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Questioning the Causal Link between Maternal Smoking during Pregnancy and Offspring Use of Psychotropic Medication: A Sibling Design Analysis

Lovisa Söderström¹, Raquel Perez-Vicente¹, Sol Juárez¹², Juan Merlo¹*

¹ Unit for Social Epidemiology, Department of Clinical Sciences, Faculty of Medicine, Lund University, Malmö, Sweden, ² Centre for Economic Demography, Lund University, Malmö, Sweden

Abstract

A recent population-based, longitudinal study from Finland observed a dose-response association between smoking during pregnancy (SDP) and use of psychotropic medications in exposed children and young adults. However, this association may be confounded by unmeasured familial characteristics related to both SDP and offspring mental health. Consequently, we aim to investigate the effect of SDP by means of a sibling design that to some extent allows controlling for unknown environmental and genetic confounders. Using the Swedish Medical Birth Register (1987–1993), which was linked to the Swedish Prescribed Drugs Register (July 2005–December 2008), we investigated 579,543 children and among them 39,007 were discordant for use of psychotropic medication and 4,021 siblings discordant for both use of psychotropic medication and for smoking exposure. Replicating the Finnish study using traditional logistic regression methods we found an association between exposure to ≥10 cigarettes per day during pregnancy and psychotropic drug use (odds ratio = 1.61, 95% confidence interval 1.56, 1.66). Similar in size to the association reported from Finland (odds ratio = 1.63; 95% confidence interval 1.53, 1.74). However, in the adjusted sibling analysis using conditional logistic regression, the association was considerably reduced (odds ratio 1.22; 95% confidence interval 1.08, 1.38). Preventing smoking is of major public health importance. However, SDP per se appears to have less influence on offspring psychotropic drug use than previously suggested.

Introduction

Several studies have reported an association between maternal smoking during pregnancy (SDP) and offspring psychological disorders. These include mainly externalizing behavioral disorders, such as attention deficit hyperactivity disorder (ADHD), conduct disorder, and oppositional defiant disorder, but also internalizing psychopathology (i.e., depression and anxiety disorders) [1,2,3,4]. Ekblad et al have recently observed a dose-dependent association between maternal SDP and offspring use of psychotropic medication during childhood and up to young adulthood [5]. Their hypothesis was that prenatal smoking exposure interferes with the development of the fetal brain and, thus, increases psychiatric morbidity, leading to increased risk for use of psychotropic medications. Compared to children unexposed to SDP, the authors found odds ratios (ORs) of 1.36 and 1.63, respectively, for exposure to less than, and more than, 10 cigarettes per day. Their analysis was adjusted for sex, maternal age, obstetric characteristics, and for smoking exposure. Replicating the Finnish study using traditional logistic regression methods we found an association between exposure to ≥10 cigarettes per day during pregnancy and psychotropic drug use (odds ratio = 1.61, 95% confidence interval 1.56, 1.66). Similar in size to the association reported from Finland (odds ratio = 1.63; 95% confidence interval 1.53, 1.74). However, in the adjusted sibling analysis using conditional logistic regression, the association was considerably reduced (odds ratio 1.22; 95% confidence interval 1.08, 1.38). Preventing smoking is of major public health importance. However, SDP per se appears to have less influence on offspring psychotropic drug use than previously suggested.

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between maternal and paternal SDP because paternal SDP does not cause direct intrauterine exposure to tobacco. Using this epidemiological design, a small study by Nomura, Marks, and Halperin [18] found that only maternal SDP was associated with ADHD symptoms. However, Langley, Heron, Smith, and Thapar [19] observed an association between both maternal and paternal smoking and ADHD symptoms, suggesting that the association between maternal SDP and psychiatric outcomes may be due to genetic or household-level confounding rather than to the causal intrauterine effect of SDP.

If the association between maternal SDP and psychiatric morbidity in the offspring was causal, this would further support the evidence that maternal smoking in this critical period of life puts the fetus at risk. If not, prevention should also be focused on improving those socioeconomic and psychosocial circumstances of the mother that are common causes of both SDP and offspring mental ill health.

