respiratory failure appear to be uncommon following MDMA consumption. One case of acute pulmonary oedema[326] and one asthma-related death[35] have been reported (although, in the latter case, the causal relationship between the exposure and the outcome is unclear). Two other instances of respiratory complication that have been cited elsewhere[1] appear to be related to consumption of MDEA.[329,330]

Liver failure

Critical hepatic dysfunction is a notable consequence of hyperthermia and extensive hepatic necrosis is an invariable postmortem finding in MDMA deaths.[206] In addition, it is well established that MDMA-induced acute liver failure can also occur without thermoregulatory dysfunction.[199,231,331–338] This type of acute hepatic failure (the term *fulminant* liver failure is also used, either synonymously or in reference to the most rapidly symptomatic cases[339]) develops over a slightly longer period than in hyperthermic liver failure, with cases becoming symptomatic a matter of days, rather than hours, after MDMA ingestion. In most reported cases, acute hepatitis appears to develop following a history of repeated MDMA use. However, cases involving very limited exposure (including, ostensibly, consumption of a single tablet) have also been described.[199,332,333,335]

Spontaneous resolution of symptoms can be expected in some cases; however, failure can also be irreversible, leading to death or requiring salvage liver transplantation.[334] It has been emphasised that, in common with other hepatotoxic substances, MDMA could be expected to cause silent liver damage in a number of cases over and above those that are clinically evident.[200]

One retrospective case series reported acute liver failure in the absence of hyperthermia. This was based on consecutive non-paracetamol-induced fulminant hepatic failure presenting at the Scottish Liver Transplant Unit (which serves the whole of Scotland) in 1992–2004.[340] Of 30 cases, six were related to ecstasy use and had not been preceded by hyperthermia, and two of these proved fatal. Of the four survivors, two had a liver transplant.[231] One other study reported on a successful liver transplant in a 25-year-old woman with liver and kidney failure.[231]

Kidney failure and other urinary tract abnormalities

It is thought that MDMA-induced kidney dysfunction can occur in the absence of hyperthermia or hyponatraemia. A similar causative mechanism to that postulated in respect of cerebral vasculitis (see above) may be implicated because renal arteritis has been demonstrated in postmortem examinations.[341] However, we did not identify any fatal cases with acute renal failure that did not also record hyperthermia. One fatal case study of chronic renal failure reported on a 30-year-old man in the UK who presented 1 week after having taken ecstasy and other amphetamines.[341] He was reportedly apyrexial although no temperature is given, was hypertensive and had pulmonary oedema. Postmortem revealed necrotising angiitis confined to the kidney.

Transient urinary retention is a relatively common characteristic of the 24 hours following MDMA consumption, with catheterisation occasionally required to resolve symptoms.[244,342–344] All four cases we identified were under 20 years (mean 18, range 17–19) and three were men.

Suicide

It is postulated that impaired serotoninergic function as a result of ecstasy use could lead to depression and suicide.[345] We identified 10 cases of suicide related to ecstasy use in the literature either as a means of overdose, or reported as having been taken in the run-up to suicide by other means.[177,210,214,345–350] Eight cases were in men, aged 17–53 years (mean 31), and two were in women, whose ages were not recorded. One woman hanged herself in jail after a 3-day session of injecting ecstasy. The other woman committed suicide having been admitted to a psychiatric ward as the result of paranoid delusions after ingesting an unknown quantity of ecstasy.[345] She is reported as having a long history of undefined 'drug abuse'.

In three cases, MDMA was deliberately taken as the means of suicide, following a personal crisis or imprisonment.[210,214,349] In two cases, MDMA was found at autopsy but no further details about its use are provided – in one of these cases, heroin and antidepressants were also found and, in the other, suicide was assumed after the man died under a train.[177] In five cases, MDMA had been consumed before expression of suicidal intention.[345–347,350] In three of these cases, ecstasy use seemed to precipitate a psychotic episode leading to suicide (although there was also some reporting of prior emotional distress or depression[345,346]), in one case within 3 hours, in another within 8 days, this latter following admission to and discharge from psychiatric hospital. One case was in the UK, in a 17-year-old boy, who was apparently a first-time user.[347]

Other psychiatric effects

We identified one retrospective case series based on audit data from a psychiatric admission ward in Cardiff. Over a 12-month period, this records that 50 out of 390 admissions were drug related, and that ecstasy was implicated in 35 cases (70% of all drug-related admissions).[351] Usual presentations included panic attacks, restlessness and psychotic behaviour. Most were initially treated with tranquillisers with behaviour change seen 48 to 72 hours later. The authors report that eight (23%) of this sample were still receiving treatment from psychiatric services 8 months after admission, including two as inpatients. None of these eight had any previous history of mental illness.[351]

We also identified 25 cases of acute psychiatric episodes in 15 case reports and case series.[296,298,301,352–362] Four cases in two series were from the UK.[358,359] Reports were published fairly evenly from 1986 to 2005 and cases were among those aged 17–52 years (mean 25.4), of whom 18 were men (72%). No prior history of psychiatric disorder was recorded in 22/25 cases. Two cases were reported after first-time use of ecstasy[353,362] and, in a further two, ecstasy was taken unintentionally for the first time following friends 'spiking' drinks.[350,354]

Commonly reported presentations were panic attacks (reported in 12/25 cases), auditory and/or visual hallucinations (11/25) and paranoid delusions or psychosis (7/25); other symptoms included delirium, aggression, obsessional behaviour, self-harm and suicide ideation. Additional physical symptoms such as palpitations, hyperthermia and seizures were also reported.

In only two cases was ecstasy the only substance taken, although this is not reported in four papers. Reported co-used substances included alcohol (3/21), cannabis (9/21), cocaine (4/21), heroin (1/21, with a further two having a prior history of heroin addiction), methadone (2/21), LSD (2/21), other amphetamines (1/21), benzodiazepine (1/21), citalopram (1/21), valium (1/21) and opioid-based painkillers (1/21) – in six cases multiple substances were co-used.

Symptoms manifested from minutes to days after ingesting ecstasy and persisted for hours, days or months with treatment. Most papers report full recovery, after 3 hours to 7 months of treatment, but five papers report symptoms remaining at 1–9 months.[301,359,360,363]

Chapter 4
Discussion

Statement of principal findings

This systematic review assesses the health harms of the recreational use of MDMA. We adopted a much broader remit than previous syntheses, encompassing and expanding on previous areas of interest. In addition, our review provides greater detail about the methods used for meta-analysis and we use innovative methods to pool data and to examine possible confounders between study arms. We also distinguish between polydrug-using and drug-naïve controls, which was not the case in all previous meta-analyses.

We include a large number of studies that have investigated a wide range of possible chronic harmful effects of ecstasy on recreational users of the drug. There is good agreement in the results of these studies, whether they emanate from previous meta-analyses or from meta-analyses undertaken for this review of either individual outcome measures or composite outcomes. Ecstasy users consistently perform worse than controls across a wide range of neurocognitive tests and psychopathological instruments. The effects are most consistent and marked for memory, particularly measures of verbal and working memory, but are also seen particularly strongly in self-rated measures of depression, memory, anxiety and impulsivity. While the commonest comparison made in studies is that of current recreational users of ecstasy with polydrug-using controls (subjects who use other legal and illegal drugs but not ecstasy), similar results are seen when current ecstasy users are compared to controls naïve to illegal drugs and when former ecstasy users are compared to either control group. Substantial caution, however, should be taken in interpreting these results, the key reasons for which are outlined below.

Key registry data about drug-related deaths is available from the np-SAD and GMR registry databases. These data are not directly comparable because of differences in data sources and recording of drug use. In the 10 years to 2006, the np-SAD recorded an average of 50 drug-related deaths in which ecstasy was mentioned as present (69 in 2006): 5% of the total for the year (see *Figure 87*). Ecstasy was the sole drug implicated in an average of 10 deaths annually over the same time period (other amphetamines implicated as the sole drug in an annual average of 10 deaths, cocaine in 22 and heroin in 187).

The GMR reports an average annual number of all drug-related deaths between 1993 and 2006 of 2727, about two-thirds of which were in men. There were, on average, 17 deaths a year in this period where ecstasy was recorded as the sole drug involved (2.5% of all deaths ascribed to a single drug) and an additional 33 per year where it was reported as co-drug use (see *Table 45*). Ecstasy deaths appear to have increased up to 2001, but to have stabilised thereafter, while cocaine deaths are increasing year on year. Heroin and morphine, as expected, account for the great majority of drug-related deaths (65.6%).

The typical victim of an ecstasy death is an employed white male in his twenties, who is a known drug addict co-using a number of other substances (see *Table 46*). Given the paucity of data about scale and patterns of use, the risk associated with taking an ecstasy tablet is very difficult to assess.

Methodological considerations

The controlled observational studies (Level II evidence) included in the report investigated the chronic harmful effects of recreational ecstasy use, largely neurocognitive effects and depressive symptomatology. All these studies, apart from one with a prospective design, are cross-sectional in nature and compare ecstasy users either with users of other legal and illegal drugs or with users who were naïve to illegal drugs.

We did not identify any Level II evidence concerning the acute harmful effects of ecstasy: all the included literature on this aspect of the review consisted of Level III evidence, either case series or case reports.

Chronic harms

Our systematic review has included many more studies of controlled observational data than previous meta-analyses: 110 compared to 28 in the largest of the previous relevant meta-analyses we have included. The range of health outcomes considered is also broader, with previous reviews focused on self-reported depression or neurocognitive damage generally, and memory specifically. In addition, we have provided more detailed critical appraisal of the included studies, which are all cross-sectional in design, except one prospectively conducted study, and have numerous significant methodological flaws, which are discussed in detail (see Chapter 3, Assessment of the quality of studies).

Inclusion/exclusion criteria

With the time constraints of this project, we had to confine our review to studies published in the English language, which may have led to the exclusion of relevant studies published in other languages. It is difficult to predict what effect this exclusion may have on our results: papers in other languages may be more likely to report negative findings which would weaken the associations we have found. We have found some evidence of publication bias in the outcomes we have assessed (especially in comparisons between ecstasy users and drug-naïve controls), suggesting that there may be other unpublished studies reporting negative findings, which would also weaken our findings.

We excluded laboratory-based studies for two main reasons: recreational use of ecstasy means that the dangers of pills taken as ecstasy need to be considered, regardless of their actual purity or dose; and the impact of ecstasy, in terms of both acute and chronic harms, is influenced by the environment in which it is taken. While these are strengths in interpreting the data, they also cause limitations in that the actual impact of MDMA, as opposed to other substances, may not be being measured. Many laboratory studies also focus on the acute pleasurable effects of taking ecstasy, which are beyond the scope of this review.

We excluded studies which assess the health harms of the recreational use of amphetamines generally if it was not possible to identify which results specifically assessed the harms of ecstasy.

Outcome measures

We identified a huge number of wide-ranging outcome measures: 915 different outcome measures were used in the included studies, many of which were ostensibly measuring the same attribute, sometimes in the same study. In addition, some papers used subscales while others used the full scale of the same instrument. Some scales have revised or amended versions, and a mixture of the original and the revised scales was used in the included studies. It is not possible to determine what the impact of pooling across these scales might be. In addition, it is unclear what we should be trying to measure. It is possible that some understanding of impact on total brain function is important, rather than the specific domains (such as memory, cognition or behaviour) on which studies tend to focus.

We identified only eight outcome measures for which a meaningful number of studies had used the same instrument and the same scales, all of which were measures of verbal memory or intelligence; all except one compared ecstasy-using groups to polydrug-using controls.

Where several different outcome measures were used to measure the same attribute, we categorised and collapsed these into similar domains to allow meta-analysis. These domains and the identification of outcomes that were appropriate to include within them were based initially on reviewers' classification and then validated by our expert advisory group. Necessarily, some of these classifications are matters of judgment and other investigators may have chosen to group outcomes differently.

Many of the outcomes used in the studies, especially those assessing personality dimensions and mood, rely on self-reports of a characteristic rather than objective measurement. This may be a particular problem in self-selected study groups, who may participate because of preconceived notions of the effect of ecstasy. In pooled analyses, self-rated measures showed the greatest impact of ecstasy use in comparison to both polydrug-using and drug-naïve controls.

To pool data from different studies using disparate scales to measure the same outcome, effect sizes were converted to a standardised mean difference. One consequence of this strategy is to complicate the interpretation of the analyses further, because it is unclear how to decipher the clinical meaning of a difference of any magnitude.

There was substantial heterogeneity in study design, which may have implications for the meta-analyses, although we used random-effects models for all analyses to account for the expected heterogeneity.

There were a number of outcome domains for which data were not sufficient to pool for meta-analysis. Narrative synthesis only was possible for some of these outcomes while other individual outcomes have not been considered in the review.

Confounding

As all the included studies were observational, it is unlikely that potential confounders (such as age, exposure to other drugs, educational status, etc.) are equally distributed in the study arms. We used metaregression techniques to explore the impact of such potential confounders, in univariate analyses only. Multivariate analyses would be desirable in future syntheses, but availability of covariate data was too patchy to enable such an approach in this case. In addition to standard metaregression techniques, we examined the effect of imbalances in arm characteristics on the exposure effect estimated in studies (a technique that, as far as we are aware, has not been used previously). The benefit of this approach is that it should enable us to identify the extent to which observed differences in outcomes may be confounded by factors other than exposure to ecstasy.

Despite these analyses, it has not been possible to explore or control for all possible confounders, because of the variable and incomplete documentation of possible confounders in the literature. In addition, confounders are measured at population levels rather than individual levels, and attempts to extrapolate to individuals may lead to ecological fallacy.

The small size of many of the studies together with the suggestion of publication bias in several analyses suggest that caution is needed in interpreting the results, which may be subject to Type I errors (false rejection of the null hypothesis). We found that imbalances in baseline intelligence had a significant impact on observed outcomes in a number of cases: where ecstasy-using groups were, on average, less intelligent than their control arms, they tended to perform worse in neurocognitive tests. Other drug use, mainly amphetamines, cocaine and cannabis, may affect the results in either direction, with no consistent pattern, suggesting that these findings may be artefacts. It is possible, however, that these drugs may act to ameliorate the impact of ecstasy by lessening its hyperthermic effects. This is seen in some studies of acute harms (see Chapter 3, Hyperthermia) and chronic effects could also be influenced by increases in body temperature. In addition, metaregression in 25 analyses found that increased co-use of alcohol was associated with reduced negative effects. As discussed earlier (see Chapter 3, Inter-arm differences), it is possible that alcohol use is a marker of different patterns of drug use, or that alcohol consumption may beneficially attenuate the hyperthermic effects of ecstasy, leading to less long-term damage. These are speculative suggestions which should be treated with caution.

One Hong Kong study, by Yip and Lee,[128] indicated a much bigger impact of ecstasy use for delayed verbal and visual memory outcomes than other studies included in these meta-analyses. The characteristics of this study's participants might mean that this represents a unique insight into the pure effects of ecstasy, as this study was able to recruit clubbing cohorts of ecstasy-only users and drug-naïve controls, neither of which were exposed to other substances, including alcohol and tobacco. It would be very useful to have more studies with comparisons between such groups; however, these have proved very difficult to recruit in European settings. Other qualities might also account for these outlying results, as this is the only study to use the Chinese version of the RAVLT measure. In addition, ketamine contamination was reportedly common in pills sold as ecstasy in Hong Kong at that time.

Acute harms

We did not identify any controlled observational studies concerning acute health harms of ecstasy that met our inclusion criteria. There was, however, a large number of uncontrolled case series and case reports which met our inclusion criteria, including several case series of deaths and hospital admissions, based on data from death registers, coroners' reports, emergency department databases and hospital statistics. We obtained additional information from authors who maintain the np-SAD in the UK, to bring the data on UK deaths from ecstasy as up-to-date as possible. Establishing cause of death caused particular difficulties because death registers record the underlying cause of death only as due to poisoning, rather than stating the immediate cause or mode of death, such as hyperthermia or renal failure.

Inclusion/exclusion criteria

As outlined in the protocol, we did not consider indirect harms of ecstasy, for example the role of ecstasy in accidental deaths due to road traffic accidents, or users' vulnerability to acquiring sexually transmitted infections following unsafe sex. An assessment of such outcomes would

contribute to a more complete picture of all possible harms relating to ecstasy use.

Confounding

Three-quarters of deaths recorded in registries relate to ecstasy use among known drug users. From the data, it is not possible to ascertain whether the minority who die with ecstasy as the sole drug in their system were also known drug users. In any event, it seems that those most at risk of death related to ecstasy are also co-using other drugs or have a history of polydrug abuse.

Analysis

The weak nature of the evidence-base, in terms of both study design and poor and incomplete reporting of outcomes and confounders, made a detailed synthesis of the acute harms unfeasible. We have therefore confined ourselves to describing the case series of deaths from ecstasy in a narrative way. As the case series and case reports of non-fatal acute harms were so heterogeneous, selective in their reporting of outcomes and unlikely to be generalisable to the whole population of recreational ecstasy users, we have made no attempt to report or calculate frequencies of individual health harms and have confined ourselves simply to listing the main effects documented.

Strengths and limitations of the evidence: chronic harms

As outlined earlier in this chapter (see Statement of principal findings), there was a small but consistent negative effect of ecstasy use across a large number of studies. The fact that this effect was seen across so many different outcome measures suggests that there is a real association of ecstasy with impairment of neurocognitive function, particularly some aspects of memory, and with increased psychopathological symptomatology. There are, however, very substantial cautions attached to such an interpretation. With one exception, the evidence on which these findings are drawn is based on cross-sectional studies, so that causation cannot be inferred. There are also significant methodological flaws in many of the studies. The weakness in the study designs is also apparent in the difficulty in controlling for the many possible confounders in these studies.

In assessing whether the association between ecstasy and poor neurocognitive function and increased psychopathological symptomatology (such as anxiety, depression and impulsivity) is real and attributable to the recreational use of ecstasy, the quality of the evidence is discussed below according to relevant criteria for assessing causality:[364]

- strength and consistency of the effect
- dose–response effect
- temporal relationship
- plausibility and coherence.

Strength and consistency of effect

The detrimental effects of ecstasy on memory, depression, anxiety and impulsivity are consistently identified in previous meta-analyses and the meta-analyses undertaken for this review, for both individual outcome measures and composite measures derived by pooling outcomes measuring the same domain. This is despite different focus, outcome groupings and inclusion criteria between this systematic review and those previously published. The three previous meta-analyses of neurocognitive function all found that ecstasy users performed worse than controls in all domains: verbal learning and memory, attention, non-verbal learning and memory, psychomotor speed, executive systems function, short-term memory, long-term memory and visual memory.[59,60,73] The greatest deficits ('moderate 'to 'large' using Cohen's guidelines) were seen for verbal learning in all three reviews. Effect sizes were not modified by lifetime exposure to ecstasy, but former users were not analysed in these studies so further exploration of dose–response is not possible. It is worth noting that Verbaten confined his analysis to heavy users of ecstasy where possible and his effect sizes were larger than other meta-analyses. Our analyses do not suggest the presence of such a dose–response effect.

Sumnall and Cole's previous review of depressive symptoms also found very similar results to our analyses of such outcomes, including suggestions of publication bias.[58] Again, this review found a positive association with lifetime exposure to ecstasy and, while we found a weak association between ETLD and depression effect size when ecstasy users were compared with drug-naïve controls, there was no such evidence in the comparison with polydrug-using controls.

The commonest comparison made in our analyses is between current ecstasy users and polydrug-using controls. Polydrug-using controls are those who use legal and illegal drugs, but not ecstasy, and have generally been recruited in the same way as ecstasy users. While, given the observational nature of all the evidence available, it is not possible to

be certain that both groups come from the same population, it seems reasonable to assume that polydrug-using controls and ecstasy users are fairly similar in most respects apart from ecstasy use. This assumption is generally borne out by the reported levels of other drug use and sociodemographic variables in the individual studies.

Drug-naïve controls, on the other hand, are a more heterogeneous group and while, in some cases, they may have been recruited in a similar way to the ecstasy users, there are also instances in which they have been drawn from very different populations, such as researchers and hospital workers. While ecstasy users also perform worse than this control group on neurocognitive tests and have more psychopathological symptomatology, it is likely that unidentified (and therefore uncontrolled) confounders may be modifying this effect to a greater extent than with polydrug-using controls. It is also impossible to disentangle the effects of ecstasy from those of the other drugs to which the 'ecstasy' arms of these trials have been exposed.

Although consistent in direction, the size of all identified effects is generally small. For individual outcome measures, the mean effects in both user groups (current and former ecstasy users) and both control groups (polydrug users and drug-naïve controls) are within the normal range of the tests used. For the composite outcome domains, the effect sizes generally fall in the range classified as 'small' according to the Cohen guidelines.[119] This statement is true for all comparisons of ecstasy users with polydrug-using controls, with the exception of self-rated memory, where the difference is 0.51 SD (a 'moderate' effect according to Cohen). The range of differences is 0.15–0.51 SD.

Differences between users and drug-naïve controls are larger, with those for immediate and delayed verbal memory, 0.84 and 1.04 SD, being classified as 'large' (range of differences 0.27–1.04 SD). Self-rated depression, memory and impulsivity also produced 'moderate' to 'large' differences for this comparison. Less weight should be attached to self-rated measures than to objective outcomes, even though the effect is consistent.

We remain uncertain of the clinical meaning or relevance of any of these identified differences between ecstasy users and control groups. It is not clear what, if any, impact the 'deficits' described might have on everyday living or quality of life. None of the included studies collected data directly reflecting the quality of life of participants. Similarly, we found no attempts to assess the clinical meaningfulness of any inter-cohort differences, and it is difficult for us to assess this on the basis of aggregate level data alone. As we are not aware that ecstasy users present in any great numbers to drug services, unlike other drug misusers, it seems unlikely that the differences described cause major clinical or functional problems for the majority of consumers.

Methodological flaws in the included studies may also partially explain the effects seen, particularly because the effects are generally small. None of the included studies stated whether the researchers were blind to the ecstasy-using status of each subject; while some of the outcomes are sufficiently objective to make this weakness unlikely to lead to significant observer bias, other outcomes are more open to interpretation. Observer bias cannot therefore be excluded as a partial explanation of our findings. In addition, it not clear what information on the nature of the study was given to subjects at recruitment. As subjects in these studies cannot be blind to their own ecstasy-using status, they may have prior beliefs or expectations about its effects that could influence their performance. The effect of such beliefs could affect our results in either direction: subjects may accept that ecstasy causes memory problems or may be keen to demonstrate that ecstasy use has no effect, or a beneficial effect, on their brain function.

Our metaregression analyses did not consistently identify confounders, although other drug use and differences between study arms in age, sex and intelligence do affect some analyses, in some cases in a counterintuitive direction. Such inconsistent findings weaken the associations identified and strengthen the methodological concerns about the included studies. The apparently consistent, positive effect of additional alcohol consumption may be explained either as a direct chemical effect or as an indicator of more casual modes of ecstasy consumption, as discussed above.

Many of the included studies were very small, which means that they are subject to substantial uncertainty. However, in common with all conventional meta-analyses, our syntheses give weight to contributing studies according to their precision, which is directly influenced by the size of the sample on which they are based. These methods were developed for synthesising the results of randomised controlled trials, where

it can be assumed that, as long as they are well conducted, larger studies are more likely to provide an accurate estimate of treatment effect. This assumption does not necessarily hold true in observational studies: a large study may very well be more biased than a small one.[72] As a result our meta-analyses can only reflect the biases inherent in underlying evidence.

While the total number of outcome measures reported in the studies is very large, it is not clear to what extent they are truly independent measures. The consistency of the effects seen may be artefactually strengthened by the interdependence of the outcomes. In addition, we are aware that many studies do not report results for all of the outcomes they state have been measured. Selective reporting of outcomes may also apparently strengthen any effects, as negative findings are perhaps less likely to be reported.

Significant evidence of small-study bias was found in a few analyses, but only in comparisons between ecstasy users and ecstasy-naïve controls. This may be a chance finding, or it may reflect a lower level of methodological rigour in such studies, leading to biased findings. Selective outcome reporting – which one would expect to find in low-quality studies – might be a contributory factor. There appears to be especially strong evidence that the meta-analysis of depression in ecstasy users compared to drug-naïve controls may be distorted by this bias (see Chapter 3, Depression (self-rated) – MDMA users versus drug-naïve controls).

Finally, subjects have been recruited for the individual studies in a number of ways, none of which suggests that they can be considered truly representative of the ecstasy-using population as a whole. Those participating are self-selected populations, often recruited through snowball methods which may exaggerate any specific, local qualities of the sample, particularly because individual study sizes are often very small. Generalising these effects to the total population of ecstasy users is therefore problematic.

Dose–response

If the associations seen are real and causally linked, we would expect to find greater effects in cases where more ecstasy has been consumed. In addition, the effects in former ecstasy users might diminish the longer they abstain from ecstasy use. In fact, we found very little evidence that studies in which subjects were exposed to more ecstasy reported greater deficits in neurocognitive function or psychopathological symptomatology. Most metaregression analyses showed no impact of exposure, and of the two that did show a relationship, one showed a positive effect and the other a negative effect; chance findings are therefore a possibility.

Ecstasy exposure has been defined in various ways: as total lifetime exposure measured as number of tablets consumed, as duration of ecstasy use, as frequency of ecstasy consumption and as number of tablets consumed on each occasion. Measuring exposure to ecstasy is difficult. All our included studies rely on self-reported consumption of tablets sold as ecstasy, sometimes over a period of several years. Such information is highly subject to recall bias, with both overestimates and underestimates of consumption likely. Compounding this is the lack of knowledge of the exact composition of any tablet sold as ecstasy. Amount of MDMA present varies and other psychoactive and non-psychoactive substances may also be present. All estimates of ecstasy use are likely to be inaccurate indications of MDMA consumption. As a result, it may not be surprising that we cannot demonstrate a dose–response effect in current ecstasy users.

As most ecstasy users co-use other drugs or use other drugs at other times, isolation of an effect particular to ecstasy is very difficult. Use of other drugs is clearly an important potential confounder; however, details about the frequency, volume and combinations of consumptions are varied and subject to the same difficulties of accurate estimate seen for ecstasy use. The importance of co-use, as opposed to poly-use on separate occasions, is not known.

Contrary to expectation when looking for a dose–response effect, former ecstasy users appear to have a disadvantage comparable to – and, in some instances, significantly greater than – current users. We suggest that this may be an artefact of the self-selection process, with people worried about the impact of former drug use more likely to volunteer to participate. Additionally, negative experiences with ecstasy use may cause people to stop taking it. In all cases, the number of studies providing data for pooling about former ecstasy users is smaller than for current users and so the sample of studies may be subject to greater chance variation.

Similarly, we have not demonstrated any effect of length of abstinence on effect size. While it is possible that any effect of ecstasy is permanent and does not improve after exposure ceases, a number of methodological explanations should also be considered. Some studies established quit

status objectively, while others relied on self-report, and both methods could result in inaccuracies of measurement over longer periods of time. In other studies, it is not clear how long subjects had abstained from ecstasy consumption. The sampling biases discussed in the previous paragraph may also apply.

On the other hand, the nature of our analysis, combining data at study level rather than individual level, means that any large effects seen in a small number of individuals would not be identified. It is possible that a minority of ecstasy users are substantially affected by the drug. Such idiosyncratic responses have been noted in the acute effects of ecstasy with some people experiencing severe, even fatal, responses to doses tolerated by others. Unfortunately, such subgroup analysis is not possible with the aggregate-level data identified for this review.

Temporal relationship

Cross-sectional studies, which make up the bulk of available evidence about possible chronic health harms of ecstasy, do not permit causal relationships to be inferred, as it is never possible to ascertain if exposure preceded outcome. The one prospective study that we identified for this review found small deficits in memory and increased self-rated depression in a group of subjects who started using ecstasy in the year after they were recruited to a longitudinal study (although test results for all participants were comfortably within the range of normal function).[84,90,91] The comparison group for this study comprised matched controls that had not started using ecstasy. The reported cumulative dose of ecstasy in this group is small (averaging only three to six tablets), which makes their findings important if such a small exposure to ecstasy can result in defects of measurable magnitude, even if their clinical significance appears to be extremely minor. Controls and ecstasy users did not differ at baseline and were recruited at the same time and in the same way without investigators knowing which would become ecstasy users. However, it is not clear whether researchers at the follow-up testing were aware of the ecstasy-using status of the subjects, so observer bias is a possibility that cannot be excluded. Nevertheless, the methodological quality of this study is good, and we should give more weight to its findings than to those of other studies. We can cautiously suggest, therefore, that a small causal effect of ecstasy on neurocognitive function is possible. The fact that the results from this study support those from the meta-analyses in this review adds to the consistency of findings (see Strength and consistency of effect).

Other longitudinal studies have investigated the performance of ecstasy users over time in comparison to controls. Most of them, however, started by recruiting pre-existing users and controls using the same sort of methods as the cross-sectional studies, making it as difficult to establish causation as in the rest of the literature, despite their subsequent longitudinal nature.[365–369] All five studies are small, but did follow up subjects for between 1 and 2 years after recruitment, noting those who became abstinent during follow-up. The largest study was subject to substantial drop-out (only 38/60 users were tested at the 18-month follow-up), a finding likely to substantially bias the results, as the authors acknowledge.[368] Overall, the results from these longitudinal studies are conflicting: one reported no change over time in task performance for current or ex-users,[81] another showed no difference between ecstasy users and ecstasy abstainers at follow-up,[368] another showed that ex-users failed to improve over time while current users did not deteriorate[366] and two showed that scores remained static or improved for ex-users while they declined for current users.[366,369] These studies are also as subject to confounding as the rest of the literature and their small size makes their evidence very weak. Overall, they cannot be taken as providing any evidence of a causal link between ecstasy use and neurocognitive deficits.

One final longitudinal study provides substantially better evidence that mental disorders are more likely to precede illegal drug use than develop as a consequence.[80] This study used a pre-existing population-based longitudinal study of young people being followed for the early development of mental disorders to investigate symptomatology with and without exposure to ecstasy and other amphetamines. As it is not possible to separate out results relating to ecstasy use, we have not included the study's results in our meta-analyses. It did not include any neurocognitive testing in its methods. Nevertheless, the size and methodological quality of this study suggest that we should give weight to these results, which show outcome preceding exposure in the majority of cases (that is to say, participants started using ecstasy after the onset of psychopathological symptoms). These findings suggest that amphetamines generally do not cause mental disorders, but rather that their use follows the onset of such disorders.

Plausibility and coherence

The link between ecstasy and neurocognitive deficits in particular is plausible and can be predicted from animal, pharmacological and experimental studies which have not been reviewed for this report.

The consistent confounding effect of alcohol on the associations was initially surprising, but may be explained in two ways (either as a direct neuroprotective effect or via the existence of different populations with different consumption patterns), as outlined in Chapter 3, Inter-arm differences.

Strengths and limitations of the evidence: acute harms

Registry data for the UK provides an indication of the scale of ecstasy-related deaths; however, without detailed understandings of the scale and nature of ecstasy use, it is not possible to assess the risk of taking any ecstasy tablet. This uncertainty is compounded by apparent idiosyncratic responses in some people which cause acute harms including, in some cases, death, after ingesting doses that are tolerated by others. We identified no studies that offered ways of identifying those most at risk of fatal effects. The variable content of ecstasy tablets is also an issue.

Two-thirds of those deaths recorded in registry data as having ecstasy as a contributory factor were in individuals who were also found to have consumed other drugs. In nearly 60% of these cases, heroin, methadone or other opiates were also found. In populations recruited for the comparative studies about chronic harms of ecstasy use, heroin was not a commonly co-used drug. It is possible that the majority of those fatal cases involving ecstasy use are in those who are opiate abusers who also use other drugs, a subgroup which is not representative of the majority of ecstasy users.

There are few audits of presentations in emergency rooms related to ecstasy use and only one of these was from the UK, in which no fatal cases were recorded. In other such hospital-based audits, fatalities are seen in between 0 and 2% of presentations, suggesting that most adverse effects resolve spontaneously or with treatment, even where they are severe enough to result in presentation at A&E.

Given the lack of information about cause of death in registries and the small size of hospital audit samples, we had to use other case series literature to explore the nature of acute harms. Such data are subject to a number of well-known limitations [see Chapter 3, Uncontrolled (Level III) evidence (acute harms)] Most fatal and non-fatal acute harms reported appear to be related to the main syndromes of hyperthermia and hyponatraemia – women may be more susceptible to the latter.

The scope of our review was such that transient subacute health harms of ecstasy consumption have not been reviewed. This may be particularly relevant where short-term disturbance of mood is concerned, as this phenomenon may be related to long-term depressive outcomes.[591]

Further research

Our recommendations for future research are as follows:

- Large, population-based, prospective studies are required to examine the time relationship between ecstasy exposure and neurocognitive deficits and psychopathological symptoms.
- Further research synthesis of the social and other indirect health harms of ecstasy would provide a more complete picture. Similar synthesis of the health harms of amphetamines generally would provide a useful comparison.
- Future cross-sectional studies will only add to the evidence-base if they are large, as representative as possible of the ecstasy-using population, use well-validated outcome measures, measure outcomes as objectively as possible with researchers blind to the ecstasy-using status of their subjects, report on all outcomes used, and provide complete documentation of possible effect modifiers. Cohorts should be matched for baseline factors, including IQ and exposure to alcohol.
- The heterogeneity of outcome measures used by different investigators is unhelpful: consensus on the most appropriate instruments to use should be sought. Investigators should collect data directly reflecting the quality of life of participants and/or attempt to assess the clinical meaningfulness of any inter-cohort differences.
- A registry of adverse events related to illegal intoxicants presenting to medical services (akin to the 'yellow card' system for prescription medicines) would enable useful estimation of the incidence of harmful effects of ecstasy in comparison to other substances.

- Future case reports of acute harms of ecstasy are unlikely to contribute valuable information to the evidence-base. Where novel findings are presented, care should be taken to report toxicological findings confirming the precise identity of the substance(s) consumed by the individual(s) in question.

Conclusions

Chronic harms

The one prospective study identified for this review (the Netherlands XTC study) found that subjects using ecstasy had a poorer performance on neurocognitive testing of various aspects of memory and reported increased depressive symptomatology, when compared to subjects who had not used ecstasy.

Previous meta-analyses of cross-sectional studies report small to medium decreases in performance on various neurocognitive outcomes concerned with memory, and an increase in depressive symptomatology.

Meta-analyses undertaken for this review also find the same deficits, whether for individual outcome measures or for pooled outcomes measuring the same function (e.g. immediate or delayed memory). These neurocognitive deficits remain largely within the normal range for individual measures or are classified mostly as small effects, with some verging on medium-sized effects. Slightly larger effect differences are generally (but not universally) seen when current ecstasy users are compared to users naïve to illegal drugs rather than users of other illegal drugs. The differences are frequently slightly larger for former ecstasy users compared to both control groups than for current ecstasy users.

As all the data for these meta-analyses are derived from cross-sectional studies, no causal inference can be made. Metaregression shows that differences in baseline intelligence and consumption of other drugs, particularly alcohol, partially explain the difference between groups, although not necessarily in the expected direction (e.g. higher consumption of alcohol amongst ecstasy-using cohorts appears to be associated with better relative performance in neurocognitive tests). Level of education, intelligence, age and gender do not consistently explain the differences seen between studies.

No dose–response effect for ecstasy is seen in most of the analyses, whether dose is measured as duration or frequency of use, size of dose at each use or lifetime exposure. Period of abstinence from ecstasy before testing also has no identifiable effect. In some cases (notably the NeXT study), neurocognitive effects are demonstrable after apparently very low doses of only a few tablets. Our lack of identified dose–response effect is, perhaps, surprising. It certainly might be expected that differences exist between novice users taking only a few tablets and those who have taken hundreds of tablets over many years. The lack of identified dose–response effect may relate to the difficulties in measuring exposure, which include both recall bias in subjects and variable quantities of MDMA plus possible other psychoactive ingredients in tablets consumed as ecstasy.

Other explanations include methodological ones, such as the lack of blinding of investigators to the drug-using status of subjects: the differences tend to be greater when subjective outcomes are measured. The artificiality of separating illegal drug users into those declaring that they use ecstasy and those who do not may also contribute. Polydrug-using controls are likely to be the population of subjects from which ecstasy users are drawn, while drug-naïve controls may be quite different and more heterogeneous, making it likely that they differ markedly from the recreational ecstasy users in many unmeasured ways. In addition, our analyses will not pick up individual severe effects, as there is a big variation in exposure within most studies and the large effects in a few individuals will be averaged out (i.e. subject to the ecological fallacy).

Estimated exposure effects are consistently small or within normal ranges, suggesting that effects are unlikely to have serious clinical implications for the average user. However, there are no long-term follow-up data to monitor any persistent effects over time or any rate of comparative neurocognitive decline in these groups.

Acute harms

Death remains a rare event following exposure to ecstasy. Documentation is inconsistent and incomplete, but, such as it is, suggests that death usually occurs within a few hours of ingestion of ecstasy and is associated mainly with hyperthermia and its consequences or hyponatraemia. Occasionally, it is associated with isolated liver

failure occurring over a period of days or weeks rather than hours. It is not possible to calculate a risk of death from taking ecstasy, not least because many victims have been exposed to other drugs, both alcohol and other illegal drugs, and reporting of this is not always complete. Women appear to bemore susceptible to fatal hyponatraemia, but this phenomenon is extremely rare and is likely to be reported more completely and thoroughly than other deaths.

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Contribution of authors

Gabriel Rogers co-ordinated the project, drafted the protocol, contributed to devising the search strategy, contributed to the review (study selection; data extraction and checking; critical appraisal of studies; data synthesis), contributed to drafting the report (all sections) and compiled and edited the report. Julian Elston contributed to the review (study selection; data extraction and checking; critical appraisal of studies; data synthesis) and contributed to drafting the report (results; discussion). Ruth Garside was co-responsible for project direction, contributed to the review (study selection; data extraction and checking; critical appraisal of studies; data synthesis) and contributed to drafting the report (all sections). Chris Roome contributed to the review (data extraction and checking; critical appraisal of studies; data synthesis) and contributed to drafting the report (results). Rod Taylor contributed to the design, implementation and checking of quantitative synthesis, contributed to the review (data checking), and contributed to drafting the report (methods). Paula Younger devised the search strategy, conducted the literature searches and contributed to drafting the report (methods; results). Anna Zawada contributed to the review (critical appraisal of studies; data synthesis) and contributed to drafting the report (results). Margaret Somerville was co-responsible for project direction, contributed to the review (data checking; critical appraisal of studies; data synthesis) and contributed to drafting the report (all sections).

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Appendix 1

Expert Advisory Group

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Appendix 2

Review protocol

Title of the project

The harmful health effects of recreational ecstasy: a systematic review of observational evidence

Name of TAR team and project lead

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Plain English summary

Street-drugs known as *ecstasy* have been sold for about 20 years in the UK. The active substance that such tablets contain – or purport to contain – is 3,4-methylenedioxymethamphetamine (MDMA). MDMA does not exist in nature; it can only be made chemically. Shortly after consumption, MDMA releases chemicals in the brain that tend to bring about a sense of euphoria, exhilaration and increased intimacy with others. In the UK, MDMA has been a Class A illegal substance for 30 years. This means that it is classified among the most dangerous drugs, and serious penalties are imposed for possession or supply. Most people who take ecstasy also use other legal and illegal drugs, sometimes at the same time. Ecstasy is commonly taken in nightclubs and at parties, and is very often associated with extended sessions of dancing.

Along with the pleasurable effects sought by users of MDMA, it has become clear that the drug can cause a range of unintended harms. In the short term, the most serious dangers arise when MDMA interferes with the body's ability to maintain a constant temperature. In severe cases, multiple organ failure can develop, and this can prove swiftly fatal. To counteract this danger, ecstasy users are advised to drink plenty of fluid. However, some people overcompensate, drinking excessive amounts, and a condition can result in which the excess fluid leaks into the brain, causing it to swell, often with fatal consequences. A variety of other adverse events have been reported in the immediate aftermath of MDMA consumption, including heart failure, brain haemorrhage, and liver failure.

Consumption of MDMA may also have long-term consequences, especially as regards users' mental health. People who have taken ecstasy in the past may have increased susceptibility to depression, and their memory may also be affected. There are other possible psychiatric effects, some of them serious.

This project will systematically review the medical literature detailing the harms to human health from ecstasy. Electronic databases will be searched for journal articles describing the incidence and impact of adverse events. The identified material will be analysed and summarised. Consideration will be given to the features of the evidence that may make its interpretation complex (for example: to what extent is it possible to isolate the long-term harms of MDMA from those of the other substances that users have almost always taken?) If several papers report the same kind of numerical information, these data will be combined by meta-analysis. An effort will also be made to analyse

factors that might make some types of user more or less likely to suffer an adverse event.

Scope of the review

Review question

What are the harmful health effects of taking 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) for recreational use?

Background

Ecstasy is the common street-name for drugs that contain – or purport to contain – 3,4-methylenedioxymethamphetamine (MDMA) as their active ingredient. Following the convention of Gowing *et al*.,[P1] the term *ecstasy* is used here to denote the drug as it is sold on the street, whereas *MDMA* refers to the known chemical substance.

Pharmacology

MDMA is an entirely synthetic chemical belonging to the amphetamine family, a group of phenethylamines. Several substances that are closely related in chemical structure are also commonly used as recreational drugs:

- amphetamine ('speed', 'whizz')
- methamphetamine (MA; 'crystal meth')
- paramethoxyamphetamine (PMA)
- 3,4-methylenedioxyamphetamine (MDA)
- 3,4-methylenedioxy-*N*-ethylamphetamine (MDEA; 'Eve')
- 3,4-methylenedioxy-phenyl-*N*-methylbutanamine (MBDB).

Drugs sold as 'ecstasy' frequently contain one or more of these substances, instead of or in addition to MDMA.[P2] The intended effects for which ecstasy users take the drug are described in terms of euphoria, exhilaration and a sense of increased intimacy and empathy with others.[P3] The neuropharmacological mechanisms by which these effects are produced involve the release of extracellular serotonin and dopamine,[P4] neurotransmitters that are commonly associated with the mood and pleasure systems of the brain.

The physiological effects of MDMA in humans have been studied in controlled conditions. Heart rate rises to a peak an average of 20–30 beats per minute higher than baseline[P5–P7] approximately an hour after consumption of doses similar to those taken recreationally. Blood pressure increases over a similar period (systolic by 25–40 mmHg, diastolic by 10–20 mmHg).[P5–P7] Body temperature also rises (by 0.3–1.0°C), but this effect is less immediate, with a peak several hours after consumption.[P5,P7,P8]

The apparently non-linear nature of MDMA pharmacokinetics has been emphasised; blood concentrations of MDMA rise disproportionately as dosage is increased.[P9]

History

The first documentary record of the synthesis of MDMA is the 1912 German patent application of Merck pharmaceuticals in relation to haemostasis,[P10] but it was not tested on humans until 1960.[P10] Following very sporadic reports in the 1970s, recreational use of MDMA became more widespread during the 1980s,[P11] with discussion proliferating in the popular press in 1985.[P12] The term *ecstasy* first appeared in print in reference to MDMA in 1985[P13] and in the British media in 1987.[P14]

The US Drug Enforcement Administration classified MDMA as a Schedule 1 controlled substance with effect from 1 July 1985,[P15] In the UK, it had already been criminalised; a statutory instrument of 1977, without naming MDMA in particular, categorised all ring-substituted phenethylamines as Class A substances under the Misuse of Drugs Act.[P16]

In the UK, reported ecstasy consumption has remained relatively stable over the past decade, with somewhere in the region of 2% of 16- to 59-year-olds reporting ecstasy use in the preceding 12 months (Office for National Statistics crime survey). This makes it the third most-used illegal drug in the UK. It has been estimated that somewhere between 500000 and 2 million doses of ecstasy are consumed each week in the UK.[P17]

Usage

The overwhelming pattern of ecstasy usage is as a part of polydrug consumption.[P18] A 2003 survey of UK ecstasy-using respondents also reported extensive concomitant use of alcohol (88%), amphetamines (83%), cannabis (82%), cocaine (58%) and amyl nitrate (51%), and there was also some use of LSD, ketamine, fluoxetine, crack cocaine, herbal highs and sildenafil. In addition, various substances were used in the 'comedown' period following ecstasy consumption, most notably cannabis (82%), alcohol (60%), benzodiazepines (18%) and heroin (2%).

Ecstasy tablets as sold on the street contain a variable amount of MDMA, ranging from none to around 150 mg.[P2] As noted above, some tablets contain MDEA, MDA and/or amphetamine in addition to or instead of MDMA. Ecstasy tablets may also be 'cut' with unrelated substances.

Many of these are pharmacologically weak (e.g. caffeine, paracetamol); however, there are reports of stronger psychoactive substances (e.g. atropine, opiates, phenylbutanamine and dextromethorphan).[P2] One US source analysed tablets in 2005–7 and found them to have approximately a one in three chance of containing only MDMA, MDMA along with other active ingredients, or no MDMA at all.[P19]

As a result of these factors, it is not possible to isolate exposure to MDMA in particular in any individual history or in characteristics across cohorts. Even if there were such a thing as an identifiable group of individuals whose ecstasy consumption alone distinguished them from the general population, it would still be impossible to ascertain to which chemicals they had been exposed, and at what dosage.

Safety

Reports from investigators assessing the psychotherapeutic potential of MDMA in 1986 suggested that the drug was 'apparently physically safe', despite some 'undesirable' effects.[P20] Within a year of such claims, the first reports of ecstasy-related deaths appeared in the medical literature.[P21] In the UK, the first reported fatalities came in 1991.[P22,P23] Over the past 20 years, a wide variety of fatal and non-fatal complications have been ascribed to consumption of ecstasy.

Acute harms

Major syndromes

The most critical acute complications of MDMA consumption are, in a majority of cases, related to two well recognised syndromes, each involving serious derangement of homeostasis leading to multiple organ failure: hyperthermia and hyponatraemia.

Hyperthermia Derangements of thermoregulation are a widely reported feature of MDMA toxicity,[P24] with temperatures as high as 43°C reported in some cases.[P25–P29] In this context, the association between MDMA use and prolonged dancing may be important because core temperature rises during intensive exercise.[P30]

The physiological manifestations of MDMA-induced hyperthermia are similar to those seen in severe heatstroke.[P31] The most noteworthy effects are rhabdomyolysis, disseminated intravascular coagulopathy (DIC), acute renal failure (ARF) and acute liver failure.

Hyponatraemia When the hyperthermogenic properties of MDMA are combined with intense physical activity, profuse sweating inevitably results, and substantial amounts of sodium can be lost in perspiration. This problem is significantly compounded by the tendency of MDMA users to drink large quantities of water. The combination of sodium loss and excess water consumption may also be exacerbated by excess fluid retention (as the result of inappropriate secretion of antidiuretic hormones and/or impairment of renal function[P32]). The resultant hyponatraemic state sees a fall in serum osmolar pressure, allowing intracellular displacement of water, the most hazardous result of which is cerebral oedema.[P32]

The early clinical manifestations of hyponatraemic cerebral oedema are headache and nausea, progressing to confusion and seizures.[P32–P35] If not corrected the syndrome will commonly progress to tentorial herniation, respiratory arrest, cerebral hypoxia and death.

