Association of prenatal exposure to benzodiazepines and child internalizing problems: A sibling-controlled cohort study

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters.

Citation
Brandlistuen, Ragnhild E., Eivind Ystrom, Sonia Hernandez-Diaz, Svetlana Skurtveit, Randi Selmer, Marte Handal, and Hedvig Nordeng. 2017. “Association of prenatal exposure to benzodiazepines and child internalizing problems: A sibling-controlled cohort study.” PLoS ONE 12 (7): e0181042. doi:10.1371/journal.pone.0181042. http://dx.doi.org/10.1371/journal.pone.0181042.

Published Version
doi:10.1371/journal.pone.0181042

Citable link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:34375336

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA
Association of prenatal exposure to benzodiazepines and child internalizing problems: A sibling-controlled cohort study

Ragnhild E. Brandlistuen1,2 *, Eivind Ystrom2,3, Sonia Hernandez-Diaz4, Svetlana Skurtveit2, Randi Selmer2, Marte Handal2, Hedvig Nordeng1,2

1 Pharmacoepidemiology and Drug Safety Research Group, School of Pharmacy, PharmaTox Strategic Research Initiative, Faculty of Mathematics and Natural Sciences, University of Oslo, Oslo, Norway, 2 Norwegian Institute of Public Health, Oslo, Norway, 3 Department of Psychology, Faculty of Social Sciences, University of Oslo, Oslo, Norway, 4 Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States of America

* Ragnhild.Eek.Brandlistuen@fhi.no

Abstract

Background
During pregnancy, many women experience sleep problems and anxiety that require treatment. The long-term safety for the child of maternal benzodiazepine (BZD) and z-hypnotic use during pregnancy remains controversial.

Method
We conducted a cohort and a sibling control study using data from the Norwegian Mother and Child Cohort Study. Data on use of BZD and z-hypnotics, internalizing and externalizing outcomes, and covariates were collected from mothers at gestational weeks 17 and 30 and when children were 0.5, 1.5, and 3 years of age. The total sample consisted of 71,996 children (19,297 siblings) at 1.5 years and 55,081 children (13,779 siblings) at 3 years. Short-term use was defined as use in one pregnancy period only. Long-term use was defined as use in two or more pregnancy periods. Linear full cohort random-effect and sibling-matched fixed-effect regression models were used to compare internalizing and externalizing behavior in children prenatally exposed compared to those unexposed in the full cohort of pregnancies accounting for family clusters, as well as within sibling clusters comparing pregnancies with discordant exposures. Propensity score (PS) adjustment included variables on indication for use (sleep problems, symptoms of anxiety and depression) and other potential confounding factors.

Results
Long-term prenatal exposure to BZD or z-hypnotics was associated with increased internalizing behavior in crude cohort analyses and at age 1.5 years after PS adjustment in sibling-matched fixed-effect models [β 0.60, 95% confidence interval 0.17–0.95]. Analyses on specific drug groups showed that prenatal exposure to BZD-anxiolytics was associated with...
increased internalizing problems at both 1.5 years [$\beta$ 0.25, 0.01–0.49] and 3 years [$\beta$ 0.26, 0.002–0.52] while exposure to z-hypnotics was not associated with any adverse outcomes after adjustment.

**Conclusion**

The findings suggest a moderate association between BZD-anxiolytic exposure and child internalizing problems that is not likely due to stable familial confounding factors.

**Introduction**

Up to 20% of women are estimated to experience sleep problems and symptoms of anxiety during pregnancy [1, 2]. Between 1 and 3% of Norwegian women use benzodiazepine (BZD) or z-hypnotic drugs to treat anxiety disorders or insomnia while pregnant [3]. These medications have sedative, hypnotic, anxiolytic, anticonvulsant, and muscle-relaxing effects depending primarily on how long they act on the gamma-aminobutyric acid (GABA$_A$) receptor [4]. BZDs and z-hypnotics cross the placenta and have the potential to bind to receptors in the developing embryonal/fetal central nervous system [5]. It has been proposed that exposure to medications that mimic GABA at GABA$_A$ receptors also trigger apoptotic neurodegeneration in the developing brain [6].

In the 1980s, a number of rat studies consistently showed that prenatal exposure to BZDs resulted in behavioral deficits and altered brain function [7–11]. Withdrawal syndrome and floppy infant syndrome have been reported in babies after maternal use of BZDs towards the end of pregnancy [12–15]. Results of previous studies on mental health outcomes in the offspring following prenatal exposure to BZDs or z-hypnotic drugs have been conflicting [16–18]. A sibling-matched study found no association with behavioral deviation in children at age 8–12 months after prenatal exposure to medazepam [16]. In contrast, a study on 1.5-year-old children showed reduced personal-social behavior abilities in children exposed to BZDs [17]. The only published investigation of behavioral outcomes in children older than 1.5 years following prenatal exposure to BZDs was a retrospective study based on 15 exposed children, which found no effects on behavior at the age of 9–10 years [18]. None of these studies controlled for indication for use in the mother.

