Cite this article as: BMJ, doi:10.1136/bmj.38743.539398.3A (published 24 February 2006)

Research

Symptoms of anxiety and depression in childhood and use of MDMA: prospective, population based study

Anja C Huizink, Robert F Ferdinand, Jan van der Ende, Frank C Verhulst

Abstract

Objective To investigate whether using ecstasy (3,4-methylenedioxymethamphetamine, MDMA) is preceded by symptoms of behavioural and emotional problems in childhood and early adolescence.

Design Prospective, longitudinal, population based study

Setting The Dutch province of Zuid-Holland.

Participants A sample of 1580 individuals, followed up across a 14 year period, from childhood into adulthood.

Main outcome measures The first assessment took place in 1983 before MDMA appeared as a recreational drug in the Netherlands and included the child behaviour checklist to obtain standardised parents' reports of their children's behavioural and emotional problems. Use of the drug was assessed with the composite international diagnostic interview 14 years later.

Results Eight syndrome scales of childhood behaviour were examined. Scores in the deviant range for the scales designated as anxious or depressed in childhood were significantly related to use of MDMA in adolescents and adults, resulting in an increased risk (hazard ratio 2.22, 95% confidence interval 1.20 to 4.11, P = 0.01).

Conclusions Individuals with childhood symptoms of anxiety and depression may have an increased tendency to use MDMA in adolescence or young adulthood. Its effects are supposed to include enhanced feelings of bonding with other people, euphoria, or relaxation. Especially individuals with symptoms of anxiety or depression may be susceptible to these positive effects.

Introduction

Ecstasy (3,4-methylenedioxymethamphetamine, MDMA) emerged as a new drug in Europe more than a decade ago. In the Netherlands, the drug became available at dance parties from 1985 onwards. Its most frequent users are adolescents who go out to dance parties.[1] In the Netherlands, the age of users is 20-24. In this age group, the number of users has grown in the past few years, with a lifetime prevalence of 13.2% in 2001 compared with 6.2% in 1997. The prevalence of MDMA use in the preceding month also increased, from 1.9% in 1997 to 2.9% in 2001.[2] Recently, the adverse effects of using MDMA have raised considerable interest, including its neurotoxic effects.[3] Several studies have indicated that using MDMA is associated with emotional health problems, such as depression, psychotic symptoms, and anxiety disorders.[4–7] These associations may represent two basic temporal pathways: either emotional problems are a consequence of using MDMA, or emotional problems lead to ecstasy use—for example, in order to "self medicate" symptoms. These two pathways do not exclude each other. Links between emotional problems and MDMA use may run in both directions, from emotional problems towards use of the drug and vice versa. Since most studies were cross sectional and based on clinical samples, we lack insight in these temporal pathways. Most authors argue for the first option and refer to neurotoxic effects of MDMA on serotonergic neurones.[8–12] However, a study by Lieb et al has shown that the first use of MDMA was secondary to phobias, somatoform disorders, dysthymia, and panic disorder or agoraphobia.[5] The study did not focus on other psychiatric disorders, such as delinquent, aggressive behaviour, or attention problems in relation to ecstasy use.

We investigated whether use of MDMA is preceded by symptoms of behavioural and emotional problems in childhood and early adolescence. For this purpose, we assessed MDMA use in a sample of 1580 individuals, who were followed up for a period of 14 years, from childhood into adulthood. The first assessment took place in 1983 before MDMA appeared as a recreational drug in the Netherlands. The subjects in our study had therefore probably not used MDMA at the first assessment. This offered us the unique opportunity to investigate if a pathway from behavioural and emotional problems leading to MDMA use exists.

Methods

Participants

This study was part of an ongoing longitudinal general population study that started in 1983 in the Dutch province of Zuid-Holland. The investigators drew a random sample of 2600 children and adolescents aged 4-17 from municipal registers that list all residents. Of the 2447 parents who were contacted, 2076 (84.8%) cooperated. After the first measurement (1983), the sample was approached again in 1985, 1987, 1989, 1991, and 1997. More details on the initial data collection are presented elsewhere.[13 14]

In 1997 (at follow-up) we reassessed 1580 individuals with the computerised version of the composite international diagnostic interview[15] to determine psychiatric diagnoses according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV).[16] The response rate was 79% after correction for deceased subjects (n = 8), mentally retarded subjects (n = 12), and emigrated subjects (n = 59). Scores for 1983 from the child behaviour checklist scores were similar for dropouts and for children who remained in the study.[17]