Subgroup effects may be an issue. Regardless of cause, hyponatraemia is known to be most hazardous in women, especially during menstruation.[P36]

Isolated acute harms

Acute cardiovascular dysfunction Tachycardia is an invariable response to MDMA consumption, and is the most frequently reported clinical symptom in series detailing acute admissions in accident and emergency departments.[P37,P38] There are reports of MDMA-related myocardial infarction[P39–P42] and sudden cardiac death.[P43] The importance of excluding concomitant use of other drugs (especially cocaine, which is well known to induce critical cardiovascular dysfunction) has been emphasised.[P44]

Acute neurological dysfunction (seizures) Seizures are a recognised manifestation of both hyponatraemia and hyperthermia (see above). Cases have also been reported of MDMA-induced seizures which apparently do not involve either of these underlying causes.[P45]

Intracranial haemorrhage There are several reports of intracranial haemorrhage following consumption of MDMA. Such events are commonly associated with pre-existing cerebrovascular vulnerabilities (e.g. aneurysm[P46,P47] or arteriovenous malformation[P48,P49]); however, cases have also been reported in which no such features were identified.[P49,P50]

Respiratory dysfunction Chest pain secondary to pneumomediastinum (leakage from the airways into the mediastinum; also known as mediastinal emphysema) is a relatively commonly reported condition in those presenting for medical attention following MDMA consumption.[P51–P63] Less frequently, pneumothorax[P55,P59] and pneumopericardium[P58] have also been reported.

Acute liver failure Critical hepatic dysfunction is a notable consequence of hyperthermia (see above), and extensive hepatic necrosis is an invariable post mortem finding in MDMA deaths.[P64] In addition, it is well established that MDMA-induced acute liver failure can also occur without thermoregulatory dysfunction.[P28,P65–P74] This type of acute hepatic failure develops over a slightly longer period than in hyperthermic liver failure, with cases becoming symptomatic a matter of days, rather than hours, after MDMA ingestion.

Renal failure and other urinary tract abnormalities Occasionally, MDMA-induced kidney dysfunction can occur in the absence of hyperthermia or hyponatraemia. Such cases are frequently associated with severe hypertension.[P75–P77]

Rhabdomyolysis A few cases of isolated rhabdomyolysis without evidence of hyperthermia have been reported.[P78,P79]

Acute ophthalmic injury There are reports of ocular problems arising from MDMA consumption, including retinal haemorrhage,[P80] keratopathy,[P81] glaucoma,[P82] diplopia[P83] and myopia.[P84]

Long-term harms

For all potential long-term harms, it is extremely difficult to disentangle the long-term effects of MDMA use from those of the other legal and illegal substances with which the histories of users are invariably confounded.[P85]

Neuropsychiatric sequelae

While short-term depression of mood in the few days following MDMA use is a common finding in qualitative[P86,P87] and observational[P88] literature, the long-term neuropsychiatric effects of MDMA use are the subject of much research and are widely believed to be irreversible.[P89] Some biochemical analyses have shown depletion of serotonin metabolites in the cerebrospinal fluid of human MDMA users, from which permanent impairment of serotonergic function is inferred.[P90] The impact of MDMA consumption on dopamine activity has been a more controversial topic. A variety of clinical manifestations may result. Studies have most commonly examined the impact of MDMA use on depression, neurocognitive impairment (with a particular focus on both short- and long-term memory), psychomotor dysfunction and psychotic symptomatology.

Depression It is hypothesised that, if MDMA use compromises serotonergic function, long-term consumption can be expected to result in chronic depression of mood.[P91]

Neurocognition It is suggested that recreational MDMA use is associated with deficits in general neurocognitive function,[P92] with particularly strong evidence of short- and long-term memory impairment.[P92–P94]

Psychomotor symptoms Psychomotor symptoms, such as tremor and even Parkinson's disease, appear to be more common in those with a history of MDMA use.[P95,P96–P100]

Psychosis and other psychiatric disorders Paranoia and anxiety are recognised characteristics of the short-term experience of MDMA.[P86,P87,P101] Specific persistent psychiatric abnormalities lasting beyond the acute phase are also recorded.

Other long-term harms

Dental damage Trismus and bruxism are very frequent characteristics of MDMA intoxication,[P3] and excessive toothwear can result. The problem may be exacerbated by consumption of carbonated drinks, which is common.[P102]

Long-term susceptibility to seizure There is some discussion about whether long-term exposure to MDMA predisposes users to epilepsy.[P33]

Methods for systematic review of evidence

Inclusion/exclusion criteria

The relevance of all evidence will be appraised with respect to the following criteria.

Population

Included

- Users of recreational drugs in the UK or in populations relevant to the UK.

Excluded

- Animal studies.
- Non-drug-using volunteers enrolled in prospective research.

- Gamma-hydroxybutyric acid (GHB, 'liquid ecstasy').

Exposures

Included

- Recreational use of substances shown or believed by the investigator(s) to contain MDMA.

Excluded

- Use of street-drugs shown or believed by the investigator(s) not to contain MDMA, whether referred to as 'ecstasy' or not.
- Therapeutic use of MDMA.
- Generic drug-using populations in which it is not possible to isolate a subgroup with exposure to MDMA in particular.

Comparators

Some uncontrolled evidence will be considered in the review, where appropriate (see below). Where comparative evidence is reviewed, studies with comparator arm(s) meeting the following characteristics will be eligible.

Included

- Recreational users of drugs other than MDMA.
- Non-drug-users.

Outcomes

Included

- Death
- Acute, clinically observable health harms, including (but not limited to)
  - hyperpyrexia
  - hyponatraemia
  - acute cardiovascular dysfunction
  - acute neurological dysfunction (seizures)
  - acute renal failure/anuria
  - acute liver failure (including 'subacute' liver failure and hepatitis)
  - intracranial haemorrhage
  - respiratory dysfunction (including pneumomediastinum and pneumothorax)
  - rhabdomyolysis
  - disseminated intravascular coagulopathy
  - acute ophthalmic injury (including retinal haemorrhage, keratopathy, glaucoma, diplopia, myopia).
- Long term, clinically observable health harms, including (but not limited to)
  - neuropsychiatric sequelae (including depression, psychosis, memory impairment, disorders of neurocognition, psychomotor symptoms)
- Dental damage.

Excluded

- Surrogate measures of harm (e.g. neuroimaging studies, biochemical markers), where there is no explicit correlation to observed effect
- Biochemical indices of MDMA consumption (e.g. testing for MDMA use in blood or hair samples)
- Studies reporting therapeutic measures for adverse events without providing data on individuals suffering such complications
- Subjective measures of psychostimulation (i.e. studies of the drug's intended short-term intoxicative effects)
- Indirect harms
  - accidental injury where ecstasy consumption is detected/implicated
  - health consequences of high-risk sexual behaviour contributed to by ecstasy consumption
- Birth defects secondary to maternal exposure to MDMA.

Methods

Except where otherwise specified, the general methods of the review will follow the guidance on the conduct of systematic reviews published by the Centre for Reviews and Dissemination.[P103]

Identification of evidence

The search strategy will comprise the following main elements:

- searching of electronic databases
- contact with experts in the field
- scrutiny of bibliographies of retrieved papers.

Search strategy for electronic databases

A comprehensive search syntax using indexed keywords (e.g. MeSH, EMTREE) and free-text terms will be developed. This will build upon the search syntax devised and used for the scoping searches (Preliminary search strategy).

Databases to be searched

The electronic databases that will be searched include: MEDLINE, EMBASE and PsycINFO (all via Dialog DataStar); PubMed (limited to recent publications and in-process citations); Web of Knowledge; the Cochrane Library (including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register); DARE; NHS HTA database. Simple keywords (e.g. 'Ecstasy'; 'MDMA') will also be used to consult research registers, to identify any relevant prospective studies.

Inclusion of relevant evidence

The outputs of searches will be considered against the prespecified inclusion/exclusion criteria, with a sample of citations screened by a second reviewer, to appraise validity of assessment. Studies that can confidently be identified as not meeting eligibility criteria on the basis of title and abstract will be excluded. The full texts of all other papers will be obtained. Two reviewers will independently assess whether these studies fulfil the inclusion criteria, with disagreements resolved by consensus.

Papers in languages other than English

As a result of the time restraints on this project, only studies published in English will be included in the review.

Meeting abstracts

Reports published as meeting abstracts will only be included in the review if sufficient methodological details are reported to allow critical appraisal of study quality.

Methods of analysis/synthesis

General approach

Initially, all included evidence will be reviewed to establish a taxonomy of reported outcomes. For each outcome, the available evidence will be categorised in a predefined hierarchy of research design:

- *Level I* Pre-existing systematic research syntheses (systematic reviews, meta-analyses, syntheses of qualitative data)
- *Level II* Controlled observational studies (cohort studies, case–control studies, etc.)
- *Level III* Uncontrolled observational evidence (case reports and case series).

Where it is adequately designed and conducted (see below for methods of critical appraisal), Level I evidence will be preferred. Any such synthesis of primary research can be expected to include consideration of all relevant Level II evidence, if it is appropriately comprehensive. Accordingly, where reasonable-quality Level I evidence is available for a given outcome, Level II evidence will only be considered to the extent that it supplements the pre-existing syntheses. For example, Level II studies that post-date the higher-level evidence will be reviewed and appraised. Where possible and appropriate, attempts will be made to extend any quantitative analyses contained in Level I evidence to include such additional evidence. Where no adequate Level I evidence is identified for a given outcome, any Level II evidence will be systematically reviewed. The quality of research will be appraised and described, and findings reported. Where possible and appropriate, quantitative synthesis of study outcomes will also be undertaken (for methods, see below). A brief tabulation and/or summary of Level III evidence will be provided.

Where neither Level I nor Level II evidence is available, Level III evidence will be systematically surveyed.

Critical appraisal of evidence

The internal validity of included studies will be assessed using methods appropriate to study design.

Level I: systematic research syntheses Systematic reviews of observational evidence will be appraised with reference to a quality assessment instrument adapted from the recommendations of the MOOSE (Meta-analysis of Observational Studies in Epidemiology) proposal.[P104]

Level II: controlled observational studies Cohort studies and case–control studies will be appraised using a bespoke quality assessment instrument, which will be constructed with reference to recommendations made by Levine *et al*.,[P105] Downs and Black,[P106] the NHS Centre for Reviews and Dissemination (2004)[P103] and Mallen *et al*.[P107]

Level III: Uncontrolled observational studies Case series and case reports will be appraised using a bespoke quality assessment instrument, which will be constructed with reference to the findings of Dalziel *et al*.[P108]

Data extraction

Data will be extracted using a bespoke database. Recorded information, where available, will include:

- study design (e.g. design, country, setting, dates, length of follow-up)
- details of study participants, including
  - baseline demographics (e.g. age, gender)
  - previous exposure to ecstasy and other legal and illegal substances)
- details of exposure, including
  - details of ecstasy consumed (e.g. number of tablets, MDMA content, other substances contained in tablets)
  - other substances consumed (e.g. alcohol, other recreational drugs)
- outcome data, including
  - quantitative data describing key study outcomes
- inter-cohort comparisons.

All extracted data will be checked by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

Quantitative synthesis

Where it is possible and appropriate, meta-analysis will be carried out using random-effects models by default. If there is statistical evidence of inter-study homogeneity and no reason to suspect clinical heterogeneity, sensitivity analyses using fixed-effects models will be undertaken. STATA software will be used to pool results and estimate an overall effect measure. Heterogeneity will be explored through consideration of the study populations, methods and exposures, by visualisation of results and, in statistical terms, by the chi-squared test for homogeneity and the I^2 statistic. Small-study effects (including publication bias) will be assessed and quantified.

Subgroup effects

For all outcomes, consideration will be given to the possibility of differential effects existing in subgroups (e.g. by age group, by gender, by exposure to other substances, etc.) Where quantitative synthesis is undertaken, stratified analyses and metaregression, using potential predictors of effect size as covariates, will be considered.

Expertise in the review team

Peninsula Technology Assessment Group

The Peninsula Technology Assessment Group is part of the Institute of Health and Social Care Research at the Peninsula Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments for the UK HTA Programme and other local and national decision-makers. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Peninsula Medical School is part of the Peninsula College of Medicine and Dentistry within the Universities of Plymouth and Exeter.

Team members

The PenTAG team members who will undertake the project have previously produced reports for NICE, the Health Technology Assessment Programme and the Department of Health. These projects have included Technology Assessment Reports, National Guidelines, and short reports. The members of the project team and their role in the project are listed below.

Mr Gabriel Rogers, Associate Research Fellow	Responsible for project coordination Responsible for drafting the protocol Contributor to devising the search strategy Contributor to review (study selection; data extraction and checking; critical appraisal of studies; data synthesis) Contributor to drafting report (all sections) Responsible for compiling and editing report
Dr Julian Elston, Academic Specialist Trainee in Public Health/ Honorary Research Fellow	Contributor to review (study selection; data extraction and checking; critical appraisal of studies; data synthesis) Contributor to drafting report (results; discussion)
Ms Paula Younger, Electronic Resources Librarian[a]	Responsible for devising the search strategy Responsible for conducting the literature searches Contributor to drafting report (methods; results)
Ms Ruth Garside, Research Fellow	Co-responsible for project direction Contributor to drafting report (executive summary; discussion)
Dr Margaret Somerville, Principal Lecturer and Consultant in Public Health	Co-responsible for project direction Contributor to drafting report (executive summary; discussion)

a Exeter Health Library, Royal Devon and Exeter NHS Foundation Trust (1st Floor, Peninsula Medical School Building, Barrack Road, Exeter EX2 5DW)

Competing interests of authors

None.

Timetable

The report will be delivered to NCCHTA by 20 December 2007.

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Preliminary search strategy

The following search was run in MEDLINE only (via PubMed) on 15 August 2007, with 2204 hits identified. The review's final search strategy will build upon this approach and syntax.

```
"n-methyl-3,4-methylenedioxyamphetamine/adverse effects"[MH]
OR
   (("n-methyl-3,4-methylenedioxyamphetamine"[MH] OR MDMA[TW] OR Ecstasy[TW])
   AND (
        (
        (hyperthermia[TW] OR "fever"[MH] OR pyrexia[TW] OR "fever"[TW] OR "Heat
           Exhaustion"[MH] OR "Heat Stress Disorders"[MH] OR heatstroke[TW] OR heat
           stroke[TW])
        OR (hyponatremia[TW] OR hyponatraemia[TW] OR "hyponatremia"[MH])
        OR ("seizures"[MH] OR seizure*[TW] OR fit[TW])
        OR ("cardiovascular system"[MH] OR cardiovascular[TW] OR "heart"[MH] OR
           cardiac[TW] OR heart[TW])
        OR ("intracranial hemorrhages"[MH] OR brain haemorrhage[TW] OR brain
           hemorrhage[TW])
        OR respiratory[All Fields]
        OR (mediastinal[TW] OR pneumomediastinum[TW] OR (intra-alveolar[TW] AND
           pressure[TW]))
        OR (ophthalm*[TW] OR "cornea"[MH] OR cornea*[TW])
        OR ("tooth"[MH] OR tooth*[TW] OR teeth*[TW] OR "bruxism"[MH] OR bruxism[TW])
        OR ("liver"[MH] OR liver[TW] OR "hepatitis"[MH] OR hepatitis[TW])
        OR ("death"[MH] OR death*[TW])
        OR (rhabdomyolysis[MH] OR rhabdomyoly*[TW])
        OR (hyponatremia[MH] OR hyponatremia[TW] OR hyponatraemia[TW])
        OR (Kidney[MH] OR Kidney[tw] OR renal[tw] OR nephro*[tw])
        OR (Hematologic-diseases[MH] OR (disseminated[tw] AND intravascular[tw] AND
           coagul*[TW]) OR DIC)
        OR ("Mental Disorders"[MH] OR depress*[TW] OR neuropsych*[TW] OR
           psychopatholog*[TW] OR neurocogniti*[TW] OR cogniti*[TW] OR psychiatric[TW]
           OR panic*[TW] OR delus*[TW] OR memory[TW] OR motor[TW] OR psychomotor[TW]
           OR attention[TW] OR concentration[TW])
        )
     OR
        ("street drugs/adverse effects"[MH]
        OR "substance-related disorders/epidemiology"[MH]
        OR "Designer Drugs/adverse effects"[MH])
     )
   )
```

No study design filters or language restrictions applied.

Appendix 3

Literature search: strategy and results

Dialog DataStar (MEDLINE; EMBASE; PsycINFO); run 19 September 2007

No.	Database	Search term	Results
1	MEDLINE	(N-METHYL–3–4-METHYLENEDIOXYAMPHETAMINE-AE OR N-METHYL–3–4-METHYLENEDIOXYAMPHETAMINE-PO OR N-METHYL–3–4-METHYLENEDIOXYAMPHETAMINE-TO).DE.	928
2	MEDLINE	N-METHYL–3–4-METHYLENEDIOXYAMPHETAMINE#.DE. OR (methylenedioxymethamphetamine OR MDMA OR ecstasy OR ecstasy OR ectasy OR ectacy).TI,AB.	3251
3	MEDLINE	2 AND ((DESIGNER-DRUGS-AE OR DESIGNER-DRUGS-PO OR DESIGNER-DRUGS-TO OR STREET-DRUGS-AE OR STREET-DRUGS-PO OR STREET-DRUGS-TO).DE. OR (adverse OR harm OR harms OR harmful OR safety OR consequence$OR outcome$OR sequel$).TI,AB.)	643
4	MEDLINE	2 AND (DEATH#.DE. OR (death OR deaths OR fatal$OR mortal$).TI,AB.)	290
5	MEDLINE	2 AND ((FEVER# OR HEAT-STROKE#).DE. OR (hyperthermi$OR pyrexi$OR hyperpyrexia$OR fever OR febrile OR heatstroke OR heat ADJ stroke).TI,AB.)	299
6	MEDLINE	2 AND (WATER-ELECTROLYTE-IMBALANCE#.DE. OR (hyponatraemia OR hyponatremia OR water ADJ intoxication).TI,AB.)	55
7	MEDLINE	2 AND ((CARDIOVASCULAR-SYSTEM# OR CARDIOVASCULAR-DISEASES#).DE. OR (heart OR cardiovascular OR cardiac).TI,AB.)	270
8	MEDLINE	2 AND ((RESPIRATORY-SYSTEM# OR RESPIRATORY-TRACT-DISEASES# OR MEDIASTINAL-EMPHYSEMA# OR PNEUMOTHORAX#).DE. OR (respiratory OR respiration OR lung OR lungs OR pulmonary OR pneumomediastin$OR pneumothora$).TI,AB.)	99
9	MEDLINE	2 AND ((LIVER# OR LIVER-DISEASES#).DE. OR (liver OR hepatic OR hepatitis OR hepatotox$).TI,AB.)	187
10	MEDLINE	2 AND ((KIDNEY# OR KIDNEY-DISEASES#).DE. OR (kidney OR renal).TI,AB.)	97
11	MEDLINE	2 AND (RHABDOMYOLYSIS#.DE. OR (rhabdomyoly$OR myoglobinur$).TI,AB.)	70
12	MEDLINE	2 AND ((NEUROLOGIC-MANIFESTATIONS# OR EPILEPSY# OR SEIZURES#).DE. OR (seizure OR seizures OR fit OR fits OR fitting OR convuls$).TI,AB.)	271
13	MEDLINE	2 AND (INTRACRANIAL-HEMORRHAGES#.DE. OR ((brain OR cerebral OR intracerebral OR intracranial OR subarachnoid) ADJ (haemorrhage OR hemorrhage OR bleed OR bleeds OR bleeding)).TI,AB.)	19
14	MEDLINE	2 AND (DISSEMINATED-INTRAVASCULAR-COAGULATION.DE. OR (disseminated ADJ intravascular ADJ (coagulation OR coagulopathy OR clotting) OR DIC).TI,AB.)	31
15	MEDLINE	2 AND ((EYE# OR EYE-DISEASES#).DE. OR (eye OR ophthalmic OR ophthalmol$OR retina OR retinas OR retinal OR cornea OR corneas OR corneal OR keratopath$OR glaucoma OR diplopi$OR myopi$).TI,AB.)	58
16	MEDLINE	2 AND (WOUNDS-AND-INJURIES#.DE. OR (accident$OR trauma OR traumas OR traumatic).TI,AB.)	88
17	MEDLINE	2 AND (MENTAL-DISORDERS#.DE. OR (neuropsychi$OR neuropsycho$OR psychology OR psychologic$OR psychiatric OR psychiatry OR psychopatholog$OR neurocogniti$OR cognitive OR cognition OR psychosis OR psychoses OR depression OR depressive OR depressed OR panic OR delus$OR hallucinat$OR memory OR mood OR impulsiv$OR motor OR psychomotor OR parkinson OR parkinsons OR parkinsonism).TI,AB.)	1380
18	MEDLINE	2 AND ((TOOTH# OR TOOTH-DISEASES#).DE. OR (tooth OR teeth OR toothgr$OR teethgr$OR toothwear OR dental OR Bruxism).TI,AB.)	23

continued

No.	Database	Search term	Results
19	MEDLINE	1 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 17 OR 18	2297
20	MEDLINE	19 NOT (ANIMAL=YES NOT HUMAN=YES)	1812
21	EMBASE	(3–4-METHYLENEDIOXYMETHAMPHETAMINE-CO OR 3–4-METHYLENEDIOXYMETHAMPHETAMINE-SI OR 3–4-METHYLENEDIOXYMETHAMPHETAMINE-AE OR 3–4-METHYLENEDIOXYMETHAMPHETAMINE-TO).DE.	1368
22	EMBASE	3–4-METHYLENEDIOXYMETHAMPHETAMINE#.DE. OR (methylenedioxymethamphetamine OR MDMA OR ecstasy OR ecstasy OR ectasy OR ectacy).TI,AB.	4109
23	EMBASE	22 AND ((DESIGNER-DRUG-CO OR DESIGNER-DRUG-SI OR DESIGNER-DRUG-AE OR DESIGNER-DRUG-TO OR STREET-DRUG-CO OR STREET-DRUG-SI OR STREET-DRUG-AE OR STREET-DRUG-TO).DE. OR (adverse OR harm OR harms OR harmful OR safety OR consequence$OR outcome$OR sequel$).TI,AB.)	650
24	EMBASE	22 AND (DEATH#.DE. OR (death OR deaths OR fatal$OR mortal$).TI,AB.)	448
25	EMBASE	22 AND (BODY-TEMPERATURE-DISORDER#.DE. OR (hyperthermi$OR pyrexi$OR hyperpyrexia$OR fever OR febrile OR heatstroke OR heat ADJ stroke).TI,AB.)	429
26	EMBASE	22 AND ((DISORDERS-OF-MINERAL-ELECTROLYTE-AND-METAL-METABOLISM# OR ABNORMAL-SUBSTRATE-CONCENTRATION-IN-BLOOD#).DE. OR (hyponatraemia OR hyponatremia OR water ADJ intoxication).TI,AB.)	171
27	EMBASE	22 AND ((CARDIOVASCULAR-SYSTEM# OR CARDIOVASCULAR-DISEASE#).DE. OR (heart OR cardiovascular OR cardiac).TI,AB.)	540
28	EMBASE	22 AND ((RESPIRATORY-TRACT-DISEASE# OR PNEUMOMEDIASTINUM#).DE. OR (respiratory OR respiration OR lung OR lungs OR pulmonary OR pneumomediastin$OR pneumothora$).TI,AB.)	243
29	EMBASE	22 AND ((LIVER# OR LIVER-DISEASE#).DE. OR (liver OR hepatic OR hepatitis OR hepatotox$).TI,AB.)	312
30	EMBASE	22 AND ((KIDNEY# OR KIDNEY-DISEASE#).DE. OR (kidney OR renal).TI,AB.)	159
31	EMBASE	22 AND (RHABDOMYOLYSIS#.DE. OR (rhabdomyoly$OR myoglobinur$).TI,AB.)	116
32	EMBASE	22 AND (SEIZURE-EPILEPSY-AND-CONVULSION#.DE. OR (seizure OR seizures OR fit OR fits OR fitting OR convuls$).TI,AB.)	234
33	EMBASE	22 AND (BRAIN-HEMORRHAGE#.DE. OR ((brain OR cerebral OR intracerebral OR intracranial OR subarachnoid) ADJ (haemorrhage OR hemorrhage OR bleed OR bleeds OR bleeding)).TI,AB.)	43
34	EMBASE	22 AND (DISSEMINATED-INTRAVASCULAR-CLOTTING.DE. OR (disseminated ADJ intravascular ADJ (coagulation OR coagulopathy OR clotting) OR dic).TI,AB.)	46
35	EMBASE	22 AND ((EYE# OR EYE-DISEASE#).DE. OR (eye OR ophthalmic OR ophthalmol$OR retina OR retinas OR retinal OR cornea OR corneas OR corneal OR keratopath$OR glaucoma OR diplopi$OR myopi$).TI,AB.)	152
36	EMBASE	22 AND (INJURY#.DE. OR (accident$OR trauma OR traumas OR traumatic).TI,AB.)	543
37	EMBASE	22 AND ((MENTAL-DISEASE# OR MENTAL-FUNCTION#).DE. OR (neuropsychi$OR neuropsycho$OR psychology OR psychologic$OR psychiatric OR psychiatry OR psychopatholog$OR neurocogniti$OR cognitive OR cognition OR psychosis OR psychoses OR depression OR depressive OR depressed OR panic OR delus$OR hallucinat$OR memory OR mood OR impulsiv$OR motor OR psychomotor OR parkinson OR parkinsons OR parkinsonism).TI,AB.)	2140
38	EMBASE	22 AND (MOUTH-AND-TEETH#.DE. OR (tooth OR teeth OR toothgr$OR teethgr$OR toothwear OR dental OR Bruxism).TI,AB.)	18
39	EMBASE	21 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38	3253
40	EMBASE	39 NOT (ANIMAL=YES NOT HUMAN=YES)	2600
41	PsycINFO	METHYLENEDIOXYMETHAMPHETAMINE#.DE. OR (methylenedioxymethamphetamine OR MDMA OR ecstasy OR ecstasy OR ectasy OR ectacy).TI,AB.	1614

No.	Database	Search term	Results
42	PsycINFO	41 NOT (PO=ANIMAL NOT PO=HUMAN)	1259
43		combined sets 20, 40, 42	5671
44		dropped duplicates from 43	1840
45		unique records from 43	3831

Web of Science; run 7 October 2007

No.	Search term	Results
# 1	TS=(Methylenedioxymethamphetamine OR MDMA OR ecstasy OR ecstasy OR ectasy OR ectacy)	4424
# 2	#1 AND (TS=(adverse OR harm OR harms OR harmful OR safety OR consequence* OR outcome* OR sequel*))	518
# 3	#1 AND (TS=(death OR deaths OR fatal* OR mortal*))	369
# 4	#1 AND (TS=(hyperthermi* OR pyrexi* OR hyperpyrexia* OR fever OR febrile OR heatstroke OR (heat ADJ stroke)))	329
# 5	#1 AND (TS=(hyponatraemia OR hyponatremia OR (water ADJ intoxication)))	44
# 6	#1 AND (TS=(heart OR cardiovascular OR cardiac))	156
# 7	#1 AND (TS=(respiratory OR respiration OR lung OR lungs OR pulmonary OR pneumomediastin* OR pneumothora*))	76
# 8	#1 AND (TS=(liver OR hepatic OR hepatitis OR hepatotox*))	182
# 9	#1 AND (TS=(kidney OR renal))	68
# 10	#1 AND (TS=(rhabdomyoly* OR myoglobinur*))	65
# 11	#1 AND (TS=(seizure OR seizures OR fit OR fits OR fitting OR convuls*))	113
# 12	#1 AND (TS=((brain OR cerebral OR intracerebral OR intracranial OR subarachnoid) SAME (haemorrhage OR hemorrhage OR bleed OR bleeds OR bleeding)))	24
# 13	#1 AND (TS=((disseminated SAME intravascular SAME (coagulation OR coagulopathy OR clotting)) OR DIC))	23
# 14	#1 AND (TS=(eye OR ophthalmic OR ophthalmol* OR retina OR retinas OR retinal OR cornea OR corneas OR corneal OR keratopath* OR glaucoma OR diplopi* OR myopi*))	18
# 15	#1 AND (TS=(accident* OR trauma OR traumas OR traumatic))	72
# 16	#1 AND (TS=(neuropsychi* OR neuropsycho* OR psychology OR psychologic* OR psychiatric OR psychiatry OR psychopatholog* OR neurocogniti* OR cognitive OR cognition OR psychosis OR psychoses OR depression OR depressive OR depressed OR panic OR delus* OR hallucinat* OR memory OR mood OR impulsiv* OR motor OR psychomotor OR Parkinson OR Parkinsons OR Parkinsonism))	909
# 17	#1 AND (TS=(tooth OR teeth OR toothgr* OR teethgr* OR toothwear OR dental OR bruxism))	20
# 18	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	1879
	unique additional citations after de-duplication against Dialog DataStar results	563

Appendix 4

Updated literature search: results

Our updated literature searches identified the following potentially relevant studies, which should be considered for inclusion in any update of this review.

Ahmed M, Islam S, Hoffman GR. Widespread oral and oropharyngeal mucosal oedema induced by ecstasy (MDMA): A case for concern. *Br J Oral Maxillofac Surg* 2007;**45**:496–8.

Brown J, Edwards M, McKone E, Ward J. A long-term ecstasy-related change is visual perception. *Psychopharmacology* 2007;**193**:437–46.

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Eifinger F, Roth B, Kröner L, Rothschild MA. Life-threatening ecstasy ingestion in a young infant. *Notarzt* 2007;**23**:165–6.

Falck RS, Jichuan W, Carlson RG. Depressive symptomatology in young adults with a history of MDMA use: a longitudinal analysis. *J Psychopharmacol* 2008;**22**:47–54.

Feldman KW, Mazor S. Ecstasy ingestion causing heatstroke-like, multiorgan injury in a toddler. *Pediatr Emerg Care* 2007;**23**:725–6.

Golding JF, Groome DH, Rycroft N, Denton Z. Cognitive performance in light current users and ex-users of ecstasy (MDMA) and controls. *Am J Drug Alcohol Abuse* 2007;**33**:301–7.

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Guillot C. Is recreational ecstasy (MDMA) use associated with higher levels of depressive symptoms? *J Psychoactive Drugs* 2007;**39**:31–9.

Hanson K. Neurocognitive and personality function in MDMA and polydrug users: evidence of nonspecific impairments. *Dissertation Abstracts International: Section B: The Sciences and Engineering* 2007;**67**:4105.

Hoshi R, Cohen L, Lemanski L, Piccini P, Bond A, Curran HV. Ecstasy (MDMA) does not have long-term effects on aggressive interpretative bias: A study comparing current and ex-ecstasy users with polydrug and drug-naive controls. *Exp Clin Psychopharmacol* 2007;**15**:351–8.

Hoshi R, Mullins K, Boundy C, Brignell C, Piccini P, Curran HV. Neurocognitive function in current and ex-users of ecstasy in comparison to both matched polydrug-using controls and drug-naïve controls. *Psychopharmacology* 2007;**194**:371–9.

Jager G, de Win MM, Vervaeke H, Schilt T, Kahn R, van den Brink W, *et al*. Incidental use of ecstasy: No evidence for harmful effects on cognitive brain function in a prospective fMRL study. *Psychopharmacology* 2007;**193**:403–14.

Jager G, de Win MML, van der Tweel I, Schilt T, Kahn RS, van den Brink W, *et al*. Assessment of cognitive brain function in ecstasy users and contributions of other drugs of abuse: results from an fMRI study. *Neuropsychopharmacology* 2008;**33**:247–58.

Kalechstein A, De La Garza R II, Mahoney J, Fantegrossi W, Newton T. MDMA use and neurocognition: a meta-analytic review. *Psychopharmacology* 2007;**189**:531–7.

Krebs T, Johansen P. No evidence of decrease in cognitive function in users of low-dose ecstasy. *Arch Gen Psychiatry* 2008;**65**:236.

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Nicolato R, Pacheco J, Boson L, Leite R, Salgado JV, Romano S, *et al*. Cotard's syndrome induced by ecstasy. *J Bras Psiquiatr* 2007;**56**:64–6.

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Sauvageau A. Death from a possible anaphylactic reaction to ecstasy. *Clin Toxicol (Philadelphia PA)* 2008;**46**:156.

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Silins E, Copeland J, Dillon P. Qualitative review of serotonin syndrome, ecstasy (MDMA) and the use of other serotonergic substances: hierarchy of risk. *Aust NZ J Psychiatry* 2007;**41**:649–55.

Stull BW. Spontaneous pneumomediastinum following ecstasy ingestion and sexual intercourse. *Emerg Med J* 2008;**25**:113–14.

Wareing M, Fisk J, Montgomery C, Murphy P, Chandler M. Information processing speed in ecstasy (MDMA) users. *Hum Psychopharmacol Clin Exp* 2007;**22**:81–8.

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Appendix 5

Mapping of outcome measures into composite domains

Domain	Instrument	Abbreviation	Outcome measure
Aggression/anger	Aggression questionnaire[370]	AQ	Anger
			Hostility
			Physical
			Total
			Verbal
	Aggression Rating Scale[371]	ARS	Overall score
	Angry Stories Task[372]	AST	Reading time – angry endings – ms
			Reading time – non-angry endings – ms
	Buss–Durkee Hostility Inventory[373]	BDHI	Direct
			Guilty
			Irritability
			Total
	Interpretative Bias test[154,374]	IB	Reaction time
			Reaction time – aggressive – ms
			Reaction time – neutral – ms
			Sentences correctly identified
			Time to endorse as seen
			Time to endorse as seen – aggressive – ms
			Time to endorse as seen – neutral – ms
	Multidimensional Anger Inventory[375]	MAI	Anger–arousal
			Anger–in
			Anger–out
			Hostile outlook
			Range
			Total
	Point Subtraction Aggression Paradigm[376]	PSAP	Aggressive responding – study end
	Symptom Check List (SCL-90-R)[377]	SCL-90-R	Aggression/hostility score
Anxiety	Beck Anxiety Inventory[378]	BAI	Overall score
	DSM-IV[379]	DSM-IV	Current anxiety disorder
			Lifetime anxiety disorder
	Hospital Anxiety and Depression scale[380]	HADS	Anxiety score
	Hamilton Anxiety Rating Scale[381]	HARS	Overall score
	Mood Rating Scale (visual analogue scale)[382]	MRS–VAS	Anxiety vs calmness score
	NS	NS	In-test state anxiety

continued

Domain	Instrument	Abbreviation	Outcome measure
			Medication for anxiety disorder
	Profile of Mood States (visual analogue scale)[383]	POMS	Anxiety score
	Symptom Check List (SCL-90)	SCL-90	Anxiety score
			Phobic anxiety score
	Symptom Check List (SCL-90-R)[377]	SCL-90-R	Anxiety score
			Phobic anxiety score
	Symptom Check List – Brief Symptom Inventory[384]	SCL– BSI	Anxiety
			Anxiety score
			Phobic anxiety
			Phobic anxiety score
	Self-rated	S-R	Anxiety
	State–Trait Anxiety Inventory[385]	STAI	State anxiety
			Trait anxiety
	State–Trait Anxiety Inventory (Dutch)[385,386]	STAI-DY	Trait anxiety
Attention (general)	Speed of Comprehension Test[387]	SCT	Sentences correct
	Wechsler Memory Scale – Revised[388]	WMS-R	Attention and concentration index score
Attention–focus-execute	Automated Performance Test System[389]	APTS	AREACT
	CANTAB intradimensional/extra-dimensional test[390]	CANTAB 3D-ID/ED	Errors – simple dimensional
			Errors – simple dimensional – reversal
			Latency – simple dimensional
			Latency – simple dimensional – reversal
	Cognitive Drug Research battery[391]	CDR	Choice 1 – correct [%]
			Choice 1 – reaction time [ms]
			Choice 2 – correct [%]
			Choice 2 – reaction time [ms]
			Simple reaction time [ms]
	FePsy[392]	FePsy	Auditive reaction time – dominant hand [ms]
			Auditive reaction time – non-dominant hand [ms]
			Binary choice – errors [*n*]
			Binary choice – reaction time [ms]
			Visual reaction time – dominant hand [ms]
			Visual reaction time – non-dominant hand [ms]
	Matching Familiar Figures Task-20[393]	MFFT-20	Latency to first response [s]
			Total errors [*n*]
	NS	NS	Binary choice task – reaction time [ms]
			Complex reaction time [ms]
			Double digit cancellation – time – s
			Immediate memory task – correct [*n*]
			Letter cancellation – commission errors
			Letter cancellation – omission errors
			Letter cancellation – time – s

Domain	Instrument	Abbreviation	Outcome measure
			Letter comparison speed task – three-letter – correct [%]
			Letter comparison speed task – three-letter – correct [*n*]
			Letter comparison speed task – three-letter – errors [*n*]
			Letter comparison speed task – six-letter – correct [%]
			Letter comparison speed task – six-letter – correct [*n*]
			Letter comparison speed task – six-letter – errors [*n*]
			Letter comparison speed task – nine-letter – correct [%]
			Letter comparison speed task – nine-letter – correct [*n*]
			Letter comparison speed task – nine-letter – errors [*n*]
			Pattern comparison speed task – three-pattern – correct [*n*]
			Pattern comparison speed task – three-pattern – errors [*n*]
			Pattern comparison speed task – six-pattern – correct [*n*]
			Pattern comparison speed task – six-pattern – errors [*n*]
			Pattern comparison speed task – nine-pattern – correct [*n*]
			Pattern comparison speed task – nine-pattern – errors [*n*]
			Simple auditory reaction time [ms]
			Simple visual reaction time [ms]
			Visual reaction time [ms]
			Visual search – time [s]
	Ruff 2 and 7 Selective Attention Test[394]	Ruff 2 and 7	Controlled search accuracy
			Controlled search speed
			Total accuracy
			Total speed
	Symbol Digit Modalities test[395]	SDMT	Correct [*n*]
			Overall score
	Stroop test[396]	Stroop	Colour reading – errors [*n*]
			Colour reading – time [ms]
			Colour reading – time [s]
			Word reading – errors [*n*]
			Word reading – time [ms]
			Word reading – time [s]
	Test for Attentional Performance[397]	TAP	1 – phasic reaction time [ms]

continued

Domain	Instrument	Abbreviation	Outcome measure
			1 – tonic reaction time [ms]
	Test of Everyday Attention[398]	TEA	Map search 1
			Map search 2
			Telephone search
	Trailmaking Test[399–401]	TMT	Part A – errors
			Part A – time
			Part B – errors
			Part B – part A – time
			Part B – time
			Part B – T-score
	Colour trails test[402]	TMT-C	Part 1 – time
			Part 2 – time
	Wechsler Adult Intelligence Scale – Third Edition[403]	WAIS-III	Digit symbol [standard score units]
	Wechsler Adult Intelligence Scale – Revised[404]	WAIS-R	Digit symbol
			Digit symbol [age-corrected scaled score]
	Walter Reed Army Institute of Research Performance Assessment Battery[405]	WRAIR PAB	Code substitution
Attention–sustain	CANTAB intradimensional/extra-dimensional test[390]	CANTAB 3D-ID/ED	Errors – compound dimensional
			Errors – compound dimensional – reversal
			Errors – intradimensional
			Errors – intradimensional – reversal
			Latency – compound dimensional
			Latency – compound dimensional – reversal
			Latency – intradimensional
			Latency – intradimensional – reversal
	Affective Go/No-go task[406]	CANTAB A-G/N-G	Omission errors [*n*]
	Cognitive Drug Research battery[391]	CDR	Number vigilance – correct [%]
			Number vigilance – reaction time [ms]
	Go/No-Go task[397,407]	G/N-G	Correct responses
			Punishment-reward – omission errors
			Reward-punishment – omission errors
			Summed conditions – omission errors
	Rapid visual information processing[408]	RVIP	10-minute task – correct [*n*]
	Test for Attentional Performance[397]	TAP	Visual scanning – accuracy/speed correlation [z-score]
			Visual scanning – critical trials – correct [*n*]
			Visual scanning – critical trials – time [ms]
			Visual scanning – non-critical trials – correct [*n*]
			Visual scanning – non-critical trials – time [ms]
			Visual scanning – time/accuracy correlation [z-score]
	Test of Everyday Attention[398]	TEA	Elevator counting

Domain	Instrument	Abbreviation	Outcome measure
			Elevator counting with distraction
			Elevator counting with reversal
Decision-making	Iowa Gambling Task[409,410]	IGT	Block 1
			Block 2
			Block 3
			Block 4
			Block 5
			Net score
	Rogers Gambling Task[411]	RGT	High loss – choices
			High loss – latency – ms
			High probability – choices
			High probability – latency – ms
			High win – choices
			High win – latency – ms
			Low loss – choices
			Low loss – latency – ms
			Low probability – choices
			Low probability – latency – ms
			Low win – choices
			Low win – latency – ms
			Overall – choices
			Overall – latency – ms
	Revised Strategy Applications Test[412]	R-SAT	Total 1 – all pages
			Total 2 – not including first two pages
Depression	Beck Depression Inventory[413]	BDI	Median
			Overall score
	Beck Depression Inventory II[414]	BDI-II	Cognitive subscale
			Cognitive–affective subscale
			Overall score
			Somatic subscale
	Composite International Diagnostic Interview[415]	CIDI	Current diagnosis [*n*]
	Hospital Anxiety and Depression Scale[380]	HADS	Depression score
	Hamilton Depression Rating Scale[416]	HDRS	Overall score
	Minnesota Multiphasic Personality Inventory[417]	MMPI	Overall score
	Minnesota Multiphasic Personality Inventory – 2[418]	MMPI 2	Overall score
	NS	NS	Medication for depression
	Symptom Check List (SCL-90)	SCL-90	Depression score
	Symptom Check List (SCL-90-R)[377]	SCL-90-R	Depression score

continued

Domain	Instrument	Abbreviation	Outcome measure
	Symptom Check List – Brief Symptom Inventory[385]	SCL–BSI	Depression
			Depression score
	Self-rated	S-R	Depression
Disinhibition	Frontal Systems Behavioral scale[419]	FrSBe	Overall score
Executive function (general)	Behavioural Assessment of the Dysexecutive Syndrome – Dysexecutive questionnaire[420]	DEX	Dysexecutive function score
	Frontal Systems Behavioral scale[419]	FrSBe	Executive dysfunction
	Random letter generation[421,422]	Random letter generation	Alphabetical sequences – 1 s
			Alphabetical sequences – 2 s
			Alphabetical sequences – 4 s
			Alphabetical sequences [standardised score]
			Composite score [standardised score]
			Letters [standardised score]
			Number of letters – 1 s
			Number of letters – 2 s
			Number of letters – 4 s
			Redundancy – 1 s –%
			Redundancy – 2 s –%
			Redundancy – 4 s –%
			Redundancy [standardised score]
			Repeated sequences – 1 s
			Repeated sequences – 2 s
			Repeated sequences – 4 s
			Repeated sequences [standardised score]
			Vowels – 1 s – %
			Vowels – 2 s – %
			Vowels – 4 s – %
Executive function – inhibition of return	NS	NS	Mean slowing [ms]
Executive function – planning	Behavioural Assessment of the Dysexecutive Syndrome[420]	BADS	Action program test
			Key search test
			Modified six elements test
			Temporal judgement test
			Total profile score
			Zoo map test
	Plan-A-Day simulation[423]	Plan-A-Day	End score
			Peak – end score
			Peak score
			Sequences of deletions
			Single deletions
			Use of F2 key
	CANTAB Stockings of Cambridge[424]	SOC	Initial thinking time [ms]

Domain	Instrument	Abbreviation	Outcome measure
	Tower of London[425]	ToL	Errors – *n*
			Excess moves
			Excess moves – %
			Initial thinking time – ms
			Perfect solutions
			Planning time – s
			Solution time – s
			Subsequent thinking time – ms/move
			Total moves
			Total time – s
			Trials completed – n
Executive function – processing speed	NS	NS	Letters – correct [*n*]
			Patterns – correct [*n*]
			Total errors [*n*]
Executive function – response inhibition	Affective Go/No-go task[408]	CANTAB A-G/N-G	Commission errors – non-shift block
			Commission errors – shift block
			Commission errors [*n*]
	Go/No-Go task[397,407]	G/N-G	Commission errors
			Punishment–reward – commission errors
			Punishment–reward – gain
			Reaction time – ms
			Reward–punishment – commission errors
			Reward–punishment – gain
			Summed conditions – Σ commission errors
			Summed conditions – Σ gain
	Huizinga and van der Molen – Eriksen Flankers test[426,427]	HvdM EF	EF – Eriksen Flankers – correct – %
			EF – Eriksen Flankers – reaction time – ms
	Huizinga and van der Molen – stop signal[428]	HvdM SS	Stop signal – reaction time – ms
	Stroop test[396]	Stroop	Colour naming – time [s]
			Inhibition/switching contrast [s]
			Interference – errors [*n*]
			Interference – negative priming – time [ms]
			Interference – no negative priming – time [ms]
			Interference – switching time difference [s]
			Interference – time [ms]
			Interference – time [s]
			Interference – time difference [s]
			Interference + switching – errors [*n*]
			Interference + switching – time [s]
			Switching – time [ms]
	Test for Attentional Performance[397]	TAP	Selective visual attention – sustain – time [ms]

continued

Domain	Instrument	Abbreviation	Outcome measure
Executive function – shifting	Behavioural Assessment of the Dysexecutive Syndrome[420]	BADS	Rule shift cards test
	Brixton Spatial Anticipation task[429]	BSA	Errors [*n*]
	CANTAB intradimensional/extra-dimensional test[390]	CANTAB 3D–ID/ED	Errors – extra-dimensional
			Errors – extradimensional – reversal
			Latency – extra-dimensional
			Latency – extra-dimensional – reversal
	Huizinga and van der Molen – dots–triangles[47]	HvdM DT	Dots–triangles – correct – %
			Dots–triangles – response time – ms
	Huizinga and van der Molen – local–global[47]	HvdM LG	Local–global – correct – %
			Local–global – response time – ms
	NS	NS	Number/letter switch cost
			Plus/minus task switch cost
	Test of Everyday Attention[398]	TEA	Telephone search with counting
	Wisconsin Card-Sorting Test[430]	WCST	Categories
			Conceptual level responses [%]
			Failure to maintain set
			Learning-to-learn score
			No. ambig. error
			No. correct ambig.
			Non-perseverative errors
			Non-perseverative errors – %
			Perseverative errors
			Perseverative errors –%
			Perseverative responses
			Total no. correct
			Total no. errors
			Total no. trials
			Trials to first category
Executive function – updating	Keep Track Test[51]	Keep Track Test	Words correct [*n*]
	NS	NS	Consonant updating – score
			Non-spatial associative learning
Executive function – visual fluency	Delis–Kaplan Executive Function System[431]	D-KEFS	Closed
			Open
			Switching
			Total accuracy
			Total score
	Ruff Figural Fluency Test[432]	RFFT	Repeated designs [*n*]
			Unique designs – total [*n*]
	Rey–Osterrieth Complex Figure Test[433,434]	R-OCFT	Copy score
Impulsivity	Barratt Impulsiveness Scale[435,436]	BIS	Total
	Barratt Impulsiveness Scale-II[437]	BIS-II	Attentional