Therefore, applying the sibling design, we aimed to revisit the association between maternal SDP and increased psychotropic drug use in children and young adults recently reported by Ekblad et al [5]. The sibling design is suited to study causal associations since it approximates a counterfactual situation of exposure [20]. This design assesses the impact of maternal SDP on the offspring use of psychotropic medication in individuals who are genetically related and share a similar social environment [21,22]. Sibling designs are, therefore, able of adjusting for unmeasured and even unknown factors that are a common cause of both maternal SDP and offspring use of psychotropic medication [23].

For doing these sibling analyses we applied conditional logistic regression (CLR). CLR is suitable for matched case-control studies. In our case, we can understand the sibling analysis as a matched case-control study where one of the siblings is a “case” (i.e., use psychotropic drugs) and the other sibling the “control” (i.e., non-use of psychotropic drugs), and the matching variable is the mother. In the CLR analyses the estimations are obtained in siblings with discordant outcome (i.e., cases and controls) and exposure (smoking vs non-smoking). The association between SDP and psychotropic drugs is, by design, adjusted for the matching variable (mother). Therefore, the CLR identifies the correlation of the information between the case and control siblings.

However, the similarity between siblings and, thereby, the capacity of the sibling design for confounding adjustment should not be exaggerated [22,24]. From this perspective it is necessary to control for variables that change between pregnancies and that may be a common cause of both maternal SDP and offspring use of psychotropic medication.


Materials and Methods

Study Population and Ethics Statement

The Swedish Medical Birth Register collects standardized information on the antenatal care, delivery, and medical examination of newborn babies. It includes about 98.6% of all pregnancies in Sweden that culminate in delivery [25,26]. The National Board of Health and Welfare, in coordination with Statistics Sweden, links the Swedish Medical Birth Register to a number of other national databases: the Swedish Prescribed Drugs Register, the National Mortality Register, the Emigration Register, the National Inpatient Register, and the Income and Asset Register. This record linkage was performed by the Swedish authorities using a unique personal identification number given to each person residing in Sweden. However, in the data we analyzed, the identification numbers were replaced with arbitrary numbers to safeguard the anonymity of the subjects.

The construction of the record linkage database used in our study was approved by The Regional Ethical Review Board in Southern Sweden, The National Board of Health and Welfare and Statistics Sweden. Lund University signed a contract of confidentiality with the Swedish Authorities. Active informed consent was waived as a requirement for the construction of the database.

We identified all 811,599 children born between January 1st, 1987, and December 31st, 1993, recorded in the Swedish Medical Birth Register. We excluded every non-singleton child (n = 19,162), Measurement of psychotropic drug use using administrative registries reflects both access to healthcare and the presence of psychological disorder, which may originate information bias when studying the effect of smoking. Therefore, we also excluded every child with an immigrant parent (n = 157,856) because children of immigrants have been reported to use less psychotropic medication in relation to their needs (see elsewhere for a more detailed discussion [22]).

We furthermore excluded children whose mothers’ identification number was missing (n = 16), children who had died (n = 4,514) or emigrated (n = 3,958) before December 31st, 2008, and children with missing information on maternal SDP (n = 36,827). To further increase the homogeneity of our study, we also excluded children with major congenital abnormalities (n = 9,723). The final study population for performing traditional analyses consisted of 579,543 subjects. The sibling analyses were done on a sample of 39,007 siblings with discordant outcome (Figure 1). Out of these, 4,021 were siblings with contrast of exposure and outcome.

The individuals were between 11 and 21 years of age when we gathered information about their use of psychotropic medication.

Assessment of Outcome Variable

The Swedish Prescribed Drug Register contains all dispensed medication prescribed in outpatient settings in Sweden since July 2005. It does not contain over the counter medication or medication given in hospitals and nursing homes [27]. From this registry, we identified six different categories of psychotropic medication, according to the Anatomical Therapeutic Chemical (ATC) classification system: antipsychotics (N05A), anxiolytics (N05B), hypnotics and sedatives (N05C), antidepressants (N06A), psychostimulants (N06B), and medication used in addictive disorders (N07B). We defined the outcome as at least one dispensed prescription (“yes”/“no”) of one of these medications during the period from July 1st, 2005, to December 31st, 2008.