Well-designed observational studies and randomized controlled trials (RCTs) have been called for to resolve these conflicting findings [19], but because RCTs involving pregnant women are ethically problematic, observational studies addressing confounding by indication and other potential confounders take precedent [20]. In this study, using data from the Norwegian Mother and Child cohort study (MoBa), we aimed to evaluate whether prenatal exposure to BZDs and z-hypnotics affects internalizing or externalizing behavior problems in children at ages 1.5 and 3 years. Such problems are characterized respectively by negative mood states and behavioral inhibition and by behavioral disinhibition [21]. Genetic or familial environmental determinants might result in an increased risk of both mood disorders and anxiety in the mother and behavioral problems in the infant, and living with a mother with these disorders could affect a child’s behavior. To reduce confounding by family conditions, we performed sibling-matched analyses using fixed-effect (FE) models as a conservative approach to adjust for shared familial confounding. To control for indications that vary over time and could confound the sibling comparisons, we used propensity scores (PS) to adjust for
indication for use (sleep problems, symptoms of anxiety and depression) and other potential confounding factors.

Materials and methods

Data collection

Data were extracted from the ongoing MoBa study conducted by the Norwegian Institute of Public Health. MoBa is a prospective population-based cohort study following over 100,000 pregnancies [22]. Enrollment in the study started in 1999 and was completed in 2008. The participation rate at first assessment was 40.6%. Mothers reported a range of sociodemographic, medical, and psychological information by filling out questionnaires at gestational weeks (gw) 17 and 30 and at 6, 18, and 36 months postpartum (with response rates of 95%, 92%, 87%, 77%, and 62%, respectively). We used the seventh version of the dataset, which is quality-assured and was released in 2013 [http://www.fhi.no/moba-en].

The Medical Birth Registry of Norway (MBRN) includes information on pregnancy, delivery, and neonatal health on all births in Norway [23]. The MoBa and MBRN data were linked via personal identification numbers.

The research project is approved by the Regional Committees for Medical and Health Research Ethics (REK) (2015/1897), and the MoBa study has a license from the Norwegian Data Inspectorate. Written informed consent was obtained from all participants.

Study population

This study was based on data for 71,996 children whose mothers had returned the 1.5-year follow-up questionnaire and 55,081 children whose mothers had returned the 3-year follow-up questionnaire. Within this cohort, a total of 19,297 siblings were included at 1.5 years and 13,779 siblings at 3 years. All live-born singletons were included in the study population; twins and triplets (N = 4305) and infants born with major malformations (N = 2970) (Fig 1) were excluded.

BZD and z-hypnotics exposure

BZDs included drugs classified in Anatomical Therapeutic Chemical (ATC) groups N05BA (diazepam, oxazepam, alprazolam), N05CD (nitrazepam, midazolam, flunitrazepam), N03AE01 (clonazepam). Z-hypnotics included drugs classified in the ATC group N05CF (zopiclone and zolpidem). Drug classification was based on the ATC classification system developed by the WHO Collaborating Centre for Drug Statistics Methodology [24]. Women reported information about illnesses they experienced throughout their pregnancy and medication used for these illnesses in two prenatal (17 gw, 30 gw) and one postnatal questionnaire (6 months postpartum) covering three time periods: 0 to 13 gw and 14 to 29 gw, and from 30 gw to birth. The women were defined as users of BZDs and z-hypnotics if they had reported use of any BZD or z-hypnotic drug (ATC groups N05BA, N05CD, N05CF, and N03AE01) during pregnancy on at least one of the three questionnaires. Short-term use was defined as reported use in one pregnancy period only (0–13, 14–29, 30–birth), and long-term use was defined as reported use in two or more pregnancy periods. Separate analyses were also performed for the most commonly reported drug groups: BZD-anxiolytics and z-hypnotics. The drug groups of BZDs and z-hypnotics used, as well as the number of siblings discordantly exposed, are described in Table 1.
Behavior outcomes

The Child Behavior Checklist (CBCL), a validated and widely used measure of child behavior, was used at 1.5 and 3 years [25]. In MoBa, a shortened version of the CBCL was used; it covers both externalizing (i.e., aggression, attention problems) and internalizing behavior (i.e., anxiousness, emotional reactivity, somatic complaints) and is representative of the full scale [26]. Items were selected by a team of four clinical and developmental psychologists, based on clinical and theoretical standards, as well as empirical representativeness (high factor loadings) for behavior problems. The questionnaire consisted of 13 items at 1.5 years and 21 items at 3 years, covering externalizing behavior and internalizing behavior. Externalizing behavior was measured by eight items at 1.5 years and 12 items at 3 years, and internalizing behavior was measured by five items at 1.5 years and nine items at 3 years. These domains predict later psychopathology in children and adolescents [27]. The questions were answered on a 3-point scale, as follows: 1 = not true; 2 = somewhat or sometimes true; and 3 = very true or often true.
Mean scores were calculated for externalizing and internalizing behaviors, respectively, and standardized z-scores then were computed for both behavioral outcomes.

**Potential confounders**

Confounders were identified by means of a literature review and through use of directed acyclic graphs [28] [29] (http://www.dagitty.net/dags.html) [30]. All potential confounders considered are listed in Tables 2 and 3. Information regarding maternal age and parity was retrieved from the MBRN. Information on maternal years of formal education, marital status, pre-pregnancy BMI, sleep problems, chronic disease, and use of folic acid supplements in early pregnancy was retrieved from the first pregnancy questionnaire. Information on alcohol use, illicit drug consumption during pregnancy, and smoking was retrieved from all three pregnancy questionnaires.