Domain	Instrument	Abbreviation	Outcome measure
			Cognitive
			Motor
			Non-planning
			Total
	Impulsivity self-rating scale[382]	ISRS	Overall score
	Adult impulsiveness, venturesomeness and empathy scale[438]	IVE	Overall score
	Matching Familiar Figures Task[439]	MFFT	Efficiency score
			Impulsivity score
	Matching Familiar Figures Task–20[393]	MFFT-20	Impulsivity score
	NS	NS	Bets16 – risk-taking score
			Delayed memory task – adjusted commision errors [*n*]
			Immediate memory task – adjusted commission errors [*n*]
	Rogers Gambling Task[411]	RGT	Gains only – latency [ms]
			Gains only – latency – ms
			Gains only – risk-averse choices
			Losses only – latency [ms]
			Losses only – latency – ms
			Losses only – risk-averse choices
			Losses only – risk-seeking choices
Intelligence	Kaufman Brief Intelligence Test[440]	K-BIT	Overall score
	Mill Hill Vocabulary Scale[441]	Mill Hill	Vocabulary
	Mehrfachwahl-Wortschatz-Intelligenztest (Multiple Choice Verbal Intelligence Test)[442,443]	MWT-B	Verbal IQ
	National Adult Reading Test [444,445]	NART	0
			IQ
			Overall score
	National Adult Reading Test (Dutch version)[444–446]	NART-D	IQ
	Quick Test[447]	Quick	Verbal IQ
	Raven's Progressive Matrices[448]	RPM	D
			E
			Total correct – C+D+E
			Total correct – D+E
			Total score
	Shipley Institute of Living Scale[449,450]	SILS	Abstraction
			IQ
			Verbal
	Spot the Word[451]	STW	Overall score

continued

Domain	Instrument	Abbreviation	Outcome measure
	Test of non-verbal intelligence (TONI-3)[452]	TONI-3	Overall score
	Wechsler Adult Intelligence Scale – Third Edition[403]	WAIS-III	Full-scale IQ
			Performance IQ
			Similarities
			Verbal IQ
			Vocabulary
	Wechsler Adult Intelligence Scale – Revised[404]	WAIS-R	Full-scale IQ
			General knowledge [information]
			Performance IQ
			Verbal IQ
			Vocabulary
			Vocabulary [median]
	Wechsler Abbreviated Scale of Intelligence[403]	WASI	Vocabulary
	Woodcock–Johnson Revised Test of Achievement[453]	WJR	Letter-word identification
			Letter-word identification – standard score
			Word attack
			Word attack – standard score
Memory (general)	Rivermead Behavioural Memory Test[454]	RBMT	Total score
	Wechsler Memory Scale – III[455]	WMS-III	General index score
	Wechsler Memory Scale – Revised[388]	WMS-R	General index score
Memory (general) – delayed	Lern- und Gedächtnis-test[456]	LGT-3	City map test
			German–Turkish test
			Library test
			Logos test
	Wechsler Memory Scale – III[455]	WMS-III	Auditory index score
	Wechsler Memory Scale – Revised[388]	WMS-R	Index score
	Walter Reed Army Institute of Research Performance Assessment Battery[405]	WRAIR PAB	Overall score
Memory – self-rated	Cognitive Failures Questionnaire[457]	CFQ	Other-rated – slips reported [%]
			Other-rated – total score
			Self-rated – slips reported [%]
			Self-rated – total score
	Everyday Memory Questionnaire[458]	EMQ	Overall score
	Fragebogen zum Alltagsgedächtnis (questionnaire on everyday memory)[459]	FZ–EMQ	Overall score
	Prospective Memory Questionnaire[460]	PMQ	Internally cued
			Long-term
			Long-term episodic
			Short-term

Domain	Instrument	Abbreviation	Outcome measure
			Short-term habitual
			Strategies
	Rivermead Behavioural Memory Test[454]	RBMT	Appointment
			Belonging
			First/second name
			Message
	Uplifts/hassles questionnaire[461]	Uplifts/hassles	Cognitive failures
	Virtual Week[462]	VW	All tasks – correct
			All tasks – correct – frequent ecstasy users
			All tasks – correct – infrequent ecstasy users
			All tasks – late
			All tasks – missed
			All tasks – wrong
			Irregular task – correct
			Irregular task – late
			Irregular task – missed
			Irregular task – wrong
			Regular task – correct
			Regular task – late
			Regular task –missed
			Regular task – wrong
			Time-check task – correct
			Time-check task – late
			Time-check task – missed
			Time-check task – wrong
Memory (general) – immediate	Automated Performance Test System[389]	APTS	Sternberg numbers – correct – n
			Sternberg numbers – speed [s]
	Cognitive Drug Research battery[391]	CDR	Sternberg numbers – speed [ms]
	FePsy[392]	FePSY	Sternberg figures – serial
			Sternberg figures – simultaneous
			Sternberg words – serial
			Sternberg words – simultaneous
	Lern- und Gedächtnis-test[456]	LGT-3	City map test
			German–Turkish test
			Library test
			Logos test
	Wechsler Memory Scale – III[455]	WMS-III	Auditory index score
			Index score
Memory – learning performance	Buschke selective reminding task[463]	Buschke	Trial 3 – trial 1
	Rey Auditory Verbal Learning Test[464]	RAVLT	Learning – trial 5 – trial 1

continued

Domain	Instrument	Abbreviation	Outcome measure
	Rey Auditory Verbal Learning Test – German version[464,465]	RAVLT-G	Learning – trial 5 – trial 1
			Repetitions required for learning – n
	VIG: visuospatial memory[466]	VIG	Learning – trial 5 – trial 1
			Repetitions required for learning – n
	Wechsler Memory Scale – III[455]	WMS-III	Logical memory – verbal learning slope
Memory – verbal (general)	California Verbal Learning Test – Second Edition[467]	CVLT-II	Total recognition – z-score
Memory – verbal delayed	Automated Performance Test System[389]	APTS	Overall score
	Buschke selective reminding task[463]	Buschke	Overall score
	Cognitive Drug Research battery[391]	CDR	Word recall [*n*]
	California Verbal Learning Test – Second Edition[467]	CVLT-II	Long-delay cued recall – z-score
			Long-delay cued recall correct
			Long-delay false positives
			Long-delay free recall – z-score
			Long-delay free recall correct
			Long-delay recognition hits
	NS	NS	Prose recall
			Prose retained – %
	Rey Auditory Verbal Learning Test[464]	RAVLT	Overall score
			Recognition
			Recognition – errors – list A
			Recognition – errors – list B
			Recognition – list A
			Recognition – list B
			Trial 8
	Rey Auditory Verbal Learning Test – Chinese version[464]	RAVLT-C	Overall score
			Recognition
			Trial 8
	Rey Auditory Verbal Learning Test – Dutch version[464,468]	RAVLT-D	Recognition
			Trial 8
	Rey Auditory Verbal Learning Test – German version[464,465]	RAVLT-G	Trial 8
	Rivermead Behavioural Memory Test[454]	RBMT	Prose recall
			Prose recall (est)
			Prose recall (sum of two tests)
	Wechsler Memory Scale – adapted[388]	WMS adapted	Logical memory
	Wechsler Memory Scale – III[455]	WMS-III	Auditory index score
			Index score
			Logical memory
			Logical memory – story A recall unit score
			Logical memory – verbal % ret
			Verbal paired associates

Domain	Instrument	Abbreviation	Outcome measure
	Wechsler Memory Scale – Revised[388]	WMS-R	Logical memory
			Verbal paired associates
			Verbal reproduction
Memory – verbal immediate	Auditory Consonant Trigrams[469]	ACT	Score
	Automated Performance Test System[389]	APTS	Overall score
	Buschke selective reminding task[465]	Buschke	Trial 1
			Trial 2
			Trial 3
	Cognitive Drug Research battery[391]	CDR	Word recall [*n*]
	California Verbal Learning Test – Second Edition[467]	CVLT-II	Short-delay cued recall – z-score
			Short-delay cued recall correct
			Short-delay free recall – z-score
			Short-delay free recall correct
			Total intrusions
			Total list B correct
			Total list B plus trial 1 correct
			Total repetitions
			Total trials 1–5 correct – *n*
			Trial 1 correct – *n*
			Trial 5 correct – *n*
			Trial B correct – *n*
	Matched verbal recall/ recognition[470]	MRR	Recall – hits – intrusions
			Recognition – hits – false alarms
	NS	NS	Computation span
			Digit span – backwards
			Digit span – forwards
			Free recall
			Letter span – forwards
			Prose recall
			Verbal paired associates – perseverative responses – *n*
			Verbal paired associates – total forgotten – *n*
			Verbal paired associates – trials to completion
			Verbal paired associates – errors trial 1
			Verbal paired associates – errors trial 2
			Verbal paired associates – errors trial 3
			Verbal paired associates – errors trial 4
			Verbal paired associates – trial 1- correct – *n*
			Word span
	Rey Auditory Verbal Learning Test[464]	RAVLT	Adjusted list A
			Adjusted list B

continued

Domain	Instrument	Abbreviation	Outcome measure
			Interference – trial 5 – trial 7
			List B
			Proactive interference – trial 1 – trial 6
			Recall consistency –%
			Retroactive interference – trial 5 – trial 6
			Sum of trials 1–5
			Trial 1
			Trial 1 – errors
			Trial 2
			Trial 2 – errors
			Trial 3
			Trial 3 – errors
			Trial 4
			Trial 4 – errors
			Trial 5
			Trial 5 – errors
			Trial 6
			Trial 6 – errors
			Trial 6 – interference list
			Trial 7
			Trial 7 – errors
			Trial 7 – post-interference
	Rey Auditory Verbal Learning Test – Chinese version[464]	RAVLT-C	Items recalled in all trials 1–5
			Overall score
	Rey Auditory Verbal Learning Test – Dutch version[464,468]	RAVLT-D	Sum of trials 1–5
	Rey Auditory Verbal Learning Test – German version[464,465]	RAVLT-G	Interference – trial 5 – trial 7
			Trial 1
	Rivermead Behavioural Memory Test[454]	RBMT	Prose recall
			Prose recall (est)
			Prose recall (sum of two tests)
	Recognition memory tests (Warrington)[471]	RMT	Recognition
	Wechsler Adult Intelligence Scale – Third Edition[403]	WAIS-III	Digit span – forwards
	Wechsler Adult Intelligence Scale – Revised[404]	WAIS-R	Digit span – backwards
			Digit span – forwards
	Wechsler Memory Scale – adapted[388]	WMS adapted	Logical memory
	Wechsler Memory Scale – III[455]	WMS-III	Auditory index score
			Index score
			Logical memory
			Logical memory – story A
			Logical memory – story B
			Logical memory 1 – 1st recall total score – stories A and B1

Domain	Instrument	Abbreviation	Outcome measure
			LOGICAL memory 1 – recall total score – sum recall unit scores stories A, B1, B2
			Verbal paired associates
	Wechsler Memory Scale – Revised[388]	WMS-R	Digit span – total
			Index score
			Logical memory
			Verbal paired associates
Memory – visual delayed	Aggie figures learning test[472]	AFLT	Overall score
			Recognition
	Memory for Designs[473]	MFD	Correct – *n*
	CANTAB Pattern recognition memory[474]	PRM	Correct – %
			Latency – ms
	Rivermead Behavioural Memory Test[454]	RBMT	Face recognition
			Picture recognition
			Route
	Rey–Osterrieth Complex Figure Test[433,434]	R-OCFT	Retained –%
			Total score
	Wechsler Memory Scale – III[455]	WMS-III	Visual
			Visual reproduction
	Wechsler Memory Scale – Revised[388]	WMS-R	Visual paired associates
			Visual reproduction
Memory – visual immediate	Aggie figures learning test[472]	AFLT	Overall score
	Automated Performance Test System[389]	APTS	ACODES – correct – *n*
			ACODES – speed – s
	Benton Visual Retention Test – Fifth edition[475]	BVRT	Correct – *n*
			Errors – *n*
	CANTAB Delayed match to sample[476]	CANTAB DMTS	All delayed – latency – ms
			Delayed – 0s – correct –%
			Delayed – 12s – correct –%
			Delayed – 4s – correct –%
			Delayed – latency – ms
			Simultaneous – correct –%
			Simultaneous – latency – ms
	CANTAB Spatial Span test[477]	CANTAB SS	Spatial span
	Corsi Block Tapping Test[478]	Corsi Block	Span
			Span plus one
	Continuous visual memory test[479]	CVMT	d´
			False alarms
			Hits
			Recognition
			Total
	Memory for Designs[473]	MFD	Correct – *n*

continued

Domain	Instrument	Abbreviation	Outcome measure
			Trials to completion – *n*
	NS	NS	Paired associates – memory score – six-box trial
			Paired associates – memory score – eight-box trial
			Pattern recognition – correct [%]
			Pattern recognition – latency [s]
			Spatial recognition – correct [%]
			Spatial recognition – latency [s]
			Spatial span
			Visual paired associates – six-box trial – errors [*n*]
			Visual paired associates – six-box trial – trials to completion
			Visual paired associates – eight-box trial – errors [*n*]
			Visual paired associates – eight-box trial – trials to completion
	CANTAB Pattern recognition memory[474]	PRM	Correct – %
			Latency – ms
	Rey Auditory Verbal Learning Test[464]	RAVLT	List B
			Sum of trials 1–5
			Trial 6 – interference list
	Rivermead Behavioural Memory Test[454]	RBMT	Route
	Recognition memory tests (Warrington)[471]	RMT	Recognition
	Rey–Osterrieth Complex Figure Test[433,434]	R-OCFT	Total score
	VIG: visuospatial memory[466]	VIG	Recall
	Wechsler Memory Scale – III[455]	WMS-III	Spatial span – visual backwards
			Spatial span – visual forwards
			Spatial span – visual total
			Visual
			VISUAL reproduction
	Wechsler Memory Scale – Revised[388]	WMS-R	Figural memory
			Index score
			Visual memory span
			Visual paired associates
			Visual reproduction
			Visual reproduction% ret.
			Visual reproduction 1
Memory – working	Huizinga and van der Molen – mental counters[480]	HvdM MC	MC – mental counters – correct – %
			MC – mental counters – reaction time – ms
	Huizinga and van der Molen – tic-tac-toe[480]	HvdM TTT	Tic-tac-toe – correct – %
			Tic-tac-toe – reaction time – ms
	n-back test (NS)	*n*-back	0-back – correct responses – n
			0-back – reaction time – ms

Domain	Instrument	Abbreviation	Outcome measure
			1-back – correct responses – *n*
			1-back – reaction time – ms
			1-back and 2-back – auditory – correct responses – simple – %
			1-back and 2-back – auditory – reaction time – simple – ms
			1-back and 2-back – divided – correct responses – %
			1-back and 2-back – divided – reaction time – ms
			1-back and 2-back – divided – reaction time – ms
			1-back and 2-back – visual – correct responses – selective – %
			1-back and 2-back – visual – correct responses – simple – %
			1-back and 2-back – visual – reaction time – selective – %
			1-back and 2-back – visual – reaction time – selective – ms
			1-back and 2-back – visual – reaction time – simple – ms
			2-back – correct responses – *n*
			2-back – figures – correct responses – *n*
			2-back – figures – reaction time – ms
			2-back – letters – correct responses – *n*
			2-back – letters – reaction time – ms
			2-back – reaction time – ms
	NS	NS	Affective – correct – 500 ms delay – %
			Affective – correct – 8000 ms delay – %
			Affective – latency – 500 ms delay – ms
			Affective – latency – 8000 ms delay – ms
			Computation span
			Delayed memory task – correct [*n*]
			Reading span
			Serial subtraction – SS7 – correct – *n*
			Serial subtraction – SS7 – errors [*n*]
			Spatial recall – correct – *n*
			Spatial task – between errors–four-box trial
			Spatial task – between errors–six-box trial
			Spatial task – between errors–eight-box trial
			Spatial task – error score – 4000 ms delay
			Spatial task – error score – 4000–500 ms difference
			Spatial task – error score – 500 ms delay
			Spatial task – error score – 8000 ms delay
			Spatial task – error score – 8000–500 ms difference

continued

Domain	Instrument	Abbreviation	Outcome measure
			Spatial task – latency – 4000 ms delay – ms
			Spatial task – latency – 4000–500 ms difference – ms
			Spatial task – latency – 500 ms delay – ms
			Spatial task – latency – 8000 ms delay – ms
			Spatial task – latency – 8000–500 ms difference – ms
			Spatial task – search strategy score
			Spatial task – within errors–four-box trial
			Spatial task – within errors–six-box trial
			Spatial task – within errors–eight-box trial
			Visuospatial span
			Visuospatial span – alphabetic generation
			Visuospatial span – control – no dual task
			Visuospatial span – overall mean
			Visuospatial span with random letter generation
	Paced Auditory Serial Addition Test[481]	PASAT	Hits – 1.6 s
			Hits – 2.4 s
	Rapid visual information processing[408]	RVIP	5-minute task
	Test for Attentional Performance[397]	TAP	5 – divided attention – time [ms]
			8 – intermodal integration – time [ms]
	Wechsler Adult Intelligence Scale – Third Edition[403]	WAIS-III	Letter number sequencing – scaled score
	Wechsler Memory Scale – III[455]	WMS-III	Index score
			Mental control
	Wechsler Memory Scale – Revised[388]	WMS-R	Mental control
	Walter Reed Army Institute of Research Performance Assessment Battery[405]	WRAIR PAB	Matching to sample task
			Serial add and subtract test
Mood	Affective Go/No-go task[406]	CANTAB A-G/N-G	Affective bias [ms]
	EWL Mood Rating Scale[482]	EWL	Activity
			Depressiveness
			Emotional excitability
			Extro-/introversion
			Inactivation
			Well-being
	Frontal Systems Behavioral Scale[416]	FrSBe	Apathy
	Mood Rating Scale (visual analogue scale)[382]	MRS	Discontentedness
			Sedation
	Nowlis Mood Adjective Checklist[483]	NMAC	Overall score
	Profile Of Mood States (Visual Analogue Scale)[383]	POMS	Anger–hostility
			Confusion
			Depression–dejection

Domain	Instrument	Abbreviation	Outcome measure
			Fatigue
			Friendliness
			Tension
			Vigour
	Symptom Check List (SCL-90)	SCL-90	Positive moods
	Self-rated	S-R	Abnormal
			Calm
			Clearheaded
			Depressed
			Drowsy
			Energetic
			Good tempered
			Ill
			Interested
			Quick witted
			Sad
			Sober
			Steady
			Unpleasant
			Unsociable
			Well co-ordinated
Motor function	Automated Performance Test System[389]	APTS	ATAP – finger tapping test – non-dominant hand
			BTAP – finger tapping test – non-dominant hand
	Grooved pegboard[484]	Grooved pegboard	Time – dominant hand
			Time – left hand
			Time – non-dominant hand
			Time – right hand
	NS	NS	Finger tapping test – dominant hand
			Finger tapping test – non-dominant hand
Orientation	Rivermead Behavioural Memory Test[454]	RBMT	Date
			Orientation
Perceptual organisation	Automated Performance Test System[389]	APTS	PATRNC correct – *n*
			PATRNC speed – s
	Judgment of Line Orientation[485]	JOLO	Pairs
	Mental Rotation test[486]	Mental rotation test	Completely perfect [*n*]
			Mirror – errors [*n*]
			Mirror – latency [ms]
			Reaction time [ms]
			Standard – errors [*n*]
			Standard – latency [ms]
	NS	NS	Heading task – angle 1 – correct [%]
			Heading task – angle 2 – correct [%]
			Heading task – angle 4 – correct [%]

continued

Domain	Instrument	Abbreviation	Outcome measure
			Heading task – angle 8 – correct [%]
	Wechsler Adult Intelligence Scale – Revised[404]	WAIS-R	Block design
			Block test – tile manipulation – copy – moves per problem
			Block test – tile manipulation – copy – no. completely perfect
			Block test – tile manipulation – copy – reaction time
			Block test – tile manipulation – copy – thinking time
			Block test – tile manipulation – mental rotation – moves per problem
			Block test – tile manipulation – mental rotation – no. completely perfect
			Block test – tile manipulation – mental rotation – thinking time
			Block test – tile manipulation – mirror – errors
			Block test – tile manipulation – mirror – latency – ms
			Block test – tile manipulation – mirror – moves per problem
			Block test – tile manipulation – mirror – no. completely perfect
			Block test – tile manipulation – mirror – reaction time
			Block test – tile manipulation – mirror – thinking time
	Walter Reed Army Institute of Research Performance Assessment Battery[405]	WRAIR PAB	Manikin task
			Time wall task
Personality	Eysenck Personality Questionnaire[487]	EPQ	Extroversion
			Lies
			Neuroticism
			Psychoticism
	Goldberg's Big Five questionnaire – Dutch version[488]	GB5	Agreeableness
			Conscientiousness
			Emotional stability
			Extroversion
			Open experiences
	Adult impulsiveness, venturesomeness and empathy scale[438]	IVE	Empathy
			Venturesomeness
	Sensation-Seeking Scale [489]	SSS	Sensation-seeking – boredom susceptibility
			Sensation-seeking – disinhibition
			Sensation-seeking – experience seeking
			Sensation-seeking – overall
			Sensation-seeking – thrill and adventure seeking
	Sensation-Seeking Scale – Dutch version[489,490]	SSS-D	Sensation-seeking – boredom susceptibility
			Sensation-seeking – disinhibition

Domain	Instrument	Abbreviation	Outcome measure
			Sensation-seeking – experience seeking
			Sensation-seeking – general
			Sensation-seeking – thrill and adventure seeking
	Tridimensional Personality Questionnaire[491]	TPQ	Harm avoidance
			Novelty seeking
			Reward dependence
Psychopathology	DSM-III-R – Structured Clinical Interview[492]	DSM-III-R SCI	Axis 1 disorders
			Axis 2 disorders
	DSM-IV[379]	DSM-IV	ADHD – current
			ADHD – lifetime
			Adjustment disorder – current
			Adjustment disorder – lifetime
			Affective disorder – current
			Affective disorder – lifetime
			Eating disorder – current
			Eating disorder – lifetime
			SIDP – axis II disorders
	ICD-10	ICD-10	Psychosis
	Personality Diagnostic Questionnaire – Revised[493]	PDQ-R	Overall score
	Symptom Check List (SCL-90)	SCL-90	Agoraphobia
			Anger–hostility
			Appetite
			Death cognitions
			Early waking
			Global score index
			Guilt
			Hostility
			Insomnia
			Insufficency
			Interpersonal sensitivity
			MDMA side effects
			Negative psychobiology
			Obessionality
			Obsession–compulsion
			Obsessive–compulsive
			Overeating
			Paranoid ideation
			Positive life experiences
			Positive psychobiology
			Psychoticism
			Sensitivity
			Sociability

continued

Domain	Instrument	Abbreviation	Outcome measure
			Somatisation
			Total
			Total negative
			Total positive
	Symptom Check List (SCL-90-R)[377]	SCL-90-R	Anger-hostility
			GSI
			Interpersonal sensitivity
			Obsessive–compulsive
			Overall score
			Paranoid ideation
			PSDI score
			Psychoticism
			Sensitivity
			Somatisation
	Symptom Check List – Brief Symptom Inventory[384]	SCL–BSI	Anger–hostility
			Global severity index
			Global severity index – moderate
			Global severity index – severe
			Hostility – moderate
			Hostility – severe
			Interpersonal sensitiveness
			Obsessive–compulsive
			Obsessive–compulsive – moderate
			Obsessive–compulsive – severe
			Paranoid ideation
			Paranoid ideation – moderate
			Paranoid ideation – severe
			Positive symptom total
			Positive symptoms distress index
			Psychoticism
			Psychoticism – moderate
			Psychoticism – severe
			Somatic complaints – moderate
			Somatic complaints – severe
			Somatisation
Reasoning	Automated Performance Test System[389]	APTS	AREASON – correct – *n*
			AREASON – speed – s
	Leistungsprüfsystem–4[466,494]	LPS–4	Logical thinking/problem solving
	NS	NS	Syllogistic reasoning – correct – NVC – *n*
			Syllogistic reasoning – correct – one model – *n*
			Syllogistic reasoning – correct – three model – *n*
			Syllogistic reasoning – correct – three model/ NVC – *n*
			Syllogistic reasoning – correct – total – %

Domain	Instrument	Abbreviation	Outcome measure
			Syllogistic reasoning – correct – two/three model – *n*
			Syllogistic reasoning – incorrect – NVC – *n*
			Syllogistic reasoning – incorrect – one model – *n*
			Syllogistic reasoning – incorrect – three model – *n*
			Syllogistic reasoning – incorrect – total – s
			Syllogistic reasoning – *n*o response – NVC – *n*
			Syllogistic reasoning – *n*o response – one model – *n*
			Syllogistic reasoning – *n*o response – three model – *n*
			Syllogistic reasoning – *n*o response – total – *n*
	Wechsler Adult Intelligence Scale – Third Edition[403]	WAIS-III	Matrix reasoning – scaled score
	Wechsler Abbreviated Scale of Intelligence[403]	WASI	Matrix reasoning
	Walter Reed Army Institute of Research Performance Assessment Battery[405]	WRAIR PAB	Logical reasoning task
Sleep	Epworth sleepiness scale[495]	Epworth SS	Total score
	NS	NS	Hours/night
			Morning/evening type
			Quality
			Refreshed
			REM latency [min]
			Sleep efficiency [%]
			Sleep latency – min
			Sometimes miss out a night
			Total sleep time – min
			Wake time after sleep onset – min
	Rechtschaffen and Kales sleep rating procedures[496]	Rechtschaffen and Kales	NREM – min
			REM – min
			Stage 1 – min
			Stage 2 – min
			Stage 3/4 – min
			Stage REM – min
			TST – min
	Symptom Check List (SCL-90)	SCL-90	Self-reported sleep disturbances
	Self-rated	S-R	Scale 1–5
			Sleep disorder
Verbal skills	Boston naming test[497]	BNT	Naming fluency
	Controlled Oral Word Association ('FAS' test) (NS)	COWA	Fluency – category – animals [*n*]
			Fluency – category [*n*]
			Fluency – errors [*n*]

continued

Domain	Instrument	Abbreviation	Outcome measure
			Fluency – inappropriate words [*n*]
			Fluency – letter – FAS [*n*]
			Fluency – letter [*n*]
			Fluency – perseverative errors [*n*]
			Fluency – switching [*n*]
			Fluency – total [*n*]
			Fluency – total perseverations [*n*]
	Chicago Word Fluency Test[498]	CWF	Fluency – letter – C4 [*n*]
			Fluency – letter – S [*n*]
	Delis–Kaplan Executive Function System[431]	D–KEFS	Fluency – category
			Fluency – FAS
			Fluency – switching
	NS	NS	Anagrams – correct [*n*]
			Anagrams – In – time – [s]
			Anagrams – time [s]
			Fluency – category [*n*]

CANTAB, Cambridge Neuropsychological Test Automated Battery; DSM-V, *Diagnostic and Stastical Manual IV*; ms, milliseconds; NS, not specified (or a bespoke test); s, seconds.

Appendix 6

Datasets used in meta-analyses of composite outcome measures

TABLE 51 *Verbal memory – immediate (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs polydrug controls											
Parrott and Lasky 1998[121]	Free recall	(+)	(1) Users (regular) vs controls	15	12	2.324	7.5	15.1	3.098	–1.195	(–2.145 to –0.245)
			(2) Users (novice) vs controls	15	13.9	2.711	7.5	15.1	3.098	–0.423	(–1.309 to 0.463)
Bolla *et al*. 1998[93]	RAVLT: sum of trials 1–5	(+)		24	53.2	7.8	24	56	8.2	–0.350	(–0.920 to 0.220)
	WMS-R: digit span – total	(+)		24	18.1	3.2	24	18.8	3.9	–0.196	(–0.763 to 0.371)
	WMS-R: logical memory	(+)		24	26.2	6.1	24	29.9	6.3	–0.597	(–1.175 to –0.018)
	WMS-R: verbal paired associates	(+)		24	21.3	3.6	24	22.1	2.1	–0.271	(–0.840 to 0.297)
Morgan 1999[102]	RBMT: prose recall	(+)		25	6.14	2.23	22	8.09	1.86	–0.944	(–1.549 to –0.339)
Rodgers 2000[122]	WMS-R: index score	(+)		15	86.4	12.8	15	88.07	10.46	–0.143	(–0.860 to 0.574)
Gouzoulis *et al*. 2000[99]	RAVLT-G: interference – trial 5 – trial 7	(–)		28	2.14	2.07	28	1.5	1.77	–0.332	(–0.860 to 0.195)
	RAVLT-G: trial 1	(+)		28	7.82	1.93	28	8.71	2.03	–0.449	(–0.980 to 0.081)
	WAIS-R: digit span – backwards	(+)		28	7	2.34	28	8	1.87	–0.472	(–1.003 to 0.059)
	WAIS-R: digit span – forwards	(+)		28	8.54	1.84	28	8.93	1.51	–0.232	(–0.757 to 0.294)
Fox *et al*. 2001[112]	MRR: recall (hits – intrusions)	(–)	(1) Users (high-dose) vs controls	11	15.8	7.2	6.67	14.5	5.3	–0.198	(–1.162 to 0.767)
			(2) Users (medium) vs controls	14	14.9	5.6	6.67	14.5	5.3	–0.073	(–0.995 to 0.850)
			(3) Users (low) vs controls	14	15.4	4.3	6.67	14.5	5.3	–0.195	(–1.119 to 0.730)
	MRR: recognition (hits – false alarms)	(–)	(1) Users (high-dose) vs controls	11	11.9	6.8	6.67	16.3	5.2	0.702	(–0.291 to 1.695)
			(2) Users (medium) vs controls	14	13.1	5.4	6.67	16.3	5.2	0.599	(–0.343 to 1.541)
			(3) Users (low) vs controls	14	14.9	5.4	6.67	16.3	5.2	0.262	(–0.664 to 1.188)
	WMS adapted: logical memory	(+)	(1) Users (high-dose) vs controls	11	19.5	7.8	6.67	19.8	4.6	–0.044	(–1.006 to 0.918)
			(2) Users (medium) vs controls	14	17.7	5.9	6.67	19.8	4.6	–0.379	(–1.309 to 0.551)
			(3) Users (low) vs controls	14	21.4	4.4	6.67	19.8	4.6	0.359	(–0.571 to 1.288)

Study	Measure	(+/–)	Comparison	MDMA users			Controls			SMD	(95% CI)
				n	Mean	SD	*n*	Mean	SD		
Croft *et al.* 2001[94]	Digit span – backwards	(+)		11	8	2.6	18	7.9	1.8	0.047	(–0.703 to 0.797)
	Digit span – forwards	(+)		11	9.2	1.6	18	9.6	1.5	–0.260	(–1.013 to 0.493)
	RAVLT: list B	(+)		11	7.3	2.6	18	6.5	2.2	0.340	(–0.416 to 1.095)
	RAVLT: sum of trials 1–5	(+)		11	57.2	11.3	18	56.3	9	0.091	(–0.660 to 0.841)
	RAVLT: trial 6 – interference list	(+)		11	12.2	2.7	18	11.8	3	0.138	(–0.613 to 0.889)
	RMT: recognition	(+)		11	45.5	7	18	48.3	1.8	–0.623	(–1.391 to 0.145)
Reneman *et al.* 2001[95]	RAVLT: sum of trials 1–5	(+)		8	45.8	9.3	7	53.8	6.6	–0.980	(–2.062 to 0.102)
Simon and Mattick 2002[123]	WMS-III: auditory index score	(+)		40	106.4	13.4	37	112.4	14.7	–0.427	(–0.880 to 0.025)
Morgan *et al.* 2002[103]	RBMT: prose recall	(+)		18	7.7	3.182	8	8.5	3	–0.256	(–1.092 to 0.580)
Curran and Verheyden 2003[104]	Buschke: trial 1	(+)		32	6.155	1.93	16	6.785	2.245	–0.309	(–0.913 to 0.294)
	RBMT: prose recall	(+)		32	8.56	3.483	16	8.14	4.455	0.110	(–0.491 to 0.710)
Gouzoulis *et al.* 2003[108]	Digit span – backwards	(+)	(1) Users (heavy) vs controls	30	8	2.3	15	8.8	2.3	–0.348	(–0.972 to 0.276)
			(2) Users (moderate) vs controls	30	8.8	2	15	8.8	2.3	0.000	(–0.620 to 0.620)
Zakzanis *et al.* 2003[101]	RBMT: prose recall	(+)		15	1.5	0.7	17	1.7	0.5	–0.332	(–1.032 to 0.367)
Halpern *et al.* 2004[106]	CVLT-II: total trials 1–5 correct – *n*	(+)	(1) Users (heavy) vs controls	11	63	9.6	8	66.5	8.8	–0.377	(–1.297 to 0.542)
			(2) Users (moderate) vs controls	12	66.2	7.3	8	66.5	8.8	–0.038	(–0.933 to 0.857)
	CVLT-II: trial B correct – *n*	(+)	(1) Users (heavy) vs controls	11	7.9	3.2	8	8.9	2.6	–0.337	(–1.255 to 0.581)
			(2) Users (moderate) vs controls	12	9.5	3.1	8	8.9	2.6	0.206	(–0.691 to 1.103)
	WAIS-R: digit span – backwards	(+)	(1) Users (heavy) vs controls	11	8.1	3.3	8	9.1	2.1	–0.349	(–1.267 to 0.569)
			(2) Users (moderate) vs controls	12	8.7	1.6	8	9.1	2.1	–0.221	(–1.118 to 0.677)
	WAIS-R: digit span – forwards	(+)	(1) Users (heavy) vs controls	11	9	2	8	9.9	1.6	–0.488	(–1.413 to 0.438)
			(2) Users (moderate) vs controls	12	9.7	2.2	8	9.9	1.6	–0.101	(–0.996 to 0.795)
	WMS-III: logical memory	(+)	(1) Users (heavy) vs controls	11	49.1	11.5	8	52.8	6.9	–0.375	(–1.294 to 0.544)
			(2) Users (moderate) vs controls	12	52	9.1	8	52.8	6.9	–0.096	(–0.991 to 0.799)

continued

TABLE 51 *Verbal memory – immediate (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis (continued)*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
	WMS-III: verbal paired associates	(+)	(1) Users (heavy) vs controls	11	24.9	6.2	8	28.7	3.1	–0.737	(–1.681 to 0.207)
			(2) Users (moderate) vs controls	12	25.2	6.4	8	28.7	3.1	–0.653	(–1.572 to 0.267)
McCardle *et al*. 2004[100]	Digit span – backwards	(+)		17	5.12	1.65	15	5.53	1.25	–0.278	(–0.975 to 0.420)
	Digit span – forwards	(+)		17	6.41	0.87	15	7.07	0.96	–0.723	(–1.441 to –0.005)
	RAVLT: trial 1	(+)		17	7.47	1.84	15	8.07	2.37	–0.285	(–0.983 to 0.413)
	RAVLT: trial 2	(+)		17	9.94	2.05	15	10.53	2.5	–0.260	(–0.957 to 0.438)
	RAVLT: trial 3	(+)		17	12	2.03	15	12.07	1.79	0.036	(–0.731 to 0.658)
	RAVLT: trial 4	(+)		17	12.76	1.89	15	13.4	1.3	–0.390	(–1.091 to 0.311)
	RAVLT: trial 5	(+)		17	12.41	1.97	15	13.4	1.55	–0.554	(–1.263 to 0.154)
	RAVLT: trial 7	(+)		17	11.65	2.42	15	11.93	2.46	–0.115	(–0.810 to 0.580)
Dafters *et al*. 2004[75]	Free recall	(+)	(1) Heavy users vs controls	16	8.85	2.15	7.5	9.6	2.15	–0.349	(–1.222 to 0.525)
			(2) Light users vs controls	19	9.3	2.55	7.5	9.6	2.15	–0.122	(–0.968 to 0.723)
	RBMT: prose recall	(+)	(1) Heavy users vs controls	16	4.6	1.7	7.5	4.3	1.9	0.170	(–0.699 to 1.039)
			(2) Light users vs controls	19	5.1	1.6	7.5	4.3	1.9	0.475	(–0.381 to 1.330)
Medina *et al*. 2005[124]	CVLT-II: short-delay cued recall (z-score)	(+)		48	–0.57	0.95	17	–0.03	0.8	–0.591	(–1.153 to –0.028)
	CVLT-II: short-delay free recall (z-score)	(+)		48	–0.38	0.99	17	–0.06	0.61	–0.352	(–0.909 to 0.204)
Thomasius *et al*. 2005[96]	RAVLT: sum of trials 1–5	(+)	Data from secondary pub.[105]	30	58.8	9.585	14.5	53.6	9.424	0.545	(–0.092 to 1.183)
	RBMT: prose recall	(+)	Data from secondary pub.[105]	30	9.5	3.286	14.5	9.5	3.096	0.000	(–0.627 to 0.627)
Montgomery *et al*. 2005[120]	Verbal paired associates – perseverative responses – *n*	(–)	(1) High lifetime dose vs controls	18	0.67	1.28	31	0.16	0.66	–0.547	(–1.138 to 0.045)
			(2) Low lifetime dose vs controls	17	0.71	1.05	31	0.16	0.66	–0.673	(–1.280 to –0.066)
	Verbal paired associates – trials to completion	(–)	(1) High lifetime dose vs controls	18	5.67	1.28	31	4.32	1.46	–0.966	(–1.579 to –0.353)
			(2) Low lifetime dose vs controls	17	6.59	2.4	31	4.32	1.46	–1.232	(–1.875 to –0.589)

Study	Measure	(+/–)	Comparison	MDMA users			Controls			SMD	(95% CI)
				n	Mean	SD	*n*	Mean	SD		
	Verbal paired associates – errors Trial 1	(–)	(1) High lifetime dose vs controls	18	0.72	0.83	31	0.39	0.75	–0.423	(–1.010 to 0.164)
			(2) Low lifetime dose vs controls	17	1	1.22	31	0.39	0.75	–0.649	(–1.255 to –0.042)
	Verbal paired associates – errors Trial 2	(–)	(1) High lifetime dose vs controls	18	0.06	0.24	31	0.1	0.35	0.127	(–0.454 to 0.708)
			(2) Low lifetime dose vs controls	17	0.47	0.87	31	0.1	0.35	–0.632	(–1.237 to –0.026)
	Verbal paired associates – Trial 1 – correct – *n*	(+)	(1) High lifetime dose vs controls	18	2.67	1.81	31	4.32	2.01	–0.850	(–1.456 to –0.245)
			(2) Low lifetime dose vs controls	17	3.29	2.2	31	4.32	2.01	–0.496	(–1.096 to 0.104)
Reneman *et al.* 2006[97]	RAVLT: sum of trials 1–5	(+)	(1) Users (heavy) vs controls	22	47	8.6	4.33	60	6.8	–1.552	(–2.671 to –0.433)
			(2) Users (moderate) vs controls	15	51.2	8.6	4.33	60	6.8	–1.062	(–2.188 to 0.064)
	RBMT: prose recall (sum for 2 tests)	(+)	(1) Users (heavy) vs controls	22	17.9	3.8	4.33	17.9	6.1	0.000	(–1.030 to 1.030)
			(2) Users (moderate) vs controls	15	16.1	5.2	4.33	17.9	6.1	–0.334	(–1.409 to 0.740)
Reay *et al.* 2006[109]	Digit span – backwards	(+)		15	5.61	1.19	15	6.59	1.4	–0.754	(–1.497 to –0.012)
Quednow *et al.* 2006[83]	RAVLT: adjusted list A	(+)		19	0.85	0.1	19	0.93	0.05	–1.012	(–1.689 to –0.334)
	RAVLT: adjusted list B	(+)		19	0.74	0.03	19	0.84	0.02	–3.922	(–5.029 to –2.815)
	RAVLT: sum of trials 1–5	(+)		19	56.2	8.16	19	64.8	6.21	–1.186	(–1.878 to –0.494)
Lamers *et al.* 2006[98]	RAVLT: sum of trials 1–5	(+)		11	51.5	7.6	15	52.3	7.1	–0.109	(–0.888 to 0.669)
de Win *et al.* 2005[84]	RAVLT-D: sum of trials 1–5	(+)	Follow-up. Data from secondary pub.[90]	58	59.6	6.5	60	61.7	5.9	–0.339	(–0.702 to 0.025)
	WAIS-R: digit span – backwards	(+)	Follow-up. Data from secondary pub.[90]	58	11.8	2.4	60	11.4	2.9	0.150	(–0.211 to 0.511)
	WAIS-R: digit span – forwards	(+)	Follow-up. Data from secondary pub.[90]	58	15.5	2.8	60	15.1	2.2	0.159	(–0.202 to 0.521)
McCann *et al.* 2007[117]	WMS-III: logical memory (recall total score)	(+)		25	39.72	10.52	23	46.56	6.84	–0.764	(–1.352 to –0.177)
Hoshi *et al.* 2007[125]	Buschke: trial 1	(+)		25	5.35	1.5	14.5	5.2	1.62	0.097	(–0.550 to 0.744)
	Buschke: trial 2	(+)		25	7.6	2	14.5	8.1	2.69	–0.220	(–0.869 to 0.429)
	Buschke: trial 3	(+)		25	9.1	2	14.5	10	2.96	–0.377	(–1.029 to 0.276)

continued

TABLE 51 *Verbal memory – immediate (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis (continued)*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Groth *et al.* 2007[124]	WMS-III: index score	(+)		26	107.4	15.2	26	113.2	11.6	–0.429	(–0.979 to 0.121)
Former users vs polydrug controls											
Morgan *et al.* 2002[103]	RBMT: prose recall	(+)		15	6.1	3.679	8	8.5	3	–0.692	(–1.575 to 0.191)
Curran and Verheyden 2003[104]	Buschke: trial 1	(+)		32	5.755	1.607	16	6.785	2.245	–0.560	(–1.171 to 0.051)
	RBMT: prose recall	(+)		32	6.83	2.973	16	8.14	4.455	–0.372	(–0.976 to 0.233)
Thomasius *et al.* 2005[96]	RAVLT: sum of trials 1–5	(+)	Data from secondary pub.[105]	31	53.6	8.352	14.5	53.6	9.424	0.000	(–0.624 to 0.624)
	RBMT: prose recall	(+)	Data from secondary pub.[105]	31	8.2	2.617	14.5	9.5	3.096	–0.469	(–1.100 to 0.163)
Reneman *et al.* 2006[97]	RAVLT: sum of trials 1–5	(+)		16	48	12.5	4.33	60	6.8	–1.028	(–2.140 to 0.084)
	RBMT: prose recall	(+)		16	16.3	5.8	4.33	17.9	6.1	–0.273	(–1.338 to 0.792)
Hoshi *et al.* 2007[125]	Buschke: trial 1	(+)		28	6.15	2.12	14.5	5.2	1.62	0.483	(–0.160 to 1.126)
	Buschke: trial 2	(+)		28	8.85	2.12	14.5	8.1	2.69	0.323	(–0.316 to 0.961)
	Buschke: trial 3	(+)		28	9.95	2.65	14.5	10	2.96	–0.018	(–0.652 to 0.616)

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TABLE 52 *Verbal memory – immediate (composite measure) – ecstasy users versus drug-naïve controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs drug-naïve controls											
Morgan 1999[102]	RBMT: prose recall	(+)		25	6.14	2.23	19	8.29	2.87	–0.852	(–1.475 to –0.228)
Rodgers 2000[122]	WMS-R: index score	(+)		15	86.4	12.8	15	109.7	12.79	–1.819	(–2.678 to –0.959)
Gouzoulis *et al*. 2000[99]	RAVLT-G: interference – trial 5 – trial 7	(–)		28	2.14	2.07	28	0.89	1.55	–0.684	(–1.223 to –0.144)
	RAVLT-G: trial 1	(+)		28	7.82	1.93	28	9.82	2.28	–0.947	(–1.500 to –0.393)
	WAIS-R: digit span – backwards	(+)		28	7	2.34	28	9.11	2.67	–0.840	(–1.388 to –0.293)
	WAIS-R: digit span – forwards	(+)		28	8.54	1.84	28	8.89	1.29	–0.220	(–0.746 to 0.305)
Bhattachary and Powell 2001[127]	Digit span – backwards	(+)	(1) Regular users vs controls	26	5.5	0.99	6.67	5.85	1.04	–0.350	(–1.206 to 0.505)
			(2) Novice users vs controls	18	5.56	1.09	6.67	5.85	1.04	–0.269	(–1.161 to 0.623)
	Prose recall	(+)	(1) Regular users vs controls	26	10.58	1.93	6.67	15.8	1.55	–2.798	(–3.900 to –1.696)
			(2) Novice users vs controls	18	14.44	1.97	6.67	15.8	1.55	–0.726	(–1.639 to 0.188)
Croft *et al*. 2001[94]	Digit span – backwards	(+)		11	8	2.6	31	9.3	2.2	–0.564	(–1.262 to 0.135)
	Digit span – forwards	(+)		11	9.2	1.6	31	10.5	1.8	–0.742	(–1.449 to –0.035)
	RAVLT: list B	(+)		11	7.3	2.6	31	8.5	2.7	–0.449	(–1.143 to 0.246)
	RAVLT: sum of trials 1–5	(+)		11	57.2	11.3	31	62.4	7.7	–0.595	(–1.295 to 0.105)
	RAVLT: trial 6 – interference list	(+)		11	12.2	2.7	31	13.2	1.6	–0.517	(–1.214 to 0.180)
	RMT: recognition	(+)		11	45.5	7	31	48.3	2.3	–0.695	(–1.400 to 0.009)
Morgan *et al*. 2002[103]	RBMT: prose recall	(+)		18	7.7	3.182	7.5	9.95	3.873	–0.664	(–1.537 to 0.208)
Dafters *et al*. 2004[75]	Free recall	(+)	(1) Heavy users vs controls	16	8.85	2.15	9.5	12.4	2.15	–1.651	(–2.582 to –0.720)
			(2) Light users vs controls	19	9.3	2.55	9.5	12.4	2.15	–1.276	(–2.128 to –0.425)
	RBMT: prose recall	(+)	(1) Heavy users vs controls	16	4.6	1.7	9.5	6.3	2.7	–0.803	(–1.638 to 0.032)
			(2) Light users vs controls	19	5.1	1.6	9.5	6.3	2.7	–0.594	(–1.389 to 0.201)

continued

TABLE 52 *Verbal memory-immediate (composite measure) – ecstasy users versus drug-naive controls: dataset used in meta-analysis (continued)*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Thomasius *et al.* 2005[96]	RAVLT: sum of trials 1–5	(+)	Data from secondary pub.[105]	30	58.8	9.585	15	60.3	8.216	–0.164	(–0.784 to 0.457)
	RBMT: prose recall	(+)	Data from secondary pub.[105]	30	9.5	3.286	15	10.75	3.286	–0.380	(–1.005 to 0.245)
Yip and Lee 2005[128]	Digit span – backwards	(+)		100	9.38	1.01	100	9.57	1.03	–0.186	(–0.464 to 0.092)
	Digit span – forwards	(+)		100	6.66	0.96	100	6.75	1.02	–0.091	(–0.368 to 0.186)
	RAVLT-C: items recalled in all trials 1–5	(+)		100	5.2	0.8	100	10.51	1.45	–4.535	(–5.060 to –4.009)
Quednow *et al.* 2006[83]	RAVLT: adjusted list A	(+)		19	0.85	0.1	19	0.9	0.08	–0.552	(–1.201 to 0.096)
	RAVLT: adjusted list B	(+)		19	0.74	0.03	19	0.81	0.03	–2.333	(–3.167 to –1.500)
	RAVLT: sum of trials 1–5	(+)		19	56.2	8.16	19	64.7	5.72	–1.206	(–1.901 to –0.512)
Lamers *et al.* 2006[98]	RAVLT: sum of trials 1–5	(+)		11	51.5	7.6	15	60	5.3	–1.336	(–2.201 to –0.471)
Hoshi *et al.* 2007[125]	Buschke: trial 1	(+)		25	5.35	1.5	13.5	7.1	2.08	–1.017	(–1.719 to –0.315)
	Buschke: trial 2	(+)		25	7.6	2	13.5	10.45	2.6	–1.282	(–2.006 to –0.557)
	Buschke: trial 3	(+)		25	9.1	2	13.5	11.6	2.6	–1.124	(–1.835 to –0.414)
Former users vs drug-naïve controls											
Bhattachary and Powell 2001[127]	Digit span – backwards	(+)		16	5.44	0.96	6.67	5.85	1.04	–0.417	(–1.330 to 0.495)
	Prose recall	(+)		16	11.09	1.86	6.67	15.8	1.55	–2.646	(–3.857 to –1.434)
Morgan *et al.* 2002[103]	RBMT: prose recall	(+)		15	6.1	3.679	7.5	9.95	3.873	–1.029	(–1.960 to –0.098)
Thomasius *et al.* 2005[96]	RAVLT: sum of trials 1–5	(+)	Data from secondary pub.[105]	31	53.6	8.352	15	60.3	8.216	–0.806	(–1.445 to –0.167)
	RBMT: prose recall	(+)	Data from secondary pub.[105]	31	8.2	2.617	15	10.75	3.286	–0.896	(–1.540 to –0.251)
Hoshi *et al.* 2007[125]	Buschke: trial 1	(+)		28	6.15	2.12	13.5	7.1	2.08	–0.451	(–1.108 to 0.206)
	Buschke: trial 2	(+)		28	8.85	2.12	13.5	10.45	2.6	–0.701	(–1.368 to –0.033)
	Buschke: trial 3	(+)		28	9.95	2.65	13.5	11.6	2.6	–0.626	(–1.290 to 0.038)