Because we use psychotropic medication as a proxy of psychiatric disorders and the therapeutic profiles of the different medication groups overlap each other (i.e., different psychiatric disorders can be treated with the same drug group), we study psychotropic medication as a group.

Assessment of Maternal Smoking during Pregnancy

From the Swedish Medical Birth Register, we obtained information on self-reported SDP. This information was retrieved at the first antenatal care visit (i.e., between gestational weeks 8 and 12) [28]. Smoking during pregnancy was categorized as no smoking, 1–9 cigarettes per day, and ≥10 cigarettes per day.

Assessment of Other Variables

From the Swedish Medical Birth Register, we collected information on parental relationship status, parity, birth order,
Apgar score, the mother’s age at delivery, gestational age (GA) in weeks, birth weight, and birth weight adjusted for GA. Information on parents’ relationship status is reported by the mother at the first antenatal care visit. Apgar score is rated on a scale of 1–10 at 1, 5, and 10 minutes after birth. A score of 10 indicates a delivery without fetal distress. In the analyses, we used the 5-minute Apgar score. The variable “birth weight adjusted for GA” is categorized in the Swedish Medical Birth Register as small for gestational age (SGA), appropriate for gestational age (AGA), and large for gestational age (LGA). Small for gestational age and LGA are defined as a birth weight below or above 2 standard deviations (SDs) from the average birth weight for those born at that GA in Sweden.

From the Income and Asset Register, we obtained information on whether the parents were receiving social welfare the year before the birth of the child. We also obtained information on the income of the parents the year before and after the birth of the child. We created a combined variable categorized into four groups using income tertiles and adding a fourth category for parents receiving social welfare. Using the National Inpatient Register, we collected data on maternal history of psychiatric diagnosis (i.e., sex, GA, birth weight, 5-minute Apgar score, maternal age, parity, and maternal psychiatric diagnosis) in a traditional multiple logistic regression analysis. The outcome of our analysis was very similar to the outcome used by Ekblad et al [5].

Since we did not fully agree with the variables that Ekblad et al [5] used in their adjusted analysis, in model c, we performed another traditional multiple logistic regression analysis, excluding variables such as birth weight and 5-minute Apgar, which could be affected by smoking and could therefore, be on the causal path between SDP and psychopathology in the offspring. If these variables were mediators, adjusting for them could underestimate the effect of smoking. In this model, we included demographic (the birth year of the children, maternal age, parity, birth order, and maternal psychiatric diagnosis) and socioeconomic variables (e.g., parental relationship status and household income) that could be considered as a common cause of both maternal SDP and later use of psychotropic medication by the children/adolescents. These models (a, b, c) were intentionally performed by applying the traditional logistic regression analysis, which do not take into consideration the dependence between siblings within mothers.

Applying a sibling design (model d), we next analyzed siblings with discrepant use of psychotropic medication. We compared siblings using a conditional logistic regression analysis with the mother as the grouping variable. In the final model e, we expanded model d and included birth year of the children, birth order, maternal age, relationship status of the parents, and household income since these variables may change between pregnancies and can be related to both maternal SDP and later use of psychotropic medication by the children/adolescents. The conditional logistic regression is a suitable method to perform sibling analysis [24], because it takes into account the correlation of the information between siblings within mothers, and therefore provides proper adjustment and estimations of the standard errors.

For all analyses, we used Stata version 12 (StatCorp LP. 2011. College Station, TX). We repeated the analyses in “R” version 2.15.1.

Results

Characteristics of the Population

Table 1 indicates the characteristics of the offspring population by maternal SDP and use of psychotropic medication in 2005–2008 for both the full and sibling samples. Almost every fourth person in our study population (n = 142,379) had been exposed to maternal SDP, and these children were using psychotropic medication more frequently than those not exposed to maternal SDP. However, while the exposure to maternal SDP was similar for girls and boys, the consumption of psychotropic medication was more frequent in girls.