Maternal symptoms of depression and anxiety during the pregnancy were reported via a validated short version of the Hopkins Symptom Checklist, the SCL-5, at 17 and 30 gw [31]. The 5-item version (SCL-5) has a 0.92 correlation with the original 25-item version. Items in the SCL are scored on a Likert scale ranging from 1 (not at all bothered) to 4 (very much bothered), and scores were calculated as the mean value of the five items. The presence of symptoms of anxiety and depression during pregnancy was defined as 85th percentile or above.

Maternal concomitant use of other drugs (opioids, selective serotonin reuptake inhibitors (SSRIs), antipsychotics, triptans, nonsteroidal anti-inflammatory drugs (NSAIDs), and paracetamol) were reported at 17 and 30 gw and 6 months after birth. Because we previously found...
### Table 2. Maternal characteristics by use of BZDs and z-hypnotics during pregnancy in the 1.5 year MoBa sample.

|                              | Use of BZDs and z-hypnotics | 1.5-year sample |
|------------------------------|-----------------------------|------------------|
|                              | No                          | N = 71,419       | Yes   | N = 557 |
| Maternal age in years        |                             |                  |       |         |
| <25                          | 6,948                       | 9.7              | 41    | 7.1     |
| 25–29                        | 23,807                      | 33.3             | 149   | 25.8    |
| 30–34                        | 28,130                      | 39.4             | 237   | 41.1    |
| ≥35                          | 12,534                      | 17.6             | 150   | 26.0    |
| Maternal formal education in years |                         |                  |       |         |
| <12                          | 4,229                       | 6.3              | 55    | 10.2    |
| 12                           | 17,931                      | 26.6             | 126   | 23.3    |
| 13–16                        | 28,576                      | 42.4             | 226   | 41.9    |
| ≥17                          | 16,594                      | 24.7             | 133   | 24.6    |
| Marital status               |                             |                  |       |         |
| Married or cohabitant        | 68,416                      | 98.1             | 518   | 93.0    |
| Single                       | 1,357                       | 1.9              | 36    | 7.0     |
| Maternal BMI                 |                             |                  |       |         |
| <25                          | 47,712                      | 69.2             | 398   | 71.5    |
| 25–29                        | 14,936                      | 21.7             | 111   | 19.9    |
| 30–34                        | 4,618                       | 6.7              | 41    | 7.4     |
| ≥35                          | 1,643                       | 2.4              | 7     | 1.3     |
| Parity                       |                             |                  |       |         |
| 0                            | 32,999                      | 46.2             | 282   | 48.9    |
| 1                            | 24,914                      | 34.9             | 171   | 29.6    |
| ≥2                           | 13,506                      | 18.9             | 124   | 21.5    |
| Maternal smoking             |                             |                  |       |         |
| No                           | 66,159                      | 92.6             | 486   | 84.2    |
| Yes                          | 5,260                       | 7.4              | 91    | 15.8    |
| Maternal alcohol use         |                             |                  |       |         |
| No                           | 32,563                      | 45.8             | 176   | 30.7    |
| Yes, occasionally            | 35,958                      | 50.6             | 340   | 59.2    |
| Yes, often                   | 2,509                       | 3.6              | 58    | 10.1    |
| Maternal symptoms of anxiety/depression 17 gw\(^a\) | |       | | |
| No                           | 67,105                      | 94.0             | 456   | 79.0    |
| Yes                          | 4,314                       | 6.0              | 121   | 21.0    |
| Maternal symptoms of anxiety/depression 30 gw\(^a\) | |       | | |
| No                           | 67,377                      | 94.3             | 449   | 77.8    |
| Yes                          | 4,042                       | 5.7              | 128   | 22.2    |
| Lifetime history of major depression\(^b\) | |       | | |
| No                           | 56,089                      | 78.5             | 280   | 48.5    |
| Yes                          | 15,330                      | 21.5             | 297   | 51.5    |
| Maternal sleep problems      |                             |                  |       |         |
| No                           | 60,361                      | 84.5             | 328   | 56.8    |
| Yes                          | 11,058                      | 15.5             | 249   | 43.2    |
| Maternal use of illicit drugs\(^c\) | |       | | |
| No                           | 71,205                      | 99.7             | 538   | 96.6    |

(Continued)
an association between long term paracetamol exposure and behavior problems in the child we differentiated between short and long term paracetamol use[33].

### Statistical methods

First, we used random-effects linear regression models to examine crude effect estimates on behavior outcomes at 1.5 and 3 years following prenatal exposure to any BZD or z-hypnotics, short term or long term, for the full MoBa cohort. Random-effects models account for family clusters in the sample by producing standard errors that adjust for dependence between siblings. Separate analyses were performed for BZD-anxiolytics and z-hypnotics.

| Table 2. (Continued) |
|---------------------|

#### Use of BZDs and z-hypnotics

|                         | 1.5-year sample |
|------------------------|-----------------|
|                        | No              | Yes             |
|                        | N = 71,419      | N = 557         |
| Maternal opioid use in pregnancy |                  |
| No                     | 70,013          | 499             |
| Yes                    | 1,406           | 78              |
| Maternal SSRI use in pregnancy |                  |
| No                     | 70,780          | 489             |
| Yes                    | 639             | 88              |
| Maternal antipsychotic use in pregnancy |              |
| No                     | 70,780          | 489             |
| Yes                    | 639             | 88              |
| Maternal triptan use in pregnancy |                  |
| No                     | 70,778          | 559             |
| Yes                    | 641             | 18              |
| Maternal NSAID use in pregnancy |                |
| No                     | 66,542          | 485             |
| Yes                    | 4,877           | 92              |
| Maternal use of paracetamol (acetaminophen) |            |
| No use                 | 39,294          | 224             |
| 1 pregnancy period     | 24,757          | 235             |
| 2 or 3 pregnancy periods| 2,244           | 83              |
| Maternal folic acid supplements in early pregnancy |          |
| No                     | 22,830          | 183             |
| Yes                    | 48,589          | 394             |
| Maternal chronic disease<sup>d</sup> |            |
| No                     | 64,412          | 474             |
| Yes                    | 7,007           | 103             |