Procedures

In 1983 the researchers used the child behaviour checklist (CBCL) to obtain standardised parent reports of their children's behavioural and emotional problems. The checklist includes 120 problem items, which are scored 0 (not true), 1 (somewhat or sometimes true), and 2 (very true or often true), based on the preceding six months.[18] Eight syndrome scores are derived: withdrawn, somatic complaints, anxious or depressed, social problems, thought problems, attention problems, delinquent behaviour, and aggressive behaviour. Good reliability and validity of the checklist have been replicated for the Dutch translation.[19] Kasius et al reported strong associations between syndrome scores on the child behaviour checklist and DSM-IV diagnoses that were derived from standardised diagnostic interview, in a Dutch psychiatric outpatient sample of 231 youngsters aged 6-16.[20]

We dichotomised syndrome scores on the CBCL as deviant and non-deviant. To select individuals who could be regarded as deviant, we used the cut-off points reflecting the 95th percentile of the cumulative frequency distribution of these scales in a Dutch normative sample, for each age group (4-11, 12-17) and sex separately, as recommended by Achenbach.[18] These cut-off points are widely used in clinical practice and were established by comparing large samples of clinically referred children with non-referred children, to divide children on the basis of their scores into those who resemble normal children and those who resemble children with disorders.[18]

At follow-up in 1997, we used the lifetime version of the composite international diagnostic interview (CIDI), version 2.1,[15] to assess use of MDMA. This instrument allows for the standardised assessment of psychiatric symptoms, syndromes, and diagnoses of a wide range of DSM-IV substance use and mental disorders, along with information about onset, duration, and clinical and psychosocial severity. Good reliability and validity have been reported for the CIDI.[21] For this study, we defined lifetime use of MDMA as having used the drug on at least five occasions, to indicate those users only who progressed from experimentation with the drug to more regular use. The item of the CIDI regarding MDMA use represents one of the DSM-IV criteria of drug abuse. We also assessed age at first use (onset).

The investigators used a six point scale of parental occupation[22] with 1=lowest and 6=highest to measure socioeconomic status of the parents in 1983. If both parents worked we used the highest occupational level. For this study we used a dichotomised score, indicating a low socioeconomic status (scores 1-3) and a medium to high status (scores 4-6).

At each phase, all subjects who completed a questionnaire (parents and youths) gave written informed consent after the procedure had been fully explained.

Statistical analyses

We used SAS, version 9.1 (SAS Institute, Cary, NC, 2002-2003) to conduct Cox regression analyses.[23] In the analysis, we determined whether behavioural and emotional problems in childhood or early adolescence, measured in 1983, were a risk factor for later use of MDMA. During interviews, the age of onset could be determined only as a whole number of years, and therefore, we defined survival time in years as age at onset of use of MDMA, or, if this did not occur, as the age at the final assessment, in 1997. Since we knew the survival time only in years, we used the exact method in SAS for the treatment of ties. We assessed subjects first at ages 4-17, therefore we accounted for left truncation of survival times. We computed hazard ratios that indicate a considerable association between behavioural and emotional in 1983. We adjusted for possible cohort effects by fitting stratified Cox regressions, in which we used age groups in 1983 as strata. We further adjusted for the possible effects of socioeconomic status and tested for interaction effects of sex with the predictors. The proportional hazards assumption was not violated in any of the conducted analyses. We assumed statistical significance at the level of $P<0.05$.

Table 1 Number (percentages) of subjects in deviant range groups and number of subjects within deviant range groups that reported to have used ecstasy in 1997

CBCL scale in 1983	Boys in deviant range*	Boys in deviant range, using MDMA in 1997†	Girls in deviant range*	Girls in deviant range, using MDMA in 1997†
Withdrawn	60 (8)	4 (7)	68 (8)	2 (3)
Somatic complaints	39 (5)	3 (8)	34 (4)	0 (0)
Anxious/depressed	61 (8)	9 (15)	58 (7)	3 (5)
Social problems	66 (9)	2 (3)	79 (9)	2 (3)
Thought problems	26 (4)	3 (12)	16 (2)	0 (0)
Attention problems	95 (13)	6 (1)	75 (9)	1 (1)
Delinquent behaviour	92 (13)	13 (14)	56 (7)	0 (0)
Aggressive behaviour	99 (14)	8 (8)	87 (10)	0 (0)

In 1983, 1016 boys and 1060 girls were included in the study, and in 1997, 732 male subjects and 848 female subjects. At follow-up in 1997, 64 (9%) of male subjects and 34 (4%) of female subjects used MDMA.
*The percentages reflect the number of individuals with scores in the deviant range of the respective syndrome scales divided by the number of (male or female) individuals in 1997.
†The percentages reflect the number of individuals who used MDMA in 1997 divided by the number of individuals with scores in the deviant range of the respective syndrome scales.