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TABLE 53 *Verbal memory – delayed (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs polydrug controls											
Bolla *et al.* 1998[93]	RAVLT: recognition	(+)		24	13.8	1.3	24	14.3	0.9	–0.447	(–1.020 to 0.126)
	RAVLT: trial 8	(+)		24	11	2.9	24	12	2.3	–0.382	(–0.953 to 0.189)
	WMS-R: logical memory	(+)		24	22	7.1	24	26.9	7.3	–0.680	(–1.263 to –0.098)
	WMS-R: verbal paired associates	(+)		24	7.8	0.5	24	7.9	0.3	–0.243	(–0.810 to 0.325)
Morgan 1999[102]	RBMT: prose recall	(+)		25	5.36	2.48	22	7.23	1.9	–0.839	(–1.438 to –0.241)
Rodgers 2000[122]	WMS-R: logical memory	(+)		15	18.4	12.3	15	20.1	8.9	–0.158	(–0.875 to 0.559)
	WMS-R: verbal paired associates	(+)		15	8.5	7.8	15	16.5	4.8	–1.235	(–2.021 to –0.450)
Gouzoulis *et al.* 2000[99]	RAVLT-G: trial 8	(+)		28	13.79	1.75	28	14.43	1.07	–0.441	(–0.972 to 0.089)
Fox *et al.* 2001[112]	WMS adapted: logical memory	(+)	(1) High-dose users vs controls	11	19.8	6.1	6.67	18.2	4	0.294	(–0.673 to 1.262)
			(2) Medium-dose users vs controls	14	15.8	6.6	6.67	18.2	4	–0.405	(–1.336 to 0.527)
			(3) Low-dose users vs controls	14	20	4.3	6.67	18.2	4	0.427	(–0.505 to 1.360)
Reneman *et al.* 2001[95]	RAVLT: trial 8	(+)		8	10.6	2	7	12.8	1.9	–1.126	(–2.228 to –0.023)
Simon and Mattick 2002[123]	WMS-III: auditory index score	(+)		40	105.3	11.9	37	109.9	10.2	–0.414	(–0.866 to 0.038)
	WMS-R: verbal reproduction	(+)		40	104.5	13.4	37	106.9	12.9	–0.182	(–0.630 to 0.266)
Morgan *et al.* 2002[103]	RBMT: prose recall	(+)		18	6.2	3.394	8	7	3	–0.244	(–1.079 to 0.592)
Curran and Verheyden 2003[104]	Buschke: overall score	(+)		32	7.315	3.045	16	7.905	3.11	–0.192	(–0.794 to 0.409)
	RBMT: prose recall	(+)		32	7.565	3.528	16	7.515	4.33	0.013	(–0.587 to 0.613)
Zakzanis *et al.* 2003[101]	RBMT: prose recall	(+)		15	1.8	0.4	17	1.7	0.5	0.219	(–0.477 to 0.916)

continued

TABLE 53 *Verbal memory – delayed (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis (continued)*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Halpern *et al.* 2004[106]	WMS-III: logical memory	(+)	(1) Heavy users vs controls	11	32	8.4	8	34.8	5.8	–0.376	(–1.296 to 0.543)
			(2) Moderate users vs controls	12	34.1	4.5	8	34.8	5.8	–0.139	(–1.034 to 0.757)
	WMS-III: verbal paired associates	(+)	(1) Heavy users vs controls	11	7.5	1.3	8	7.9	0.3	–0.394	(–1.314 to 0.526)
			(2) Moderate users vs controls	12	7.6	1.4	8	7.9	0.3	–0.270	(–1.169 to 0.629)
McCardle *et al.* 2004[100]	RAVLT: trial 8	(+)		17	11.18	2.58	15	12.13	2.13	–0.399	(–1.101 to 0.303)
Dafters *et al.* 2004[75]	RBMT: prose recall	(+)	(1) Heavy users vs controls	16	4.1	1.65	7.5	3.85	1.7	0.150	(–0.718 to 1.019)
			(2) Light users vs controls	19	4.55	1.45	7.5	3.85	1.7	0.460	(–0.395 to 1.315)
Medina *et al.* 2005[124]	CVLT-II: long-delay free recall (z-score)	(+)		48	–0.57	1.1	17	0.06	0.86	–0.603	(–1.166 to –0.040)
Thomasius *et al.* 2005[96]	RAVLT: overall score	(+)	Data from secondary pub.[105]	30	12.65	2.465	14.5	11.15	2.962	0.570	(–0.069 to 1.208)
	RBMT: prose recall	(+)	Data from secondary pub.[105]	30	8.52	3.122	14.5	8.95	2.962	–0.140	(–0.768 to 0.488)
Reneman *et al.* 2006[97]	RAVLT: trial 8	(+)	(1) Heavy users vs controls	22	9.8	2.9	4.33	13.1	2.1	–1.177	(–2.259 to –0.095)
			(2) Moderate users vs controls	15	10.7	3.2	4.33	13.1	2.1	–0.795	(–1.896 to 0.306)
	RBMT: prose recall (sum for 2 tests)	(+)	(1) Heavy users vs controls	22	14.4	3.9	4.33	15.3	5.8	–0.214	(–1.246 to 0.818)
			(2) Moderate users vs controls	15	12.7	5.4	4.33	15.3	5.8	–0.475	(–1.555 to 0.606)
Quednow *et al.* 2006[83]	RAVLT: recognition – errors – list B	(–)		19	4.3	3.1	19	2.4	2	–0.728	(–1.386 to –0.071)
	RAVLT: recognition – list A	(+)		19	14	1.2	19	15	0.4	–1.118	(–1.804 to –0.432)
	RAVLT: recognition – list B	(+)		19	10.8	2.1	19	12.4	1.7	–0.837	(–1.502 to –0.173)
Lamers *et al.* 2006[98]	RAVLT: trial 8	(+)		11	11.6	2.8	15	10.7	3.5	0.279	(–0.503 to 1.061)

Study	Measure	(+/–)	Comparison	MDMA users			Controls			SMD	(95% CI)
				n	Mean	SD	*n*	Mean	SD		
de Win *et al.* 2006[91]	RAVLT-D: recognition	(+)	Follow-up. Data from secondary pub.[90]	58	29.66	0.8	60	29.93	0.3	–0.450	(–0.815 to –0.084)
	RAVLT-D: trial 8	(+)	Follow-up. Data from secondary pub.[90]	58	13.2	2	60	14.1	1.2	–0.548	(–0.916 to –0.180)
McCann *et al.* 2007[117]	WMS-III: logical memory (story A recall unit score)	(+)		25	10.24	4.8	23	13.74	3.94	–0.794	(–1.383 to –0.205)
Hoshi *et al.* 2007[125]	Buschke: overall score	(+)		25	5.2	2.5	14.5	6.55	3.23	–0.485	(–1.141 to 0.171)
Groth *et al.* 2007[126]	WMS-III: index score	(+)		26	108.4	12.1	26	112.2	9	–0.356	(–0.904 to 0.192)
Former users vs polydrug controls											
Morgan *et al.* 2002[103]	RBMT: prose recall	(+)		15	4.3	3.679	8	7	3	–0.779	(–1.668 to 0.111)
Curran and Verheyden 2003[104]	Buschke: overall score	(+)		32	5.685	2.685	16	7.905	3.11	–0.784	(–1.406 to –0.163)
	RBMT: prose recall	(+)		32	5.825	2.733	16	7.515	4.33	–0.506	(–1.115 to 0.103)
Thomasius *et al.* 2005[96]	RAVLT: overall score	(+)	Data from secondary pub.[105]	31	10.8	3.229	14.5	11.15	2.962	–0.111	(–0.735 to 0.513)
	RBMT: prose recall	(+)	Data from secondary pub.[105]	31	7.28	2.505	14.5	8.95	2.962	–0.629	(–1.266 to 0.009)
Reneman *et al.* 2006[97]	RAVLT: trial 8	(+)		16	10.1	2.9	4.33	13.1	2.1	–1.082	(–2.200 to 0.035)
	RBMT: prose recall (sum for 2 tests)	(+)		16	13.8	6.2	4.33	15.3	5.8	–0.245	(–1.309 to 0.820)
Hoshi *et al.* 2007[125]	Buschke: overall score	(+)		28	6.45	3.17	14.5	6.55	3.23	–0.031	(–0.666 to 0.603)

TABLE 54 *Verbal memory – delayed (composite measure) – ecstasy users versus drug-naïve controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs drug-naïve controls											
Morgan 1999[102]	RBMT: prose recall	(+)		25	5.36	2.48	19	7.61	2.74	–0.867	(–1.492 to –0.242)
Rodgers 2000[122]	WMS-R: logical memory	(+)		15	18.4	12.3	15	38.2	9.3	–1.816	(–2.675 to –0.957)
	WMS-R: verbal paired associates	(+)		15	8.5	7.8	15	15.3	7.6	–0.883	(–1.635 to –0.131)
Gouzoulis *et al*. 2000[99]	RAVLT-G: trial 8	(+)		28	13.79	1.75	28	14.21	1.03	–0.293	(–0.819 to 0.234)
Reneman *et al*. 2001[111]	RAVLT: trial 8	(+)	Data from secondary pub.[499]	5	8.14	3.4	9	12.3	1.8	–1.696	(–2.983 to –0.410)
Bhattachary and Powell 2001[127]	Prose recall	(+)	(1) Regular users vs controls	26	8.94	1.76	6.67	14.33	2.01	–2.980	(–4.111 to –1.848)
			(2) Novice users vs controls	18	13.31	1.98	6.67	14.33	2.01	–0.513	(–1.414 to 0.388)
	Prose retained [%]	(+)	(1) Regular users vs controls	26	84.96	10.59	6.67	90.67	8.46	–0.558	(–1.420 to 0.304)
			(2) Novice users vs controls	18	92.22	6.84	6.67	90.67	8.46	0.213	(–0.678 to 1.104)
Morgan *et al*. 2002[103]	RBMT: prose recall	(+)		18	6.2	3.394	7.5	8.6	3.873	–0.679	(–1.553 to 0.194)
Dafters *et al*. 2004[75]	RBMT: prose recall	(+)	(1) Heavy users vs controls	16	4.1	1.65	9.5	5.95	2.25	–0.979	(–1.829 to –0.129)
			(2) Light users vs controls	19	4.55	1.45	9.5	5.95	2.25	–0.801	(–1.610 to 0.007)
Thomasius *et al*. 2005[96]	RAVLT: overall score	(+)	(1) Data from primary pub.	30	12.65	2.465	15	12.95	2.574	–0.120	(–0.740 to 0.500)
	RBMT: prose recall	(+)	(2) Data from secondary pub.[105]	30	8.52	3.122	15	9.45	3.012	–0.301	(–0.924 to 0.322)
Yip and Lee 2005[128]	RAVLT-C: recognition	(+)		100	5.64	1.93	100	12.8	1.22	–4.435	(–4.952 to –3.917)
	RAVLT-C: trial 8	(+)		100	5.28	1.57	100	13.52	1.26	–5.789	(–6.423 to –5.155)

Study	Measure	(+/–)	Comparison	MDMA users			Controls			SMD	(95% CI)
				n	Mean	SD	*n*	Mean	SD		
Quednow *et al.* 2006[83]	RAVLT: recognition – errors – list A	(–)		19	0.2	0.5	19	0.2	0.3	0.000	(–0.636 to 0.636)
	RAVLT: recognition – errors – list B	(–)		19	4.3	3.1	19	3.4	2.5	–0.320	(–0.960 to 0.321)
	RAVLT: recognition – list A	(+)		19	14	1.2	19	14.8	0.5	–0.870	(–1.537 to –0.203)
	RAVLT: recognition – list B	(+)		19	10.8	2.1	19	12.1	2.7	–0.537	(–1.185 to 0.110)
Lamers *et al.* 2006[98]	RAVLT: trial 8	(+)		11	11.6	2.8	15	13.1	1.5	–0.701	(–1.504 to 0.102)
Hoshi *et al.* 2007[125]	Buschke: overall score	(+)		25	5.2	2.5	13.5	8.35	3.64	–1.071	(–1.777 to –0.365)
Former users vs drug-naïve controls											
Bhattachary and Powell 2001[127]	Prose recall	(+)		16	10.38	1.66	6.67	14.33	2.01	–2.241	(–3.373 to –1.108)
	Prose retained [%]	(+)		16	93.89	6.83	6.67	90.67	8.46	0.440	(–0.473 to 1.354)
Morgan *et al.* 2002[103]	RBMT: prose recall	(+)		15	4.3	3.679	7.5	8.6	3.873	–1.149	(–2.094 to –0.205)
Thomasius *et al.* 2005[96]	RAVLT: overall score	(+)	(1) Data from primary pub.	31	10.8	3.229	15	12.95	2.574	–0.708	(–1.342 to –0.074)
	RBMT: prose recall	(+)	(2) Data from secondary pub.[105]	31	7.28	2.505	15	9.45	3.012	–0.811	(–1.450 to –0.171)
Hoshi *et al.* 2007[125]	Buschke: overall score	(+)		28	6.45	3.17	13.5	8.35	3.64	–0.571	(–1.233 to 0.090)

TABLE 55 *Visual memory – immediate (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs polydrug controls											
Bolla *et al.* 1998[93]	WMS-R: figural memory	(+)		24	7.3	1.1	24	7.5	1.3	–0.166	(–0.733 to 0.401)
	WMS-R: visual memory span	(+)		24	18.6	2.2	24	17.9	2.5	0.297	(–0.272 to 0.866)
	WMS-R: visual paired associates	(+)		24	15.2	3.9	24	16.2	1.8	–0.329	(–0.899 to 0.241)
	WMS-R: visual reproduction	(+)		24	36.8	2.2	24	37.6	3.2	–0.291	(–0.860 to 0.278)
Morgan 1998[110]	CANTAB SS: spatial span	(+)	Study 1	16	6.87	1.02	12	6	1.41	0.725	(–0.049 to 1.499)
Rodgers 2000[122]	WMS-R: index score	(+)		15	113.3	7.5	15	110.3	7.62	0.397	(–0.326 to 1.120)
Gouzoulis *et al.* 2000[99]	Corsi Block: span	(+)		28	5.82	0.77	28	6.18	0.9	–0.430	(–0.960 to 0.100)
	VIG: recall	(+)		28	4.54	1.62	28	5.57	1.53	–0.654	(–1.192 to –0.116)
Croft *et al.* 2001[94]	RAVLT: list B	(+)		11	6.5	2.1	18	7.3	2.1	–0.381	(–1.138 to 0.376)
	RAVLT: sum of trials 1–5	(+)		11	40.4	4.2	18	34.9	8.6	0.755	(–0.022 to 1.531)
	RAVLT: trial 6 – interference list	(+)		11	7.7	2.5	18	7.3	2.1	0.177	(–0.574 to 0.929)
	RMT: recognition	(+)		11	40.9	5.6	18	40.7	3.7	0.044	(–0.706 to 0.795)
Verkes *et al.* 2001[129]	Corsi Block: span plus one	(+)	(1) Heavy users vs controls	21	5.5	0.9	10	6.4	1.1	–0.931	(–1.721 to –0.141)
			(2) Moderate users vs controls	21	5.7	1	10	6.4	1.1	–0.678	(–1.451 to 0.095)
	Corsi Block: span	(+)	(1) Heavy users vs controls	21	5	1.1	10	6.1	1.3	–0.944	(–1.735 to –0.152)
			(2) Moderate users vs controls	21	5.2	1.2	10	6.1	1.3	–0.731	(–1.507 to 0.046)
Fox *et al.* 2002[130]	Paired associates – memory score (six-box trial)	(+)		20	4.7	1.5	20	4.5	1.8	0.121	(–0.500 to 0.741)
	Paired associates – memory score (eight-box trial)	(+)		20	4.6	2.2	20	5	1.6	–0.208	(–0.830 to 0.414)
	Pattern recognition – correct [%]	(+)		20	87.5	8.9	20	95.2	4.5	–1.092	(–1.759 to –0.425)

Study	Measure	(+/–)	Comparison	MDMA users			Controls			SMD	(95% CI)
				n	Mean	SD	*n*	Mean	SD		
	Pattern recognition – latency [s]	(–)		20	2.05	0.47	20	2.09	0.45	0.087	(–0.533 to 0.707)
	Spatial recognition – correct [%]	(+)		20	85.8	6.5	20	84	8.2	0.243	(–0.379 to 0.865)
	Spatial recognition – latency [s]	(–)		20	2.4	0.77	20	2.29	0.51	–0.168	(–0.789 to 0.453)
	Visual paired associates – six-box trial – errors [*n*]	(–)		20	1.7	2.1	20	2.2	2.9	0.197	(–0.424 to 0.819)
	Visual paired associates – six-box trial – trials to completion	(–)		20	1.7	0.8	20	1.8	1	0.110	(–0.510 to 0.731)
	Visual paired associates – eight-box trial – errors [*n*]	(–)		20	7.7	7	20	4.7	2.9	–0.560	(–1.192 to 0.073)
	Visual paired associates – eight-box trial – trials to completion	(–)		20	3.8	2.5	20	2.9	1.1	–0.466	(–1.095 to 0.163)
Simon and Mattick 2002[123]	WMS-III: visual	(+)		40	98.2	11.1	37	97.8	11.9	0.035	(–0.412 to 0.482)
Zakzanis *et al.* 2003[101]	RBMT: route	(+)		15	1.9	0.5	17	1.9	0.2	0.000	(–0.694 to 0.694)
Halpern *et al.* 2004[106]	R-OCFT: total score	(+)	(1) Heavy users vs controls	11	20.5	7.4	8	22.3	6	–0.262	(–1.177 to 0.653)
			(2) Moderate users vs controls	12	20.2	5.4	8	22.3	6	–0.372	(–1.275 to 0.531)
	WMS-III: spatial span – visual total	(+)	(1) Heavy users vs controls	11	18.4	3.7	8	21.6	2.9	–0.943	(–1.907 to 0.021)
			(2) Moderate users vs controls	12	19.8	2.4	8	21.6	2.9	–0.691	(–1.613 to 0.232)
	WMS-III: visual reproduction	(+)	(1) Heavy users vs controls	11	94.9	3.7	8	96.8	4.8	–0.454	(–1.377 to 0.470)
			(2) Moderate users vs controls	12	94.1	7.9	8	96.8	4.8	–0.393	(–1.297 to 0.510)
Medina *et al.* 2005[124]	BVRT: correct – *n*	(+)		48	7.8	1.5	17	8.2	1.3	–0.276	(–0.831 to 0.280)
	BVRT: errors – *n*	(–)		48	2.8	2.2	17	2.2	1.8	–0.285	(–0.840 to 0.270)

continued

TABLE 55 *Visual memory – immediate (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis (continued)*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Wareing *et al.* 2005[131]	Spatial span	(+)		36	4.56	0.94	15.5	4.84	1.13	–0.280	(–0.878 to 0.318)
Reneman *et al.* 2006[97]	Corsi Block: span plus one	(+)	(1) Heavy users vs controls	22	6	1.1	4.33	5.6	0.6	0.383	(–0.653 to 1.418)
			(2) Moderate users vs controls	15	5.9	1	4.33	5.6	0.6	0.320	(–0.754 to 1.395)
	Corsi Block: span	(+)	(1) Heavy users vs controls	22	5.6	1.3	4.33	5.2	0.7	0.324	(–0.710 to 1.358)
			(2) Moderate users vs controls	15	5.7	1.1	4.33	5.2	0.7	0.483	(–0.598 to 1.564)
	WMS-R: visual reproduction	(+)	(1) Heavy users vs controls	22	38.4	2.6	4.33	39.4	1.9	–0.398	(–1.434 to 0.639)
			(2) Moderate users vs controls	15	39.2	1.8	4.33	39.4	1.9	–0.110	(–1.179 to 0.960)
de Win *et al.* 2006[91]	MFD: correct – n	(+)	Follow-up. Data from secondary pub.[90]	58	94.4	7.8	60	96.8	6.6	–0.333	(–0.696 to 0.031)
	MFD: trials to completion – n	(–)	Follow-up. Data from secondary pub.[90]	58	3.3	1.3	60	3.1	1.4	–0.148	(–0.509 to 0.213)
Groth *et al.* 2007[126]	WMS-III: visual	(+)		26	97.1	13.6	26	99.9	10.4	–0.231	(–0.777 to 0.314)
Roiser *et al.* 2007[118]	CANTAB DMTS: delayed – latency – ms	(–)		30	2418	488	15	2815	842.6	0.635	(0.001–1.269)
	CANTAB DMTS: delayed (0 s) – correct [%]	(+)		30	90.3	8.1	15	89	14.5	0.122	(–0.498 to 0.743)
	CANTAB DMTS: delayed (12 s) – correct [%]	(+)		30	80.3	16.5	15	77.3	15.1	0.187	(–0.434 to 0.808)
	CANTAB DMTS: delayed (4 s) – correct [%]	(+)		30	88.7	14.6	15	86.7	13.2	0.141	(–0.479 to 0.762)

Study	Measure	(+/–)	Comparison	MDMA users			Controls			SMD	(95% CI)
				n	Mean	SD	*n*	Mean	SD		
	CANTAB DMTS: simultaneous – correct [%]	(+)		30	96.7	6.1	15	95	7.3	0.261	(–0.361 to 0.883)
	CANTAB DMTS: simultaneous – latency – ms	(–)		30	3020	818.8	15	3244	648.4	0.293	(–0.330 to 0.916)
	PRM: correct [%]	(+)		30	88.9	15.1	15	91.4	10.7	–0.181	(–0.802 to 0.440)
	PRM: latency – ms	(–)		30	1753	372.4	15	1673	383.3	–0.215	(–0.836 to 0.407)
Former users vs polydrug controls											
Wareing *et al.* 2005[131]	Spatial span	(+)		12	4.08	1.51	15.5	4.84	1.13	–0.581	(–1.352 to 0.189)
Reneman *et al.* 2006[97]	Corsi Block: span plus one	(+)		16	6	1.2	4.33	5.6	0.6	0.359	(–0.709 to 1.426)
	Corsi Block: span	(+)		16	5.7	1.3	4.33	5.2	0.7	0.412	(–0.658 to 1.482)
	WMS-R: visual reproduction	(+)		16	37.7	3.2	4.33	39.4	1.9	–0.566	(–1.643 to 0.511)
Roiser *et al.* 2007[118]	CANTAB DMTS: delayed – latency – ms	(–)		20	2609	604	15	2815	842.6	0.289	(–0.384 to 0.962)
	CANTAB DMTS: delayed (0 s) – correct [%]	(+)		20	88	10.6	15	89	14.5	–0.081	(–0.750 to 0.589)
	CANTAB DMTS: delayed (12 s) – correct [%]	(+)		20	76.5	19	15	77.3	15.1	–0.046	(–0.715 to 0.624)
	CANTAB DMTS: delayed (4 s) – correct [%]	(+)		20	87.5	15.2	15	86.7	13.2	0.056	(–0.614 to 0.725)
	CANTAB DMTS: simultaneous – correct [%]	(+)		20	94.5	8.9	15	95	7.3	–0.061	(–0.730 to 0.609)
	CANTAB DMTS: simultaneous – latency – ms	(–)		20	3165	1226	15	3244	648.4	0.078	(–0.592 to 0.748)
	PRM: correct [%]	(+)		20	86.2	14.9	15	91.4	10.7	–0.392	(–1.068 to 0.285)
	PRM: latency – ms	(–)		20	1730	504.3	15	1673	383.3	–0.125	(–0.795 to 0.545)

TABLE 56 *Visual memory – immediate (composite measure) – ecstasy users versus drug-naïve controls: dataset used in meta-analysis*

				MDMA users		Controls				
Study	**Measure**	**(+/–)**	**Comparison**	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs drug-naïve controls										
Morgan 1998[110]	CANTAB SS: spatial span	(+)	Study 1	6.87	1.02	16	6.69	1.35	0.150	(–0.544 to 0.844)
Rodgers 2000[122]	WMS-R: index score	(+)		113.3	7.5	15	109.5	11.98	0.380	(–0.342 to 1.103)
Gouzoulis *et al*. 2000[99]	Corsi Block: span	(+)		5.82	0.77	28	6.04	1.04	–0.240	(–0.766 to 0.285)
	VIG: recall	(+)		4.54	1.62	28	5.71	1.24	–0.811	(–1.357 to –0.265)
Croft *et al*. 2001[94]	RAVLT: list B	(+)		6.5	2.1	31	6.7	2	–0.099	(–0.787 to 0.589)
	RAVLT: sum of trials 1–5	(+)		40.4	4.2	31	39.9	6.5	0.083	(–0.605 to 0.771)
	RAVLT: trial 6 – interference list	(+)		7.7	2.5	31	8.2	1.7	–0.259	(–0.949 to 0.431)
	RMT: recognition	(+)		40.9	5.6	31	43	3.3	–0.525	(–1.222 to 0.173)
Yip and Lee 2005[128]	AFLT: overall score	(+)		5.44	1.58	100	6.54	2	–0.610	(–0.894 to –0.327)
Roiser *et al*. 2007[118]	CANTAB DMTS: delayed – latency – ms	(–)		2418	488	15	2609	610.3	0.360	(–0.265 to 0.984)
	CANTAB DMTS: delayed (0 s) – correct [%]	(+)		90.3	8.1	15	89.3	9.8	0.115	(–0.505 to 0.735)
	CANTAB DMTS: delayed (12 s) – correct [%]	(+)		80.3	16.5	15	77.7	16.3	0.158	(–0.462 to 0.779)
	CANTAB DMTS: delayed (4 s) – correct [%]	(+)		88.7	14.6	15	89	11.2	–0.022	(–0.642 to 0.598)
	CANTAB DMTS: simultaneous – correct [%]	(+)		96.7	6.1	15	94.7	7.3	0.307	(–0.316 to 0.930)
	CANTAB DMTS: simultaneous – latency – ms	(–)		3020	818.8	15	3121	628.9	0.133	(–0.488 to 0.753)
	PRM: correct [%]	(+)		88.9	15.1	15	92.2	7.3	–0.252	(–0.874 to 0.370)
	PRM: latency – ms	(–)		1753	372.4	15	1713	356.9	–0.109	(–0.729 to 0.511)

Study	Measure	(+/–)	Comparison	MDMA users Mean	MDMA users SD	Controls *n*	Controls Mean	Controls SD	SMD	(95% CI)
Former users vs drug-naïve controls										
Roiser *et al.* 2007[118]	CANTAB DMTS: delayed – latency – ms	(–)		2609	604	15	2609	610.3	0.000	(–0.669 to 0.670)
	CANTAB DMTS: delayed (0 s) – correct [%]	(+)		88	10.6	15	89.3	9.8	–0.127	(–0.797 to 0.544)
	CANTAB DMTS: delayed (12 s) – correct [%]	(+)		76.5	19	15	77.7	16.3	–0.067	(–0.737 to 0.603)
	CANTAB DMTS: delayed (4 s) – correct [%]	(+)		87.5	15.2	15	89	11.2	–0.110	(–0.780 to 0.560)
	CANTAB DMTS: simultaneous – correct [%]	(+)		94.5	8.9	15	94.7	7.3	–0.024	(–0.694 to 0.645)
	CANTAB DMTS: simultaneous – latency – ms	(–)		3165	1226	15	3121	628.9	–0.043	(–0.713 to 0.626)
	PRM: correct [%]	(+)		86.2	14.9	15	92.2	7.3	–0.489	(–1.169 to 0.191)
	PRM: latency – ms	(–)		1730	504.3	15	1713	356.9	–0.037	(–0.706 to 0.633)

TABLE 57 *Visual memory – delayed (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs polydrug controls											
Bolla *et al*. 1998[93]	R-OCFT: total score	(+)		24	20	6.6	24	20.3	5.6	–0.049	(–0.615 to 0.517)
	WMS-R: visual paired associates	(+)		24	5.8	0.5	24	5.9	0.3	–0.243	(–0.810 to 0.325)
	WMS-R: visual reproduction	(+)		24	33.2	4.7	24	35.9	4.1	–0.612	(–1.192 to –0.033)
Rodgers 2000[122]	WMS-R: visual paired associates	(+)		15	6.3	7.6	15	12.1	4.3	–0.939	(–1.696 to –0.183)
	WMS-R: visual reproduction	(+)		15	38.7	11.9	15	39	8.7	–0.029	(–0.744 to 0.687)
Simon and Mattick 2002[123]	WMS-III: visual	(+)		40	96	12.4	37	97	11.8	–0.083	(–0.530 to 0.365)
Zakzanis *et al*. 2003[101]	RBMT: picture recognition	(+)		15	1.9	0.3	17	1.8	0.5	0.239	(–0.458 to 0.936)
	RBMT: route	(+)		15	1.9	0.5	17	1.9	0.2	0.000	(–0.694 to 0.694)
Halpern *et al*. 2004[106]	R-OCFT: total score	(+)	(1) Heavy users vs controls	11	21.6	6.4	8	22.3	6.3	–0.110	(–1.022 to 0.801)
			(2) Moderate users vs controls	12	21	3.5	8	22.3	6.3	–0.272	(–1.171 to 0.627)
	WMS-III: visual reproduction	(+)	(1) Heavy users vs controls	11	80.5	16.5	8	90.6	11.6	–0.688	(–1.628 to 0.252)
			(2) Moderate users vs controls	12	87.4	9.1	8	90.6	11.6	–0.315	(–1.216 to 0.585)
Reneman *et al*. 2006[97]	WMS-R: visual reproduction	(+)	(1) Heavy users vs controls	22	35.4	5.6	4.33	36.4	3.4	–0.187	(–1.218 to 0.845)
			(2) Moderate users vs controls	15	36.2	5.5	4.33	36.4	3.4	–0.039	(–1.108 to 1.030)

Study	Measure	(+/–)	Comparison	MDMA users			Controls			SMD	(95% CI)
				n	Mean	SD	*n*	Mean	SD		
Lamers *et al.* 2006[98]	R-OCFT: total score	(+)		11	20.6	7.6	15	22.3	6.8	–0.238	(–1.019 to 0.543)
de Win *et al.* 2006[91]	MFD: correct – n	(+)	Follow-up. Data from secondary pub.[90]	58	20.8	0.5	60	20.9	0.3	–0.244	(–0.606 to 0.119)
Groth *et al.* 2007[126]	WMS-III: visual	(+)		26	99.2	11.2	26	100.3	9.2	–0.107	(–0.651 to 0.437)
Roiser *et al.* 2007[118]	PRM: correct [%]	(+)		30	88.3	8.4	15	87.9	12.4	0.040	(–0.579 to 0.660)
	PRM: latency – ms	(–)		30	1702	346.7	15	1749	472.9	0.120	(–0.500 to 0.740)
Former users vs polydrug controls											
Reneman *et al.* 2006[97]	WMS-R: visual reproduction	(+)		16	35.9	4.1	4.33	36.4	3.4	–0.126	(–1.188 to 0.937)
	PRM: correct [%]	(+)		20	83.8	16.5	15	87.9	12.4	–0.275	(–0.948 to 0.398)
Roiser *et al.* 2007[118]	PRM: latency – ms	(–)		20	1850	591.8	15	1749	472.9	–0.186	(–0.857 to 0.485)

TABLE 58 *Visual memory – delayed (composite measure) – ecstasy users versus drug-naïve controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs drug-naïve controls											
Rodgers 2000[122]	WMS-R: visual paired associates	(+)		15	6.3	7.6	15	13.4	2.6	–1.250	(–2.037 to –0.463)
	WMS-R: visual reproduction	(+)		15	38.7	11.9	15	36.9	7.6	0.180	(–0.537 to 0.898)
Bhattachary and Powell 2001[127]	R-OCFT: total score	(+)	(1) Regular users vs non-users	26	24.92	3.38	6.67	23.38	3.44	0.454	(–0.404 to 1.313)
			(2) Novice users vs non-users	18	24.11	2.8	6.67	23.38	3.44	0.246	(–0.646 to 1.137)
Yip and Lee 2005[128]	AFLT: overall score	(+)		100	5.45	1.57	100	8.81	1.99	–1.875	(–2.208 to –1.542)
Lamers *et al*. 2006[98]	R-OCFT: total score	(+)		11	20.6	7.6	15	23.7	4.2	–0.529	(–1.321 to 0.263)
Roiser *et al*. 2007[118]	PRM: correct [%]	(+)		30	88.3	8.4	15	89	9.4	–0.080	(–0.700 to 0.540)
	PRM: latency – ms	(–)		30	1702	346.7	15	1678	392.9	–0.065	(–0.685 to 0.555)
Former users vs drug-naïve controls											
Bhattachary and Powell 2001[127]	R-OCFT: total score	(+)		16	23.28	2.91	6.67	23.38	3.44	–0.033	(–0.936 to 0.871)
Roiser *et al*. 2007[118]	PRM: correct [%]	(+)		20	83.8	16.5	15	89	9.4	–0.373	(–1.049 to 0.302)
	PRM: latency – ms	(–)		20	1850	591.8	15	1678	392.9	–0.332	(–1.006 to 0.342)

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TABLE 59 *Working memory (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs polydrug controls											
Rodgers 2000[122]	WMS-R: mental control	(+)		15	4.9	3.2	15	5.3	5.1	–0.094	(–0.810 to 0.622)
Gouzoulis *et al.* 2000[99]	TAP: 5 – divided attention – time [ms]	(–)		28	671.6	57	28	625	35.1	–0.984	(–1.540 to –0.429)
	TAP: 8 – intermodal integration – time [ms]	(–)		28	412.2	80.7	28	364.9	44.8	–0.725	(–1.266 to –0.183)
Fox *et al.* 2001[112]	Spatial recall – correct – *n*	(+)	(1) High-dose users vs controls	11	24.5	3.7	6.67	28.3	2.9	–1.107	(–2.144 to –0.070)
			(2) Medium users vs controls	14	25.4	3.1	6.67	28.3	2.9	–0.954	(–1.925 to 0.018)
			(1) Light users vs controls	14	26.9	2.9	6.67	28.3	2.9	–0.483	(–1.418 to 0.452)
Fox *et al.* 2002[130]	Spatial task – between errors – four-box	(–)		20	0.6	2.1	20	0.1	0.3	–0.333	(–0.958 to 0.291)
	Spatial task – between errors – six-box	(–)		20	5.8	4.7	20	3.8	4.8	–0.421	(–1.048 to 0.206)
	Spatial task – between errors – eight-box	(–)		20	17.1	14.2	20	8.3	5.8	–0.811	(–1.457 to –0.165)
	Spatial task – search strategy score	(+)		20	32.7	5.3	20	32	4.1	0.148	(–0.473 to 0.768)
	Spatial task – within errors – four-box	(+)		20	0.1	0.2	20	0.1	0.2	0.000	(–0.620 to 0.620)
	Spatial task – within errors – six-box	(–)		20	0.9	1.6	20	0.7	1.6	–0.125	(–0.745 to 0.495)
	Spatial task – within errors – eight-box	(–)		20	2.9	3.3	20	0.7	1.1	–0.894	(–1.546 to –0.243)
Simon and Mattick 2002[123]	WMS-III: index score	(+)		40	105.1	13.1	37	107	12.5	–0.148	(–0.596 to 0.299)
Morgan *et al.* 2002[103]	Serial subtraction (SS7) – errors [*n*]	(–)		18	1.725	1.591	8	1.05	1.4	–0.439	(–1.281 to 0.403)
Curran and Verheyden 2003[104]	Serial subtraction (SS7) – correct – *n*	(+)		32	28.5	13.9	16	27.7	11.7	0.061	(–0.540 to 0.661)
	RVIP: 5-minute task – correct [*n*]	(+)		32	19.9	6.7	16	19.7	6.4	0.030	(–0.570 to 0.630)

continued

TABLE 59 *Working memory (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis (continued)*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Gouzoulis *et al*. 2003[108]	*n*-back: 2-back – figures – correct responses – *n*	(+)	(1) Heavy users vs controls	30	8.9	3.1	15	9.7	3	–0.261	(–0.883 to 0.361)
			(2) Moderate users vs controls	30	8.7	2.8	15	9.7	3	–0.349	(–0.973 to 0.275)
	n-back: 2-back – figures – reaction time – ms	(–)	(1) Heavy users vs controls	30	695.2	146.5	15	742.5	131.6	0.334	(–0.290 to 0.957)
			(2) Moderate users vs controls	30	723.4	153.4	15	742.5	131.6	0.130	(–0.490 to 0.751)
	n-back: 2-back – letters – correct responses – *n*	(+)	(1) Heavy users vs controls	30	11.9	2.7	15	12.3	3.2	–0.139	(–0.760 to 0.481)
			(2) Moderate users vs controls	30	12.9	1.7	15	12.3	3.2	0.261	(–0.361 to 0.883)
	n-back: 2-back – letters – reaction time – ms	(–)	(1) Heavy users vs controls	30	641.8	149.4	15	622.2	140.9	–0.134	(–0.754 to 0.487)
			(2) Moderate users vs controls	30	630.1	153.9	15	622.2	140.9	–0.053	(–0.673 to 0.567)
Halpern *et al*. 2004[106]	WMS-III: mental control	(+)	(1) Heavy users vs controls	11	25.9	5.6	8	28.8	3.4	–0.602	(–1.535 to 0.331)
			(2) Moderate users vs controls	12	28.3	4.1	8	28.8	3.4	–0.130	(–1.026 to 0.765)
von Geusau *et al*. 2004[132]	HvdM MC: Mental counters – correct – %	(+)	(1) Female	9	89.7	1.8	21	89.7	1.2	0.000	(–0.781 to 0.781)
			(2) Male	17	89.6	1.2	12	92.9	1.6	–2.396	(–3.373 to –1.419)
	HvdM MC: Mental counters – reaction time – ms	(–)	(1) Female	9	544.7	50	21	540.3	33.1	–0.114	(–0.895 to 0.668)
			(2) Male	17	586.2	34.2	12	413.6	44.1	–4.478	(–5.883 to –3.074)
	HvdM TTT: Tic-tac-toe – correct – %	(+)	(1) Female	9	93	2.7	21	93	1.8	0.000	(–0.781 to 0.781)
			(2) Male	17	91.1	2.2	12	94.9	2.4	–1.664	(–2.526 to –0.802)
	HvdM TTT: Tic-tac-toe – reaction time – ms	(–)	(1) Female	9	376.8	20	21	379.1	13.1	0.149	(–0.632 to 0.931)
			(2) Male	17	385.6	16.1	12	376.6	17.4	–0.541	(–1.294 to 0.212)
Wareing *et al*. 2004[107]	Computation span	(+)		42	3.12	1.85	15.5	5.23	2.1	–1.100	(–1.717 to –0.482)
	Reading span	(+)		42	2.57	0.94	15.5	3.1	1.16	–0.529	(–1.120 to 0.062)

Study	Measure	(+/–)	Comparison	MDMA users			Controls			SMD	(95% CI)
				n	Mean	SD	*n*	Mean	SD		
Medina *et al.* 2005[124]	WAIS-III: letter number sequencing – scaled score	(+)		48	10.1	2.2	17	10.5	3	–0.165	(–0.719 to 0.389)
de Win *et al.* 2006[91]	PASAT: hits – 1.6 s	(+)	Follow-up. Data from secondary pub.[90]	58	45.5	8	60	46.3	8.4	–0.097	(–0.459 to 0.264)
	PASAT: hits – 2.4 s	(+)	Follow-up. Data from secondary pub.[90]	58	55	5	60	54.9	5	0.020	(–0.341 to 0.381)
Groth *et al.* 2007[126]	WMS-III: index score	(+)		26	107.6	14.6	26	105.5	8.2	0.177	(–0.367 to 0.722)
Former users vs polydrug controls											
Morgan *et al.* 2002[103]	Serial subtraction (SS7) – errors [*n*]	(–)		15	1.35	1.356	8	1.05	1.4	–0.219	(–1.080 to 0.642)
Curran and Verheyden 2003[104]	Serial subtraction (SS7) – correct – n	(+)		32	22.8	5.4	16	27.7	11.7	–0.611	(–1.224 to 0.002)
	RVIP: 5-min task – correct [*n*]	(+)		32	13.7	5.8	16	19.7	6.4	–1.000	(–1.634 to –0.366)
Wareing *et al.* 2004[107]	Computation span	(+)		17	2.82	1.63	15.5	5.23	2.1	–1.290	(–2.051 to –0.529)
	Reading span	(+)		17	3.06	1.39	15.5	3.1	1.16	–0.031	(–0.719 to 0.657)

TABLE 60 *Working memory (composite measure) – ecstasy users versus drug-naïve controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs drug-naïve controls											
Rodgers 2000[122]	WMS-R: mental control	(+)		15	4.9	3.2	15	5.4	5.1	–0.117	(–0.834 to 0.599)
Gouzoulis *et al*. 2000[99]	TAP: 5 – divided attention – time [ms]	(–)		28	671.6	57	28	638.7	69.7	–0.517	(–1.050 to 0.016)
	TAP: 8 – intermodal integration – time [ms]	(–)		28	412.2	80.7	28	380.5	49.2	–0.474	(–1.006 to 0.057)
Moeller *et al*. 2002[133]	Delayed memory task – correct [*n*]	(+)	(1) Heavy users vs controls	8	77.5	15.15	10	90	9.127	–1.030	(–2.026 to –0.034)
			(2) Infrequent users vs controls	8	96	5.772	10	90	9.127	0.765	(–0.201 to 1.732)
Morgan *et al*. 2002[103]	Serial subtraction (SS7) – errors [*n*]	(–)		18	1.725	1.591	7.5	0.325	0.678	–1.000	(–1.899 to –0.102)
Jacobsen *et al*. 2004[134]	*n*-back: 1-back and 2-back (auditory) – correct responses (simple) [%]	(+)		6	0.88	0.14	6	0.89	0.06	–0.093	(–1.225 to 1.039)
	n-back: 1-back and 2-back (auditory) – reaction time (simple) [ms]	(–)		6	1500	141.9	6	1208	119.2	–2.224	(–3.717 to –0.730)
	n-back: 1-back and 2-back (divided) – correct responses [%]	(+)		6	0.77	0.15	6	0.78	0.07	–0.085	(–1.218 to 1.047)
	n-back: 1-back and 2-back (visual) – correct responses (selective) [%]	(+)		6	0.89	0.1	6	0.97	0.05	–1.012	(–2.227 to 0.203)
	n-back: 1-back and 2-back (visual) – correct responses (simple) [%]	(+)		6	0.92	0.03	6	0.92	0.09	0.000	(–1.132 to 1.132)
	n-back: 1-back and 2-back (visual) – reaction time (simple) [ms]	(–)		6	1272	212.1	6	932.7	95.8	–2.064	(–3.512 to –0.615)
Former users vs drug-naïve controls											
Morgan *et al*. 2002[103]	Serial subtraction (SS7) – errors [*n*]	(–)		15	1.35	1.356	7.5	0.325	0.678	–0.866	(–1.782 to 0.050)

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TABLE 61 *Attention – focus–execute (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95%CI)**
Current users vs polydrug controls											
Parrott and Lasky 1998[121]	Visual search – time [s]	(–)	(1) Regular users vs controls	15	2.7	0.775	7.5	2.5	0.775	–0.258	(–1.138 to 0.622)
			(2) Novice users vs controls	15	2.7	0.775	7.5	2.5	0.775	–0.258	(–1.138 to 0.622)
Morgan 1998[110]	MFFT-20: latency to first response [s]	(–)	(1) Study 1	16	12.48	6.64	12	14.73	5.27	0.369	(–0.386 to 1.124)
			(2) Study 2	25	12	3.71	20	13.16	3.76	0.311	(–0.281 to 0.902)
	MFFT-20: total errors [*n*]	(–)	(1) Study 1	16	11.81	7.57	12	4.83	2.25	–1.176	(–1.990 to –0.363)
			(2) Study 2	25	11.73	5.88	20	8.25	4.44	–0.658	(–1.262 to –0.053)
Rodgers 2000[122]	Complex reaction time [ms]	(–)		15	1090	261.7	15	951.5	122.8	–0.679	(–1.416 to 0.058)
	Simple auditory reaction time [ms]	(–)		15	272	77.49	15	292.3	95.47	0.233	(–0.485 to 0.952)
	Visual reaction time [ms]	(–)		15	357.5	71.78	15	349.6	96.97	–0.093	(–0.809 to 0.623)
Gouzoulis *et al.* 2000[99]	TAP: 1 – phasic reaction time [ms]	(–)		28	214.8	24.8	28	214	26.7	–0.031	(–0.555 to 0.493)
	TAP: 1 – tonic reaction time [ms]	(–)		28	218.9	28.2	28	221.1	26.3	0.081	(–0.443 to 0.605)
Fox *et al.* 2001[112]	Simple visual reaction time [ms]	(–)	(1) High-dose users vs controls	11	291.2	35.4	6.67	277.9	25.4	–0.415	(–1.388 to 0.558)
			(2) Medium users vs controls	14	301	28.2	6.67	277.9	25.4	–0.845	(–1.807 to 0.116)
			(3) Low users vs controls	14	292.2	33.5	6.67	277.9	25.4	–0.459	(–1.393 to 0.475)
Croft *et al.* 2001[94]	Stroop: word reading – time [s]	(–)		11	19.5	4.9	18	17.9	2.7	–0.436	(–1.195 to 0.323)

continued

TABLE 61 *Attention – focus–execute (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis(continued)*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95%CI)**
Verkes *et al.* 2001[129]	Binary choice task – reaction time [ms]	(–)	(1) Heavy users vs controls	21	364	72	10	326	42	–0.592	(–1.360 to 0.176)
			(2) Moderate users vs controls	21	347	64	10	326	42	–0.362	(–1.120 to 0.397)
	Simple auditory reaction time [ms]	(–)	(1) Heavy users vs controls	21	247	36	10	224	23	–0.707	(–1.482 to 0.068)
			(2) Moderate users vs controls	21	239	33	10	224	23	–0.496	(–1.260 to 0.268)
	Simple visual reaction time [ms]	(–)	(1) Heavy users vs controls	21	273	39	10	246	27	–0.756	(–1.534 to 0.022)
			(2) Moderate users vs controls	21	258	37	10	246	27	–0.351	(–1.109 to 0.408)
Fox *et al.* 2002[130]	CANTAB 3D – ID/ED: errors – simple dimensional (reversal)	(–)		20	2.5	3.3	20	1.5	1.2	–0.403	(–1.029 to 0.224)
	CANTAB 3D – ID/ED: errors – simple dimensional	(–)		20	0.7	1.1	20	0.2	0.5	–0.585	(–1.219 to 0.048)
	CANTAB 3D – ID/ED: latency – simple dimensional (reversal)	(–)		20	3.02	1.97	20	2.03	0.73	–0.666	(–1.304 to –0.029)
	CANTAB 3D – ID/ED: latency – simple dimensional	(–)		20	3.91	2.27	20	2.56	1.3	–0.730	(–1.371 to –0.089)
Morgan *et al.* 2002[103]	MFFT-20: latency to first response [s]	(–)		18	8.5	4.667	8	13	5.2	0.932	(0.058–1.806)
	MFFT-20: total errors [*n*]	(–)		18	15.8	5.091	8	9.2	7.6	–1.112	(–2.003 to –0.222)
	TMT: Part B – errors (*n*)	(–)		18	0.95	1.57	8	0.13	0.32	–0.615	(–1.466 to 0.235)
Curran and Verheyden 2003[104]	Double digit cancellation – time [s]	(–)		32	81.34	17.52	16	86.25	27.83	0.229	(–0.373 to 0.831)
Halpern *et al.* 2004[106]	Stroop: colour reading – errors [*n*]	(–)	(1) Heavy users vs controls	11	1.7	1.3	8	0.9	1.3	–0.615	(–1.549 to 0.319)
			(2) Moderate users vs controls	12	1.5	1.5	8	0.9	1.3	–0.421	(–1.326 to 0.484)
	Stroop: colour reading – time [s]	(–)	(1) Heavy users vs controls	11	61.3	10.8	8	51.7	5.3	–1.072	(–2.052 to –0.093)
			(2) Moderate users vs controls	12	53.7	8	8	51.7	5.3	–0.283	(–1.182 to 0.617)
	Stroop: word reading – errors [*n*]	(–)	(1) Heavy users vs controls	11	1.1	1.1	8	0.6	0.7	–0.523	(–1.451 to 0.404)