SSRI, selective serotonin reuptake inhibitors; NSAID, nonsteroidal anti-inflammatory drug

<sup>a</sup> Mean score of >2 on the Hopkins Symptom Checklist (SCL-5)

<sup>b</sup> Measured in pregnancy week 17; defined as ever having three co-occurring symptoms of depression for at least 2 weeks and admitting to sad mood

<sup>c</sup> Illicit drug use included hashish, amphetamine, ecstasy, cocaine, or heroin

<sup>d</sup> Chronic disease included asthma, diabetes treated with insulin, Crohn’s disease, arthritis, lupus, epilepsy, multiple sclerosis, or cancer

<sup>https://doi.org/10.1371/journal.pone.0181042.t002</sup>
Table 3. Maternal characteristics by use of BZDs and z-hypnotics during pregnancy in the 3-year MoBa sample.

| Use of BZDs and z-hypnotics | 3-year sample |
|-----------------------------|---------------|
| No                         | N = 54,641    | Yes | N = 440 |
| N                          | %            | N   | %        |

Maternal age in years

| <25 | 5,058 | 9.2 | 31 | 7.0 |
| 25–29 | 18,170 | 33.3 | 117 | 26.6 |
| 30–34 | 21,720 | 39.8 | 175 | 39.8 |
| ≥35 | 9,693 | 17.7 | 117 | 26.6 |

Maternal formal education in years

| <12 | 2,902 | 5.6 | 37 | 9.0 |
| 12 | 13,112 | 25.4 | 89 | 21.5 |
| 13–16 | 22,467 | 43.5 | 178 | 43.1 |
| ≥17 | 13,164 | 25.5 | 109 | 26.4 |

Marital status

| Married or cohabitant | 52,455 | 98.2 | 396 | 93.2 |
| Single | 976 | 1.8 | 29 | 6.8 |

Maternal BMI

| <25 | 36,649 | 69.4 | 292 | 68.9 |
| 25–29 | 11,439 | 21.7 | 92 | 21.7 |
| 30–34 | 3,498 | 6.6 | 33 | 7.8 |
| ≥35 | 1,249 | 2.4 | 7 | 1.7 |

Parity

| 0 | 25,851 | 47.3 | 229 | 52.0 |
| 1 | 18,889 | 34.6 | 120 | 27.3 |
| ≥2 | 9,901 | 18.1 | 91 | 20.7 |

Maternal smoking

| No | 50,852 | 93.1 | 376 | 85.5 |
| Yes | 3,789 | 6.9 | 64 | 14.5 |

Maternal alcohol use

| No | 25,671 | 47.3 | 147 | 33.5 |
| Yes, occasionally | 26,712 | 49.2 | 251 | 57.2 |
| Yes, often | 1,946 | 3.6 | 41 | 9.3 |

Maternal symptoms of anxiety/depression 17 gw* 

| No | 51,510 | 94.3 | 344 | 78.2 |
| Yes | 3,131 | 5.7 | 96 | 21.8 |

Maternal symptoms of anxiety/depression 30 gw* 

| No | 51,662 | 94.6 | 340 | 77.3 |
| Yes | 2,979 | 5.5 | 100 | 22.7 |

Lifetime history of major depressionb 

| No | 43,096 | 78.9 | 213 | 48.4 |
| Yes | 11,545 | 21.1 | 227 | 51.6 |

Maternal sleep problems

| No | 46,014 | 84.2 | 246 | 55.9 |
| Yes | 8,627 | 15.8 | 194 | 44.1 |

Maternal use of illicit drugsc 

| No | 51,071 | 99.8 | 395 | 96.8 |

(Continued)
Second, we performed PS-adjusted random-effect linear regression analyses by including PS as covariates in the analyses. PS were determined with logistic regression models within the complete cohort at 1.5 years and 3 years separately, in which use of any BZD or z-hypnotics was the outcome variable and the predictors were the variables previously selected (see Tables 2 and 3) as confounders during multivariable model building [34].