The use of psychotropic medication increased with age. Smoking during pregnancy declined between 1987 and 1993, meaning that older children in this study population had also been more often exposed to SDP more often. Children born to women <20 years of age had the highest psychotropic drug use, and these young mothers were also the ones most often smoking during pregnancy. It seems that women who had delivered more than three children were more likely to smoke during pregnancy, and their children had higher use of psychotropic medication later on.

Statistical Methods

We analyzed the association between maternal SDP and use of psychotropic medication in a series of steps. Firstly (model a), we performed a traditional simple logistic regression analysis. Thereafter (model b), we replicated the study by Ekblad et al [3], by adjusting for similar variables as they did (i.e., sex, GA, birth weight, 5-minute Apgar score, maternal age, parity and maternal psychiatric diagnosis) in a traditional multiple logistic regression analysis. The outcome of our analysis was very similar to the outcome used by Ekblad et al [5].

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Table 1. Characteristics of the children and adolescents born in Sweden between 1987 and 1993 and living in Sweden between July 2005 and 2008 by maternal smoking during pregnancy (SDP) and offspring use of psychotropic medication.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Full Sample</th>
<th></th>
<th></th>
<th>Siblings Sample</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of individuals</td>
<td>Maternal SDP (%)</td>
<td>Psychotropic drug use (%)</td>
<td>Number of individuals</td>
<td>Maternal SDP (%)</td>
<td>Psychotropic drug use (%)</td>
</tr>
<tr>
<td>Study Population</td>
<td>579,543 (100.0)</td>
<td>24.6</td>
<td>7.2</td>
<td>39,007 (100.0)</td>
<td>28.6</td>
<td>47.2</td>
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<tr>
<td>Maternal smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No smoking</td>
<td>437,164 (75.4)</td>
<td>6.4</td>
<td>9.1</td>
<td>27,867 (71.4)</td>
<td>46.6</td>
<td></td>
</tr>
<tr>
<td>1–9 cigarettes/day</td>
<td>88,970 (15.5)</td>
<td>9.1</td>
<td>8.5</td>
<td>6,499 (16.7)</td>
<td>48.8</td>
<td></td>
</tr>
<tr>
<td>&gt;9 cigarettes/day</td>
<td>53,409 (9.2)</td>
<td>10.8</td>
<td>10.8</td>
<td>4,641 (11.9)</td>
<td>48.2</td>
<td></td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>297,239 (51.3)</td>
<td>24.6</td>
<td>8.6</td>
<td>20,437 (52.4)</td>
<td>28.9</td>
<td>52.8</td>
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<td>Male</td>
<td>282,304 (48.7)</td>
<td>24.5</td>
<td>5.9</td>
<td>18,570 (47.6)</td>
<td>28.3</td>
<td>41.0</td>
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<tr>
<td>Birth year (age in yrs)</td>
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<td></td>
<td></td>
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<td>1987 (17–21)</td>
<td>75,023 (13.0)</td>
<td>28.0</td>
<td>10.6</td>
<td>5,658 (14.5)</td>
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<td>1988 (16–20)</td>
<td>79,779 (13.8)</td>
<td>26.6</td>
<td>9.3</td>
<td>5,368 (13.8)</td>
<td>31.3</td>
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<td>1989 (15–19)</td>
<td>81,951 (14.1)</td>
<td>25.7</td>
<td>8.5</td>
<td>6,315 (16.2)</td>
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<td>1990 (14–18)</td>
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<td>1991 (13–17)</td>
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<td>24.0</td>
<td>6.0</td>
<td>5,994 (15.4)</td>
<td>27.5</td>
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<td>1992 (12–16)</td>
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<td>23.0</td>
<td>5.1</td>
<td>4,858 (12.5)</td>
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<td>1993 (11–15)</td>
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<td>20.4</td>
<td>4.2</td>
<td>4,295 (11.0)</td>
<td>26.0</td>
<td>31.9</td>
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<td>Maternal age at pregnancy (years)</td>
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<td>&lt;20</td>
<td>14,195 (2.5)</td>
<td>44.8</td>
<td>12.2</td>
<td>1,132 (2.9)</td>
<td>47.4</td>
<td>54.4</td>
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<td>20–29</td>
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<td>6,519 (67.6)</td>
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<td>30–39</td>
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<td>6.7</td>
<td>11,210 (28.7)</td>
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<td>42.9</td>
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<td>8.4</td>
<td>307 (0.8)</td>
<td>19.9</td>
<td>40.4</td>
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<td>6.9</td>
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<td>ND</td>
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<td>43.9</td>
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<td>&gt;4</td>
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<td>30.3</td>
<td>8.6</td>
<td>5,892 (15.1)</td>
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<td>36.7</td>
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<td>37,293 (95.6)</td>
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<td>1,714 (4.4)</td>
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<tr>
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<td>7.1</td>
<td>35,363 (90.7)</td>
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<td>47.2</td>
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<td>50.0</td>
<td>11.8</td>
<td>1,562 (4.0)</td>
<td>27.5</td>
<td>51.5</td>
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<td>2,082 (5.3)</td>
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<tr>
<td>Highest</td>
<td>193,134 (33.3)</td>
<td>16.3</td>
<td>5.0</td>
<td>10,891 (27.9)</td>
<td>18.7</td>
<td>39.0</td>
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<tr>
<td>Middle</td>
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<td>22.2</td>
<td>6.9</td>
<td>12,787 (32.8)</td>
<td>24.4</td>
<td>48.4</td>
</tr>
<tr>
<td>Lowest</td>
<td>142,679 (24.6)</td>
<td>28.4</td>
<td>8.4</td>
<td>10,120 (25.9)</td>
<td>29.6</td>
<td>53.5</td>
</tr>
<tr>
<td>Social allowance</td>
<td>46,863 (8.1)</td>
<td>57.3</td>
<td>13.9</td>
<td>5,206 (13.4)</td>
<td>57.3</td>
<td>48.9</td>
</tr>
<tr>
<td>Missing</td>
<td>15 (0.0)</td>
<td>26.7</td>
<td>13.3</td>
<td>3 (0.0)</td>
<td>33.3</td>
<td>33.3</td>
</tr>
</tbody>
</table>