Study	Measure	(+/–)	Comparison	MDMA users			Controls			SMD	(95%CI)
				n	Mean	SD	*n*	Mean	SD		
			(2) Moderate users vs controls	12	1.1	1.3	8	0.6	0.7	–0.452	(–1.359 to 0.455)
	Stroop: word reading – time [s]	(–)	(1) Heavy users vs controls	11	47.1	7.8	8	41.3	5.8	–0.823	(–1.775 to 0.129)
			(2) Moderate users vs controls	12	41.4	5.9	8	41.3	5.8	–0.017	(–0.912 to 0.878)
	TMT: Part A – errors (n)	(–)	(1) Heavy users vs controls	11	0.6	0.7	8	0	0.5	–0.959	(–1.925 to 0.007)
			(2) Moderate users vs controls	12	0.4	1	8	0	0.5	–0.475	(–1.383 to 0.433)
	TMT: Part A – time (s)	(–)	(1) Heavy users vs controls	11	24.7	9.9	8	22.1	6.3	–0.302	(–1.219 to 0.614)
			(2) Moderate users vs controls	12	21.8	4.9	8	22.1	6.3	0.055	(–0.840 to 0.949)
	TMT: Part B – errors (n)	(–)	(1) Heavy users vs controls	11	0.7	0.6	8	0.3	0.4	–0.759	(–1.705 to 0.187)
			(2) Moderate users vs controls	12	0.3	0.7	8	0.3	0.4	0.000	(–0.895 to 0.895)
	TMT: Part B – time (s)	(–)	(1) Heavy users vs controls	11	58.5	13.6	8	48.2	15.4	–0.717	(–1.659 to 0.225)
			(2) Moderate users vs controls	12	52.6	17.4	8	48.2	15.4	–0.264	(–1.163 to 0.635)
	WAIS-R: digit symbol	(+)	(1) Heavy users vs controls	11	62.4	10.3	8	69.6	12.5	–0.640	(–1.575 to 0.296)
			(2) Moderate users vs controls	12	69.8	12.7	8	69.6	12.5	0.016	(–0.879 to 0.910)
McCardle *et al.* 2004[100]	?WAIS: digit symbol	(+)		17	64.06	8.74	15	66.07	10.89	–0.205	(–0.901 to 0.491)
	TMT: Part A – time (s)	(–)		17	34.02	9.99	15	24.49	8.05	–1.043	(–1.786 to –0.300)
	TMT: Part B – time (s)	(–)		17	68.09	15.47	15	64.7	25.35	–0.164	(–0.859 to 0.532)
Medina *et al.* 2005[124]	Ruff 2 and 7: total accuracy –T-score	(+)		48	44.9	10.3	17	45.4	7.5	–0.052	(–0.605 to 0.502)
	Ruff 2 and 7: total speed –T-score	(+)		48	46.3	8.9	17	48.6	7.9	–0.266	(–0.821 to 0.289)
	Stroop: colour reading – time [s]	(–)		48	10.2	2	17	10.6	2.3	0.192	(–0.362 to 0.746)
	Stroop: word reading – time [s]	(–)		48	10.4	3.1	17	10.5	3.2	0.032	(–0.521 to 0.585)
	TMT: Part B –T-score	(+)		48	52.7	10.9	17	53.5	13.3	–0.069	(–0.623 to 0.484)

continued

TABLE 61 *Attention – focus–execute (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis (continued)*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95%CI)**
Morgan *et al.* 2006[115]	MFFT–20: latency to first response [s]	(–)		20	13.1	5.814	20	17.9	6.037	0.810	(0.164–1.456)
	MFFT–20: total errors [*n*]	(–)		20	12.5	6.485	20	7.85	5.367	–0.781	(–1.425 to –0.137)
Dafters 2006[137]	Stroop: colour reading – time [ms]	(–)		33	713	134	17	724	120	0.085	(–0.500 to 0.670)
	Stroop: word reading – time [ms]	(–)		33	683	133	17	684	124	0.008	(–0.577 to 0.593)
Reneman *et al.* 2006[97]	FePsy: auditive reaction time – dominant hand [ms]	(–)	(1) MDMA users (heavy) vs control	22	245.2	30.2	4.33	242.5	22.1	–0.092	(–1.123 to 0.938)
			(2) MDMA users (moderate) vs control	15	246.7	28.3	4.33	242.5	22.1	–0.154	(–1.224 to 0.916)
	FePsy: auditive reaction time – non-dominant hand [ms]	(–)	(1) MDMA users (heavy) vs control	22	245.5	26.8	4.33	244.4	34.6	–0.039	(–1.069 to 0.991)
			(2) MDMA users (moderate) vs control	15	250.1	24.1	4.33	244.4	34.6	–0.216	(–1.287 to 0.856)
	FePsy: binary choice – errors [*n*]	(–)	(1) MDMA users (heavy) vs control	22	5	7.2	4.33	2.5	3.4	–0.367	(–1.403 to 0.668)
			(2) MDMA users (moderate) vs control	15	2.6	3.1	4.33	2.5	3.4	–0.032	(–1.101 to 1.037)
	FePsy: binary choice – reaction time [ms]	(–)	(1) MDMA users (heavy) vs control	22	353.7	67.9	4.33	382.9	112.6	0.386	(–0.650 to 1.422)
			(2) MDMA users (moderate) vs control	15	368.2	53	4.33	382.9	112.6	0.214	(–0.857 to 1.286)
	FePsy: visual reaction time – dominant hand [ms]	(–)	(1) MDMA users (heavy) vs control	22	257.4	30.7	4.33	282.1	52.2	0.717	(–0.333 to 1.767)
			(2) MDMA users (moderate) vs control	15	287.7	55.2	4.33	282.1	52.2	–0.102	(–1.172 to 0.967)
	FePsy: visual reaction time – non-dominant hand [ms]	(–)	(1) MDMA users (heavy) vs control	22	268.7	31.7	4.33	316	92.8	1.045	(–0.026 to 2.117)
			(2) MDMA users (moderate) vs control	15	298.6	56.2	4.33	316	92.8	0.268	(–0.804 to 1.341)
	Stroop: colour reading – time [s]	(–)	(1) MDMA users (heavy) vs control	22	53.2	9	4.33	53.9	9	0.078	(–0.953 to 1.108)
			(2) MDMA users (moderate) vs control	15	56.7	10.5	4.33	53.9	9	–0.274	(–1.347 to 0.799)

Study	Measure	(+/–)	Comparison	MDMA users			Controls			SMD	(95%CI)
				n	Mean	SD	*n*	Mean	SD		
	TMT: Part A – time (s)	(–)	(1) MDMA users (heavy) vs control	22	19.9	3.7	4.33	24.8	7.5	1.109	(0.033–2.185)
			(2) MDMA users (moderate) vs control	15	20.6	6.5	4.33	24.8	7.5	0.627	(–0.463 to 1.716)
	TMT: Part B – time (s)	(–)	(1) MDMA users (heavy) vs control	22	46.4	15.7	4.33	47.9	12.5	0.098	(–0.932 to 1.128)
			(2) MDMA users (moderate) vs control	15	49.7	14.5	4.33	47.9	12.5	–0.127	(–1.197 to 0.942)
Quednow *et al*. 2006[83]	MFFT–20: latency to first response [s]	(–)	Data from secondary pub.[500]	19	49.5	19.3	19	53.3	21.7	0.185	(–0.452 to 0.822)
	MFFT–20: total errors [*n*]	(–)	Data from secondary pub.[500]	19	8.16	4.09	19	5.95	4.36	–0.523	(–1.170 to 0.124)
Lamers *et al*. 2006[98]	TMT: Part A – time (s)	(–)		11	26.8	9.7	15	22.3	8.5	–0.499	(–1.290 to 0.292)
	TMT: Part B – part A – time (s)	(–)		11	24.2	3.8	15	22.7	2.5	–0.483	(–1.272 to 0.307)
	TMT: Part B – time (s)	(–)		11	51	17.7	15	45	13.3	–0.392	(–1.178 to 0.393)
Wareing *et al*. 2007[135]	Letter comparison speed task – three-letter – correct [*n*]	(+)		29	26	3.7	23	26.91	4.95	–0.212	(–0.761 to 0.337)
	Letter comparison speed task – three-letter – errors [*n*]	(–)		29	1.61	1.24	23	1.09	1.01	–0.454	(–1.009 to 0.100)
	Letter comparison speed task – six-letter – correct [*n*]	(+)		29	14.91	1.6	23	15.53	3.17	–0.256	(–0.806 to 0.293)
	Letter comparison speed task – six-letter – errors [*n*]	(–)		29	1.28	1.09	23	0.75	0.54	–0.595	(–1.154 to –0.035)
	Letter comparison speed task – nine-letter – correct [*n*]	(+)		29	10.72	2.04	23	10.96	2.29	–0.111	(–0.659 to 0.436)
	Letter comparison speed task – nine-letter – errors [*n*]	(–)		29	1.43	1.47	23	0.94	0.9	–0.391	(–0.944 to 0.161)
	Pattern comparison speed task – three-pattern – correct [*n*]	(+)		29	21.34	3.6	23	19.96	5.37	0.309	(–0.242 to 0.860)
	Pattern comparison speed task – three-pattern – errors [*n*]	(–)		29	1.23	0.94	23	0.91	1.19	–0.303	(–0.853 to 0.248)
	Pattern comparison speed task – six-pattern – correct [*n*]	(+)		29	5.35	2.8	23	14.4	3.49	–2.898	(–3.687 to –2.110)

continued

TABLE 61 *Attention – focus–execute (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis (continued)*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95%CI)**
	Pattern comparison speed task – six-pattern – errors [*n*]	(–)		29	1.59	1.27	23	1.33	1.27	–0.205	(–0.753 to 0.344)
	Pattern comparison speed task – nine-pattern – correct [*n*]	(+)		29	13.74	1.74	23	13.08	3.03	0.276	(–0.274 to 0.826)
	Pattern comparison speed task – nine-pattern – errors [*n*]	(–)		29	1.73	1.54	23	1.31	1.67	–0.263	(–0.812 to 0.287)
Former users vs polydrug controls											
Morgan *et al.* 2002[103]	MFFT-20: latency to first response [s]	(–)		15	10.2	4.648	8	13	5.2	0.579	(–0.297 to 1.454)
	MFFT-20: total errors [*n*]	(–)		15	14.4	5.035	8	9.2	7.6	–0.865	(–1.762 to 0.032)
	TMT: Part B – errors (*n*)	(–)		15	0.64	0.891	8	0.13	0.32	–0.680	(–1.562 to 0.203)
Curran and Verheyden 2003[104]	Double digit cancellation – time [s]	(–)		32	93.62	25.07	16	86.25	27.83	–0.283	(–0.886 to 0.320)
Reneman *et al.* 2006[97]	FePsy: auditive reaction time – dominant hand [ms]	(–)		16	244.1	29.3	4.33	242.5	22.1	–0.057	(–1.118 to 1.005)
	FePsy: auditive reaction time – non-dominant hand [ms]	(–)		16	254.3	32.3	4.33	244.4	34.6	–0.302	(–1.368 to 0.763)
	FePsy: binary choice – errors [*n*]	(–)		16	2.6	1.9	4.33	2.5	3.4	–0.044	(–1.106 to 1.017)
	FePsy: binary choice – reaction time [ms]	(–)		16	368.3	69.5	4.33	382.9	112.6	0.185	(–0.879 to 1.248)
	FePsy: visual reaction time – dominant hand [ms]	(–)		16	270.3	46.6	4.33	282.1	52.2	0.248	(–0.817 to 1.312)
	FePsy: visual reaction time – non-dominant hand [ms]	(–)		16	279.9	53.6	4.33	316	92.8	0.577	(–0.501 to 1.655)
	Stroop: colour reading – time [s]	(–)		16	53.5	7.9	4.33	53.9	9	0.049	(–1.012 to 1.111)
	TMT: Part A – time (s)	(–)		16	24	11.6	4.33	24.8	7.5	0.073	(–0.989 to 1.135)
	TMT: Part B – time (s)	(–)		16	52.5	13.5	4.33	47.9	12.5	–0.345	(–1.413 to 0.722)

Study	Measure	(+/–)	Comparison	MDMA users			Controls			SMD	(95%CI)
				n	Mean	SD	*n*	Mean	SD		
Wareing *et al.* 2007[135]	Letter comparison speed task – three-letter – correct [*n*]	(+)		10	23.1	5	23	26.91	4.95	–0.767	(–1.534 to –0.001)
	Letter comparison speed task – three-letter – errors [*n*]	(–)		10	1.2	0.72	23	1.09	1.01	–0.118	(–0.861 to 0.625)
	Letter comparison speed task – six-letter – correct [*n*]	(+)		10	13.83	3.16	23	15.53	3.17	–0.537	(–1.291 to 0.218)
	Letter comparison speed task – six-letter – errors [*n*]	(–)		10	0.63	0.6	23	0.75	0.54	0.215	(–0.529 to 0.959)
	Letter comparison speed task – nine-letter – correct [*n*]	(+)		10	10.1	2.34	23	10.96	2.29	–0.373	(–1.121 to 0.375)
	Letter comparison speed task – nine-letter – errors [*n*]	(–)		10	0.87	0.61	23	0.94	0.9	0.085	(–0.658 to 0.827)
	Pattern comparison speed task – three-pattern – correct [*n*]	(+)		10	17.6	4.8	23	19.96	5.37	–0.453	(–1.204 to 0.298)
	Pattern comparison speed task – three-pattern – errors [*n*]	(–)		10	1.17	1.29	23	0.91	1.19	–0.213	(–0.957 to 0.531)
	Pattern comparison speed task – six-pattern – correct [*n*]	(+)		10	14.23	3.22	23	14.4	3.49	–0.050	(–0.792 to 0.693)
	Pattern comparison speed task – six-pattern – errors [*n*]	(–)		10	1.1	1.12	23	1.33	1.27	0.187	(–0.557 to 0.931)
	Pattern comparison speed task – nine-pattern – correct [*n*]	(+)		10	13.53	3.7	23	13.08	3.03	0.139	(–0.604 to 0.882)
	Pattern comparison speed task – nine-pattern – errors [*n*]	(–)		10	2.07	2.22	23	1.31	1.67	–0.412	(–1.161 to 0.338)

TABLE 62 *Attention – focus–execute (composite measure) – ecstasy users versus drug-naïve controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs drug-naïve controls											
Morgan 1998[110]	MFFT-20: latency to first response [s]	(–)	(1) Study 1	16	12.48	6.64	16	16.19	5.83	0.594	(–0.115 to 1.303)
			(2) Study 2	25	12	3.71	19	13.9	7.02	0.353	(–0.248 to 0.954)
	MFFT-20: total errors [*n*]	(–)	(1) Study 1	16	11.81	7.57	16	5.18	3.1	–1.146	(–1.897 to –0.395)
			(2) Study 2	25	11.73	5.88	19	9.68	4.93	–0.373	(–0.975 to 0.229)
Wareing *et al.* 2000[136]	Letter comparison speed task – three-letter – correct [*n*]	(+)		10	18.9	5.61	5	22.7	3.02	–0.766	(–1.879 to 0.347)
	Letter comparison speed task – six-letter – correct [*n*]	(+)		10	14.6	4.62	5	15.5	2.17	–0.223	(–1.300 to 0.854)
	Letter comparison speed task – nine-letter – correct [*n*]	(+)		10	12.9	4.65	5	12.5	1.72	0.100	(–0.974 to 1.175)
Rodgers 2000[122]	Complex reaction time [ms]	(–)		15	1090	261.7	15	953.2	120.9	–0.673	(–1.410 to 0.064)
	Simple auditory reaction time [ms]	(–)		15	272	77.49	15	279.8	67.35	0.108	(–0.608 to 0.824)
	Visual reaction time [ms]	(–)		15	357.5	71.78	15	379.3	75.96	0.295	(–0.425 to 1.015)
Gouzoulis *et al.* 2000[99]	TAP: 1 – phasic reaction time [ms]	(–)		28	214.8	24.8	28	214.7	25.2	–0.004	(–0.528 to 0.520)
	TAP: 1 – tonic reaction time [ms]	(–)		28	218.9	28.2	28	218.7	27.5	–0.007	(–0.531 to 0.517)
Croft *et al.* 2001[94]	Stroop: word reading – time [s]	(–)		11	19.5	4.9	31	16.7	2.4	–0.871	(–1.585 to –0.158)
Moeller *et al.* 2002[131]	Immediate memory task – correct [*n*]	(+)	(1) MDMA users (heavy) vs control	8	81	15.87	10	88	6.845	–0.599	(–1.551 to 0.354)
			(2) MDMA users (infrequent) vs control	8	87.5	11.54	10	88	6.845	–0.054	(–0.984 to 0.876)
Morgan *et al.* 2002[103]	MFFT–20: latency to first response [s]	(–)		18	8.5	4.667	7.5	14.3	6.584	1.101	(0.193–2.009)
	MFFT–20: total errors [*n*]	(–)		18	15.8	5.091	7.5	7.8	3.486	–1.701	(–2.682 to –0.720)
	TMT: Part B – errors (*n*)	(–)		18	0.95	1.57	7.5	0.14	0.349	–0.601	(–1.470 to 0.268)

Study	Measure	(+/–)	Comparison	MDMA users			Controls			SMD	(95% CI)
				n	Mean	SD	*n*	Mean	SD		
Yip and Lee 2005[128]	SDMT: overall score	(+)		100	60.97	4.43	100	66.3	3	–1.409	(–1.719 to –1.099)
	TMT-C: Part 1 – time (s)	(–)		100	27.62	3.33	100	27.42	3.11	–0.062	(–0.339 to 0.215)
	TMT-C: Part 2 – time (s)	(–)		100	64.44	6.92	100	63.88	7.04	–0.080	(–0.358 to 0.197)
Morgan *et al.* 2006[115]	MFFT-20: latency to first response [s]	(–)		20	13.1	5.814	19	22	11.55	0.981	(0.315–1.648)
	MFFT-20: total errors [*n*]	(–)		20	12.5	6.485	19	6.75	6.32	–0.898	(–1.558 to –0.237)
Dafters 2006[137]	Stroop: colour reading – time [ms]	(–)		33	713	134	18	699	129	–0.106	(–0.681 to 0.469)
	Stroop: word reading – time [ms]	(–)		33	683	133	18	682	117	–0.008	(–0.582 to 0.566)
Quednow *et al.* 2006[83]	MFFT-20: latency to first response [s]	(–)	Data from secondary pub.[500]	19	49.5	19.3	19	60.5	29.9	0.437	(–0.207 to 1.081)
	MFFT-20: total errors [*n*]	(–)	Data from secondary pub.[500]	19	8.16	4.09	19	6.47	4.23	–0.406	(–1.049 to 0.237)
Lamers *et al.* 2006[98]	TMT: Part A – time (s)	(–)		11	26.8	9.7	15	19	5.7	–1.023	(–1.853 to –0.193)
	TMT: Part B – part A – time (s)	(–)		11	24.2	3.8	15	19.1	6.4	–0.933	(–1.754 to –0.111)
	TMT: Part B – time (s)	(–)		11	51	17.7	15	38.1	9.3	–0.959	(–1.783 to –0.135)
Former users vs drug-naïve controls											
Wareing *et al.* 2000[136]	Letter comparison speed task – three-letter – correct [*n*]	(+)		8	20	2	5	22.7	3.02	–1.115	(–2.326 to 0.095)
	Letter comparison speed task – six-letter – correct [*n*]	(+)		8	14.9	3.67	5	15.5	2.17	–0.187	(–1.307 to 0.933)
	Letter comparison speed task – nine-letter – correct [*n*]	(+)		8	11.7	3.23	5	12.5	1.72	–0.288	(–1.412 to 0.836)
Morgan *et al.* 2002[103]	MFFT-20: latency to first response [s]	(–)		15	10.2	4.648	7.5	14.3	6.584	0.768	(–0.139 to 1.676)
	MFFT-20: total errors [*n*]	(–)		15	14.4	5.035	7.5	7.8	3.486	–1.435	(–2.415 to –0.454)
	TMT: Part B – errors (*n*)	(–)		15	0.64	0.891	7.5	0.14	0.349	–0.656	(–1.556 to 0.243)

TABLE 63 *Attention – sustain (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis*

Study	Measure	(+/–)	Comparison	MDMA users			Controls			SMD	(95% CI)
				n	Mean	SD	*n*	Mean	SD		
Current users vs polydrug controls											
Gouzoulis *et al*. 2000[99]	TAP: visual scanning – critical trials – time [ms]	(–)		28	1959	493.7	28	1921	445.7	–0.079	(–0.603 to 0.445)
	TAP: visual scanning – non-critical trials – time [ms]	(–)		28	3281	1017	28	3416	868.2	0.143	(–0.382 to 0.667)
Fox *et al*. 2002[130]	CANTAB 3D – ID/ED: errors – compound dimensional (reversal)	(–)		20	1.9	1.7	20	1.3	0.5	–0.479	(–1.108 to 0.150)
	CANTAB 3D – ID/ED: errors – compound dimensional	(–)		20	2.2	3.7	20	1.4	1.7	–0.278	(–0.901 to 0.345)
	CANTAB 3D – ID/ED: errors – intradimensional (reversal)	(–)		20	1.4	0.9	20	1.1	0.3	–0.447	(–1.075 to 0.181)
	CANTAB 3D – ID/ED: errors – intradimensional	(–)		20	1.2	1	20	0.9	0.9	–0.315	(–0.939 to 0.308)
	CANTAB 3D – ID/ED: latency – compound dimensional (reversal)	(–)		20	2.37	0.91	20	1.85	0.52	–0.702	(–1.341 to –0.062)
	CANTAB 3D – ID/ED: latency – compound dimensional	(–)		20	3.42	3.01	20	3.17	3.59	–0.075	(–0.695 to 0.545)
	CANTAB 3D – ID/ED: latency – intradimensional (reversal)	(–)		20	1.92	0.77	20	1.57	0.49	–0.542	(–1.174 to 0.089)
	CANTAB 3D – ID/ED: latency – intradimensional	(–)		20	2.6	0.93	20	2.15	0.9	–0.492	(–1.121 to 0.138)
Curran and Verheyden 2003[104]	RVIP: 10 min task – correct [*n*]	(+)		32	32.4	7.8	16	30.5	8.1	0.241	(–0.362 to 0.843)
Gouzoulis *et al*. 2003[108]	G/N-G: correct responses	(+)	(1) Heavy E users vs controls	30	19.7	0.5	15	19.4	0.9	0.456	(–0.171 to 1.084)
			(2) Moderate E users vs controls	30	19.5	0.7	15	19.4	0.9	0.130	(–0.491 to 0.750)
	TAP: visual scanning – critical trials – correct [*n*]	(+)	(1) Heavy E users vs controls	30	44.8	4.1	15	45.5	3.2	–0.183	(–0.804 to 0.438)
			(2) Moderate E users vs controls	30	44.8	3.5	15	45.5	3.2	–0.206	(–0.827 to 0.416)

Study	Measure	(+/–)	Comparison	MDMA users			Controls			SMD	(95% CI)
				n	Mean	SD	*n*	Mean	SD		
	TAP: visual scanning – critical trials – time [ms]	(–)	(1) Heavy E users vs controls	30	2756	778.2	15	2445	729.8	–0.408	(–1.034 to 0.218)
			(2) Moderate E users vs controls	30	2542	840.7	15	2445	729.8	–0.120	(–0.740 to 0.501)
	TAP: visual scanning – non-critical trials – correct [*n*]	(+)	(1) Heavy E users vs controls	30	48.2	1.1	15	48.5	1	–0.281	(–0.903 to 0.342)
			(2) Moderate E users vs controls	30	48.1	1	15	48.5	1	–0.400	(–1.026 to 0.226)
	TAP: visual scanning – non-critical trials – time [ms]	(–)	(1) Heavy E users vs controls	30	4993	1192	15	4368	1269	–0.513	(–1.143 to 0.116)
			(2) Moderate E users vs controls	30	4765	1753	15	4368	1269	–0.246	(–0.868 to 0.376)
Quednow *et al*. 2006[83]	G/N-G: summed conditions – Σ omission errors	(–)	Data from secondary pub.[500]	18	10.94	6.83	17	9.18	5.69	–0.279	(–0.946 to 0.387)
Hoshi *et al*. 2007[125]	G/N-G: correct responses	(+)		25	65	4	14.5	63.5	12.92	0.179	(–0.469 to 0.827)
Roiser *et al*. 2007[118]	CANTAB A-G/N-G: omission errors [*n*]	(–)	Data from secondary pub.[501]	30	3	2.7	15	5.2	5.1	0.601	(–0.031 to 1.234)
Former users vs polydrug controls											
Curran and Verheyden 2003[104]	RVIP: 10-min task – correct [*n*]	(+)		32	26.4	9	16	30.5	8.1	–0.470	(–1.078 to 0.137)
Hoshi *et al*. 2007[125]	G/N-G: correct responses	(+)		27	69.8	1.56	14.5	63.5	12.92	0.823	(0.159–1.486)
Roiser *et al*. 2007[118]	CANTAB A-G/N-G: omission errors [*n*]	(–)	Data from secondary pub.[501]	20	4.8	4.6	15	5.2	5.1	0.083	(–0.587 to 0.753)

TABLE 64 *Executive function – planning (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs polydrug controls											
Morgan 1998[110]	ToL: excess moves (*n*)	(–)	(1) Study 1	16	1.52	0.88	12	1.42	0.74	–0.121	(–0.871 to 0.628)
			(2) Study 2	24	1.45	0.59	20	1.65	0.66	0.321	(–0.276 to 0.919)
	ToL: initial thinking time (ms)	(–)	(1) Study 1	16	3434	2106	12	4668	3686	0.428	(–0.329 to 1.186)
			(2) Study 2	24	2337	1401	20	2521	1535	0.126	(–0.468 to 0.720)
	ToL: perfect solutions (%)	(+)	(1) Study 1	16	59.06	19.99	12	61.11	18.91	–0.105	(–0.854 to 0.644)
			(2) Study 2	24	57.51	13.19	20	56.83	14.22	0.050	(–0.544 to 0.643)
	ToL: subsequent thinking time (ms/move)	(–)	(1) Study 1	16	1561	1335	12	1541	1510	–0.014	(–0.763 to 0.734)
			(2) Study 2	24	817	951	20	710	838	–0.119	(–0.713 to 0.475)
Fox *et al.* 2001[112]	ToL: errors – *n*	(–)	(1) High-dose users vs controls	11	4.6	3.8	6.67	3.8	2.7	–0.232	(–1.198 to 0.733)
			(2) Medium users vs controls	14	5.1	3	6.67	3.8	2.7	–0.446	(–1.380 to 0.487)
			(3) Low users vs controls	14	4.1	2.2	6.67	3.8	2.7	–0.127	(–1.050 to 0.796)
	ToL: planning time – s	(–)	(1) High-dose users vs controls	11	15.3	11.6	6.67	6.5	2.9	–0.933	(–1.949 to 0.083)
			(2) Medium users vs controls	14	9.8	5.4	6.67	6.5	2.9	–0.690	(–1.639 to 0.258)
			(3) Low users vs controls	14	8.9	4.7	6.67	6.5	2.9	–0.567	(–1.507 to 0.373)
	ToL: solution time – s	(–)	(1) High-dose users vs controls	11	6.2	1.8	6.67	5.8	1.3	–0.244	(–1.210 to 0.721)
			(2) Medium users vs controls	14	6.5	1.5	6.67	5.8	1.3	–0.485	(–1.421 to 0.450)
			(3) Low users vs controls	14	6.8	1.5	6.67	5.8	1.3	–0.693	(–1.642 to 0.255)
	ToL: trials completed – *n*	(+)	(1) High-dose users vs controls	11	11.8	0.4	6.67	11.8	0.6	0.000	(–0.962 to 0.962)
			(2) Medium users vs controls	14	11.6	0.5	6.67	11.8	0.6	–0.376	(–1.306 to 0.554)
			(3) Low users vs controls	14	11.6	0.5	6.67	11.8	0.6	–0.376	(–1.306 to 0.554)

Study	Measure	(+/–)	Comparison	MDMA users			Controls			SMD	(95% CI)
				n	Mean	SD	*n*	Mean	SD		
Gouzoulis *et al*. 2003[108]	Plan-A-Day: end score	(+)	(1) Heavy users vs controls	30	24	7.1	15	25.8	7.7	–0.247	(–0.869 to 0.375)
			(2) Moderate users vs controls	30	25.1	7.6	15	25.8	7.7	–0.092	(–0.712 to 0.528)
	Plan-A-Day: sequences of deletions	(–)	(1) Heavy users vs controls	30	10.8	7.4	15	8.4	5.2	–0.355	(–0.979 to 0.269)
			(2) Moderate users vs controls	30	12.2	7.9	15	8.4	5.2	–0.533	(–1.163 to 0.097)
	Plan-A-Day: single deletions	(–)	(1) Heavy users vs controls	30	20.6	13.7	15	19.1	15.3	–0.105	(–0.726 to 0.515)
			(2) Moderate users vs controls	30	24.1	19.1	15	19.1	15.3	–0.279	(–0.901 to 0.344)
	Plan-A-Day: use of F2 key	(–)	(1) Heavy users vs controls	30	21.1	9.1	15	19.3	6.1	–0.218	(–0.840 to 0.403)
			(2) Moderate users vs controls	30	21.6	10.6	15	19.3	6.1	–0.245	(–0.867 to 0.377)
von Geusau *et al*. 2004[132]	ToL: excess moves [%]	(–)	(1) Female	9	55.6	5.1	21	55.2	3.3	–0.103	(–0.884 to 0.679)
			(2) Male	17	54.1	3.7	12	31.7	4.4	–5.600	(–7.266 to –3.934)
	ToL: planning time – s	(–)	(1) Female	9	8.8	2.3	21	10.1	1.5	0.736	(–0.068 to 1.540)
			(2) Male	17	7.7	1.7	12	14.5	2	3.720	(2.483–4.957)
	ToL: total moves	(–)	(1) Female	9	34.7	1.8	21	33.1	1.2	–1.145	(–1.981 to –0.308)
			(2) Male	17	31.9	1.3	12	27.3	1.5	–3.321	(–4.475 to –2.168)
	ToL: total time – s	(–)	(1) Female	9	33.5	2.8	21	33.4	1.9	–0.046	(–0.827 to 0.735)
			(2) Male	17	26.5	2.1	12	30.7	2.5	1.849	(0.961–2.737)
Hoshi *et al*. 2007[125]	SOC: initial thinking time [ms]	(–)		24	8400	7348	14.5	10200	5385	0.269	(–0.386 to 0.924)
Former users vs polydrug controls											
Hoshi *et al*. 2007[125]	SOC: initial thinking time [ms]	(–)		27	15000	7408	14.5	10200	5385	–0.707	(–1.364 to –0.051)

TABLE 65 *Executive function – response inhibition (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs polydrug controls											
Gouzoulis *et al*. 2000[99]	Stroop: interference – time difference [s]	(–)		28	–3.84	4.38	28	–3.86	6.13	–0.004	(–0.528 to 0.520)
	TAP: selective visual attention – time [ms]	(–)		28	532	65.4	28	484.4	57.9	–0.771	(–1.314 to –0.227)
Croft *et al*. 2001[94]	Stroop: interference – time [s]	(–)		11	22.1	5.2	18	21.5	4.2	–0.131	(–0.881 to 0.620)
Gouzoulis *et al*. 2003[108]	G/N-G: reaction time – ms	(–)	(1) Heavy users vs controls	30	398	66.1	15	382.6	54.8	–0.246	(–0.868 to 0.376)
			(2) Moderate users vs controls	30	403.8	75	15	382.6	54.8	–0.307	(–0.930 to 0.316)
Halpern *et al*. 2004[106]	Stroop: interference – errors [*n*]	(–)	(1) Heavy users vs controls	11	5.1	3.5	8	2.2	2.1	–0.965	(–1.932 to 0.001)
			(2) Moderate users vs controls	12	3	2	8	2.2	2.1	–0.392	(–1.296 to 0.511)
	Stroop: interference – time [s]	(–)	(1) Heavy users vs controls	11	115	18.9	8	91.1	15.5	–1.360	(–2.378 to –0.341)
			(2) Moderate users vs controls	12	98.7	18.7	8	91.1	15.5	–0.434	(–1.339 to 0.472)
von Geusau *et al*. 2004[132]	HvdM EF: Eriksen Flankers – correct [%]	(+)	(1) Female	9	99.3	0.9	21	96.7	0.6	3.720	(2.471–4.968)
			(2) Male	17	96.6	1.2	12	96.7	1.5	–0.075	(–0.814 to 0.664)
	HvdM EF: Eriksen Flankers – reaction time – ms	(–)	(1) Female	9	417.8	14	21	437.6	9.3	1.824	(0.909–2.740)
			(2) Male	17	445.6	12.4	12	414.6	15.4	–2.262	(–3.217 to –1.308)
	HvdM SS: stop signal – reaction time – ms	(–)	(1) Female	9	236.8	91.9	21	202.8	68.4	–0.448	(–1.238 to 0.341)
			(2) Male	17	195.2	39	12	204.9	62.6	0.194	(–0.547 to 0.935)
Medina *et al*. 2005[124]	Stroop: interference – time [s]	(–)		48	10.6	2.9	17	10	3.3	–0.200	(–0.754 to 0.355)
	Stroop: interference + switching – errors [*n*]	(–)		48	10.1	1.9	17	9.3	2.3	–0.398	(–0.956 to 0.159)
	Stroop: interference + switching – time [s]	(–)		48	10.2	2.5	17	10.2	2.7	0.000	(–0.553 to 0.553)

Study	Measure	(+/–)	Comparison	MDMA users			Controls			SMD	(95% CI)
				n	Mean	SD	*n*	Mean	SD		
Roiser *et al.* 2005[114]	CANTAB A-G/N-G: commission errors (non-shift)	(–)		66	5.413	1.055	58	5.538	0.9	0.127	(–0.226 to 0.480)
	CANTAB A-G/N-G: commission errors (shift)	(–)		66	6.345	0.927	58	6.761	1.095	0.412	(0.056–0.769)
Dafters 2006[137]	Stroop: interference – time [ms]	(–)		33	834	85	17	829	150	–0.045	(–0.630 to 0.540)
Reneman *et al.* 2006[97]	Stroop: interference – time [s]	(–)	(1) Heavy users vs controls	22	82	15.5	4.33	82.6	14.4	0.039	(–0.991 to 1.069)
			(2) Moderate users vs controls	15	83.5	12	4.33	82.6	14.4	–0.072	(–1.141 to 0.997)
Quednow *et al.* 2006[83]	G/N-G: summed conditions – Σ commission errors	(–)	Data from secondary pub.[500]	18	22.11	9.44	17	17.29	6.75	–0.585	(–1.262 to 0.093)
	G/N-G: summed conditions – Σ gain	(+)	Data from secondary pub.[500]	18	6.86	1.26	17	7.61	1.12	–0.628	(–1.308 to 0.052)
Lamers *et al.* 2006[98]	Stroop: interference – switching time difference [s]	(–)		11	40.5	9	15	39.5	9.1	–0.110	(–0.889 to 0.668)
	Stroop: interference – time difference [s]	(–)		11	16.3	17.4	15	10.6	9.8	–0.422	(–1.209 to 0.365)
Hoshi *et al.* 2007[125]	G/N-G: commission errors	(–)		25	11.8	3.5	14.5	13.6	4.31	0.472	(–0.183 to 1.128)
	G/N-G: reaction time – ms	(–)		25	355	25	14.5	359	59.24	0.098	(–0.549 to 0.745)
Roiser *et al.* 2007[118]	CANTAB A-G/N-G: commission errors [*n*]	(–)	Data from secondary pub.[501]	30	10.1	7.2	15	11.1	7	0.140	(–0.480 to 0.761)
Former users vs polydrug controls											
Reneman *et al.* 2006[97]	Stroop: interference – time [s]	(–)		16	85.5	14.4	4.33	82.6	14.4	–0.201	(–1.265 to 0.862)
Hoshi *et al.* 2007[125]	G/N-G: commission errors	(–)		27	10.2	4.68	14.5	13.6	4.31	0.746	(0.087–1.405)
	G/N-G: reaction time – ms	(–)		27	382	51.96	14.5	359	59.24	–0.422	(–1.066 to 0.223)
Roiser *et al.* 2007[118]	CANTAB A-G/N-G: commission errors [*n*]	(–)	Data from secondary pub.[501]	20	10	5.1	15	11.1	7	0.184	(–0.487 to 0.855)

TABLE 66 *Executive function – response inhibition (composite measure) – ecstasy users versus drug-naïve controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs drug-naïve controls											
Gouzoulis *et al*. 2000[99]	Stroop: interference – time difference [s]	(–)		28	–3.84	4.38	28	–3.1	6	0.141	(–0.384 to 0.665)
	TAP: selective visual attention – time [ms]	(–)		28	532	65.4	28	478.6	48.4	–0.928	(–1.480 to –0.376)
Croft *et al*. 2001[94]	Stroop: interference – time [s]	(–)		11	22.1	5.2	31	19.5	3.8	–0.620	(–1.321 to 0.081)
Yip and Lee 2005[128]	Stroop: interference – time difference [s]	(–)		100	13.7	2.38	100	13.03	0.86	–0.374	(–0.654 to –0.095)
Dafters 2006[137]	Stroop: interference – time [ms]	(–)		33	834	85	18	838	163	0.034	(–0.540 to 0.608)
Quednow *et al*. 2006[83]	G/N-G: summed conditions – Σ commission errors	(–)	Data from secondary pub.[500]	18	22.11	9.44	15	20.87	12.87	–0.112	(–0.797 to 0.574)
	G/N-G: summed conditions – Σ gain	(+)	Data from secondary pub.[500]	18	6.86	1.26	15	7.11	2.12	–0.147	(–0.833 to 0.539)
Lamers *et al*. 2006[98]	Stroop: interference – switching time difference [s]	(–)		11	40.5	9	15	48.2	9.9	0.808	(–0.003 to 1.618)
	Stroop: interference – time difference [s]	(–)		11	16.3	17.4	15	10.6	5.4	–0.476	(–1.266 to 0.313)
Hoshi *et al*. 2007[125]	G/N-G: commission errors	(–)		25	11.8	3.5	13	9.8	4.08	–0.540	(–1.222 to 0.142)
	G/N-G: reaction time – ms	(–)		25	355	25	13	385	45.89	0.897	(0.195–1.598)
Roiser *et al*. 2007[118]	CANTAB A-G/N-G: commission errors [*n*]	(–)	Data from secondary pub.[501]	30	10.1	7.2	15	13	9.6	0.360	(–0.265 to 0.984)
Former users vs drug-naïve controls											
Hoshi *et al*. 2007[125]	G/N-G: commission errors	(–)		27	10.2	4.68	13	9.8	4.08	–0.089	(–0.751 to 0.573)
	G/N-G: reaction time – ms	(–)		27	382	51.96	13	385	45.89	0.060	(–0.602 to 0.722)
Roiser *et al*. 2007[118]	CANTAB A-G/N-G: commission errors [*n*]	(–)	Data from secondary pub.[501]	20	10	5.1	15	13	9.6	0.408	(–0.269 to 1.085)

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TABLE 67 *Executive function – shifting (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs polydrug controls											
Fox *et al*. 2001[112]	WCST: categories	(+)	(1) High-dose users vs controls	11	5.5	0.7	6.67	5.3	1.3	0.208	(–0.757 to 1.173)
			(2) Medium users vs controls	14	4.6	2.1	6.67	5.3	1.3	–0.370	(–1.300 to 0.560)
			(3) Low users vs controls	14	5.3	1.8	6.67	5.3	1.3	0.000	(–0.922 to 0.922)
	WCST: failure to maintain set	(–)	(1) High-dose users vs controls	11	0.9	1.3	6.67	0.6	1.2	–0.237	(–1.203 to 0.728)
			(2) Medium users vs controls	14	0.8	0.8	6.67	0.6	1.2	–0.213	(–1.138 to 0.712)
			(3) Low users vs controls	14	0.9	1.2	6.67	0.6	1.2	–0.250	(–1.176 to 0.676)
	WCST: non-perseverative errors – %	(–)	(1) High-dose users vs controls	11	14.1	7.5	6.67	11.7	8.4	–0.306	(–1.274 to 0.662)
			(2) Medium users vs controls	14	15.9	14.4	6.67	11.7	8.4	–0.326	(–1.254 to 0.602)
			(3) Low users vs controls	14	14.6	10.3	6.67	11.7	8.4	–0.297	(–1.224 to 0.630)
	WCST: perseverative errors –%	(–)	(1) High-dose users vs controls	11	11.8	5.3	6.67	12.6	7.3	0.131	(–0.832 to 1.094)
			(2) Medium users vs controls	14	15.8	10.2	6.67	12.6	7.3	–0.340	(–1.269 to 0.589)
			(3) Low users vs controls	14	11.4	6	6.67	12.6	7.3	0.187	(–0.737 to 1.111)
	WCST: trials to first category	(–)	(1) High-dose users vs controls	11	15	9.8	6.67	14.1	6.2	–0.104	(–1.066 to 0.859)
			(2) Medium users vs controls	14	27.6	40.8	6.67	14.1	6.2	–0.395	(–1.325 to 0.536)
			(3) Low users vs controls	14	13.6	3.2	6.67	14.1	6.2	0.115	(–0.808 to 1.038)
Halpern *et al*. 2004[106]	WCST: categories	(+)	(1) Heavy users vs controls	11	7.4	1.7	8	8.9	1.2	–0.991	(–1.960 to –0.021)
			(2) Moderate users vs controls	12	8.7	1.4	8	8.9	1.2	–0.151	(–1.047 to 0.745)
	WCST: perseverative errors	(–)	(1) Heavy users vs controls	11	12.2	5.5	8	7.2	6.2	–0.862	(–1.818 to 0.093)
			(2) Moderate users vs controls	12	8.7	4.1	8	7.2	6.2	–0.299	(–1.199 to 0.601)
von Geusau *et al*. 2004[132]	HvdM DT: dots–triangles – correct – %	(+)	(1) Heavy users vs controls	9	92.3	2.7	21	86	1.8	3.004	(1.896–4.113)
			(2) Moderate users vs controls	17	94.9	2	12	89.2	2.5	2.571	(1.563–3.579)

continued

TABLE 67 *Executive function – shifting (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis (continued)*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
	HvdM DT: dots–triangles – response time – ms	(–)	(1) Heavy users vs controls	9	938.6	68.9	21	826.7	46.2	–2.086	(–3.039 to –1.133)
			(2) Moderate users vs controls	17	910.4	50.1	12	697.8	62.2	–3.841	(–5.104 to –2.578)
	HvdM LG: local–global – correct –%	(+)	(1) Heavy users vs controls	9	97.1	0.9	21	96.2	0.6	1.288	(0.437–2.138)
			(2) Moderate users vs controls	17	97	0.6	12	95.3	0.7	2.645	(1.624–3.667)
	HvdM LG: local–global – response time – ms	(–)	(1) Heavy users vs controls	9	440.3	21.9	21	457.2	13.9	1.019	(0.194–1.844)
			(2) Moderate users vs controls	17	459.2	15	12	412.1	17.9	–2.900	(–3.969 to –1.830)
	WCST: perseverative errors	(+)	(1) Heavy users vs controls	9	14.4	3	21	14.4	2	0.000	(–0.781 to 0.781)
			(2) Moderate users vs controls	17	18.8	2.2	12	11.3	2.6	–3.163	(–4.285 to –2.042)
	WCST: total no. correct	(+)	(1) Heavy users vs controls	9	75.7	3.6	21	69.2	2.3	2.376	(1.378–3.375)
			(2) Moderate users vs controls	17	70.8	2.6	12	77.1	3.1	–2.238	(–3.188 to –1.288)
Montgomery *et al*. 2005[138]	Number/letter switch cost (s)	(–)	Study 2	42	39.27	18.14	17	38.52	18.98	–0.041	(–0.604 to 0.523)
	Plus/minus task switch cost (s)	(–)	Study 2	42	28.63	19.46	17	29.58	18.18	0.050	(–0.514 to 0.613)
Reneman *et al*. 2006[97]	WCST: categories	(+)	(1) Heavy users vs controls	22	4.4	1.6	4.33	4.6	1.5	–0.126	(–1.157 to 0.905)
			(2) Moderate users vs controls	15	4.8	1.7	4.33	4.6	1.5	0.120	(–0.949 to 1.190)
	WCST: total no. errors	(–)	(1) Heavy users vs controls	22	38.8	18.3	4.33	35.3	24	–0.182	(–1.214 to 0.849)
			(2) Moderate users vs controls	15	36.7	22.8	4.33	35.3	24	–0.061	(–1.130 to 1.008)
Reay *et al*. 2006[109]	BSA: errors [*n*]	(–)		15	17	3.82	15	13.57	3.18	–0.976	(–1.736 to –0.216)
Lamers *et al*. 2006[98]	WCST: total no. errors	(–)		11	11.5	7.8	15	12.9	7.3	0.186	(–0.593 to 0.966)
Former users vs polydrug controls											
Reneman *et al*. 2006[97]	WCST: categories	(+)		16	4.7	2.1	4.33	4.6	1.5	0.050	(–1.012 to 1.111)
	WCST: total no. errors	(–)		16	35.5	19.2	4.33	35.3	24	–0.010	(–1.071 to 1.051)