Third, we restricted the sample to multiparous mothers and then carried out sibling-matched FE linear regression using the xtreg function in STATA 14 for FE linear models. As default in STATA, we used the observed information matrix to calculate 95% confidence intervals. In the FE model, each sibling’s score on the outcome variables (externalizing and internalizing behaviors) was subtracted from the average scores of all siblings in his/her

Table 3. (Continued)

| Use of BZDs and z-hypnotics | 3-year sample |          |          |
|----------------------------|---------------|----------|----------|
|                            | No | Yes | No | Yes |          |          |
| N = 54,641                 | 114 | 0.2 | 13 | 3.2 |          |          |
| Maternal opioid use in pregnancy | No | 53,558 | 98.0 | 392 | 89.1 |          |          |
| Yes | 1,083 | 2.0 | 48 | 10.9 |          |          |
| Maternal SSRI use in pregnancy | No | 54,163 | 99.1 | 363 | 82.5 |          |          |
| Yes | 478 | 0.9 | 77 | 17.5 |          |          |
| Maternal antipsychotic use in pregnancy | No | 54,546 | 99.8 | 416 | 94.6 |          |          |
| Yes | 95 | 0.2 | 24 | 5.4 |          |          |
| Maternal triptan use in pregnancy | No | 54,120 | 99.0 | 426 | 96.8 |          |          |
| Yes | 521 | 1.0 | 14 | 3.2 |          |          |
| Maternal NSAID use in pregnancy | No | 50,871 | 93.1 | 367 | 83.4 |          |          |
| Yes | 3,770 | 6.9 | 73 | 16.6 |          |          |
| Maternal use of paracetamol (acetaminophen) | No use | 27,971 | 54.0 | 151 | 35.2 |          |          |
| 1 pregnancy period | 13,933 | 26.9 | 124 | 28.9 |          |          |
| 2 or 3 pregnancy periods | 9,884 | 19.1 | 154 | 25.9 |          |          |
| Maternal folic acid supplements in early pregnancy | No | 16,250 | 29.7 | 124 | 28.2 |          |          |
| Yes | 38,391 | 70.3 | 316 | 71.8 |          |          |
| Maternal chronic disease<sup>d</sup> | No | 49,282 | 90.2 | 361 | 82.1 |          |          |
| Yes | 5,359 | 9.8 | 79 | 17.9 |          |          |

SSRI, selective serotonin reuptake inhibitors; NSAID, nonsteroidal anti-inflammatory drug
<sup>a</sup> Mean score of >2 on the Hopkins Symptom Checklist (SCL-5)
<sup>b</sup> Measured in pregnancy week 17; defined as ever having three co-occurring symptoms of depression for at least 2 weeks and admitting to sad mood
<sup>c</sup> I illicit drug use included hashish, amphetamine, ecstasy, cocaine, or heroin
<sup>d</sup> Chronic disease included asthma, diabetes treated with insulin, Crohn’s disease, arthritis, lupus, epilepsy, multiple sclerosis, or cancer

https://doi.org/10.1371/journal.pone.0181042.t003
family, and each sibling’s value of the predictor (prenatal exposure to BZDs or z-hypnotics) was subtracted from the average values of all siblings in his/her family. The new outcome variables were regressed on the new exposure variables. The sibling FE models thereby controlled for potential bias by unobserved variables that were fixed within families (constant across siblings), such as shared family environments or genetic transmission of risk (e.g., maternal personality and intellectual ability). The effect estimates are within families of siblings, and only siblings discordant on exposure and outcome contributed any information. Finally, we carried out PS-adjusted FE models to adjust for the potential confounding factors varying between siblings. All analyses were done using Stata Version 14 (Stata Corporation, College Station, TX, USA).

Results

In total, 0.8% of the children were exposed to BZDs and z-hypnotics during pregnancy ($N_{1.5\ years} = 577$ of 71,996; $N_{3\ years} = 440$ of 55,081) (Fig 1).

Internalizing behavior problems

Table 4 shows the results of full cohort (random-effect) and sibling-matched (FE) linear regression models on internalizing behavior problems predicted by in utero exposure to BZDs and z-hypnotics, short term, long term, and for BZD-anxiolytics and z-hypnotics separately. Short-term exposure to BZDs and z-hypnotics was associated with increased internalizing behavior problems in crude analyses at both 1.5 and 3 years of child age. These effects were attenuated when accounting for the factors associated with maternal use of BZDs and z-hypnotics during pregnancy by PS score adjustment. For long-term exposure, increasing associations were observed in the sibling-matched models at 1.5 years and were not attenuated after PS score adjustment. At 3 years, crude effects were observed but decreased and were not significant in the PS-adjusted model. However, in the analyses on exposure to BZD-anxiolytics specifically, effect estimates from the sibling-matched model on internalizing behavior remained elevated after adjustment at both 1.5 and 3 years. For z-hypnotics, crude increased internalizing behavior problems were attenuated after adjusting for PS scores and familial confounding in the sibling-matched models.

Externalizing behavior problems

Table 5 shows the results of full cohort (random-effect) and sibling-matched (FE) linear regression models for externalizing behavior outcomes predicted by in utero exposure to BZDs and z-hypnotics, short term, long term, and for BZD-anxiolytics and z-hypnotics separately. In crude analyses of short-term exposure to BZDs and z-hypnotics, a small increase in externalizing behavior problems was observed at child age 1.5 years, with increasing effect estimates for long-term exposure. Taking PS scores into account, all effects on externalizing behavior problems were attenuated. No effects were observed for externalizing behavior problems in the sibling-matched models for short-term and long-term exposure, accounting for familial confounding, at child age 1.5 or 3 years. In stratified analyses, crude associations with externalizing behavior were observed at 3 years for BZD-anxiolytics and 1.5 years for z-hypnotics. These associations were attenuated when accounting for PS score and familial confounding in the sibling-matched models. At 3 years of age, a beneficial effect of z-hypnotic exposure on externalizing behavior problems was observed after PS score adjustment.
In this large prospective follow-up study including siblings discordantly exposed to BZDs or z-hypnotic drugs, we found that prenatal long-term exposure to BZDs or z-hypnotics was associated with increased internalizing behavior problems among children aged 1.5 years. Of importance, when studied separately, BZD-anxiolytics exposure was associated with increased