Results

Descriptive analyses

The mean age of participants was 9.9 in 1983 (range 4-17) and 24.5 in 1997 (range 18-33). Both sexes were represented in the sample, with slightly more female than male participants (n=1060 (51.1%) *v* n=1016 (48.9%)). In 1997, data were available for 76% (n=1580) of the original sample in 1983. In 1997, 98 study participants (4.7% of the total sample)—64 male and 34 female—reported using MDMA on at least five occasions.

We dichotomised scores on all CBCL scales. Table 1 shows separately the numbers of male and female participants in the deviant range groups in 1983. In addition, it shows the numbers of male and female participants in the deviant range groups in 1983 who reported having used MDMA at least five times in 1997.

Ninety MDMA users (92%) had also experimented with other drugs, most commonly with cannabis, 58 with cocaine (59%), and 43 with psychedelic drugs (44%). Of interest is that 59 MDMA users had tried cannabis only once (60%), whereas of those who used both cocaine and ecstasy, 63 tried cocaine two to four times (64%) and those who used psychedelic drugs and MDMA, used these on two to four occasions (49%, n=48) or even on at least five occasions (49%, n=48).

Survival analyses

Firstly, we carried out separate Cox regression analyses with each dichotomised CBCL scale score as predictor and time of onset of ecstasy use as outcome, adjusting for socioeconomic status and sex, and including sex by syndrome scale interaction terms (none of which reached significance). This may be because only few events are included in our study. Therefore we deleted the interaction terms from the Cox regression analyses reported in table 2. On the basis of the associations shown in table 2, we included predictors with P values <0.10 in the next model. We therefore included scores within the deviant range of the anxious or

Table 2 Separate Cox regression analyses for each syndrome on the childhood behaviour checklist (CBCL)

CBCL scale in 1983	Hazard ratio (95% CI)	P value
Withdrawn	0.97 (0.43 to 2.24)	0.95
Somatic complaints	0.73 (0.23 to 2.30)	0.58
Anxious or depressed	2.22 (1.20 to 4.11)	0.01
Social problems	0.73 (0.27 to 2.00)	0.54
Thought problems	1.64 (0.51 to 5.22)	0.40
Attention problems	0.86 (0.39 to 1.87)	0.70
Delinquent behaviour	1.81 (1.00 to 3.28)	0.05
Aggressive behaviour	0.94 (0.45 to 1.95)	0.87

Associations were stratified for age and adjusted for socioeconomic status and sex. Associations are shown between each CBCL syndrome scale measured in 1983 and MDMA use measured in 1997.

depressed syndrome scale and delinquent behaviour syndrome scale in 1983 as predictors in the multivariate model, which was stratified for age, and adjusted for socioeconomic status and sex by syndrome scale interaction effects. The final model included only one significant predictor—scores within the deviant range of the anxious or depressed syndrome scale at baseline (1983) on MDMA use, stratified for age, and adjusted socioeconomic status and sex by syndrome scale interaction effects, resulting in an increased risk on later MDMA use (hazard ratio 2.22, 95% confidence interval 1.20 to 4.11, P = 0.01).

Discussion

We found evidence for an increased risk for use of MDMA in individuals who scored in the deviant range of the anxious or depressed scale of the child behaviour checklist in 1983. We found no associations between the other CBCL syndrome scales and use of MDMA. We studied whether behavioural and emotional problems in childhood and early adolescence preceded the use of MDMA, because the first measurement of related symptoms in childhood and early adolescence took place before MDMA appeared in the Netherlands.