TABLE 68 *Perceptual organisation (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs polydrug controls											
Gouzoulis *et al.* 2000[99]	WAIS-R: block design	(+)		28	36.11	6.09	28	40.86	5.57	–0.814	(–1.360 to –0.268)
Halpern *et al.* 2004[106]	WAIS-R: block design	(+)	(1) Heavy users vs controls	11	39.3	5.9	8	41.6	7.1	–0.358	(–1.277 to 0.560)
			(2) Moderate users vs controls	12	36.9	6.9	8	41.6	7.1	–0.674	(–1.595 to 0.248)
de Win *et al.* 2006[91]	JOLO: pairs	(+)	Follow-up. Data from secondary pub.[90]	58	24.1	3.5	60	23.3	3.8	0.219	(–0.143 to 0.581)
	Mental rotation test: completely perfect [*n*]	(+)	Follow-up. Data from secondary pub.[90]	58	26.2	8.1	60	24.4	6.4	0.247	(–0.115 to 0.609)
Roiser *et al.* 2007[118]	Mental rotation test: standard – errors [*n*]	(–)		30	5.2	4.4	15	6.4	6.4	0.234	(–0.388 to 0.855)
	Mental rotation test: standard – latency [ms]	(–)		30	694.2	105.7	15	732.8	135.7	0.332	(–0.292 to 0.956)
	Mental rotation test: mirror – errors [*n*]	(–)		30	5.5	5	15	5.6	6.5	0.018	(–0.602 to 0.638)
	Mental rotation test: mirror – latency [ms]	(–)		30	796.8	95.4	15	839.7	154.8	0.363	(–0.261 to 0.988)
	WAIS-R: block test – copy – moves per problem	(–)		30	4.2	0.34	15	4.3	0.38	0.283	(–0.340 to 0.906)
	WAIS-R: block test – copy – no. completely perfect	(+)		30	4.1	1.1	15	3.9	1.1	0.182	(–0.439 to 0.803)
	WAIS-R: block test – copy – thinking time	(–)		30	1500	590.8	15	1928	1182	0.515	(–0.114 to 1.144)
	WAIS-R: block test – mental rotation – moves per problem	(–)		30	4.8	0.76	15	4.8	0.69	0.000	(–0.620 to 0.620)
	WAIS-R: block test – mental rotation – no. completely perfect	(+)		30	2.4	1.2	15	2.1	1.3	0.243	(–0.379 to 0.865)
	WAIS-R: block test – mental rotation – thinking time	(–)		30	2387	1176	15	2983	1692	0.437	(–0.190 to 1.063)

continued

TABLE 68 *Perceptual organisation (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis (continued)*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
	WAIS-R: block test – mirror – moves per problem	(–)		30	4.5	0.56	15	4.8	0.79	0.466	(–0.162 to 1.093)
	WAIS-R: block test – mirror – no. completely perfect	(+)		30	2.6	1.2	15	2.2	1.4	0.315	(–0.308 to 0.939)
	WAIS-R: block test – mirror – thinking time	(–)		30	2416	1004	15	2979	1684	0.445	(–0.182 to 1.071)
Former users vs polydrug controls											
Roiser *et al.* 2007[18]	Mental rotation test: standard – errors [*n*]	(+)		19	6.4	4.9	15	6.4	6.4	0.000	(–0.677 to 0.677)
	Mental rotation test: standard – latency [ms]	(–)		19	693.6	106.5	15	732.8	135.7	0.326	(–0.355 to 1.008)
	Mental rotation test: mirror – errors [*n*]	(–)		19	7.4	6.9	15	5.6	6.5	–0.268	(–0.948 to 0.413)
	Mental rotation test: mirror – latency [ms]	(–)		19	824.2	105.6	15	839.7	154.8	0.120	(–0.558 to 0.797)
	WAIS-R: block test – copy – moves per problem	(–)		20	4.4	0.33	15	4.3	0.38	–0.284	(–0.957 to 0.389)
	WAIS-R: block test – copy – no. completely perfect	(+)		20	3.8	0.95	15	3.9	1.1	–0.098	(–0.768 to 0.571)
	WAIS-R: block test – copy – thinking time	(–)		20	2050	897.7	15	1928	1182	–0.119	(–0.789 to 0.551)
	WAIS-R: block test – mental rotation – moves per problem	(–)		20	4.7	0.68	15	4.8	0.69	0.146	(–0.524 to 0.817)
	WAIS-R: block test – mental rotation – no. completely perfect	(+)		20	2.2	1.1	15	2.1	1.3	0.084	(–0.586 to 0.754)
	WAIS-R: block test – mental rotation – thinking time	(–)		20	2489	923.4	15	2983	1692	0.378	(–0.297 to 1.054)
	WAIS-R: block test – mirror – moves per problem	(–)		20	4.9	0.85	15	4.8	0.79	–0.121	(–0.791 to 0.549)
	WAIS-R: block test – mirror – no. completely perfect	(+)		20	2	1.5	15	2.2	1.4	–0.137	(–0.807 to 0.533)
	WAIS-R: block test – mirror – thinking time	(–)		20	2932	1438	15	2979	1684	0.030	(–0.639 to 0.700)

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TABLE 69 *Depression – self-rated (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs polydrug controls											
Parrott *et al.* 2000[139]	SCL-90: depression score	(–)	(1) Heavy usersvs controls	12	16.4	10.6	11	10.5	9.1	–0.595	(–1.433 to 0.243)
			(2) Light users vs controls	16	16	11.4	11	10.5	9.1	–0.522	(–1.303 to 0.259)
Dughiero *et al.* 2001[140]	SCL-90: depression score	(–)		43	0.78	0.67	77	0.63	0.57	–0.247	(–0.621 to 0.128)
Parrott *et al.* 2001[141]	SCL-90: depression score	(–)	(1) Heavy users vs polydrug controls	59.5	0.93	0.7	51	0.91	0.7	–0.029	(–0.403 to 0.345)
			(2) Heavy users vs cannabis controls	59.5	0.93	0.7	48.5	0.83	0.6	–0.152	(–0.532 to 0.228)
			(3) Light users vs polydrug controls	57.5	0.86	0.7	51	0.91	0.7	0.071	(–0.306 to 0.449)
			(4) Light users vs cannabis controls	57.5	0.86	0.7	48.5	0.83	0.6	–0.046	(–0.428 to 0.336)
Verkes *et al.* 2001[129]	BDI: overall score	(–)	(1) Heavy users vs controls	21	3	3.7	10	7	6.3	0.858	(0.073–1.642)
			(2) Moderate users vs controls	21	3.9	3.3	10	7	6.3	0.696	(–0.078 to 1.470)
Gamma *et al.* 2001[142]	HDRS: overall score	(–)		16	11.7	9.2	17	5	6.1	–0.864	(–1.580 to –0.148)
Morgan *et al.* 2002[103]	SCL-90-R: depression score	(–)		18	1.06	1.146	8	0.44	0.44	–0.624	(–1.476 to 0.227)
Curran and Verheyden 2003[104]	BDI: overall score	(–)		32	6.06	5.05	16	5.59	5.77	–0.089	(–0.689 to 0.512)
von Geusau *et al.* 2004[132]	SCL-90-R: depression score	(–)	(1) Female	9	21.9	3.1	21	21.9	5.4	0.000	(–0.781 to 0.781)
			(2) Male	17	21.1	5.5	12	18.8	2.3	–0.513	(–1.265 to 0.238)

continued

TABLE 69 *Depression – self-rated (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis (continued)*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Milani *et al.* 2004[143]	SCL-90: depression score	(–)	(1) Men: heavy users vs polydrug controls	47	0.91	1.357	36	0.89	1.527	–0.014	(–0.448 to 0.420)
			(2) Men: heavy users vs cannabis controls	47	0.91	1.357	28.5	0.72	0.679	–0.165	(–0.631 to 0.301)
			(3) Men: light users vs polydrug controls	34	0.75	0.825	36	0.89	1.527	0.113	(–0.356 to 0.582)
			(4) Men: light users vs cannabis controls	34	0.75	0.825	28.5	0.72	0.679	–0.039	(–0.537 to 0.458)
			(5) Women: heavy users vs polydrug controls	10.5	1.07	0.321	14	1.01	0.423	–0.157	(–0.958 to 0.645)
			(6) Women: heavy users vs cannabis controls	10.5	1.07	0.321	19.5	0.99	0.5	–0.179	(–0.931 to 0.573)
			(7) Women: light users vs polydrug controls	22.5	1.03	0.537	14	1.01	0.423	–0.040	(–0.707 to 0.627)
			(8) Women: light users vs cannabis controls	22.5	1.03	0.537	19.5	0.99	0.5	–0.077	(–0.684 to 0.530)
McCardle *et al.* 2004[100]	BDI-II: overall score	(–)		17	12.35	9.41	15	5.53	4.64	–0.901	(–1.632 to –0.170)
Travers and Lyvers 2005[144]	BDI: overall score	(–)		43	9.5	7.05	31	6.8	5.2	–0.426	(–0.893 to 0.041)
Medina *et al.* 2005[124]	BDI-II: overall score	(–)	Data from secondary pub.[502]	48	9	8.1	17	10	7.7	0.125	(–0.429 to 0.679)
Thomasius *et al.* 2005[96]	SCL-90-R: depression score	(–)	Data from secondary pub.[105]	30	0.78	0.548	14.5	0.73	0.646	–0.086	(–0.713 to 0.541)
Fingeret *et al.* 2005[145]	HDRS: overall score	(–)		83	4.147	4.747	91	1.035	1.771	–0.885	(–1.196 to –0.573)
Roiser *et al.* 2005[114]	BDI: overall score	(–)		66	8.759	6.763	58	4.99	4.428	–0.651	(–1.013 to –0.289)
Guillot and Greenway 2006[78]	BDI-II: overall score	(–)		32	10.3	8	32	10.3	8.8	0.000	(–0.490 to 0.490)

Study	Measure	(+/–)	Comparison	MDMA users			Controls			SMD	(95% CI)
				n	Mean	SD	*n*	Mean	SD		
Lamers *et al.* 2006[98]	BDI-II: overall score	(–)		11	9.82	12	15	4.4	3.9	–0.653	(–1.453 to 0.147)
de Win *et al.* 2006[91]	BDI: overall score	(–)	Follow-up data	59	4.6	4.9	61	3.4	3.5	–0.283	(–0.642 to 0.077)
Hoshi *et al.* 2007[125]	BDI: overall score	(–)		25	5.16	3.4	14.5	6.03	4.17	0.235	(–0.414 to 0.885)
Roiser *et al.* 2007[118]	BDI-II: overall score	(–)	Data from secondary pub.[500]	30	7.9	6.5	15	6	5.4	–0.308	(–0.931 to 0.315)
Former users vs polydrug controls											
Morgan *et al.* 2002[103]	SCL-90-R: depression score	(–)		15	0.92	0.93	8	0.44	0.44	–0.600	(–1.477 to 0.277)
Curran and Verheyden 2003[104]	BDI: overall score	(–)		32	8.48	5.91	16	5.59	5.77	–0.493	(–1.101 to 0.116)
Thomasius *et al.* 2005[96]	SCL-90-R: depression score	(–)	Data from secondary pub.[105]	31	0.98	0.612	14.5	0.73	0.646	–0.401	(–1.030 to 0.228)
Hoshi *et al.* 2007[125]	BDI: overall score	(–)		28	7.57	5.49	14.5	6.03	4.17	–0.303	(–0.940 to 0.335)
Roiser *et al.* 2007[118]	BDI-II: overall score	(–)	Data from secondary pub.[500]	20	12.6	9.5	15	6	5.4	–0.823	(–1.521 to –0.125)

TABLE 70 *Depression – self-rated (composite measure) – ecstasy users versus drug-naïve controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs drug-naïve controls											
Gerra *et al.* 1998[146]	HDRS: overall score	(–)		15	14.9	3.4	15	5.1	2.2	–3.422	(–4.569 to –2.275)
	MMPI: overall score	(–)		15	64.3	3.7	15	48.5	3.2	–4.568	(–5.962 to –3.174)
Gerra *et al.* 2000[63]	HDRS: overall score	(–)	3 weeks abstinent	15	16	8.443	15	5.07	4.648	–1.604	(–2.434 to –0.774)
	MMPI 2: overall score	(–)	3 weeks abstinent	15	59.87	12.39	15	43.5	7.669	–1.588	(–2.416 to –0.761)
Parrott *et al.* 2001[141]	SCL-90: depression score	(–)	(1) Heavy users vs alcohol/tobacco controls	59.5	0.93	0.7	92.5	0.79	0.7	–0.200	(–0.527 to 0.127)
			(2) Heavy users vs drug-free controls	59.5	0.93	0.7	75	0.81	0.6	–0.186	(–0.527 to 0.155)
			(3) Light users vs alcohol/tobacco controls	57.5	0.86	0.7	92.5	0.79	0.7	–0.100	(–0.429 to 0.229)
			(4) Light users vs drug-free controls	57.5	0.86	0.7	75	0.81	0.6	–0.077	(–0.421 to 0.266)
Gerra *et al.* 2002[147]	HDRS: overall score	(–)		12	17.1	10.74	12	5.1	8.66	–1.230	(–2.109 to –0.351)
	MMPI: overall score	(–)		12	62.6	11.43	12	48.8	6.235	–1.499	(–2.413 to –0.584)
Morgan *et al.* 2002[103]	SCL-90-R: depression score	(–)		18	1.06	1.146	7.5	0.35	0.503	–0.703	(–1.578 to 0.172)
Gerra *et al.* 2003[82]	HDRS: overall score	(–)		15	12.6	2.3	15	4.1	1.5	–4.378	(–5.729 to –3.026)
	MMPI 2: overall score	(–)		15	60	3	15	46.1	2.3	–5.200	(–6.739 to –3.662)
Milani *et al.* 2004[143]	SCL-90: depression score	(–)	(1) Men: heavy users vs alcohol/tobacco controls	47	0.91	1.357	50	0.75	0.7	–0.150	(–0.548 to 0.249)
			(2) Men: heavy users vs drug-free controls	47	0.91	1.357	30	0.74	0.465	–0.154	(–0.613 to 0.304)
			(3) Men: light users vs alcohol/tobacco controls	34	0.75	0.825	50	0.75	0.7	0.000	(–0.436 to 0.436)
			(4) Men: light users vs drug-free controls	34	0.75	0.825	30	0.74	0.465	–0.015	(–0.506 to 0.476)
			(5) Women: heavy users vs alcohol/tobacco controls	10.5	1.07	0.321	42	0.98	0.642	–0.151	(–0.828 to 0.526)
			(6) Women: heavy users vs drug-free controls	10.5	1.07	0.321	44.5	0.85	0.708	–0.336	(–1.011 to 0.340)
			(7) Women: light users vs alcohol/tobacco controls	22.5	1.03	0.537	42	0.98	0.642	–0.082	(–0.595 to 0.430)
			(8) Women: light users vs drug-free controls	22.5	1.03	0.537	44.5	0.85	0.708	–0.274	(–0.784 to 0.235)

Study	Measure	(+/–)	Comparison	MDMA users			Controls			SMD	(95% CI)
				n	Mean	SD	*n*	Mean	SD		
Thomasius *et al.* 2005[96]	SCL-90-R: depression score	(–)	Data from secondary pub.[113]	30	0.78	0.548	15	0.42	0.329	–0.739	(–1.378 to –0.100)
Milani *et al.* 2005[148]	SCL–BSI: depression score	(–)	(1) MDMA polydrug (no cannabis) vs controls	44	1.07	0.87	24.2	0.73	0.77	–0.407	(–0.907 to 0.094)
			(2) MDMA polydrug (monthly cannabis) vs controls	70	0.95	0.92	24.2	0.73	0.77	–0.249	(–0.712 to 0.215)
			(3) MDMA polydrug (weekly cannabis) vs controls	31	0.79	0.9	24.2	0.73	0.77	–0.071	(–0.603 to 0.461)
			(4) MDMA polydrug (daily cannabis) vs controls	103	0.94	0.85	24.2	0.73	0.77	–0.251	(–0.695 to 0.193)
			(5) MDMA polydrug (former heavy cannabis) vs controls	32	1.01	0.95	24.2	0.73	0.77	–0.319	(–0.850 to 0.212)
Yip and Lee 2005[128]	BDI: overall score	(–)		100	1.31	1.15	100	1.48	1.01	0.157	(–0.121 to 0.435)
Lamers *et al.* 2006[98]	BDI-II: overall score	(–)		11	9.82	12	15	2.47	2.2	–0.927	(–1.748 to –0.106)
Hoshi *et al.* 2007[125]	BDI: overall score	(–)		25	5.16	3.4	13.5	4.96	5.47	–0.047	(–0.709 to 0.615)
Roiser *et al.* 2007[118]	BDI-II: overall score	(–)	Data from secondary pub.[501]	30	7.9	6.5	15	3.8	2.8	–0.736	(–1.375 to –0.097)
Former users vs drug-naïve controls											
Morgan *et al.* 2002[103]	SCL-90-R: depression score	(–)		15	0.92	0.93	7.5	0.35	0.503	–0.696	(–1.598 to 0.206)
Thomasius *et al.* 2005[96]	SCL-90-R: depression score	(–)	Data from secondary pub.[105]	31	0.98	0.612	15	0.42	0.329	–1.040	(–1.693 to –0.386)
Hoshi *et al.* 2007[125]	BDI: overall score	(–)		28	7.57	5.49	13.5	4.96	5.47	–0.476	(–1.134 to 0.182)
Roiser *et al.* 2007[118]	BDI-II: overall score	(–)	Data from secondary pub.[501]	20	12.6	9.5	15	3.8	2.8	–1.183	(–1.911 to –0.456)

TABLE 71 *Memory – self-rated (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs polydrug controls											
Parrott *et al.* 2000[139]	Uplifts/hassles: cognitive failures	(–)	(1) Heavy users vs controls	12	8.3	3.6	11	6.2	3.8	–0.568	(–1.404 to 0.268)
			(2) Light users vs controls	16	7.4	3.6	11	6.2	3.8	–0.326	(–1.099 to 0.447)
Rodgers 2000[122]	CFQ: self-rated – total score	(–)		15	45.2	8.11	15	40.8	8.23	–0.539	(–1.268 to 0.191)
Gouzoulis *et al.* 2000[99]	FZ–EMQ: overall score	(–)		28	27	10.61	28	29.86	10.95	0.265	(–0.261 to 0.791)
Heffernan *et al.* 2001[76]	PMQ: internally cued	(–)	(1) Study 1	46	4.35	1.84	46	3.09	1.18	–0.815	(–1.241 to –0.390)
			(2) Study 2	30	3.35	1.15	37	2.85	1.3	–0.405	(–0.891 to 0.082)
	PMQ: long-term	(–)	(1) Study 1	46	4.17	1.62	46	2.72	1.25	–1.002	(–1.436 to –0.568)
			(2) Study 2	30	3.45	0.91	37	2.25	0.82	–1.393	(–1.931 to –0.855)
	PMQ: short-term	(–)	(1) Study 1	46	2.37	1.03	46	1.47	0.59	–1.072	(–1.510 to –0.635)
			(2) Study 2	30	2.39	1.12	37	1.34	0.47	–1.271	(–1.800 to –0.743)
	PMQ: strategies	(–)	(1) Study 1	46	3.79	1.64	46	3.75	2.15	–0.021	(–0.430 to 0.388)
			(2) Study 2	30	2.91	1.17	37	3.33	1.61	0.294	(–0.191 to 0.778)
	CFQ: self-rated – total score	(–)	(3) Study 3	15	45.2	8.11	15	40.8	8.23	–0.539	(–1.268 to 0.191)
Montgomery and Fisk 2007[149]	CFQ: other-rated – total score	(–)		26	14.65	6.44	31	10.71	3.63	–0.772	(–1.313 to –0.231)
	CFQ: self-rated – total score	(–)		43	46.95	15.28	51	39.68	12.93	–0.517	(–0.930 to –0.105)
	EMQ: overall score	(–)		43	97.24	35.34	51	77.28	28.07	–0.632	(–1.048 to –0.216)
	PMQ: internally cued	(–)		28	2.92	1.25	35	2.3	0.76	–0.616	(–1.125 to –0.107)
	PMQ: long-term episodic	(–)		28	3.06	1.52	35	2.52	0.76	–0.466	(–0.969 to 0.038)
	PMQ: short-term habitual	(–)		28	1.26	0.32	35	1.19	0.32	–0.219	(–0.717 to 0.280)
	PMQ: strategies	(–)		28	3.29	1.65	35	2.84	1.41	–0.296	(–0.796 to 0.204)

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TABLE 72 *Anxiety – self-rated (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs polydrug controls											
Parrott *et al.* 2000[139]	SCL-90: anxiety score	(–)	(1) Heavy users vs controls	12	13.8	9.8	11	4.9	4.2	–1.162	(–2.052 to –0.271)
			(2) Light users vs controls	16	7.5	7.2	11	4.9	4.2	–0.421	(–1.197 to 0.356)
Dughiero *et al.* 2001[140]	SCL-90-R: anxiety score	(–)		43	0.81	0.59	77	0.73	0.59	–0.136	(–0.509 to 0.238)
Parrott *et al.* 2001[139]	SCL-90: anxiety score	(–)	(1) Heavy users vs polydrug controls	59.5	0.88	0.6	51	0.81	0.6	–0.117	(–0.491 to 0.258)
			(2) Heavy users vs cannabis controls	59.5	0.88	0.6	48.5	0.78	0.6	–0.167	(–0.546 to 0.213)
			(3) Light users vs polydrug controls	57.5	0.8	0.6	51	0.81	0.6	0.017	(–0.360 to 0.394)
			(4) Light users vs cannabis controls	57.5	0.8	0.6	48.5	0.78	0.6	–0.033	(–0.415 to 0.349)
Verkes *et al.* 2001[129]	STAI-DY: trait anxiety	(–)	(1) Heavy users vs controls	21	38.8	10.4	10	32.1	7	–0.707	(–1.482 to 0.068)
			(2) Moderate users vs controls	21	33.5	6.9	10	32.1	7	–0.202	(–0.957 to 0.553)
Morgan *et al.* 2002[103]	SCL-90-R: anxiety score	(–)		18	1.01	0.891	8	0.33	0.32	–0.884	(–1.753 to –0.014)
Curran and Verheyden 2003[104]	STAI: trait anxiety	(–)		32	37.09	8.91	16	37.25	9.28	0.018	(–0.582 to 0.618)
von Geusau *et al.* 2004[132]	SCL-90-R: anxiety score	(–)	(1) Female	9	13.7	1.6	21	13.8	3.2	0.035	(–0.746 to 0.816)
			(2) Male	17	13.2	3.2	12	10.6	0.9	–1.028	(–1.816 to –0.240)
Milani *et al.* 2004[143]	SCL-90: anxiety score	(–)	(1) Men: heavy users vs polydrug controls	47	0.84	0.679	36	0.79	0.509	–0.082	(–0.516 to 0.352)
			(2) Men: heavy users vs cannabis controls	47	0.84	0.679	28.5	0.74	0.679	–0.147	(–0.613 to 0.319)
			(3) Men: light users vs polydrug controls	34	0.76	0.66	36	0.79	0.509	0.051	(–0.418 to 0.520)
			(4) Men: light users vs cannabis controls	34	0.76	0.66	28.5	0.74	0.679	–0.030	(–0.528 to 0.468)
			(5) Women: heavy users vs polydrug controls	10.5	0.96	0.092	14	0.89	0.053	–0.974	(–1.823 to –0.125)

continued

TABLE 72 *Anxiety – self-rated (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis (continued)*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
			(6) Women: heavy users vs cannabis controls	10.5	0.96	0.092	19.5	0.83	0.5	–0.317	(–1.072 to 0.437)
			(7) Women: light users vs polydrug controls	22.5	0.85	0.604	14	0.89	0.053	0.084	(–0.584 to 0.751)
			(8) Women: light users vs cannabis controls	22.5	0.85	0.604	19.5	0.83	0.5	–0.036	(–0.642 to 0.571)
Medina *et al.* 2005[124]	STAI: trait anxiety	(–)	Data from secondary pub.[502]	48	53	12.2	17	53	7.3	0.000	(–0.553 to 0.553)
Thomasius *et al.* 2005[96]	SCL-90-R: anxiety score	(–)	Data from secondary pub.[105]	30	0.42	0.411	14.5	0.54	0.539	0.264	(–0.366 to 0.893)
Fingeret *et al.* 2005[145]	HARS: overall score	(–)		83	5.282	5.751	91	1.216	1.57	–0.984	(–1.300 to –0.669)
Ward *et al.* 2006[116]	BAI: overall score	(–)		31	10.1	8.88	15	8.03	8.3	–0.238	(–0.856 to 0.381)
Lamers *et al.* 2006[98]	BAI: overall score	(–)		11	10.3	10.4	15	2.9	1.9	–1.077	(–1.913 to –0.242)
Hoshi *et al.* 2007[125]	STAI: trait anxiety	(–)		25	35.52	7.55	14.5	35.76	6.93	0.033	(–0.614 to 0.680)
Former users vs polydrug controls											
Morgan *et al.* 2002[103]	SCL-90-R: anxiety score	(–)		15	0.71	0.852	8	0.33	0.32	–0.528	(–1.401 to 0.345)
Curran and Verheyden 2003[104]	STAI: trait anxiety	(–)		32	42.87	11.22	16	37.25	9.28	–0.529	(–1.139 to 0.081)
Thomasius *et al.* 2005[96]	SCL-90-R: anxiety score	(–)	Data from secondary pub.[105]	31	0.775	0.779	14.5	0.54	0.539	–0.329	(–0.957 to 0.298)
Ward *et al.* 2006[116]	BAI: overall score	(–)		30	11.87	12.21	15	8.03	8.3	–0.346	(–0.970 to 0.278)
Hoshi *et al.* 2007[125]	STAI: trait anxiety	(–)		28	37.75	9.67	14.5	35.76	6.93	–0.225	(–0.861 to 0.411)

TABLE 73 *Anxiety – self-rated (composite measure) – ecstasy users versus drug-naïve controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs drug-naïve controls											
Parrott *et al.* 2001[141]	SCL-90: anxiety score	(–)	(1) Heavy users vs alcohol/tobacco controls	59.5	0.88	0.6	92.5	0.69	0.5	–0.351	(–0.679 to –0.023)
			(2) Heavy users vs drug-free controls	59.5	0.88	0.6	75	0.65	0.5	–0.421	(–0.765 to –0.077)
			(3) Light users vs alcohol/tobacco controls	57.5	0.8	0.6	92.5	0.69	0.5	–0.204	(–0.534 to 0.126)
			(4) Light users vs drug-free controls	57.5	0.8	0.6	75	0.65	0.5	–0.275	(–0.620 to 0.070)
Morgan *et al.* 2002[103]	SCL-90-R: anxiety score	(–)		18	1.01	0.891	7.5	0.24	0.31	–0.993	(–1.891 to –0.095)
Milani *et al.* 2004[143]	SCL-90: anxiety score	(–)	(1) Men: heavy users vs alcohol/tobacco controls	47	0.84	0.07	50	0.6	0.05	–3.966	(–4.656 to –3.276)
			(2) Men: heavy users vs drug-free controls	47	0.84	0.07	30	0.57	0.07	–3.857	(–4.626 to –3.089)
			(3) Men: light users vs alcohol/tobacco controls	34	0.76	0.08	50	0.6	0.05	–2.508	(–3.089 to –1.927)
			(4) Men: light users vs drug-free controls	34	0.76	0.08	30	0.57	0.07	–2.517	(–3.178 to –1.856)
			(5) Women: heavy users vs alcohol/ tobacco controls	10.5	0.96	0.02	42	0.8	0.05	–3.487	(–4.446 to –2.528)
			(6) Women: heavy users vs drug-free controls	10.5	0.96	0.02	44.5	0.71	0.05	–5.425	(–6.657 to –4.193)
			(7) Women: light users vs alcohol/ tobacco controls	22.5	0.85	0.09	42	0.8	0.05	–0.752	(–1.280 to –0.223)
			(8) Women: light users vs drug-free controls	22.5	0.85	0.09	44.5	0.71	0.05	–2.122	(–2.747 to –1.498)
Jacobsen *et al.* 2004[134]	POMS: anxiety score	(–)		6	0.5	3.6	6	2.2	4.5	0.417	(–0.729 to 1.563)
Thomasius *et al.* 2005[96]	SCL-90-R: anxiety score	(–)		30	0.42	0.411	15	0.32	0.301	–0.264	(–0.886 to 0.358)

continued

TABLE 73 *Anxiety – self-rated (composite measure) – ecstasy users versus drug-naïve controls: dataset used in meta-analysis (continued)*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Milani *et al.* 2005[148]	SCL–BSI: anxiety score	(–)	(1) MDMA polydrug (no cannabis) vs controls	44	1.12	0.84	24.2	0.69	0.67	–0.548	(–1.053 to –0.043)
			(2) MDMA polydrug (monthly cannabis) vs controls	70	0.82	0.85	24.2	0.69	0.67	–0.161	(–0.624 to 0.302)
			(3) MDMA polydrug (weekly cannabis) vs controls	31	0.73	0.6	24.2	0.69	0.67	–0.063	(–0.595 to 0.468)
			(4) MDMA polydrug (daily cannabis) vs controls	103	0.93	0.8	24.2	0.69	0.67	–0.309	(–0.753 to 0.136)
			(5) MDMA polydrug (former heavy cannabis) vs controls	32	1.07	1.07	24.2	0.69	0.67	–0.413	(–0.947 to 0.121)
Lamers *et al.* 2006[98]	BAI: overall score	(–)		11	10.3	10.4	15	4	4.3	–0.843	(–1.657 to –0.029)
Hoshi *et al.* 2007[125]	STAI: trait anxiety	(–)		25	35.52	7.55	13.5	33.94	8.44	–0.201	(–0.864 to 0.463)
Former users vs drug-naïve controls											
Morgan *et al.* 2002[103]	SCL-90-R: anxiety score	(–)		15	0.71	0.852	7.5	0.24	0.31	–0.648	(–1.547 to 0.251)
Thomasius *et al.* 2005[96]	SCL-90-R: anxiety score	(–)		31	0.775	0.779	15	0.32	0.301	–0.683	(–1.316 to –0.051)
Hoshi *et al.* 2007[125]	STAI: trait anxiety	(–)		28	37.75	9.67	13.5	33.94	8.44	–0.410	(–1.065 to 0.246)

TABLE 74 *Impulsivity – objective measures (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs polydrug controls											
Morgan 1998[110]	MFFT-20: impulsivity score	(–)	(1) Study 1	16	1.04	2.19	12	–0.49	1.16	–0.838	(–1.620 to –0.055)
			(2) Study 2	25	0.51	1.72	20	–0.4	1.48	–0.562	(–1.162 to 0.038)
Butler and Montgomery 2004[77]	Bets16 – risk-taking score	(–)	(1) Heavy users vs polydrug controls	9	8.3	4	18	6.1	5.2	–0.454	(–1.264 to 0.356)
			(2) Heavy users vs cannabis controls	9	8.3	4	27	4.9	4.5	–0.775	(–1.551 to 0.002)
			(3) Light users vs polydrug controls	14	4.3	4.2	18	6.1	5.2	0.376	(–0.329 to 1.080)
			(4) Light users vs cannabis controls	14	4.3	4.2	27	4.9	4.5	0.136	(–0.510 to 0.782)
Morgan *et al.* 2006[115]	MFFT-20: impulsivity score	(–)		20	1.075	1.342	20	–0.23	1.342	–0.973	(–1.630 to –0.315)
	RGT: gains only – latency – ms	(+)		20	3589	1948	20	4266	2063	–0.337	(–0.962 to 0.287)
	RGT: gains only – risky choices	(–)		20	0.769	0.273	20	0.8	0.285	0.112	(–0.508 to 0.732)
	RGT: losses only – latency – ms	(+)		20	2410	1373	20	2392	868	0.016	(–0.604 to 0.635)
	RGT: losses only – risky choices	(–)		20	0.225	0.242	20	0.144	0.244	–0.334	(–0.958 to 0.290)
Quednow *et al.* 2006[83]	MFFT: impulsivity score	(–)	Data from secondary pub.[500]	19	0.76	1.43	19	0.12	1.49	–0.438	(–1.082 to 0.206)

continued

TABLE 74 *Impulsivity – objective measures (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis (continued)*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Roiser *et al.* 2007[118]	RGT: gains only – latency – ms	(+)		30	2220	1318	15	2006	776.3	0.183	(–0.438 to 0.804)
	RGT: gains only – risky choices	(–)		30	0.8	0.27	15	0.73	0.32	–0.244	(–0.866 to 0.378)
	RGT: losses only – latency – ms	(+)		30	3834	1771	15	3579	1691	0.146	(–0.474 to 0.767)
	RGT: losses only – risky choices	(–)		30	0.27	0.32	15	0.37	0.3	0.319	(–0.305 to 0.942)
Former users vs polydrug controls											
Roiser *et al.* 2007[118]	RGT: gains only – latency – ms	(+)		20	2280	1199	15	2006	776.3	0.263	(–0.410 to 0.935)
	RGT: gains only – risky choices	(–)		20	0.76	0.32	15	0.73	0.32	–0.094	(–0.764 to 0.576)
	RGT: losses only – latency – ms	(+)		20	3728	1704	15	3579	1691	0.088	(–0.582 to 0.758)
	RGT: losses only – risky choices	(–)		20	0.42	0.29	15	0.37	0.3	–0.170	(–0.841 to 0.501)

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TABLE 75 *Impulsivity – objective measures (composite measure) – ecstasy users versus drug-naïve controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs drug-naïve controls											
Morgan 1998[110]	MFFT-20: impulsivity score	(+)	(1) Study 1	16	1.04	2.19	16	–0.67	1.28	0.953	(0.220–1.687)
			(2) Study 2	25	0.51	1.72	19	–0.28	2.2	0.407	(–0.196 to 1.010)
Moeller *et al.* 2002[133]	Delayed memory task – adjusted commission errors [*n*]	(+)	(1) Heavy users vs controls	8	0.4	0.245	10	0.21	0.169	0.923	(–0.060 to 1.906)
			(2) Infrequent users vs controls	8	0.14	0.13	10	0.21	0.169	–0.457	(–1.401 to 0.486)
	Immediate memory task – adjusted commission errors [*n*]	(+)	(1) Heavy users vs controls	8	0.426	0.182	10	0.21	0.137	1.366	(0.323–2.409)
			(2) Infrequent users vs controls	8	0.22	0.159	10	0.21	0.137	0.068	(–0.862 to 0.998)
Butler and Montgomery 2004[77]	Bets16 – risk-taking score	(+)	(1) Heavy users vs controls	18	8.3	4	56.5	3.9	4.8	0.951	(0.399–1.504)
			(2) Light users vs controls	28	4.3	4.2	56.5	3.9	4.8	0.087	(–0.366 to 0.540)
Morgan *et al.* 2006[115]	MFFT-20: impulsivity score	(+)		20	1.075	1.342	19	–0.85	1.962	1.151	(0.471–1.832)
	RGT: gains only – latency – ms	(–)		20	3589	1948	19	4528	2120	0.462	(–0.175 to 1.098)
	RGT: gains only – risky choices	(+)		20	0.769	0.273	19	0.822	0.261	–0.201	(–0.830 to 0.429)
	RGT: losses only – latency – ms	(–)		20	2410	1373	19	3044	3717	0.229	(–0.401 to 0.859)
	RGT: losses only – risky choices	(+)		20	0.225	0.242	19	0.211	0.191	0.066	(–0.562 to 0.694)

continued

TABLE 75 *Impulsivity – objective measures (composite measure) – ecstasy users versus drug-naïve controls: dataset used in meta-analysis (continued)*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Quednow *et al.* 2006[83]	MFFT: impulsivity score	(+)	Data from secondary pub.[500]	19	0.76	1.43	19	0	1.77	0.472	(–0.173 to 1.118)
Roiser *et al.* 2007[118]	RGT: gains only – latency – ms	(–)		30	2220	1318	15	2353	1584	0.095	(–0.525 to 0.715)
	RGT: gains only – risky choices	(+)		30	0.8	0.27	15	0.81	0.24	–0.038	(–0.658 to 0.581)
	RGT: losses only – latency – ms	(–)		30	3834	1771	15	3566	1928	–0.147	(–0.768 to 0.473)
	RGT: losses only – risky choices	(+)		30	0.27	0.32	15	0.4	0.36	–0.390	(–1.015 to 0.235)
Former users vs drug-naïve controls											
Roiser *et al.* 2007[118]	RGT: gains only – latency – ms	(–)		20	2280	1199	15	2353	1584	0.053	(–0.616 to 0.723)
	RGT: gains only – risky choices	(+)		20	0.76	0.32	15	0.81	0.24	–0.173	(–0.844 to 0.498)
	RGT: losses only – latency – ms	(–)		20	3728	1704	15	3566	1928	–0.090	(–0.760 to 0.580)
	RGT: losses only – risky choices	(+)		20	0.42	0.29	15	0.4	0.36	0.062	(–0.607 to 0.732)

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TABLE 76 *Impulsivity – subjective measures (composite measure) – ecstasy users versus polydrug controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs polydrug controls											
Morgan 1998[110]	IVE: overall score	(–)	Study 2	25	12	4.25	20	10.7	4.29	–0.305	(–0.896 to 0.287)
Parrott *et al.* 2000[139]	IVE: overall score	(–)	(1) Heavy users vs controls	12	13.4	3.4	11	8.9	4.7	–1.105	(–1.989 to –0.222)
			(2) Light users vs controls	16	11.1	4.7	11	8.9	4.7	–0.468	(–1.247 to 0.310)
Curran and Verheyden 2003[104]	BIS-II: total	(–)	Data from secondary pub.[158]	32	59.84	13.83	16	51.03	14.29	–0.630	(–1.244 to –0.016)
Butler and Montgomery 2004[77]	IVE: overall score	(–)	(1) Heavy users vs polydrug controls	9	11.1	5.4	18.5	9.8	4.6	–0.267	(–1.067 to 0.533)
			(2) Heavy users vs cannabis controls	9	11.1	5.4	27.5	8.7	3.8	–0.568	(–1.333 to 0.197)
			(3) Light users vs polydrug controls	14	10.3	4.2	18.5	9.8	4.6	–0.113	(–0.808 to 0.582)
			(4) Light users vs cannabis controls	14	10.3	4.2	27.5	8.7	3.8	–0.406	(–1.056 to 0.243)
Travers and Lyvers 2005[144]	IVE: overall score	(–)		43	9.42	4.49	31	10.42	4.53	0.222	(–0.241 to 0.685)
Fingeret *et al.* 2005[145]	BIS-II: total	(–)		83	68.04	13.01	91	57.43	8.819	–0.964	(–1.278 to –0.649)
de Win *et al.* 2006[93]	BIS-II: total	(–)	Follow-up	59	71.3	9.8	61	68.9	10.5	–0.236	(–0.595 to 0.123)
Roiser *et al.* 2007[118]	IVE: overall score	(–)		30	8.4	4.4	15	8.6	3.5	0.048	(–0.571 to 0.668)
Former users vs drug-naïve controls											
Curran and Verheyden to 2003[104]	BIS-II: total	(–)	Data from secondary pub.[158]	32	57.63	14.49	16	51.03	14.29	–0.458	(–1.065 to 0.150)
Roiser *et al.* 2007[118]	IVE: overall score	(–)		20	10.5	5.3	15	8.6	3.5	–0.411	(–1.088 to 0.266)

TABLE 77 *Impulsivity – subjective measures (composite measure) – ecstasy users versus drug-naïve controls: dataset used in meta-analysis*

				MDMA users			Controls				
Study	**Measure**	**(+/–)**	**Comparison**	***n***	**Mean**	**SD**	***n***	**Mean**	**SD**	**SMD**	**(95% CI)**
Current users vs drug-naïve controls											
Morgan 1998[110]	IVE: overall score	(+)	Study 2	25	12	4.25	19	8.47	5.12	–0.760	(–1.379 to –0.142)
Moeller *et al.* 2002[133]	BIS-II: total	(+)	(1) Heavy users vs controls	8	73	7.937	10	62.5	9.127	–1.217	(–2.238 to –0.196)
			(2) Infrequent users vs controls	8	59	11.54	10	62.5	9.127	0.341	(–0.596 to 1.278)
Butler and Montgomery 2004[77]	IVE: overall score	(+)	(1) Heavy users vs controls	18	11.1	5.4	58	7.5	4.1	–0.812	(–1.357 to –0.267)
			(2) Light users vs controls	28	10.3	4.2	58	7.5	4.1	–0.678	(–1.140 to –0.215)
Dafters 2006[150]	BIS-II: total	(+)	(1) Light users vs controls	18	81.4	11.9	9	69.7	8.2	–1.078	(–1.932 to –0.224)
			(2) Heavy users vs controls	18	81.3	6.7	9	69.7	8.2	–1.608	(–2.524 to –0.692)
	IVE: overall score	(+)	(1) Light users vs controls	18	11.12	3.5	9	7.44	2.7	–1.127	(–1.986 to –0.268)
			(2) Heavy users vs controls	18	11.47	3.3	9	7.44	2.7	–1.291	(–2.168 to –0.415)
Roiser *et al.* 2007[118]	IVE: overall score	(+)		30	8.4	4.4	15	6.8	4.5	–0.361	(–0.985 to 0.264)
Former users vs drug-naïve controls											
Roiser *et al.* 2007[118]	IVE: overall score	(+)		20	10.5	5.3	15	6.8	4.5	–0.744	(–1.437 to –0.050)

Appendix 7

Dose–response: estimated total lifetime dose of ecstasy plotted against effect estimates

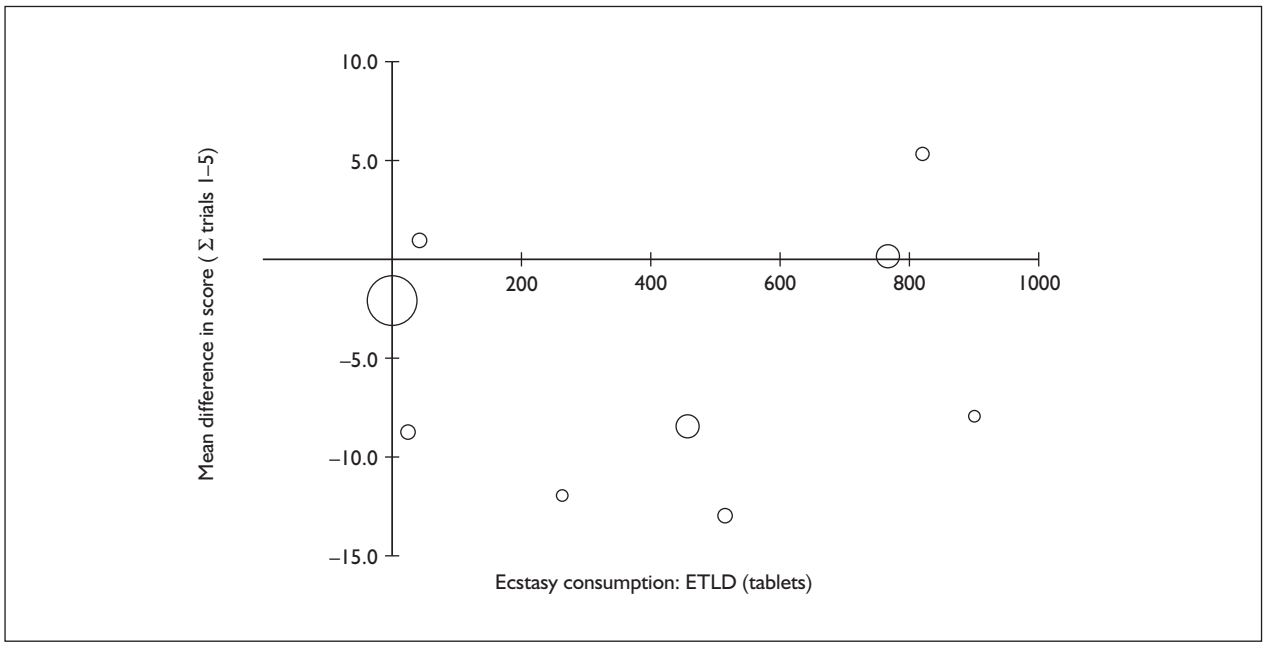

FIGURE 88 *Rey Auditory Verbal Learning Test (RAVLT) verbal recall (immediate) (sum of trials 1–5) – ecstasy users versus polydrug controls: mean difference in score against estimated total lifetime dose (ETLD) of MDMA.*

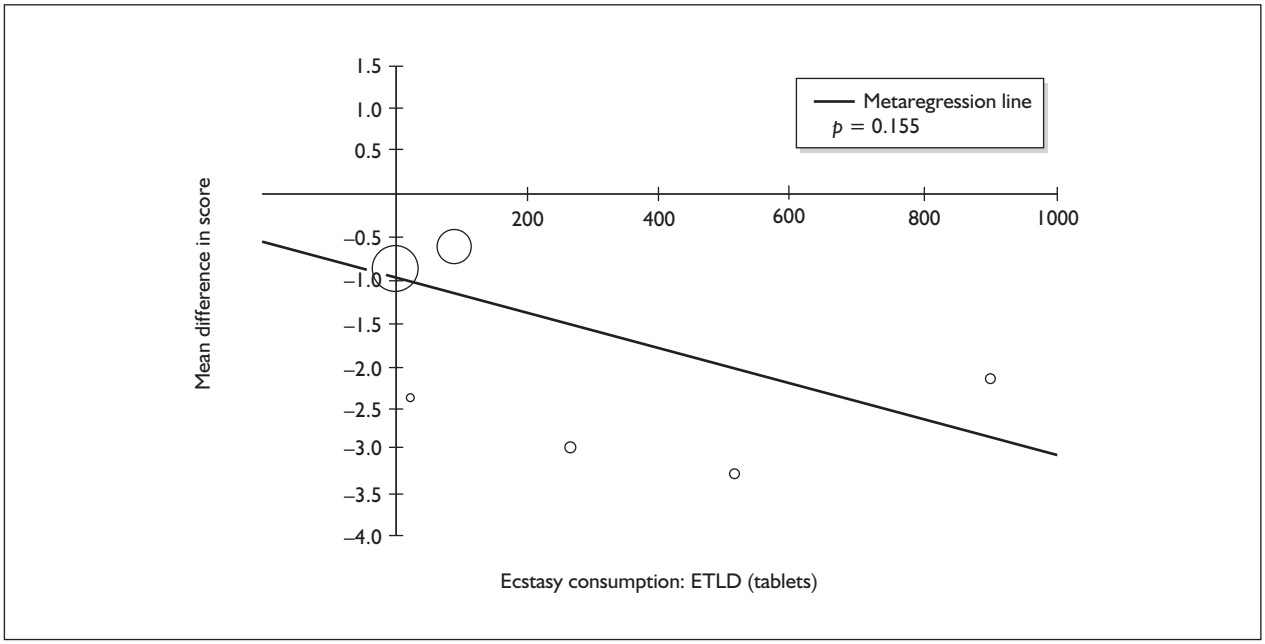

FIGURE 89 *Rey Auditory Verbal Learning Test (RAVLT) verbal recall (delayed) (trial 8) – ecstasy users versus polydrug controls: mean difference in score against estimated total lifetime dose (ETLD) of MDMA.*