doi:10.1371/journal.pone.0063420.t001
Children of women with a psychiatric diagnosis in inpatient registers were at least twice as likely to be using psychotropic medication as children born to women without such diagnoses. Women with a psychiatric diagnosis also smoked during pregnancy almost twice as often as other women. Psychotropic drug use was higher among children whose parents were not living together and in children with low family income. The same factors were also associated with SDP.

Table 2 shows the relation between obstetric characteristics, maternal SDP, and offspring use of psychotropic medication. Birth weight, GA, and birth weight adjusted for GA were correlated in a similar way to both SDP and psychotropic drug use in the offspring. These factors, however, could be on the causal path between SDP and offspring use of psychotropic medication. Apgar score was weakly related to SDP, but individuals with a low 5-minute Apgar had higher use of psychotropic medication.

Compared to the full sample, the sibling sample was rather similar across all characteristics observed in table 1 and 2. However, because the sibling sample was selected for contrast of outcome (cases and control), the proportion of psychotropic use is, as expected, substantially higher in comparison to the full sample. Moreover, because psychotropic use is highly associated to SDP, the prevalence of SDP in the sibling sample is also higher than in the full sample.

Association between Maternal Smoking during Pregnancy and Offspring use of Psychotropic Medication

Figure 2 shows the results of the logistic regression models. In the crude analysis (model a), the OR for using psychotropic medication was 1.48 for exposure to 1–9 cigarettes and 1.78 for exposure to 10 cigarettes, compared to no smoking.