Comparison with other studies

These findings partly confirm previous findings of Lieb et al, who showed that subjects with emotional disorders such as phobia, and somatoform conditions at baseline (age 14-24) showed a significantly increased risk of starting to use MDMA during a four year follow-up period.[5] We did not find a relation for somatoform conditions in childhood and use of MDMA in adolescence. Our study used a 14 year follow-up, whereas Lieb et al had a much shorter time span between determinants and outcome measures.[5] Also, in their study the assessment of the use of MDMA before their baseline measurement was retrospective and may have been subject to recall bias. In contrast, our first assessment of risk factors took place before MDMA appeared in the Netherlands, and therefore, the subjects could have started using it only after our first assessment.

We found an effect of symptoms of anxiety and depression on later MDMA use for male as well as female study participants. This finding contradicts other, mostly cross sectional, studies showing the strongest association between depressive and anxiety symptoms and substance use in young women.[24 25] However, these associations have been examined in clinical samples, including individuals with more serious psychiatric and substance use disorders than our population based sample. Examining sex specific vulnerabilities for MDMA use will be a challenge in future studies.

Meaning of the study

Although we performed multiple tests and should therefore interpret our findings cautiously, the results imply that individuals with childhood symptoms of anxiety and depression may have an increased tendency to use MDMA. The drug's effects are supposed to include enhanced feelings of bonding with other people, euphoria, or relaxation. Especially individuals with symptoms of anxiety or depression may be susceptible to these positive effects of MDMA. Studies on motivations of MDMA users showed that alleviation of depressed mood, desire for an altered state of mind, desire to escape, and self medication are among often mentioned reasons to use MDMA.[26 27] The active compound affects the serotonin system, which is known to be important in the regulation of mood. MDMA produces an acute, rapid enhancement in the release of serotonin from nerve endings in the brains of experimental animals.[28] This acute effect relates to the enhanced positive feelings. Individuals with signs of anxiety and depression may therefore use MDMA to self medicate their symptoms.

Possible reasons for using MDMA

Other studies have supported the relation between MDMA use as determinant and depression as outcome.[29–31] It has been found, for example, that in the long run, exposure to MDMA may result in increased depressive symptoms. In animals, chronic exposure to MDMA resulted in neurotoxic effects such as inhibition of serotonin reuptake into the neurone and serotonin synthesis, and destruction of serotonergic axon terminals.[32] This neurodegeneration is associated with a decline in concentrations of serotonin in the brain, and decreased availability of serotonin in the central nervous system has been proposed as the basis for the symptoms of depression.[33 34] However, our findings show that individuals who already had depressive symptoms in childhood or adolescence have an increased risk of starting to use MDMA. In turn, this may affect the serotonin system, which may increase the risk of these individuals developing a mood disorder at a later age after using MDMA. This may explain part of the association that has been found between MDMA use and later depression in other studies. Of course, other mechanisms may be involved in the relation between mood disorders and MDMA use. For example, a common underlying genetic vulnerability may account for symptoms of mood disorders and the propensity to use drugs such as ecstasy. Lieb et al showed that depression in parents is associated with depression and substance use disorders in offspring.[35]

Other factors may account for the increased tendency to use MDMA in some individuals. Their social environment will probably play a part and can include peers that take risks or use or have access to illicit drugs,[36] and therefore, the availability of ecstasy will be increased. Other potential risk factors, which we have not tested in this study, may include the desire to party, novelty seeking, other drug use of adolescents, social roles in peer groups, substance use of parents, and bad parenting practices. Furthermore, the pathway from emotional problems in childhood towards later use of MDMA may be non-specific. In our sample, many users of MDMA have also used other stimulant drugs on several occasions, such as cocaine and psychedelic drugs.

Conclusion

Our findings give evidence for a temporal pathway, in which childhood symptoms of anxiety and depression may precede use of MDMA. Focusing on the children with symptoms of anxiety and depression as vulnerable individuals in future studies will increase our insight into the potential harmful effects of MDMA

What is already known on this topic

The use of ecstasy (3,4-methylenedioxymethamphetamine, MDMA) is associated with emotional health problems, such as depression, psychotic symptoms, and anxiety disorders

Insight into temporal pathways that explain links between emotional problems and ecstasy use is lacking

What this study adds

Individuals with childhood symptoms of anxiety and depression may have an increased tendency to use ecstasy in adolescence or young adulthood

Focusing on these vulnerable individuals in future studies will increase our insight into the potential harmful effects of MDMA on brain neurotransmitter systems and associated psychopathology

on brain neurotransmitter systems and associated psychopathology. Moreover, the reward mechanisms involved in the plausible "self medication" attempts of vulnerable individuals need to be examined, to prevent adolescents and young adults from using MDMA regularly.