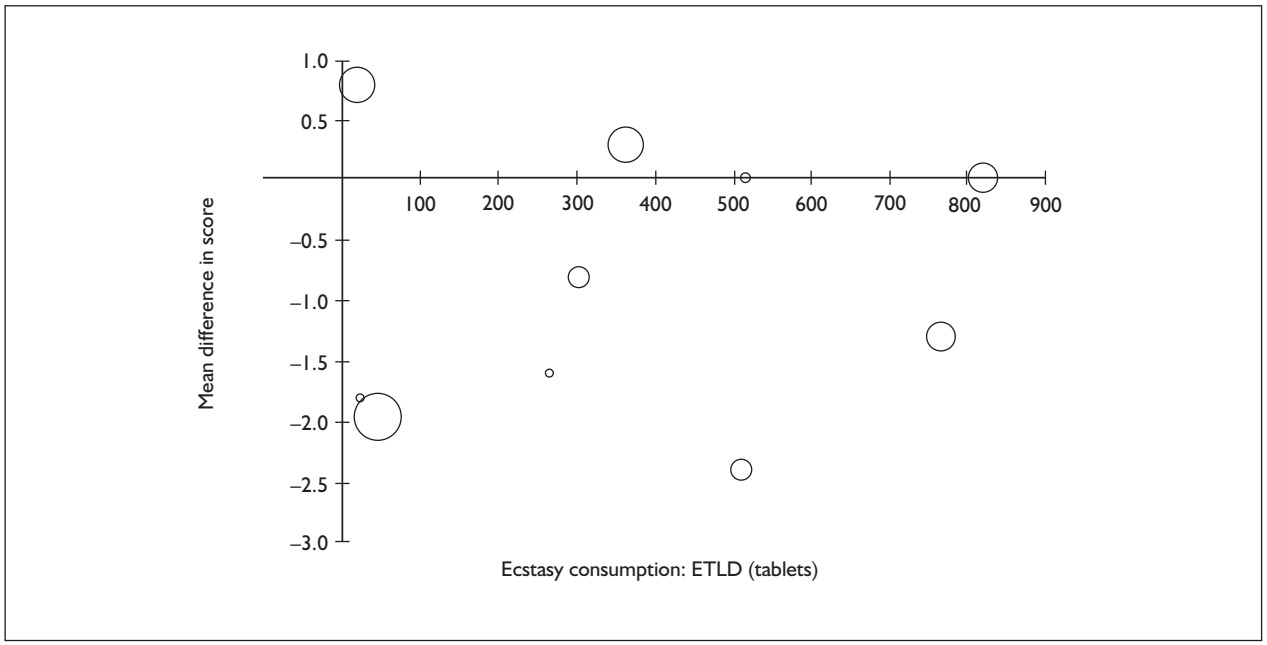

FIGURE 90 *Rivermead Behavioural Memory Test (RBMT) prose recall (immediate) – ecstasy users versus polydrug controls: mean difference in score against estimated total lifetime dose (ETLD) of MDMA.*

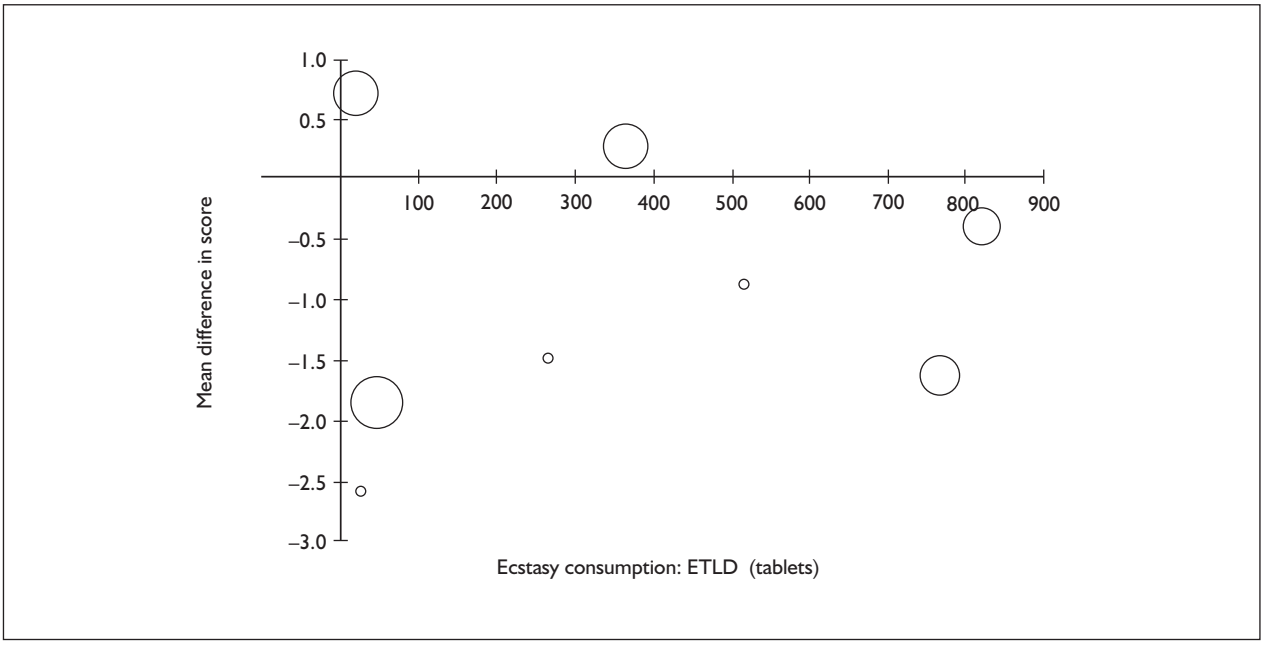

FIGURE 91 *Rivermead Behavioural Memory Test (RBMT) prose recall (delayed) – ecstasy users versus. polydrug controls: mean difference in score against estimated total lifetime dose (ETLD) of MDMA.*

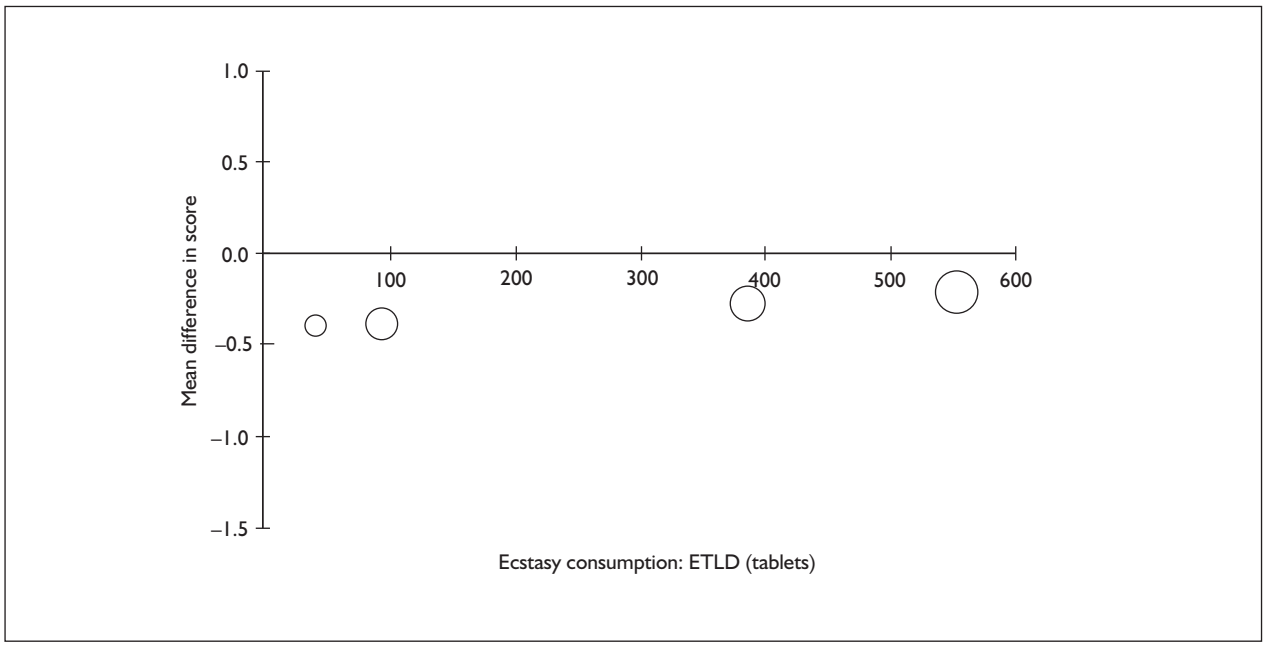

FIGURE 92 *Digit span (forwards) – ecstasy users versus polydrug controls: mean difference in score against estimated total lifetime dose (ETLD) of MDMA.*

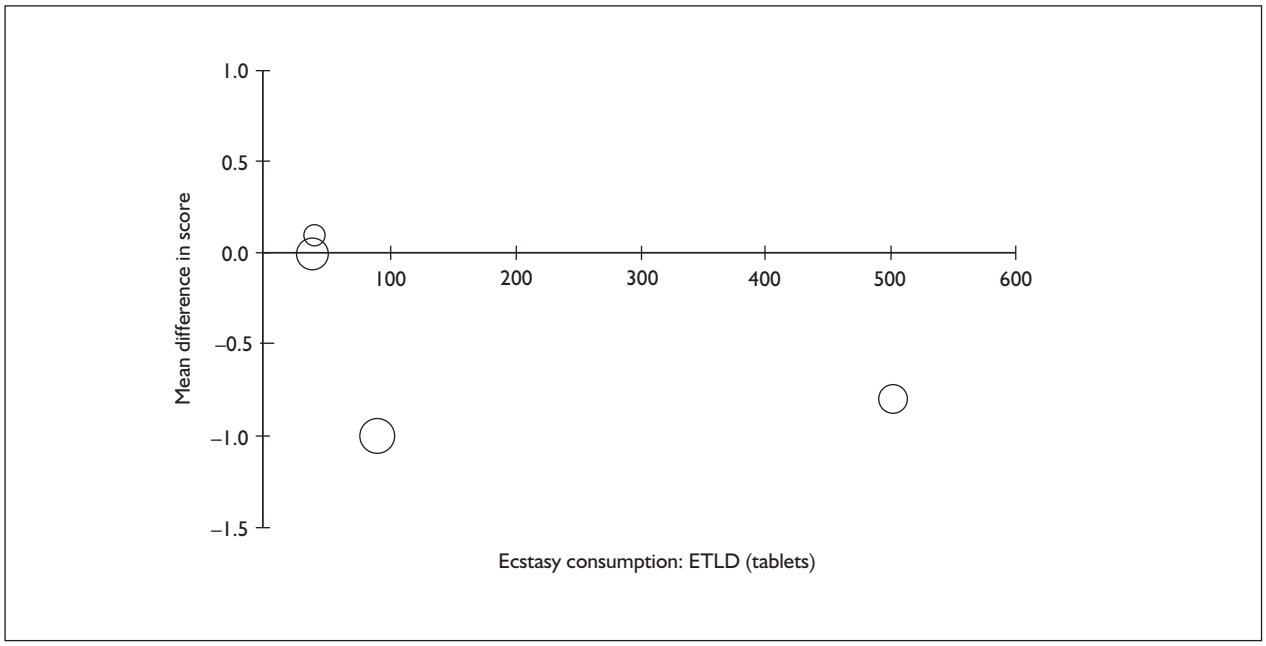

FIGURE 93 *Digit span (backwards) – ecstasy users versus polydrug controls: mean difference in score against estimated total lifetime dose (ETLD) of MDMA.*

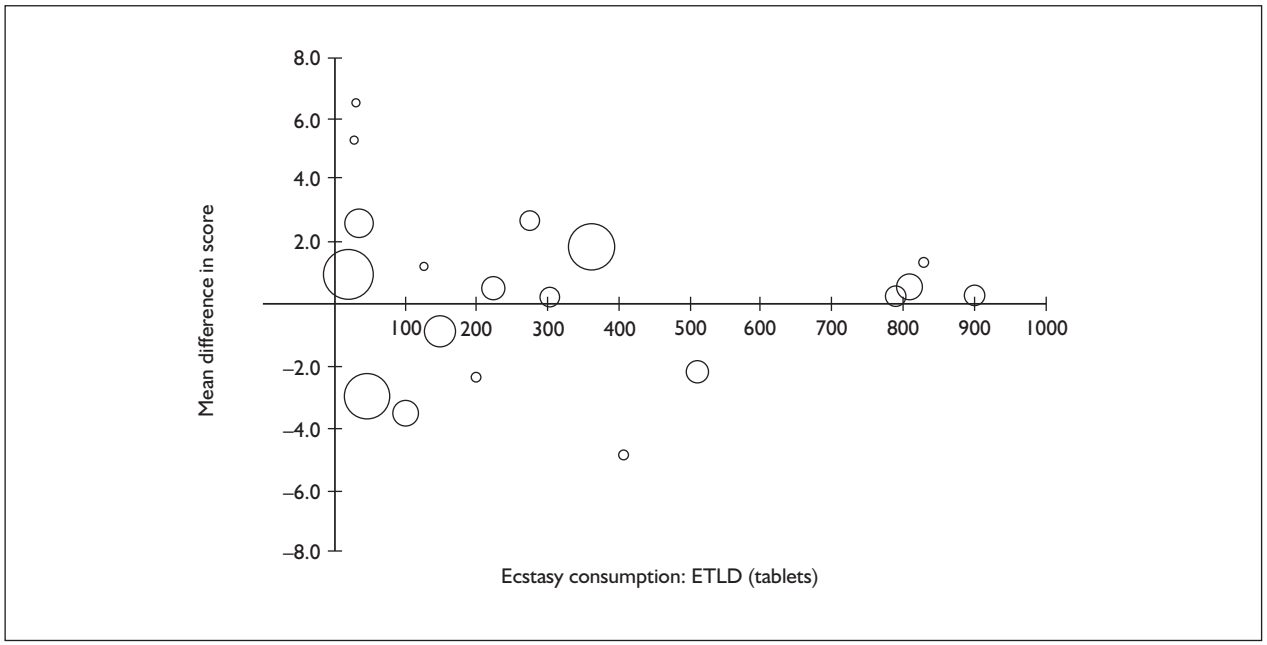

FIGURE 94 *IQ (National Adult Reading Test) – ecstasy users versus polydrug controls: mean difference in IQ against estimated total lifetime dose (ETLD) of MDMA.*

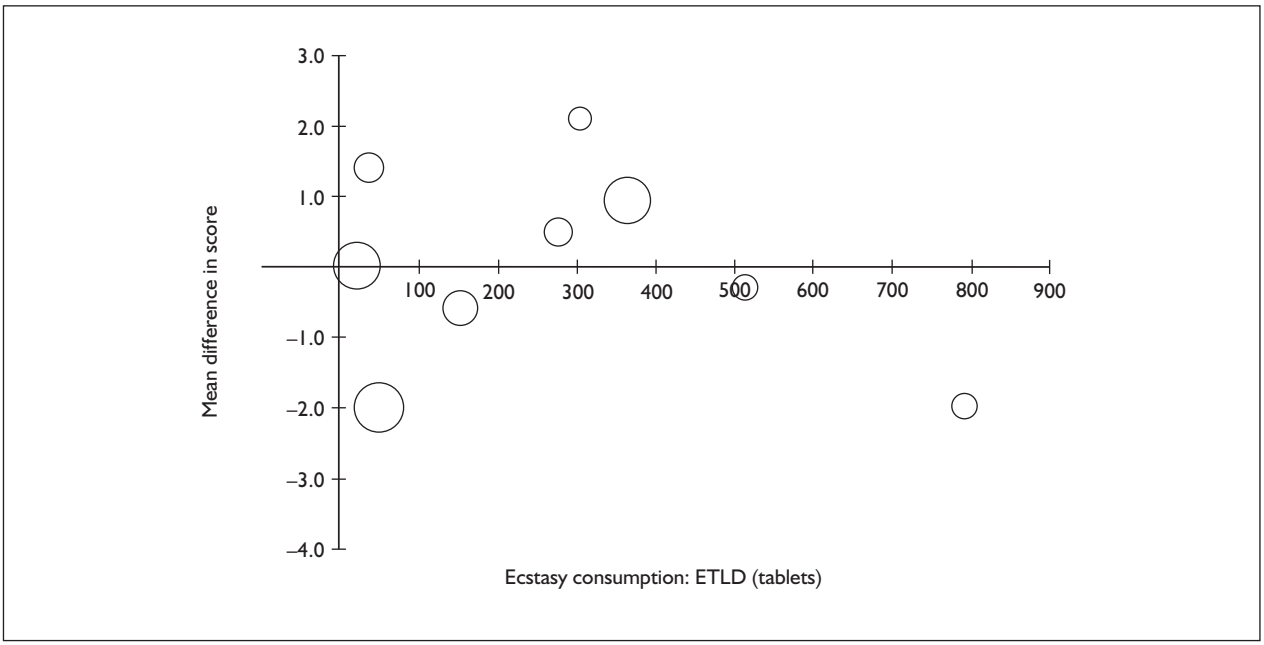

FIGURE 95 *IQ (National Adult Reading Test) – ecstasy users versus drug-naïve controls: mean difference in IQ against estimated total lifetime dose (ETLD) of MDMA.*

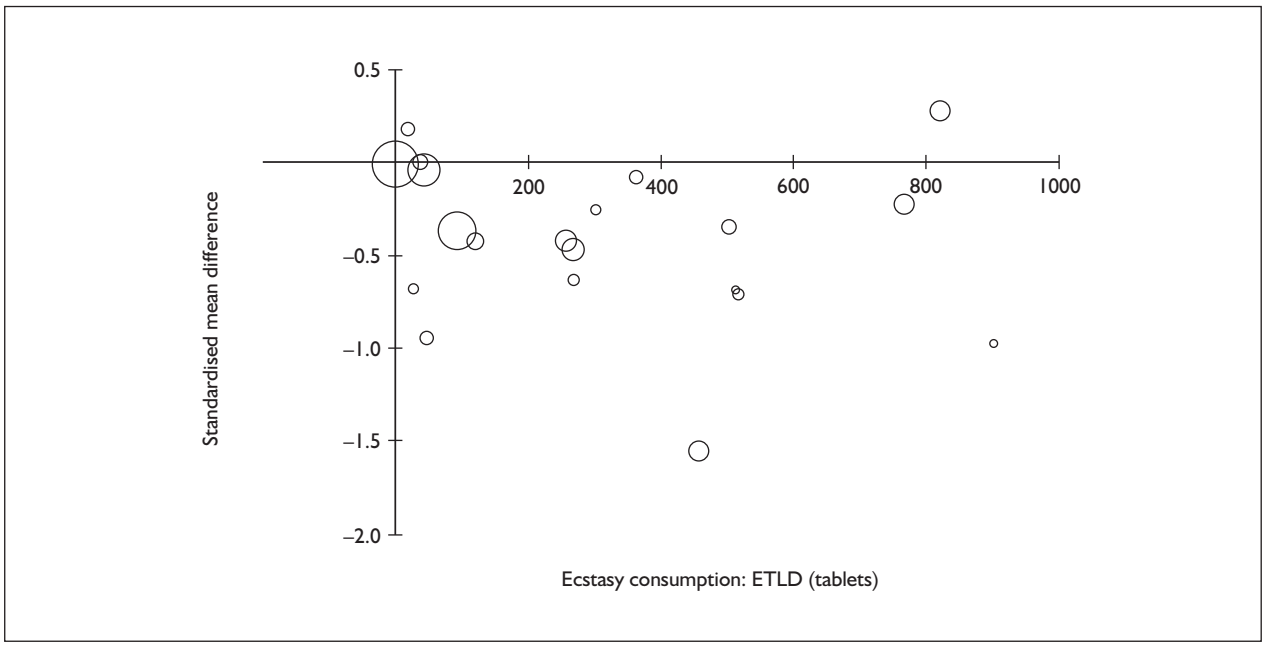

FIGURE 96 *Verbal memory – immediate (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

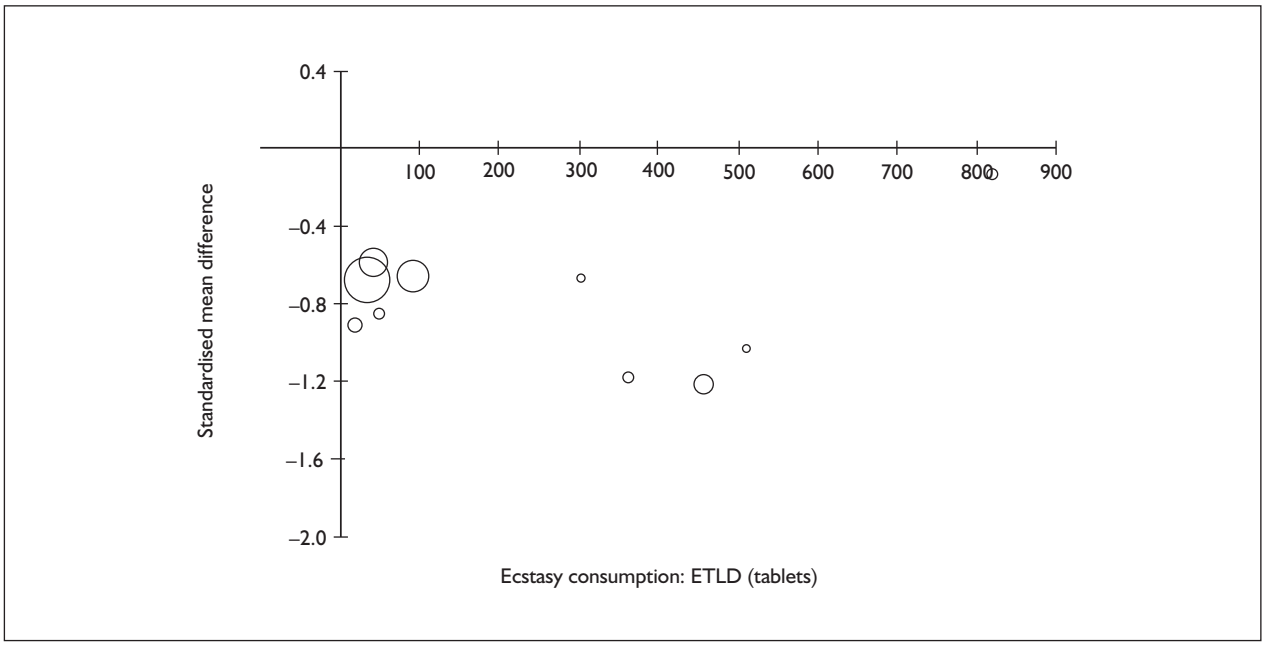

FIGURE 97 *Verbal memory – immediate (composite measure) – ecstasy users versus drug-naïve controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

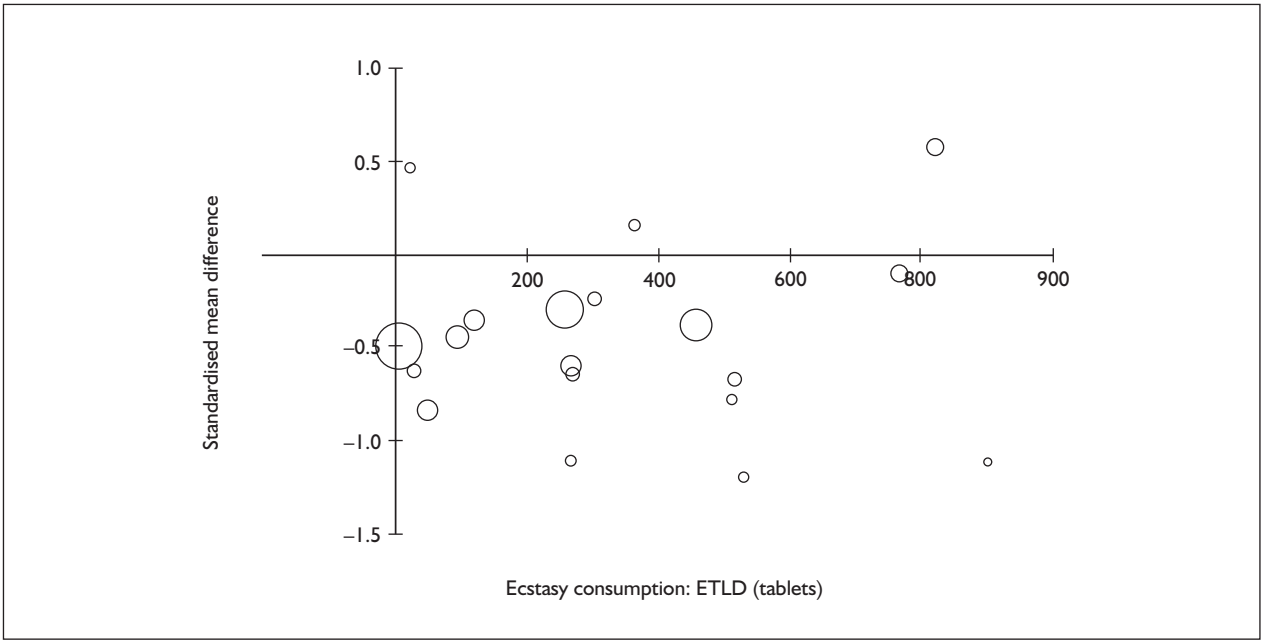

FIGURE 98 *Verbal memory – delayed (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

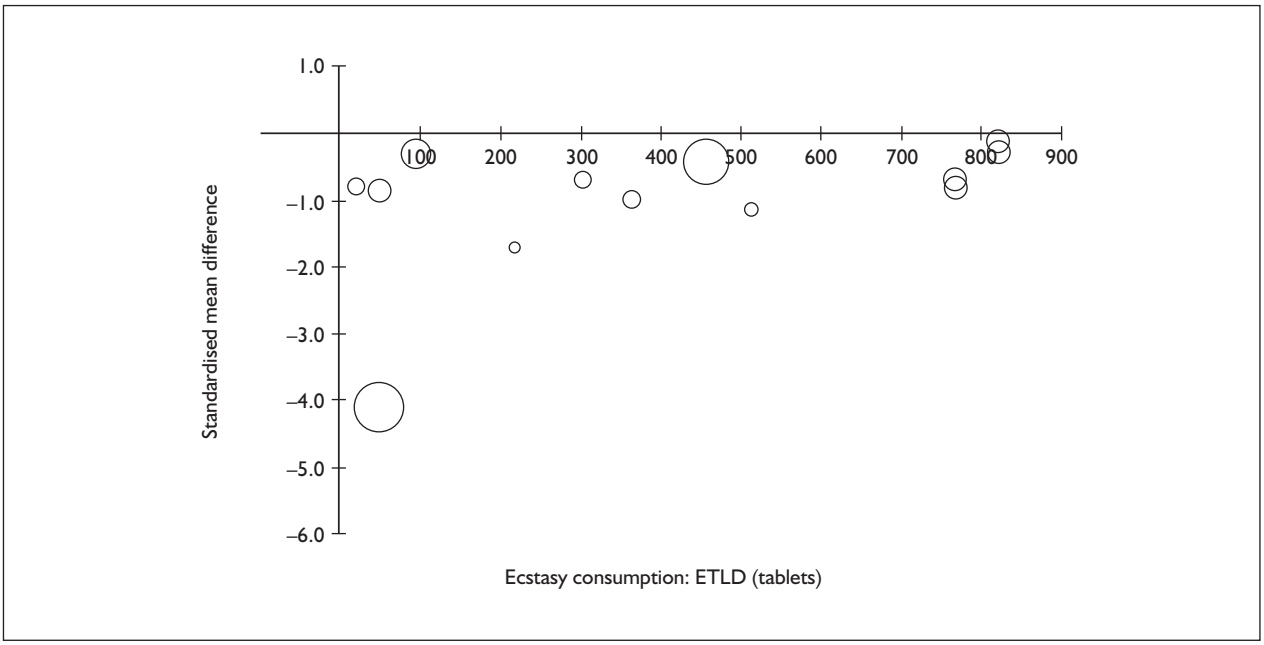

FIGURE 99 *Verbal memory – delayed (composite measure) – ecstasy users versus drug-naïve controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

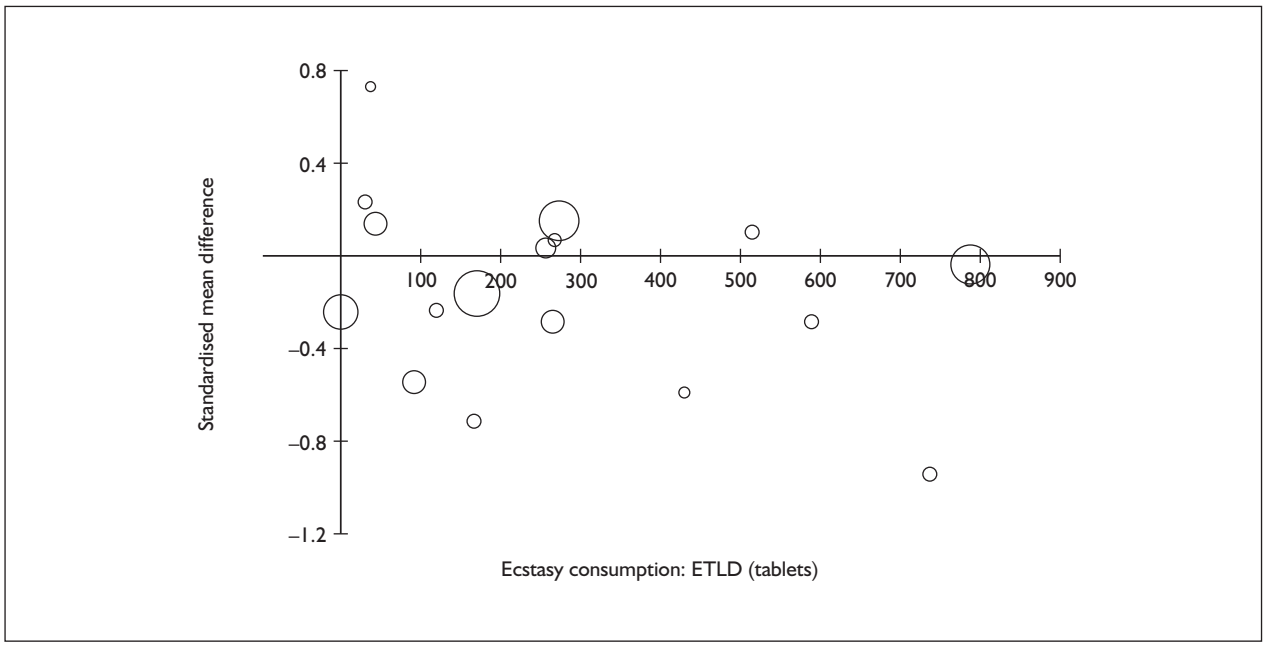

FIGURE 100 *Visual memory – immediate (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

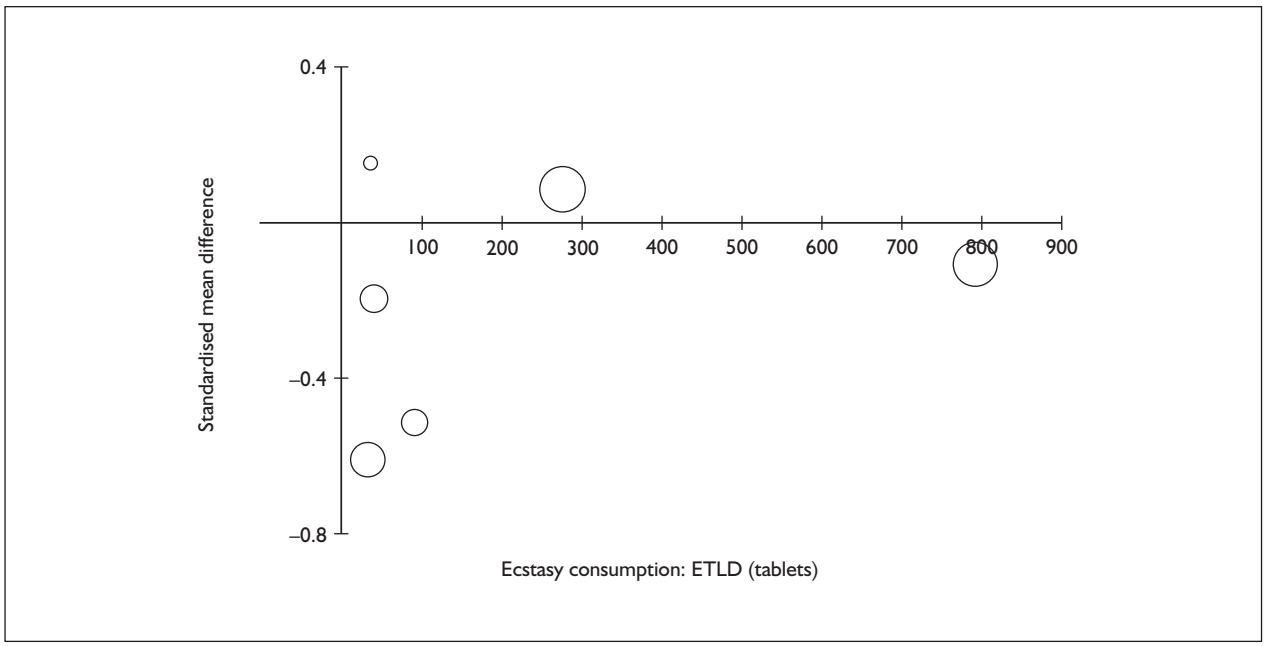

FIGURE 101 *Visual memory – immediate (composite measure) – ecstasy users versus drug-naïve controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

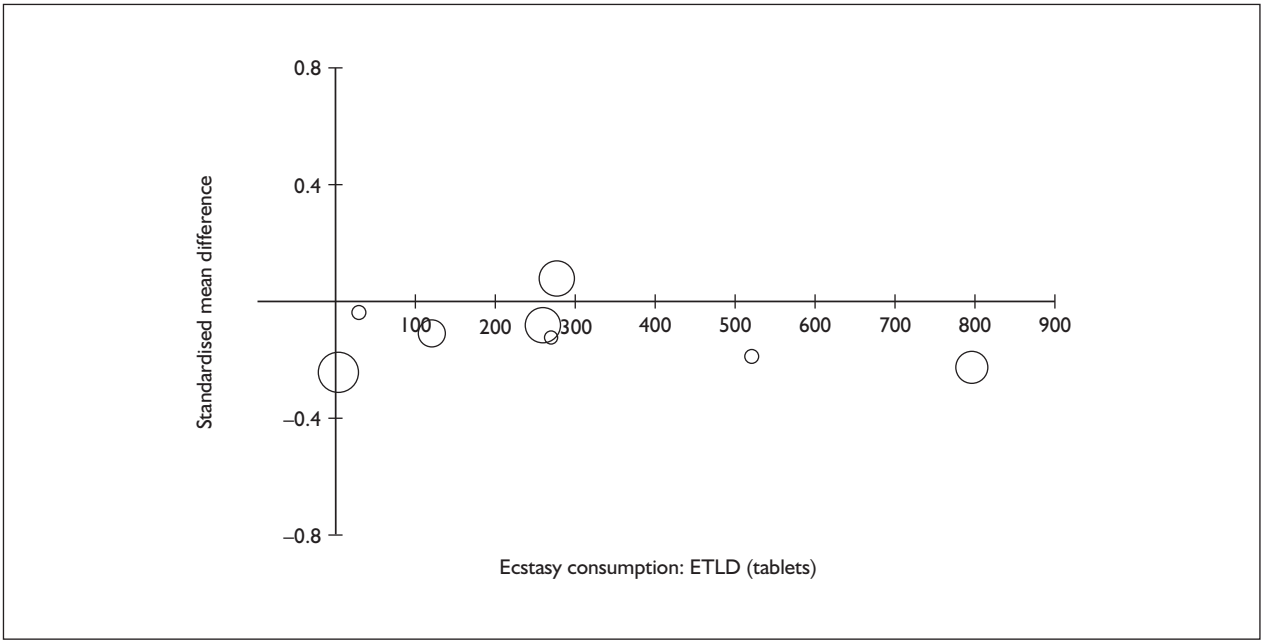

FIGURE 102 *Visual memory – delayed (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

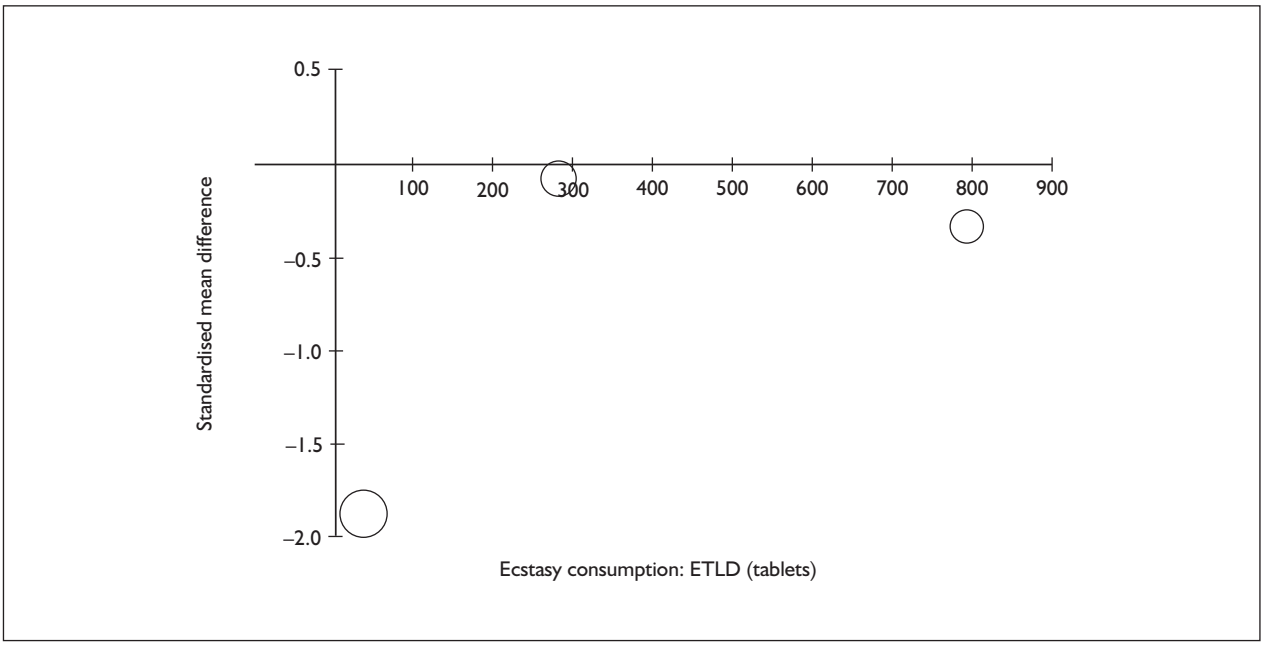

FIGURE 103 *Visual memory – delayed (composite measure) – ecstasy users versus drug-naïve controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

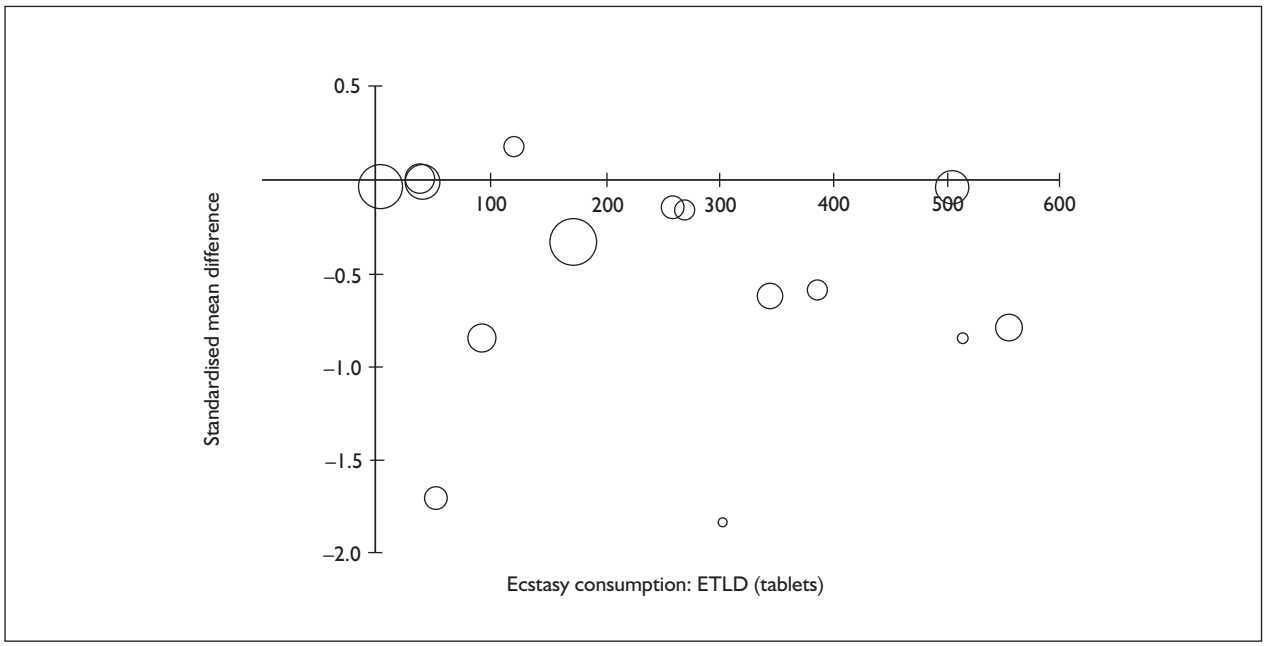

FIGURE 104 *Working memory (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

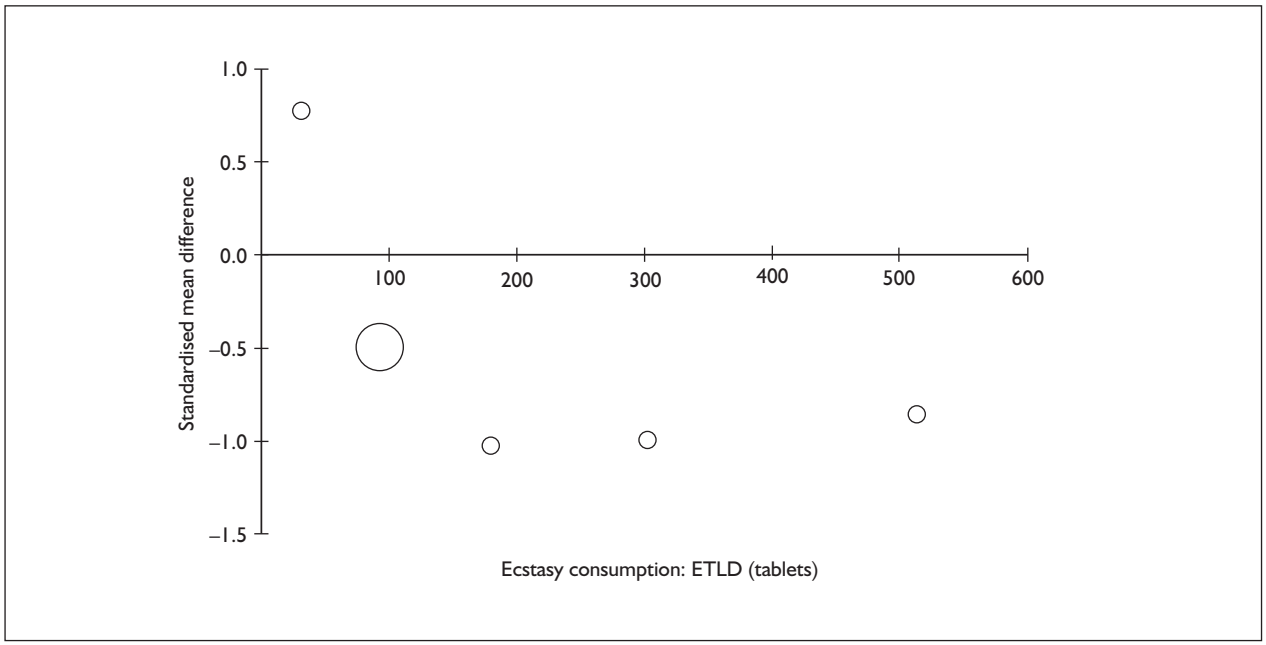

FIGURE 105 *Working memory (composite measure) – ecstasy users versus drug-naïve controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

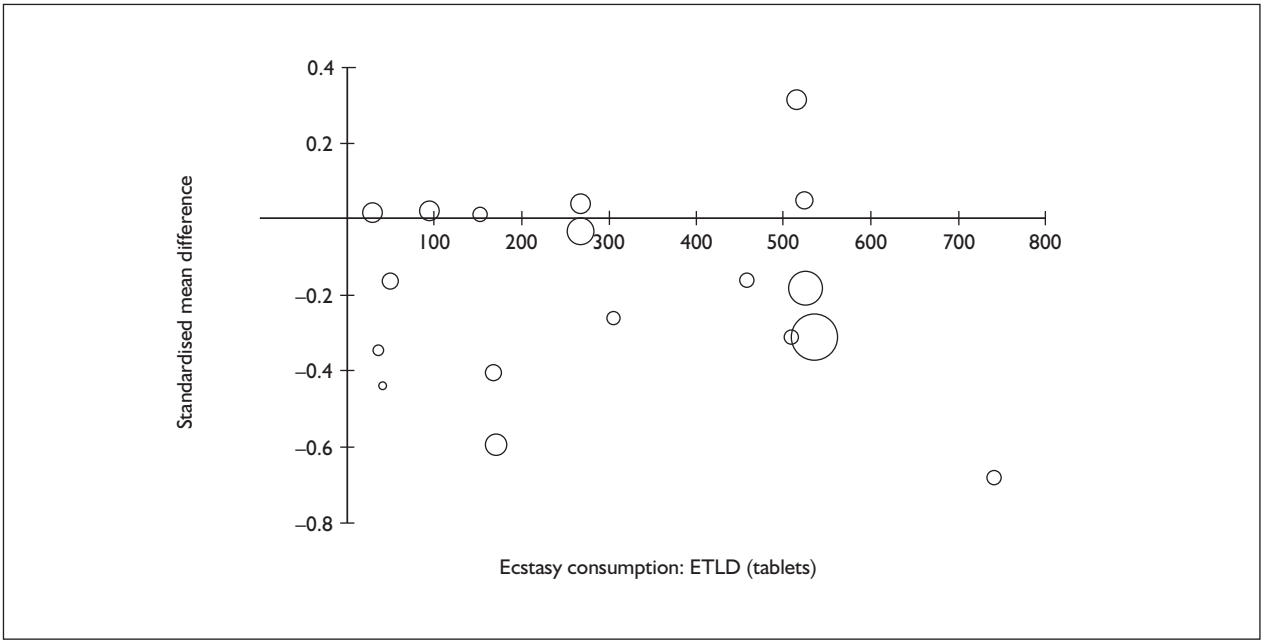

FIGURE 106 *Attention – focus–execute (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

