ABSTRACT
Objective: To determine whether use of intrapartum Pethidine pain analgesia increases the risk for substance use disorder in adult offspring.
Design: Analysis of data from a cohort study.
Setting: Academic hospital in Leiden, the Netherlands.
Participants: 133 cases and 164 control individuals, aged 18–20 years at follow-up.
Main outcome measure: Incidence of substance use disorder or use of alcohol and tobacco.
Results: The lifetime use of addictive substances in children exposed to intrapartum Pethidine analgesia was 45% of 133 children versus 48% of 164 not-exposed subjects (adjusted OR = 0.79, 95% CI 0.48 to 1.29). Recent use of alcohol, tobacco and hard drugs showed no statistical difference either.
Conclusion: Pethidine for labour pain medication appears not to be associated with substance misuse or smoking in later life.

INTRODUCTION
Analgesia during labour is common worldwide. Methods used include barbiturates, nitrous oxide, opioids, epidural analgesia, transcutaneous electric nerve stimulation, psychoprophylaxis and hypnosis. In the Netherlands, opiates had been used in 7%–15% of all deliveries between 2000 and 2007, which is in 15 000–30 000 mothers a year.1 In the 1970s, intramuscular Pethidine® was the most common drug for pain relief during labour. In recent years, a rise in the use of epidural or spinal analgesia and in PCA (patient-controlled analgesia) with very short acting opiates intravenously is observed. However, Pethidine® is the most commonly used opioid worldwide because it is cheap and easy to administer. Concerns have been raised about its effectiveness and potential maternal, fetal and neonatal side effects.2 After parenteral therapy in the mother, the opiates can be detected in cord blood with a plasma level of 50% of that of the mother. After birth, the child is often sleepy and slightly respiratory depressed for a few hours.3 4

In 1987, the issue of development of substance use disorders (SUDs) and behavioural problems in the offspring after perinatal analgesic medication was addressed.5 The authors reported ORs of 4.7 compared with individuals who did not receive perinatal analgesic drugs. These results were derived from case–control studies in patients with SUD.6–8

The SUD was attributed to the ‘imprinting hypothesis’ and was first published in the BMJ in 1990 by Jacobson et al.7 The brain, when exposed to a noxe during a window in time before or during birth, could be
affected permanently by changing neurotransmitter receptors, synaptogenesis, myelination, proliferation, apoptosis, migration of neuronal cells or by stunting of dendrite growth.9–12 An epidemiological and clinical study showed that cannabis exposure before birth is associated with impulsive and psychiatric disorders in later life.13 Conflicting results have been published about the association of autism spectrum disorders, developmental delay and learning disorders in offspring after peripartum exposure to analgesics.14–17

No long-term follow-up study in children born after opioid use of the mother during pregnancy or after opioid labour analgesia has been published. A recent Cochrane Review has been published looking at the effectiveness and side effects of intrapartum parenteral opioids.18 Short-term follow-up studies did not show sequelae in children in their development up to 5 years.19–22

We investigated the association between Pethidine® use and the risk on smoking, drinking alcohol or drug abuse in offspring 20 years after birth.

METHODS
Sample and study design
Power calculation
Considering the prevalence of drug abuse, smoking and drinking alcohol, we needed 160 participants in each group. In total, 85 individuals in each group were sufficient to detect an OR of 4.7 or more between the groups with 80% power and a type I error of 0.05,2 assuming a prevalence of major drug abuse in the control group of 5%.1 Because of the much more frequent use of tobacco and alcohol, this sample size was sufficient to detect ORs around two.

Data about lifetime prevalence and recent substance use are available for Europe23 and for the Netherlands24 (table 1).

Identification of the cohort variables
After ethical approval by the Medical Ethical Committee of the Leiden University Medical Center, the birth files from the Academic Hospital Leiden from 1986 to 1987 were used to compose two groups of participants: one cohort with and the other without labour analgesia by Pethidine®. Included were only healthy babies without congenital anomalies, born at term after an uncomplicated delivery and who had not been admitted in the paediatric ward. Information was available on maternal characteristics and obstetric history including medication as well as the postpartum condition of the newborn.

Data collection
After finding the recent addresses, we were able to send validated questionnaires about lifetime and recent (last month) use of cigarettes, alcohol and drugs. The first is the National Drugs Questionnaire as a part of the Permanent National Life Style Inquiry that is used from 1997 (with computer-assisted personal interviewing or in case of drug questions with computer-assisted self-interviewing method) that meet with the European Statistics Code of Practice. The second questionnaire is a validated questionnaire for young adults about life events, schooling and behaviour.25

Analysis
The primary analysis was a comparison of the prevalence of substance abuse at adult age between the Pethidine®-exposed and not-exposed groups. Subsequently, the results were compared with the national drug monitor study that was done in the same period. A multivariate logistic regression model was used to calculate ORs and 95% CIs for the outcome measures with age, sex, religion and parental education as potential confounders. The analyses were performed with SPSS V.11.5 for Windows (SPSS Inc).