|                | Internalizing behavior | 1.5 years |            |            | 3 years |            |            |
|----------------|------------------------|-----------|------------|------------|---------|------------|------------|
|                |                        | N         | β (95% CI) | N          | β (95% CI)|           |            |
| Any BZDs and z-hypnotics |                        |           |            |            |         |            |            |
| Short term^a   |                        |           |            |            |         |            |            |
| Crude cohort sample (re) | Any BZDs and z-hypnotics | 71,649 | 0.12 (0.06, 0.19) | 54,741 | 0.18 (0.10, 0.25) |         |            |
| PS-adjusted cohort sample (re)^b |                        | 60,964 | 0.07 (0.001, 0.14) | 47,767 | 0.08 (-0.02, 0.16) |         |            |
| PS-adjusted sibling sample (re)^b |                        | 18,193 | 0.12 (-0.01, 0.25) | 13,199 | 0.15 (-0.01, 0.29) |         |            |
| Sibling-matched sample (fe) |                        | 19,397 | 0.10 (-0.08, 0.29) | 13,711 | 0.12 (-0.07, 0.32) |         |            |
| PS-adjusted sibling-matched sample (fe)^c |                        | 18,193 | 0.13 (-0.06, 0.32) | 13,199 | 0.12 (-0.08, 0.32) |         |            |
| Long term^a    |                        |           |            |            |         |            |            |
| Crude cohort sample (re) |                        | 71,649 | 0.11 (-0.03, 0.24) | 54,741 | 0.21 (0.06, 0.36) |         |            |
| PS-adjusted cohort sample (re)^b |                        | 60,964 | 0.01 (-0.13, 0.15) | 47,767 | 0.04 (-0.12, 0.20) |         |            |
| PS-adjusted sibling sample (re)^b |                        | 18,193 | 0.21 (-0.07, 0.49) | 13,199 | 0.06 (-0.25, 0.36) |         |            |
| Sibling-matched sample (fe) |                        | 19,397 | 0.46 (0.08, 0.85) | 13,711 | 0.21 (-0.19, 0.62) |         |            |
| PS-adjusted sibling-matched sample (fe)^c |                        | 18,193 | 0.60 (0.17, 0.95) | 13,199 | 0.15 (-0.26, 0.56) |         |            |

**Stratified analyses on drug groups^d**

**BZD-anxiolytics**

|                | Internalizing behavior | 1.5 years |            |            | 3 years |            |            |
|----------------|------------------------|-----------|------------|------------|---------|------------|------------|
|                |                        | N         | β (95% CI) | N          | β (95% CI)|           |            |
| Short term^a   |                        |           |            |            |         |            |            |
| Crude cohort sample (re) | BZD-anxiolytics | 71,649 | 0.09 (0.003, 0.17) | 54,741 | 0.24 (0.14, 0.34) |         |            |
| PS-adjusted cohort sample (re)^b |                        | 60,964 | 0.05 (-0.04, 0.14) | 47,767 | 0.13 (0.03, 0.24) |         |            |
| PS-adjusted sibling sample (re)^b |                        | 18,193 | 0.24 (0.07, 0.41) | 13,199 | 0.23 (0.03, 0.43) |         |            |
| Sibling-matched sample (fe) |                        | 19,397 | 0.26 (0.02, 0.49) | 13,711 | 0.36 (0.17, 0.55) |         |            |
| PS-adjusted sibling-matched sample (fe)^c |                        | 18,193 | 0.25 (0.01, 0.49) | 13,199 | 0.26 (0.002,0.52) |         |            |

**Z-hypnotics**

|                | Internalizing behavior | 1.5 years |            |            | 3 years |            |            |
|----------------|------------------------|-----------|------------|------------|---------|------------|------------|
|                |                        | N         | β (95% CI) | N          | β (95% CI)|           |            |
| Short term^a   |                        |           |            |            |         |            |            |
| Crude cohort sample (re) | Z-hypnotics | 71,649 | 0.14 (0.05, 0.24) | 54,741 | 0.15 (0.05, 0.25) |         |            |
| PS-adjusted cohort sample (re)^b |                        | 60,964 | 0.05 (-0.05, 0.15) | 47,767 | 0.02 (-0.09, 0.13) |         |            |
| PS-adjusted sibling sample (re)^b |                        | 18,193 | 0.01 (-0.17, 0.19) | 13,199 | 0.03 (-0.17, 0.23) |         |            |
| Sibling-matched sample (fe) |                        | 19,397 | -0.05 (-0.32, 0.22) | 13,711 | 0.10 (-0.10, 0.30) |         |            |
| PS-adjusted sibling-matched sample (fe)^c |                        | 18,193 | 0.02 (-0.26, 0.30) | 13,199 | 0.05 (-0.24, 0.35) |         |            |

CI, confidence interval; re, random effects; fe, fixed effects; PS: propensity score. Effect sizes (β) for all outcomes should be interpreted as the increase in terms of standard deviations in the outcome variable (Cohen's d) in exposed children (reference group: unexposed).

a Three pregnancy periods were defined: gw 0–13, 14–29, 30–birth. Short-term use was defined as reported use in one pregnancy period only. Long-term use was defined as reported use in two or more pregnancy periods.