Contributors: ACH wrote the first draft of the manuscript, performed part of the statistical analyses, and coordinated the present study. RFF reviewed the first draft of the manuscript in detail. JvdE performed part of the statistical analyses and was responsible for the coordination of the data collection of the Zuid-Holland sample. FCV conceived the study and supervised the project. All authors interpreted the findings of this manuscript regarding their own specific field of expertise; RFF and FCV are experts in the field of child and adolescent psychiatry, and JvdE is an expert in statistical analyses of epidemiological studies. All authors helped to conceptualise ideas, interpret findings, and review drafts of the manuscripts. ACH is guarantor.

Funding: The data collection of the Zuid-Holland sample was financially supported by grant number 002827230 from the Health Research and Development Council, Netherlands (Zorgonderzoek Nederland).

Competing interests: None declared.

Ethical approval: The Dutch human subjects committee approved this study, and each assessment phase of this study was approved by the Committee for Medical Ethics, Erasmus Medical Center/Sophia Children's Hospital.

1 Griffiths P, Vingoe L, Jansen K. *New trends in synthetic drugs in the European Union*. Lisbon: European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 1997.
2 *Nationale Drugmonitor Jaarbericht [national drug monitor]*. Utrecht: Bureau NDM, 2002. www.trimbos.nl/default3698.html (accessed 26 Jan 2006).
3 Gowing LR, Henry-Edwards SM, Irvine RJ, Ali RL. The health effects of ecstasy: a literature review. *Drug Alcohol Rev* 2002;21:53-63.
4 Schifano F, DiFuria L, Forza G, Minicuci N, Bricolo R, Morgan MJ. MDMA ("ecstasy") consumption in the context of polydrug abuse: a report on 150 patients. *Drug Alcohol Dep* 1998;52:85-90.
5 Lieb R, Schuetz CG, Pfister H, Sydow K von, Wittchen H-U. Mental disorders in ecstasy users: a prospective longitudinal investigation. *Drug Alcohol Dep* 2002;68:195-207.
6 Parrott AC, Buchana T, Scholey AB, Heffernan T, Ling J, Rodgers J. Ecstasy/MDMA attributed problems reported by novice, moderate and heavy recreational users. *Hum Psychopharmacol* 2002;17:309-12.
7 Parrott AC, Milani RM, Parmar R, Turner JD. Recreational ecstasy/MDMA and other drug users from the UK and Italy: psychiatric symptoms and psychobiological problems. *Psychopharmacology (Berl)* 2001;159:77-82.
8 Ricaurte GA, Byron G, Strauss L, Seiden L, Schuster C. Hallucinogenic amphetamine selectively destroys brain serotonin nerve terminals. *Science* 1985;229:986-8.
9 Ricaurte GA, Yuan J, McCann UD. 3,4-methylenedioxymethamphetamine ("ecstasy") induced serotonin neurotoxicity: studies in animals. *Neuropsychobiology* 2000;42:5-10.
10 McCann UD, Eligulashvili V, Ricaurte GA. 3,4-methylenedioxymethamphetamine ("ecstasy") induced serotonin neurotoxicity: clinical studies. *Neuropsychobiology* 2000;42:11-6.
11 Sprague JE, Everman SL, Nichols DE. An integrated hypothesis for the serotonergic axonal loss induced by 3,4-methylenedioxymethamphetamine. *Neurotoxicology* 1998;19:427-41.
12 Vollenweider FX, Gamma A, Liechti M, Huber T. Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naive healthy volunteers. *Neuropsychopharmacology* 1998;19:241-51.
13 Verhulst FC, Akkerhuis GW, Althaus M. Mental health in Dutch children: (I). A cross-cultural comparison. *Acta Psychiatr Scand Suppl* 1985;323:1-108.
14 Verhulst FC, Berden GF, Sanders-Woudstra JA. Mental health in Dutch children: (II). The prevalence of psychiatric disorder and relationship between measures. *Acta Psychiatr Scand Suppl* 1985;324:1-45.
15 World Health Organization. *Composite international diagnostic interview (CIDI)*. Geneva: World Health Organization, 1997.
16 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV)*. Washington, DC: American Psychiatric Association, 1994.