Non-response
Non-responders received a short questionnaire about yes or no lifetime or recent use of alcohol, smoking and drugs. The individuals who responded to the short questionnaire and those who only partially filled in the questionnaire were analysed separately.

RESULTS
From a total of 715 deliveries, 91% of the addresses were found. Of these 651 individuals, 347 (53%) returned the questionnaires. One hundred and thirty-three participants with and 164 without Pethidine® analgesia could be fully evaluated (n=297, 46%). After a second call, 26 individuals with and 24 without Pethidine® analgesia completed the questionnaire and 92 (53 with and 39 without Pethidine®) completed the short questionnaire.

All together, 439 children (67% of 651 children) were analysed. Both the index and the control group showed the same distribution of age and sex. There were no differences in the distribution of parental education or religion (table 2). These were also similar to national data. The peripartum data of both groups showed no differences in birth weight, sex and Apgar scores. All newborns were healthy and none was admitted in the paediatric ward.

No differences were found in lifetime or recent use of drugs, alcohol or tobacco use between both groups. The

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Lifetime prevalence and recent tobacco, alcohol and drug use in the Netherlands24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lifetime prevalence (%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>72</td>
</tr>
<tr>
<td>Alcohol</td>
<td>90</td>
</tr>
<tr>
<td>Cannabis</td>
<td>37</td>
</tr>
<tr>
<td>XTC</td>
<td>6.2</td>
</tr>
<tr>
<td>Amfetamine</td>
<td>5</td>
</tr>
<tr>
<td>Cocaine</td>
<td>4.3</td>
</tr>
</tbody>
</table>
OR for ever drug abuse was 0.79 (95% CI 0.48 to 1.29) and for recent drug abuse 1.08 (95% CI 0.49 to 2.37). We also gathered data about alcohol use, cannabis and smoking during and after secondary school. These data did not show differences between the groups either, the adjusted ORs are presented in table 3. In total, 92 children responded to the short questionnaire and 50 children partially filled out the standard questionnaire. No difference was found in lifetime prevalence of smoking, alcohol and drug abuse between the Pethidine and the non-Pethidine group independent of the dose that ranged from 75 to 150 mg. The ORs were all close to unity, varying between 0.58 and 1.42.

DISCUSSION

This 20-year follow-up study showed that labour analgesia by Pethidine did not significantly increase the risk of SUD in offspring. We found no association for hard drugs, tranquilisers, hallucinogens, anabolics or soft drugs (including tobacco and alcohol use). This is in line with the results of the study from the Mayo clinics on the risk of learning disability after exposure to perinatal analgesia.14

The strength of this study is that it is a large, long-term follow-up study of a healthy cohort of neonates. We evaluated putative confounders, such as socioeconomic status, sex, and parental education, but did not find differences between the index and the control group. Uncontrolled confounding is always possible, but in this instance, one would expect these to lead to spurious positive associations and not to the absence of an association. Further investigation of potential confounders could be valuable. Given the result of the previous studies reporting a fivefold increased risk, our sample size with a minimal detectable RR of 2 was conservative. However, this implies that we could not detect small risk increases. Nevertheless, the most likely interpretation of our findings, which exclude a risk increase of more than 29% of lifetime drug abuse in children exposed to Pethidine, is the absence of any association.

The main limitation of the study is the low response and the possibility of selected response. It is inconceivable that drug users responded less than others. It is of some concern that response was lower in the group exposed during labour (54%) than in those who were not (42%). Still, if selective response was only associated to drug use in adult life, one would expect an attenuated effect but not the absence of any effect. Bias would have resulted from a differential response related to opioid use during delivery, irrespective of drug use later in life. This seems implausible, as most young adults will not be aware of the analgetic medication of their mothers during birth. Reassuring for the absence of major bias is the fact that the non-respondents to the first questionnaire, who responded to the second short questionnaire