When we adjusted for the same variables as used by Ekblad et al in their study [5] (i.e., sex, GA, birth weight, 5-minute Apgar score, maternal age, and maternal psychiatric diagnosis) in model b, the ORs were 1.39 and 1.61 for 1–9, and 10 cigarettes, respectively.

In the third analysis (model c), we adjusted for a different set of variables than the ones used by Ekblad et al [5]. We excluded variables that we did not consider as confounders (i.e., sex, GA, birth weight, 5-minute Apgar score), and included birth year and socioeconomic variables. The ORs in this model were 1.25 and 1.38 for 1–9 cigarettes and 10 cigarettes, respectively.

In the final part of our analysis (models d and e in Figure 2) we matched cases with control siblings. After adjusting for potential temporal confounders (i.e., birth year, birth order, household income, and parental relationship status at the time of birth), the OR dropped to 1.16 and 1.22, respectively, for 1–9 cigarettes and 10 cigarettes.

Table 2. Obstetrics characteristics of the total study population of children and adolescents born in Sweden between 1987 and 1993 and living in Sweden between July 2005 and 2008 by maternal smoking during pregnancy (SDP) and offspring use of psychotropic medication.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Full Sample</th>
<th>Maternal SDP</th>
<th>Psychotropic drug use (%)</th>
<th>Siblings Sample</th>
<th>Maternal SDP</th>
<th>Psychotropic drug use (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA, weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;28</td>
<td>407 (0.1)</td>
<td>33.7</td>
<td>13.3</td>
<td>39 (0.1)</td>
<td>46.2</td>
<td>55.7</td>
</tr>
<tr>
<td>28–31</td>
<td>2,028 (0.4)</td>
<td>33.5</td>
<td>10.6</td>
<td>127 (0.3)</td>
<td>36.2</td>
<td>55.9</td>
</tr>
<tr>
<td>32–36</td>
<td>24,385 (4.2)</td>
<td>29.6</td>
<td>8.5</td>
<td>1,787 (4.6)</td>
<td>35.8</td>
<td>48.9</td>
</tr>
<tr>
<td>34–41</td>
<td>511,055 (88.2)</td>
<td>24.4</td>
<td>7.1</td>
<td>34,403 (88.2)</td>
<td>28.4</td>
<td>46.9</td>
</tr>
<tr>
<td>&gt;41</td>
<td>41,347 (7.1)</td>
<td>23.1</td>
<td>7.2</td>
<td>2,622 (6.7)</td>
<td>25.3</td>
<td>49.0</td>
</tr>
<tr>
<td>Missing</td>
<td>321 (0.1)</td>
<td>39.6</td>
<td>10.0</td>
<td>29 (0.1)</td>
<td>48.3</td>
<td>62.1</td>
</tr>
<tr>
<td>Birth weight, gr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2000</td>
<td>4,786 (0.8)</td>
<td>36.7</td>
<td>10.3</td>
<td>319 (0.8)</td>
<td>42.3</td>
<td>54.9</td>
</tr>
<tr>
<td>2000–2999</td>
<td>68,556 (11.8)</td>
<td>37.8</td>
<td>8.5</td>
<td>4,762 (12.2)</td>
<td>45.2</td>
<td>50.7</td>
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<tr>
<td>3000–3999</td>
<td>392,377 (67.7)</td>
<td>24.7</td>
<td>7.1</td>
<td>26,265 (67.3)</td>
<td>28.6</td>
<td>47.4</td>
</tr>
<tr>
<td>&gt;3999</td>
<td>112,958 (19.5)</td>
<td>15.5</td>
<td>6.5</td>
<td>7,600 (19.5)</td>
<td>17.5</td>
<td>43.8</td>
</tr>
<tr>
<td>Missing</td>
<td>866 (0.2)</td>
<td>27.9</td>
<td>11.8</td>
<td>61 (0.2)</td>
<td>36.1</td>
<td>60.7</td>
</tr>
<tr>
<td>Birth weight adjusted for GA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGA</td>
<td>14,012 (2.4)</td>
<td>43.9</td>
<td>9.6</td>
<td>909 (2.3)</td>
<td>49.2</td>
<td>54.2</td>
</tr>
<tr>
<td>AGA</td>
<td>545,117 (94.1)</td>
<td>24.5</td>
<td>7.1</td>
<td>36,640 (93.9)</td>
<td>28.6</td>
<td>47.1</td>
</tr>
<tr>
<td>LGA</td>
<td>19,597 (3.4)</td>
<td>13.6</td>
<td>7.4</td>
<td>1,398 (3.6)</td>
<td>14.0</td>
<td>44.6</td>
</tr>
<tr>
<td>Missing</td>
<td>817 (0.1)</td>
<td>29.6</td>
<td>9.9</td>
<td>60 (0.2)</td>
<td>40.0</td>
<td>61.7</td>
</tr>
<tr>
<td>5- Minutes Apgar score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>1,255 (0.2)</td>
<td>24.1</td>
<td>10.4</td>
<td>84 (0.2)</td>
<td>34.5</td>
<td>67.9</td>
</tr>
<tr>
<td>4–6</td>
<td>3,297 (0.6)</td>
<td>27.3</td>
<td>10.1</td>
<td>225 (0.6)</td>
<td>32.9</td>
<td>57.8</td>
</tr>
<tr>
<td>7–10</td>
<td>566,571 (97.8)</td>
<td>24.5</td>
<td>7.2</td>
<td>38092 (97.7)</td>
<td>28.5</td>
<td>47.0</td>
</tr>
<tr>
<td>Missing</td>
<td>8,420 (1.5)</td>
<td>26.4</td>
<td>8.0</td>
<td>606 (1.6)</td>
<td>31.0</td>
<td>49.5</td>
</tr>
</tbody>
</table>