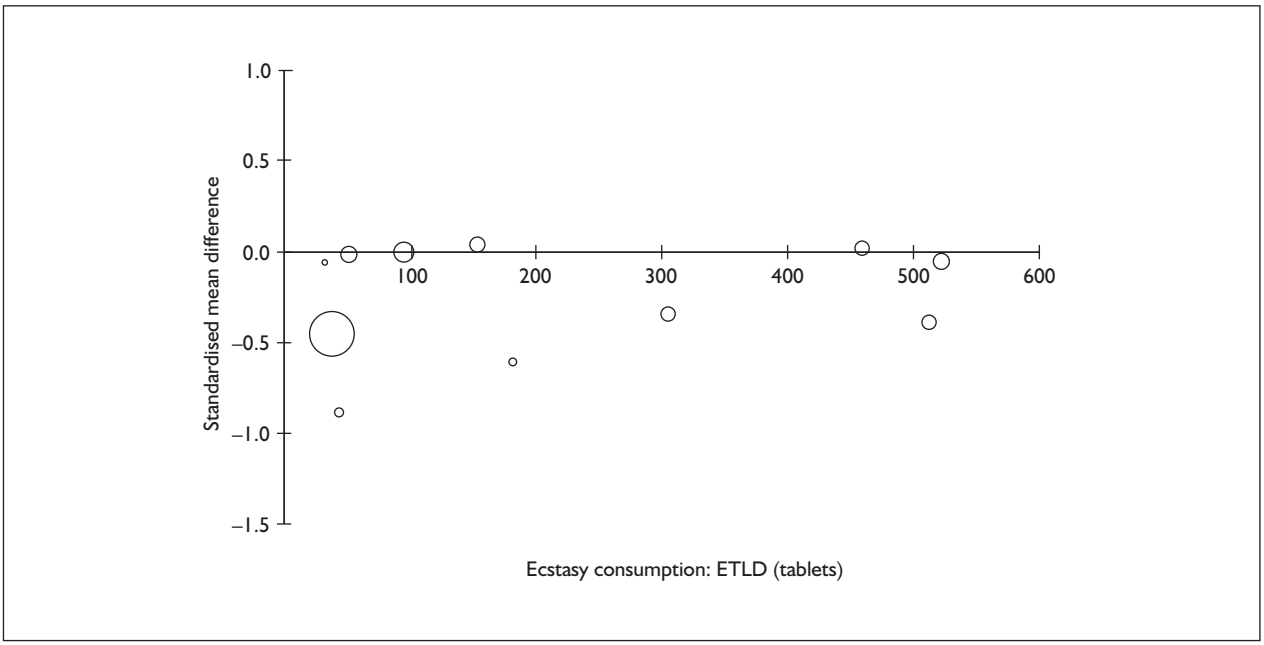

FIGURE 107 *Attention – focus–execute (composite measure) – ecstasy users versus drug-naïve controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

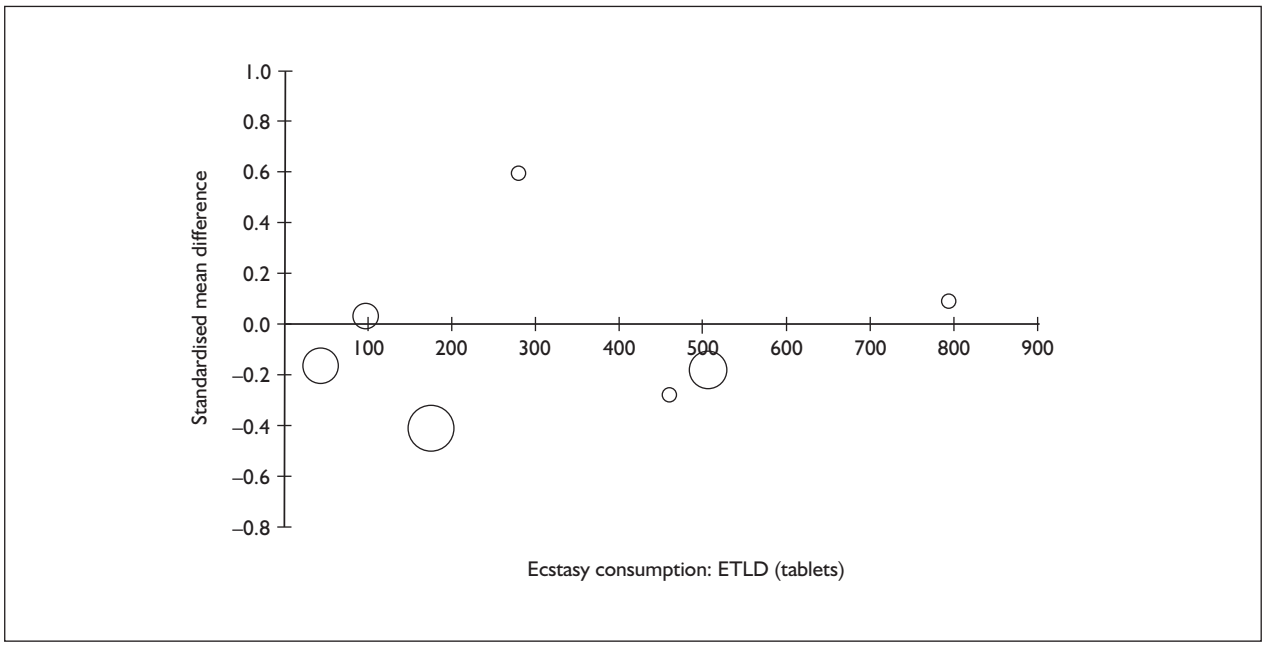

FIGURE 108 *Attention – sustain (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

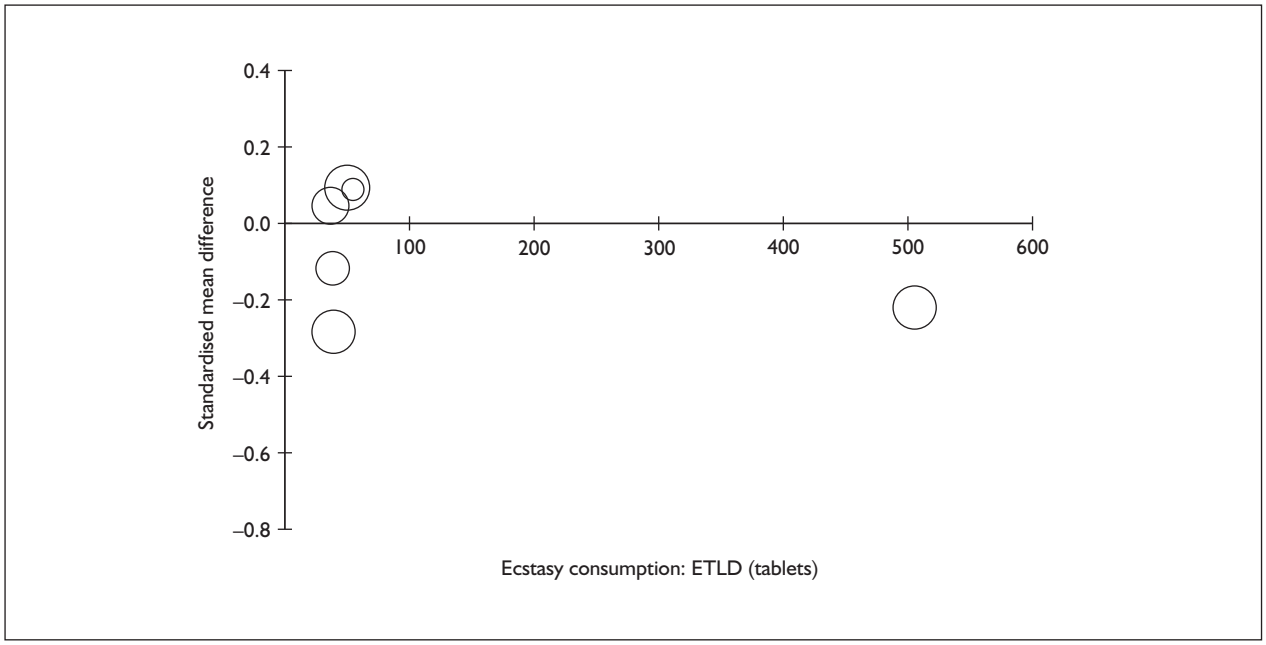

FIGURE 109 *Executive function – planning (composite measure) – ecstasy users versus drug-naïve controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

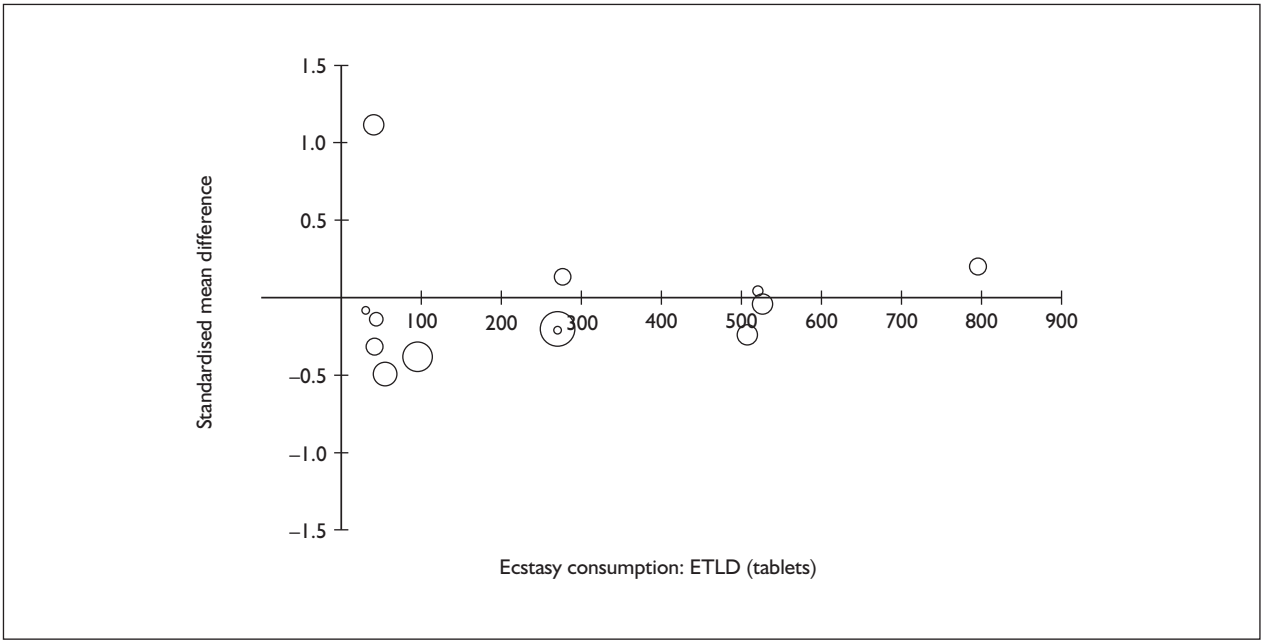

FIGURE 110 *Executive function – response inhibition (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

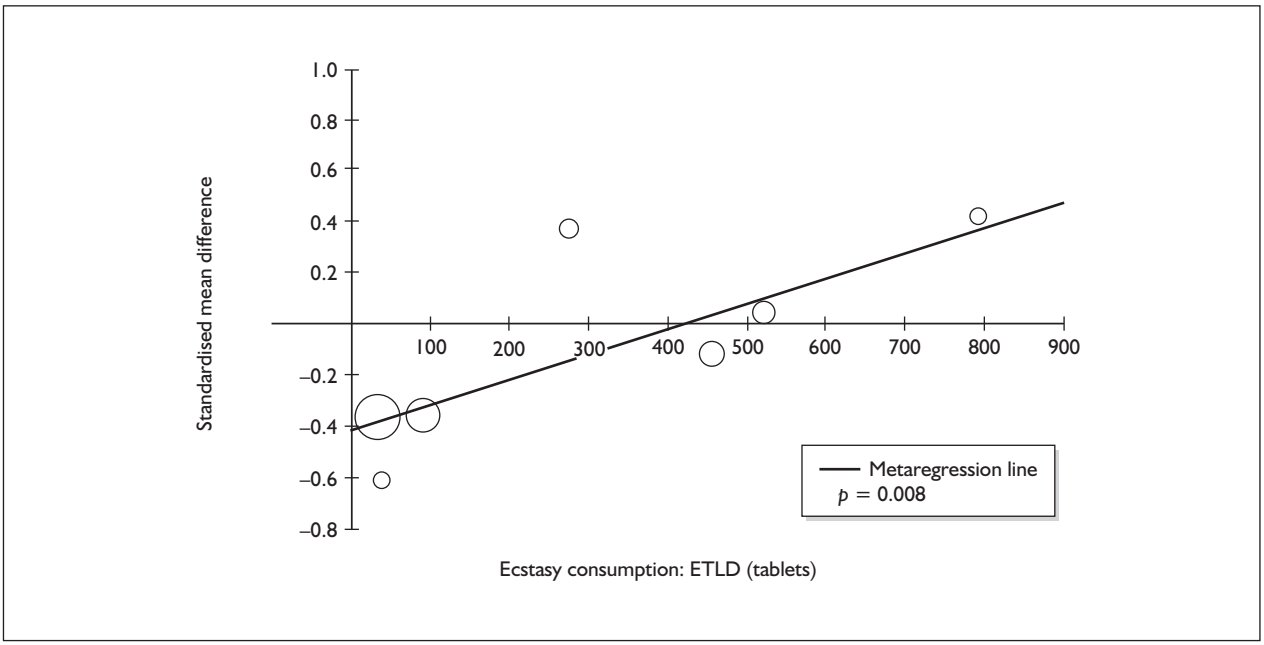

FIGURE 111 *Executive function – response inhibition (composite measure) – ecstasy users versus drug-naïve controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

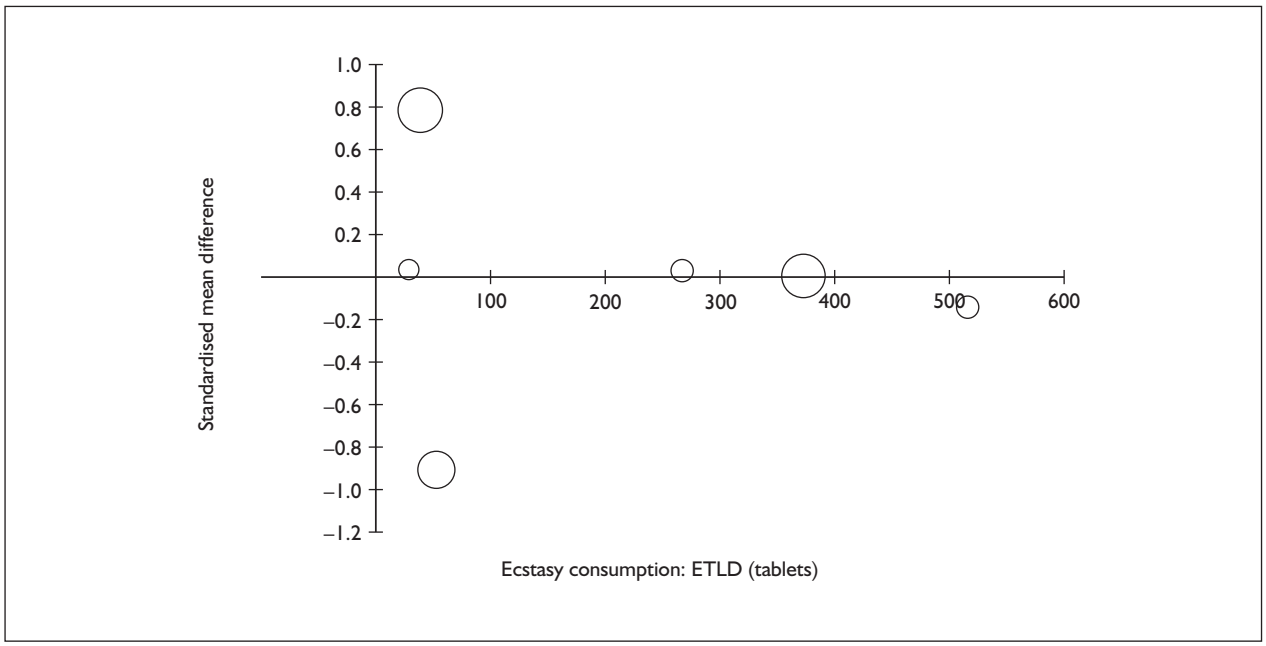

FIGURE 112 *Executive function – shifting (composite measure) – ecstasy users versus drug-naïve controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

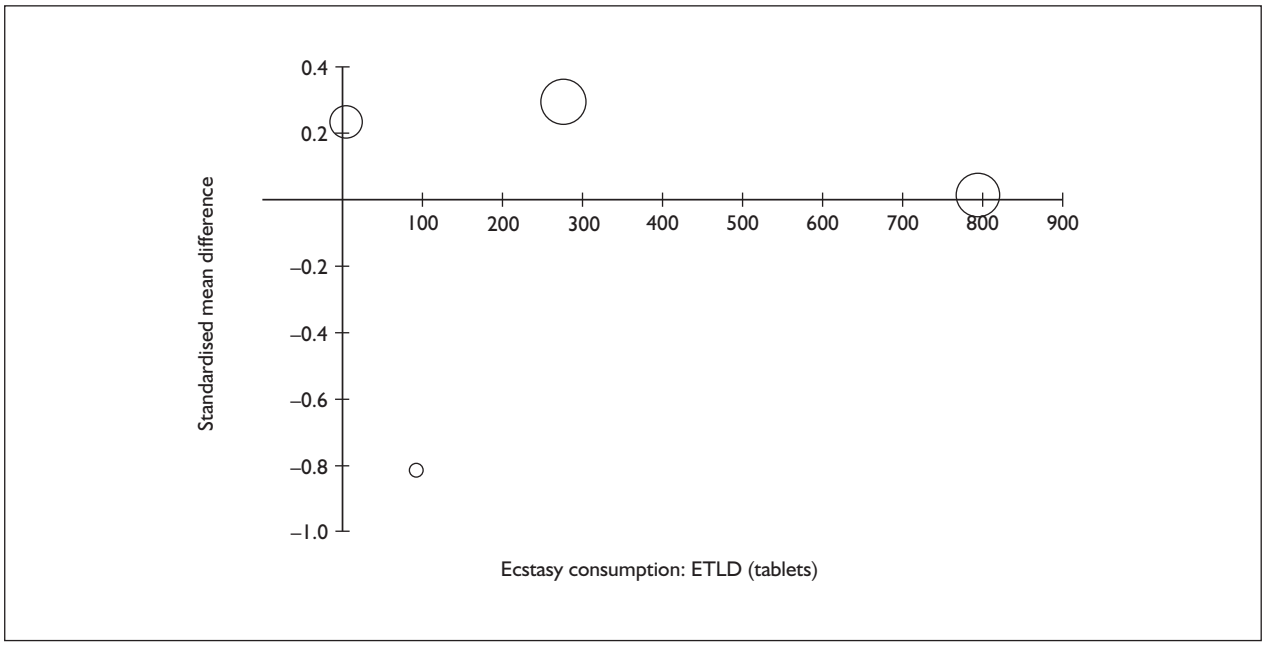

FIGURE 113 *Perceptual organisation (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

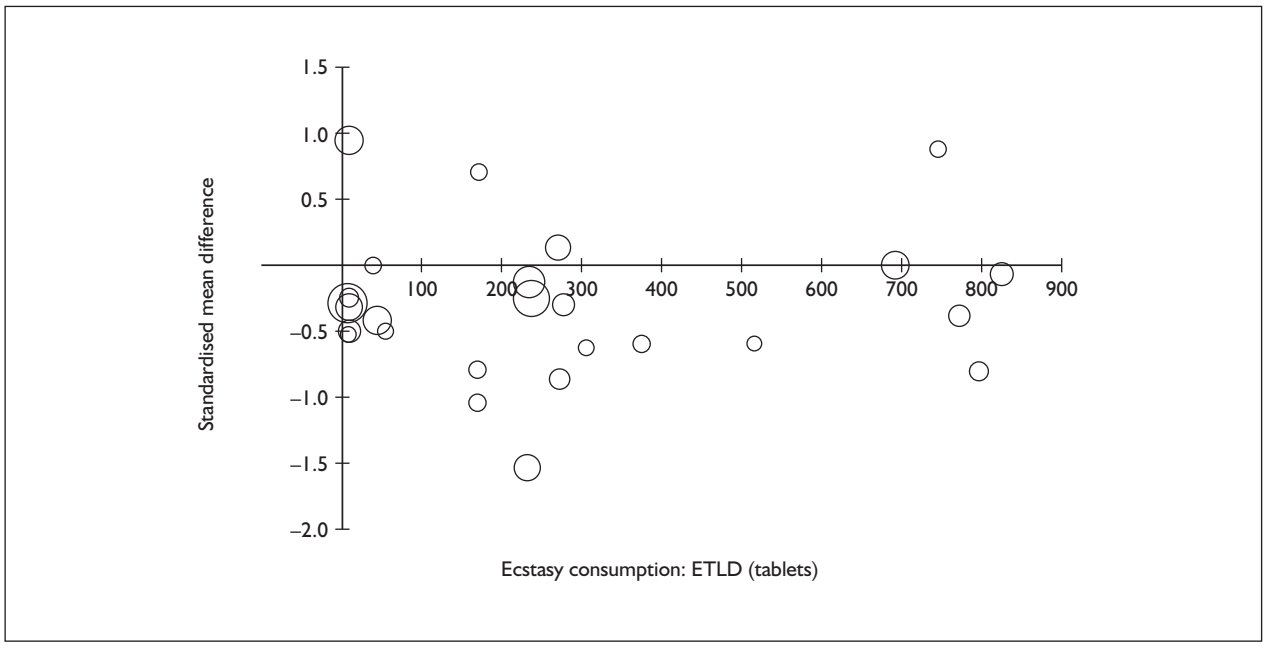

FIGURE 114 *Depression – self-rated (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

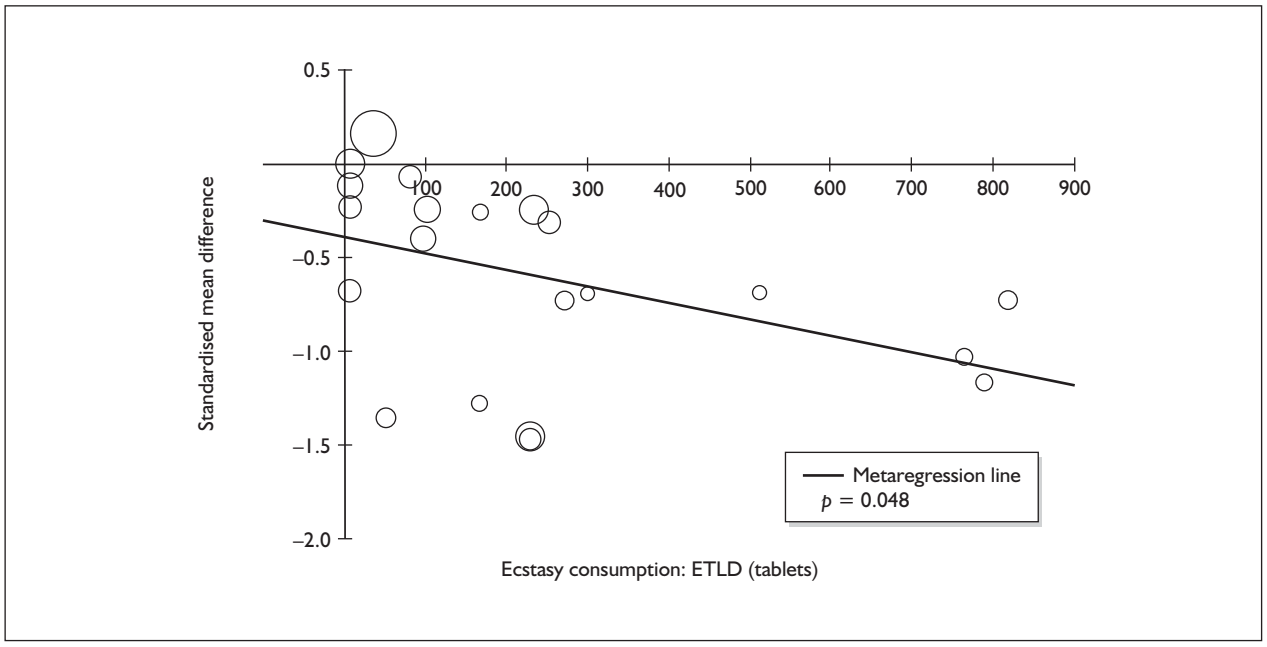

FIGURE 115 *Depression – self-rated (composite measure) – ecstasy users versus drug-naïve controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

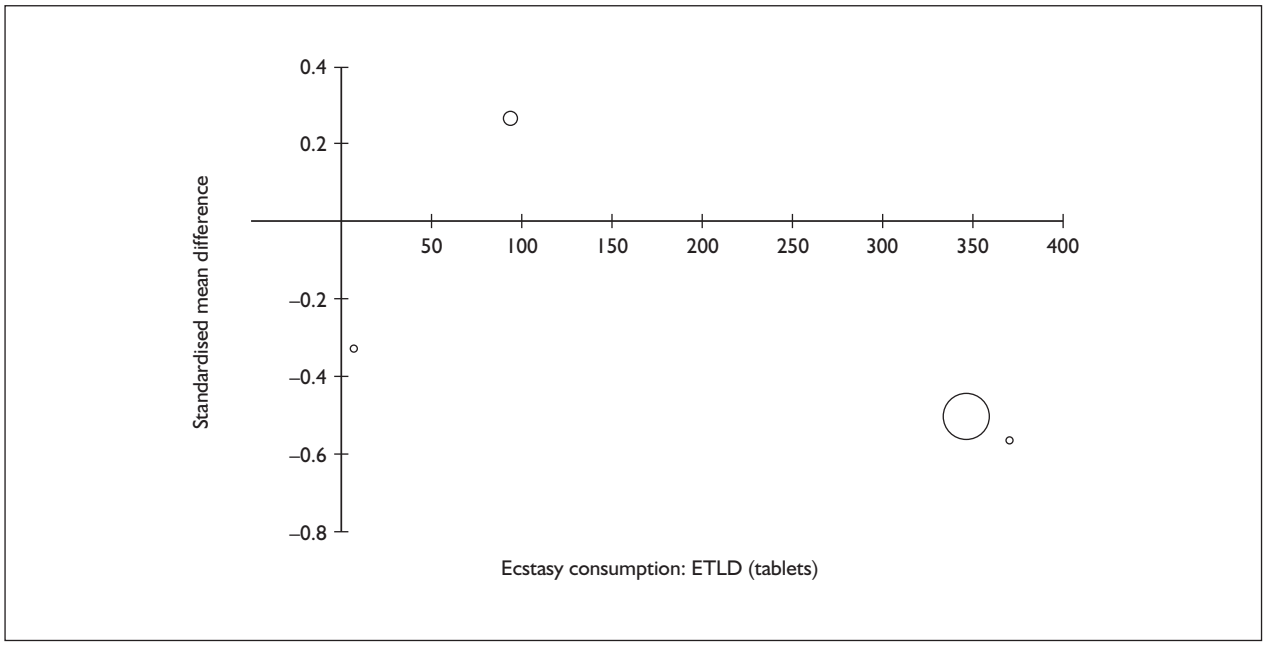

FIGURE 116 *Memory – self-rated (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

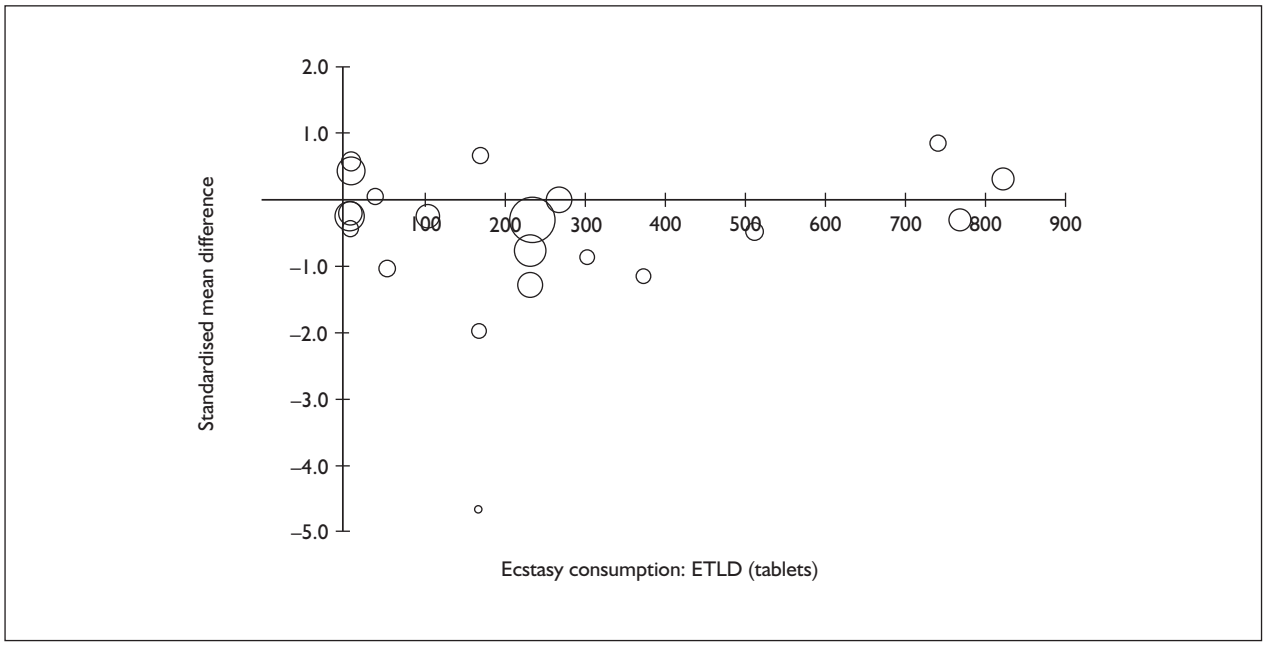

FIGURE 117 *Anxiety – self-rated (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

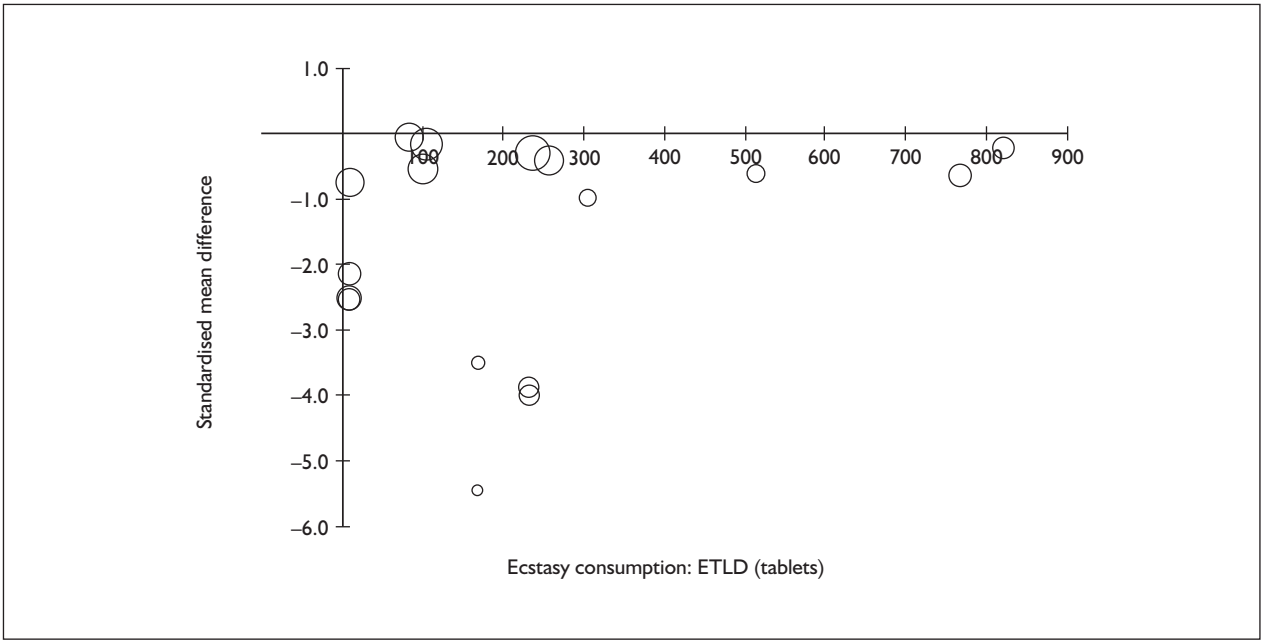

FIGURE 118 *Anxiety – self-rated (composite measure) – ecstasy users versus drug-naïve controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

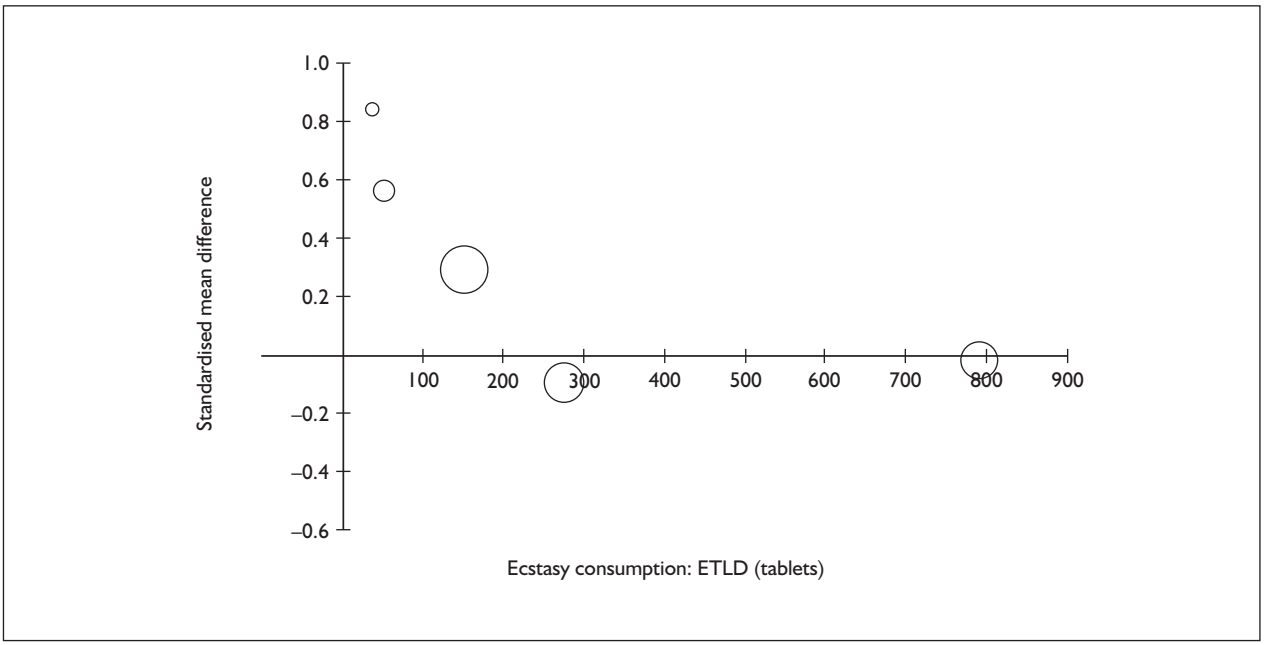

FIGURE 119 *Impulsivity – objective measures (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

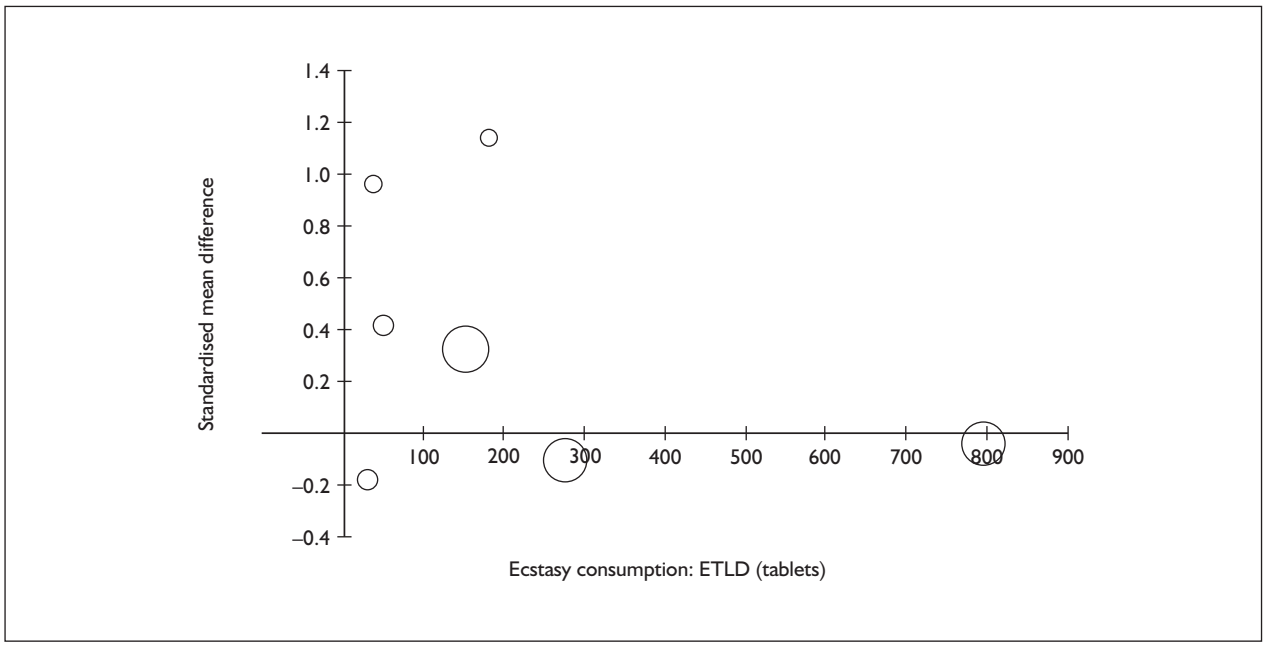

FIGURE 120 *Impulsivity – objective measures (composite measure) – ecstasy users versus drug-naïve controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

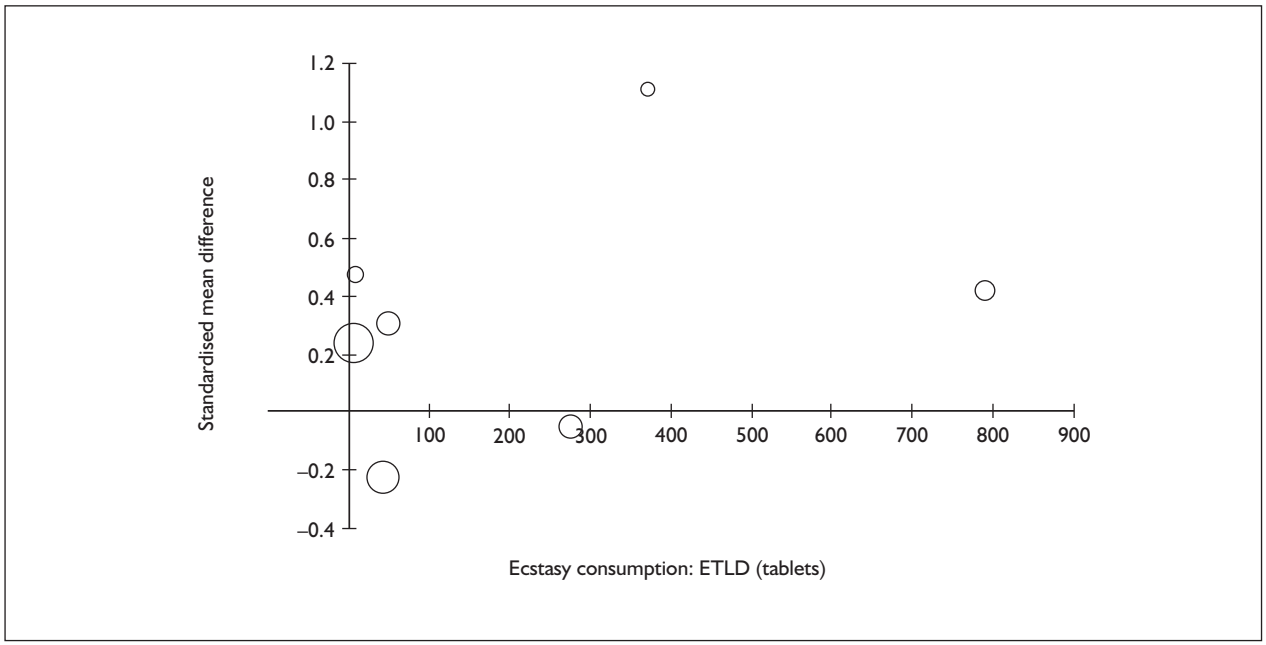

FIGURE 121 *Impulsivity – subjective measures (composite measure) – ecstasy users versus polydrug controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

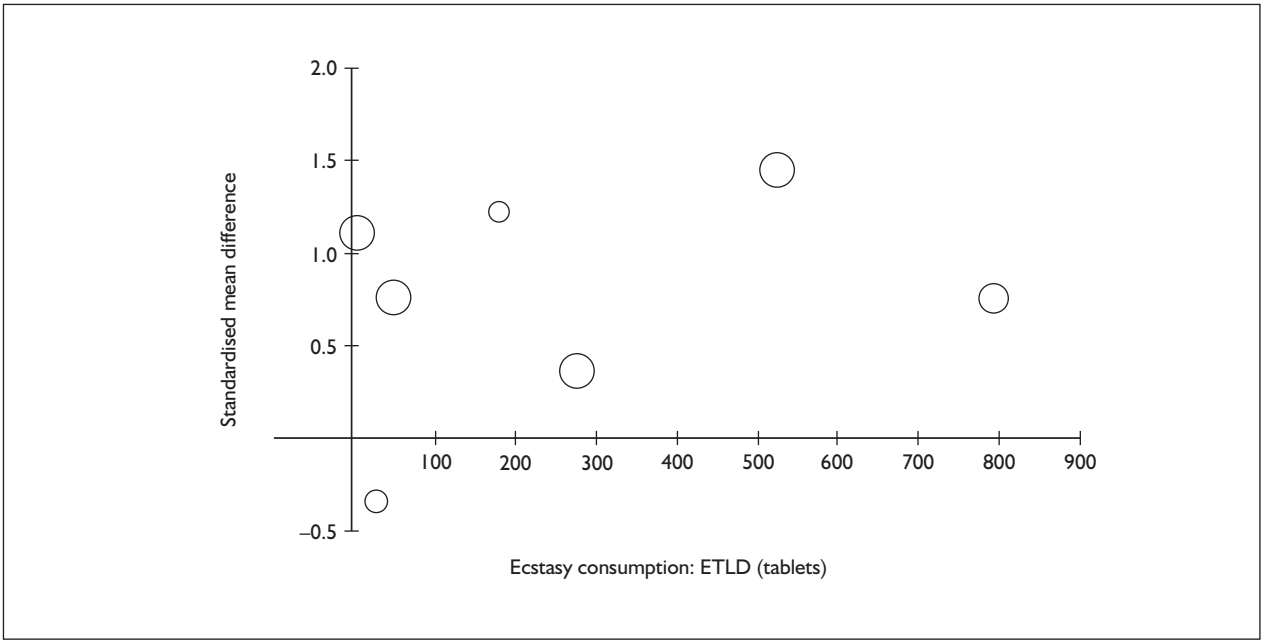

FIGURE 122 *Impulsivity – subjective measures (composite measure) – ecstasy users versus drug-naïve controls: standardised mean difference against estimated total lifetime dose (ETLD) of MDMA.*

Appendix 8

Map of Level III evidence

Outcomes identified in case series and case reports containing fatal cases

Outcome	*n*	References
Asthma exacerbation/other respiratory distress (see also: Pneumomediastinum)	1	35
Brain haemorrhage/other organic brain damage	14	169,176,195,202,204,206,207,212,213,277,281,286,292,503
Cardiac events (acute) (not sinus tachycardia)	22	176–179,188,195,196,201,203,206,208,209,212,213,215,216, 263,264,278,342,503
Central nervous system abnormalities (acute) (see also: Seizures)	5	208,213,229–231
Death	69	23,29,36,37,39,169,175–188,194–196,199,201,216,224–233, 263–265,277,281,286,292,330,340,342,345–349,503–508
Dental damage/other oral injury	3	195,201,203
Diabetic complications	1	214
Disseminated intravascular coagulopathy and other haematological disorders	17	37,168,188,196,199,201–203,205–212,214
Hyperkalaemia	3	201,211,213,215
Hyperthermia	25	37,168,176,181,188,194–196,199,201–214,216,228
Hypoglycaemia	1	286
Hyponatraemia	8	206,224–233
Hypothermia	3	188,228,230
Immunological dysfunction (aplastic anaemia, etc.)	1	188
Kidney failure	13	168,188,194,196,199,201,205,207,210,211,213,214,345
Liver failure	12	188,194–196,199,205–207,213,214,340,503
Memory (including learning)	1	224
Movement disorder (acute)(dystonia)	1	292
Psychoses/personality disorders (chronic)	1	347
Psychotic episode (acute) (including panic)	2	345,347
Rhabdomyolysis (and other muscular dysfunction)	12	168,188,196,199,202,205,209–211,213,214
Seizures	15	37,168,188,195,199,203–205,207,209,216,228,230,263,292
Suicide/attempted suicide	8	177,210,214,345–349
Vascular abnormalities	1	181

Outcomes identified in case series and case reports containing non-fatal cases

Outcome	*n*	References
Asthma exacerbation/other respiratory distress (see also: Pneumomediastinum)	1	302
Attention deficit disorder	2	509,510
Brain haemorrhage/other organic brain damage	15	222,250,276,278–280,282–285,287–291
Cardiac events (acute) (not sinus tachycardia)	14	190,266–275
Central nervous system abnormalities (acute) (see also: Seizures)	30	190,241,244,248,271,273,276,293,295,300,305–307,511–524
Dental damage/other oral injury	5	525–529
Dependency	2	530,531
Dermatological disorders	5	298,532–538
Diabetic complications	2	536,537
Disseminated intravascular coagulopathy and other haematological disorders	16	221,274,295,298,306,521,523,535,538–544
Hyperkalaemia	1	276
Hyperthermia	43	221,226,262,249,251,267,260,273,275,290,291,293,295,298,301,306, 511,512,516,519–522,540,541,544–559
Hypoglycaemia	2	290,540
Hyponatraemia	24	205–224
Hypothermia	1	220
Immunological dysfunction (aplastic anaemia, etc.)	1	560
Kidney failure	15	221,271,282,291,521,523,539,541–543,552,581,561–563
Liver failure	30	271,274,298,306,332,521,539,543,549,561,564–576
Memory (including learning)	18	221,295,365,368,371,510,525,577–602
Mood (depression, anxiety, etc.)	27	290,352,361,509,525,577,578,581,584–602
Movement disorder (acute) (dystonia)	15	190,222,244,254,280,283–285,295–299,525
Movement disorder (long-term) (including parkinsonism)	3	581,603,604
Neurocognitive function (including decision-making, attention, learning)	12	295,365,366,369,510,577–580,583,585,592
Ocular injury	4	355,605–607
Personality traits (including impulsivity, aggression, loneliness, etc.)	10	295,578,581,586,590,598,607–609
Pneumomediastinum, pneumothorax and similar	21	268,308,319,322
Psychoses/personality disorders (chronic)	32	251,280,293,300,301,351,353,357–369,509,513,514,578,581,585–587, 592–599,610–614
Psychotic episode (acute) (including panic)	19	296,298,300,301,306,350–363
Rhabdomyolysis (and other muscular dysfunction)	24	220,240,242,248,250,271,274,282,293,298,520,523,541–543,546,549, 550,555,561,615–618
Seizures	35	190,222,233–237,240,241,243,245,246,249,270,274,278,293,300,306,337, 353,363,517,520,522,531,540,541,546,547,551,554,555,619,620
Sensorineural dysfunction (auditory, optical)	9	242,289,550,593,621–625
Sexual dysfunction (chronic)	2	581,598

Outcome	*n*	References
Sleep	6	299,525,581,585,595,597
Stroke	5	300,307,600,606,627
Suicide/attempted suicide	2	350,611
Susceptibility to infection (chronic)	2	581,628
Urogenital dysfunction (including urinary retention)	6	244,344,552,629–631
Vascular abnormalities	4	308,548,625,626

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The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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