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Distribution of parental education or religion stratified by Pethidine® and no Pethidine® groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total group(n=297)</td>
</tr>
<tr>
<td>Religion</td>
<td></td>
</tr>
<tr>
<td>Christian</td>
<td>41.4</td>
</tr>
<tr>
<td>Other</td>
<td>4.4</td>
</tr>
<tr>
<td>No</td>
<td>54.2</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>38.4</td>
</tr>
<tr>
<td>Intermediate</td>
<td>27.9</td>
</tr>
<tr>
<td>High</td>
<td>33.7</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39.4</td>
</tr>
<tr>
<td>Female</td>
<td>60.6</td>
</tr>
<tr>
<td>Low, elementary school and vocational education; intermediate, high school; high, university.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Lifetime or recent use of alcohol, tobacco and drugs stratified by Pethidine® and no Pethidine® groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total group(n=297)</td>
</tr>
<tr>
<td>Smoking cigarettes ever</td>
<td>70.4</td>
</tr>
<tr>
<td>Smoking cigarettes recent</td>
<td>41.4</td>
</tr>
<tr>
<td>Alcohol ever</td>
<td>98.7</td>
</tr>
<tr>
<td>Alcohol recent</td>
<td>86.5</td>
</tr>
<tr>
<td>Smoking cannabis ever</td>
<td>46.5</td>
</tr>
<tr>
<td>Smoking cannabis recent</td>
<td>8.8</td>
</tr>
<tr>
<td>XTC ever</td>
<td>10.1</td>
</tr>
<tr>
<td>XTC recent</td>
<td>1.0</td>
</tr>
<tr>
<td>Amphetamine ever</td>
<td>5.4</td>
</tr>
<tr>
<td>Amphetamine recent</td>
<td>1.0</td>
</tr>
<tr>
<td>Cocaine ever</td>
<td>6.4</td>
</tr>
<tr>
<td>Cocaine recent</td>
<td>2.7</td>
</tr>
<tr>
<td>Drug abuse† ever</td>
<td>46.8</td>
</tr>
<tr>
<td>Drug abuse† recent</td>
<td>10.1</td>
</tr>
</tbody>
</table>

*Adjusted for age, religion and parental education. †This includes cannabis, XTC, Amphetamine and cocaine.
showed the same negative association for SUD, drinking and smoking. The non-responders showed an unequal distribution in sex compared with the responders: 41% vs 59% male/female ratio.

In this large follow-up study, we cannot confirm the results of previous studies that parenteral Pethidine® for labour pain relief is associated with SUD in later life. Because of the above-mentioned limitations, further research is needed to assess possible associations between other forms of intrapartum analgesia and SUD.

Author affiliations
1Department of Paediatrics, Maasstadziekenhuis, Rotterdam, the Netherlands
2Bouman Mental Health Care, Rotterdam, the Netherlands
3Department of Prevention and Care Netherlands Institute of Applied Sciences TNO, Leiden, the Netherlands
4Department of Obstetrics, Leiden University Medical Center, Leiden, the Netherlands
5Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands
6Department of statistics, Netherlands Institute of Applied Sciences TNO, Leiden, the Netherlands
7Netherlands Institute for Neuroscience, an Institute of the KNAW, Amsterdam, the Netherlands
8Central Office for Motor Vehicle Driving Testing (CBR), Amsterdam, the Netherlands
9Bouman Mental Health Care, Rotterdam, the Netherlands

Contributors All authors contributed to the following criteria: (1) substantial contribution to conception and design, acquisition of data or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content and (3) final approval of the version to be published.

Funding This research received no specific grant from any funding agency in public, commercial or not-for-profit sectors.

Competing interests None.

Patient consent Obtained.

Ethics approval Ethics approval was provided by Medical Ethical Committee of the Leiden University Medical Center, the Netherlands.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All data are uploaded to the Dryad data repository and available for any scientist.

REFERENCES
Parenteral Pethidine for labour pain relief and substance use disorder: 20-year follow-up cohort study in offspring

Robert Rodrigues Pereira, Humphrey Kanhai, Frits Rosendaal, Paula van Dommelen, Dick Swaab, Erik Rodrigues Pereira and Ben van de Wetering

BMJ Open 2012 2: 
doi: 10.1136/bmjopen-2011-000719

Updated information and services can be found at:
http://bmjopen.bmj.com/content/2/3/e000719

These include:

References
This article cites 20 articles, 0 of which you can access for free at:
http://bmjopen.bmj.com/content/2/3/e000719#BIBL

Open Access
This is an open-access article distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. See: http://creativecommons.org/licenses/by-nc/2.0/ and http://creativecommons.org/licenses/by-nc/2.0/legalcode.

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Addiction (160)
Anaesthesia (91)
Epidemiology (2038)
Pharmacology and therapeutics (430)
Public health (2135)
Smoking and tobacco (243)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/