AGA = appropriate for gestational age; GA = gestational age; LGA = large for gestational age; SGA = small for gestational age.
Applying a conventional multiple logistic regression and similar covariates, we were able to replicate almost exactly the findings recently published by Ekblad et al [5]. According to these results, maternal SDP increases the probability, in offspring, of using psychotropic medication from childhood until young adulthood. However, a stricter sibling analysis accounting for unknown genetic and socioeconomic characteristics of the mothers as well as for observed temporal confounding considerably reduced this association. Our results are analogous to other sibling design studies showing that the relationship between SDP and psychiatric or cognitive outcomes is mainly due to unaccounted familial confounding [12,13,14,15,16,17].

We also considered that the probability of smoking in one pregnancy may be conditioned by the experience of the mother in her previous pregnancy, we performed sensitivity analyses to explore whether the order of the exposure between siblings may influences our results. We replicated our sibling analyses in two sub-samples of mothers who had two siblings. The first subsample contained mothers who quit smoking in the second child (n = 1,840) and, the second subsample, mothers who start smoking in the second offspring (n = 1,054). The analyses show the order of the exposure has effect on the association between SDP and psychotropic use in adolescents. The adjusted model for mothers who quit smoking in the subsequent pregnancy shows an OR of 1.70 (0.62; 4.65) and 1.52 (0.54; 4.27) for 1–9 and >10 cigarettes, respectively, while the model for mothers who start smoking indicated smaller effects (ORs 1.07 (0.35; 3.29) and 1.30 (0.40; 4.23) for 1–9 and >10 cigarettes, respectively). These results are very imprecise but they suggest the existence of confounding rather than a causal effect of smoking. In fact, mothers might modify their tobacco habits (e.g., quit smoking) as consequence of health related issues that are a common causes of both changing smoking habits and early determinants of adolescent use of psychotropic drugs. This situation could explain the stronger association found in mother that quit smoking.

The negative effect of smoking on reproductive health outcomes is unquestionable and preventing SDP is of major public health relevance. However, SDP in itself appears to have less impact on offspring psychotropic drug use than suggested by previous conventional analysis. We, therefore, conclude that the results obtained by Ekblad et al [3] were in part due to residual confounding through environmental circumstances in these families or through an inherited risk for psychiatric morbidity. These findings suggest that there are common causes for SDP and use of psychotropic medication. Consequently, further research is
References