b Adjusted for the propensity for taking BZDs and z-hypnotics during pregnancy, conditional on maternal age, formal education, marital status, pre-pregnancy BMI, parity, smoking, or alcohol use during pregnancy, presence of symptoms of anxiety/depression at gw 17 and/or gw 30, lifetime history of major depression, sleep problems, use of illicit drugs, chronic disease, use of folic acid supplements, and use of other medications during pregnancy (opioids, SSRIs, antipsychotics, triptans, NSAIDs, paracetamol).

c Adjusted for the propensity for taking BZDs and z-hypnotics during pregnancy, conditional on maternal age, parity, alcohol use during pregnancy, presence of symptoms of anxiety/depression gw 17 and/or gw 30, lifetime history of major depression, sleep problems, use of illicit drugs, use of folic acid supplements, and use of other medications during pregnancy (opioids, SSRIs, antipsychotics, triptans, NSAIDs, paracetamol).

d Including both short- and long-term exposure.

https://doi.org/10.1371/journal.pone.0181042.t004

Discussion

In this large prospective follow-up study including siblings discordantly exposed to BZDs or z-hypnotic drugs, we found that prenatal long-term exposure to BZDs or z-hypnotics was associated with increased internalizing behavior problems among children aged 1.5 years. Of importance, when studied separately, BZD-anxiolytics exposure was associated with increased
internalizing problems at both 1.5 and 3 years of follow-up while z-hypnotic exposure was not associated with any adverse outcomes.

These findings are in line with previous studies reporting delayed mental functioning up to the age of 1.5 years after exposure to BZDs [17, 35, 36]. Viggledal et al. observed reduced “personal-social behavior” abilities at child age 1.5 years but found that externalizing problems

### Table 5. Full cohort and sibling-matched linear regression models for externalizing behavior predicted by in utero exposure to BZDs and z-hypnotics.

|                            | 1.5 years | 3 years |
|---------------------------|-----------|---------|
|                           | N         | β (95% CI) | N         | β (95% CI) |
| **Any BZDs and z-hypnotics** |           |          |           |          |
| Short term               |           |          |           |          |
| Crude cohort sample (re) | 71,872    | 0.08 (0.003, 0.15) | 54,709    | 0.03 (-0.06, 0.12) |
| PS-adjusted cohort sample (re) | 61,537    | 0.04 (-0.04, 0.12) | 47,741    | -0.03 (-0.13, 0.06) |
| PS-adjusted sibling sample (re) | 18,248    | 0.09 (-0.06, 0.25) | 13,191    | 0.001 (-0.19, 0.19) |
| Sibling-matched sample (fe) | 19,277    | 0.02 (-0.19, 0.22) | 13,701    | -0.16 (-0.40, 0.08) |
| PS-adjusted sibling-matched sample (fe) | 18,248    | 0.02 (-0.19, 0.23) | 13,191    | -0.15 (-0.76, 0.25) |
| Long term                |           |          |           |          |
| Crude cohort sample (re) | 71,872    | 0.22 (0.07, 0.37) | 54,709    | 0.19 (-0.05, 0.32) |
| PS-adjusted cohort sample (re) | 61,537    | 0.12 (-0.05, 0.28) | 47,741    | 0.09 (-0.10, 0.28) |
| PS-adjusted sibling sample (re) | 18,248    | 0.20 (-0.13, 0.53) | 13,191    | 0.13 (-0.25, 0.51) |
| Sibling-matched sample (fe) | 19,277    | 0.02 (-0.41, 0.44) | 13,701    | -0.26 (-0.40, 0.08) |
| PS-adjusted sibling-matched sample (fe) | 18,248    | -0.03 (-0.46, 0.40) | 13,191    | -0.25 (-0.76, 0.25) |
| **Stratified analyses on drug groups** |           |          |           |          |
| **BZD-ansxiolytics**       |           |          |           |          |
| Crude cohort sample (re) | 71,872    | 0.06 (-0.03, 0.16) | 54,709    | 0.13 (0.01, 0.24) |
| PS-adjusted cohort sample (re) | 61,537    | 0.06 (-0.05, 0.16) | 47,741    | 0.07 (-0.05, 0.20) |
| PS-adjusted sibling sample (re) | 18,248    | 0.06 (-0.14, 0.25) | 13,191    | 0.31 (0.06, 0.56) |
| Sibling-matched sample (fe) | 19,277    | -0.02 (-0.28, 0.25) | 13,701    | 0.07 (-0.24, 0.39) |
| PS-adjusted sibling-matched sample (fe) | 18,248    | -0.04 (-0.31, 0.23) | 13,191    | 0.16 (-0.17, 0.48) |
| **Z-hypnotics**            |           |          |           |          |
| Crude cohort sample (re) | 71,872    | 0.12 (0.02, 0.23) | 54,709    | 0.01 (-0.11, 0.13) |
| PS-adjusted cohort sample (re) | 61,537    | 0.04 (-0.07, 0.15) | 47,741    | -0.08 (-0.22, 0.05) |
| PS-adjusted sibling sample (re) | 18,248    | 0.08 (-0.13, 0.29) | 13,191    | -0.22 (-0.47, 0.04) |
| Sibling-matched sample (fe) | 19,277    | -0.05 (-0.35, 0.24) | 13,701    | -0.45 (-0.80, 0.10) |
| PS-adjusted sibling-matched sample (fe) | 18,248    | -0.03 (-0.34, 0.28) | 13,191    | -0.52 (-0.87, -0.15) |