17 Hofstra MB, van der Ende J, Verhulst FC. Child and adolescent problems predict DSM-IV disorders in adulthood: a 14-year follow-up of a Dutch epidemiological sample. *J Am Acad Child Adolesc Psychiatr* 2002;41:182-9.
18 Achenbach TM. *Manual for the child behaviour checklist/4-18 and 1991 profiles*. Burlington, VT: University of Vermont Department of Psychiatry, 1991.
19 Verhulst FC, Van der Ende J, Koot HM. *Handleiding voor de CBCL/4-18 [Manual for the CBCL/4-18]*. Rotterdam: Erasmus University/Department of Child and Adolescent Psychiatry, Sophia Children's Hospital, 1996.
20 Kasius MC, Ferdinand RF, van den Berg H, Verhulst FC. Associations between different diagnostic approaches for child and adolescent psychopathology. *J Child Psychol Psychiatry* 1997;38:625-32.
21 Andrews G, Peters L. The psychometric properties of the composite international diagnostic interview. *Soc Psychiatry Psychiatric Epidemiol* 1998;33:80-8.
22 Van Westerlaak JH, Kropman JA, Collaris JWM. *Beroepenklapper [Manual for occupational level]*. Nijmegen: Instituut voor Sociologie, 1975.
23 Cox DR. Regression models and life tables. *J R Stat Soc* 1972;34:187-202.
24 Brady KT, Randall CL. Gender differences in substance use disorders. *Psychiatr Clin North Am* 1999;22:241-52.
25 Latimer WW, Stone AL, Voight A, Winters KC, August GJ. Gender differences in psychiatric comorbidity among adolescents with substance use disorders. *Exp Clin Psychopharmacol* 2002;10:310-5.
26 Levy KB, O'Grady KE, Wish ED, Arria AM. An in-depth qualitative examination of the ecstasy experience: results of a focus group with ecstasy-using college students. *Subst Use Misuse* 2005;40:1427-41.
27 Boys A, Marsden J, Strang J. Understanding reasons for drug use amongst young people: a functional perspective. *Health Educ Res* 2001;16:457-69.
28 Green AR, Mechan AO, Elliott JM, O'Shea E, Colado MI. The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). *Pharmacol Rev* 2003;55:463-508.
29 McCardle K, Luebbers S, Carter JD, Croft RJ, Stough C. Chronic MDMA (ecstasy) use, cognition and mood. *Psychopharmacology (Berl)* 2004;173:434-9.
30 de Win MM, Reneman L, Reitsma JB, den Heeten GJ, Booij J, van den Brink W. Mood disorders and serotonin transporter density in ecstasy users- the influence of long-term abstention, dose, and gender. *Psychopharmacology (Berl)* 2004;173:376-82.
31 Verheyden SL, Maidment R, Curran HV. Quitting ecstasy: an investigation of why people stop taking the drug and their subsequent mental health. *J Psychopharmacol* 2003;17:371-8.
32 Pennings EJ, Konijn KZ, de Wolff FA. Clinical and toxicologic aspects of the use of ecstasy. [In Dutch.] *Ned Tijdschr Geneeskd* 1998;142:1942-6.
33 Meltzer HY, Lowy MT. The serotonin hypothesis of depression. In: Meltzer HY, ed. *Psychopharmacology: the third generation of progress*. New York: Raven, 1987:513-26.
34 Maes M, Meltzer HY. The serotonin hypothesis of major depression. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology: the fourth generation of progress*. New York: Raven Press, 1995:933-44.
35 Lieb R, Isensee B, Höfler M, Pfister H, Wittchen H-U. Parental major depression and the risk of depression and other mental disorders in offspring. *Arch Gen Psychiatry* 2002;59:365-74.
36 Fergusson DM, Swain-Campbell NR, Horwood LJ. Deviant peer affiliations, crime and substance use: a fixed effects regression analysis. *J Abnorm Child Psychology* 2002;30:419-30.

(Accepted 10 January 2006)

doi 10.1136/bmj.38743.539398.3A

Department of Child and Adolescent Psychiatry, Erasmus Medical Center Rotterdam/Sophia Children's Hospital, PO Box 2060, 3000 CB Rotterdam, Netherlands
Anja C Huizink *assistant professor*
Jan van der Ende *assistant professor*
Robert F Ferdinand *psychiatrist*
Frank C Verhulst *professor*

Correspondence to: A C Huizink a.c.huizink@erasmusmc.nl