CI, confidence interval; re, random effects; fe, fixed effects; PS: propensity score. Effect sizes (β) for all outcomes should be interpreted as the increase in terms of standard deviations in the outcome variable (Cohen’s d) in exposed children (reference group: unexposed).

a Three pregnancy periods were defined: gw 0–13, 14–29, 30–birth. Short-term use was defined as reported use in one pregnancy period only. Long-term use was defined as reported use in two or more pregnancy periods.

b Adjusted for the propensity for taking BZDs and z-hypnotics during pregnancy, conditional on maternal age, formal education, marital status, prepregnancy BMI, parity, smoking, or alcohol use during pregnancy, presence of symptoms of anxiety/depression at gw 17 and/or gw 30, lifetime history of major depression, sleep problems, use of illicit drugs, chronic disease, use of folic acid supplements, and use of other medications during pregnancy (opioids, SSRIs, antipsychotics, triptans, NSAIDs, paracetamol).

c Adjusted for the propensity for taking BZDs and z-hypnotics during pregnancy, conditional on maternal age, alcohol use during pregnancy, presence of symptoms of anxiety/depression gw 17 and/or gw 30, lifetime history of major depression, sleep problems, use of illicit drugs, use of folic acid supplements, and use of other medications during pregnancy (opioids, SSRIs, antipsychotics, triptans, NSAIDs, paracetamol).

d Including both short- and long-term exposure.

https://doi.org/10.1371/journal.pone.0181042.t005
such as hyperactivity or attention problems were not significantly different from controls [17]. This result is in line with our finding that internalizing, not externalizing, problems were reported. Moreover, our study showed effects up to 3 years of age for BZD-anxiolytics. The only previous study looking at child behavior outcomes beyond the age of 1.5 years found no effects on behavior reported at the ages of 9–10 years [18]. However, no evaluation of internalizing behavior was reported, and the sample consisted of 15 exposed children, limiting the statistical power to detect effects of exposure [18]. It is therefore unclear whether the lack of behavior problems at school age was due to diminishing symptoms, crude measures failing to capture internalizing problems, or low statistical power to detect effects. More prospective follow-up studies with larger sample sizes and measures of internalizing behavior are required to determine the stability of increased internalizing problems beyond preschool age for specific drug groups.

Of note, small associations between z-hypnotic exposure and internalizing behavior problems in the child were attenuated in adjusted analyses taking the indication for use into account. We found no increase in internalizing or externalizing problems in the sibling-matched FE models at any time point for children exposed to z-hypnotic drugs. In contrast, prenatal exposure to z-hypnotics was associated with less externalizing behavior problems at 3 years of age in the sibling-matched analyses. It is possible that using z-hypnotics to reduce sleep problems in pregnancy is beneficial for the child. To our knowledge, no previous study has examined potential long-term effects for the child of prenatal z-hypnotic exposure on behavioral outcomes, and the potential beneficial association between exposure to z-hypnotics and behavioral effects would need to be confirmed by more studies before any conclusions can be made regarding the long-term safety.

The present study has a number of strengths. It uses data from a population-based sample with the possibility of following prospectively more than 400 children prenatally exposed to BZDs and z-hypnotics and a large control group. The richness of the information available enables the opportunity to adjust for many potential confounding factors, including indication for use, which is often not available in conventional studies. Maternal use of BZDs is related to substance abuse and psychiatric problems in the mother [37]. Of importance, the sibling-matched design has a number of advantages in controlling for family factors that are difficult to measure and control for in conventional cohort designs. The intra-class correlation across pregnancies for the outcomes are 0.35 (internalizing) and 0.41 (externalizing) (both P < 0.001) [38], showing that stable factors across pregnancies are potentially strong confounders. Because socioeconomic or genetic factors are likely to confound an association between maternal psychotropic medication use during pregnancy and adverse behavioral outcomes in the child, limiting this type of confounding is an important strength.

The study also has some limitations. First, the sibling-controlled design does not rule out factors that vary between siblings, correlate with exposure within families, or correlate with the outcome [39, 40]. The inclusion of an estimated PS in the sibling analyses accounting for the observed factors shown to be associated with BZD and z-hypnotics use helped control for these factors in the current study. Although reported use of illicit drugs and substance use were controlled for, we cannot rule out confounding by more complex misuse not reported in the questionnaires. Second, the design is sensitive to measurement unreliability. Measurement error in the exposure might lead to an underestimation of the effects [41]. Moreover, the sample size was not large enough to perform analyses for specific trimesters or on single drugs instead of drug groups in a sibling-controlled design. For the same reason, stratified analyses on child gender were not possible, and gender-specific effects could therefore not be explored. The agreement between self-report and dispensed drugs registered in the Norwegian Prescription Database (NorPD) for drugs used intermittently, such as BZD-anxiolytics and z-hypnotics, is
lower than for drugs used chronically [42]. This could be because users of BZDs and hypnotics often already have the medications available from previous dispensing. More women reporting BZDs in MoBa were found with a prescription in the NorPD when a longer pre-pregnancy observation period was included [43]. In a study based on a linkage between the MBRN and the NorPD including all women giving birth in Norway, 1.5% were reported to use BZDs. In MoBa, only 0.8% reported use, indicating inclusion of healthier women in that study, which may limit the generalizability of the current findings. However, even though estimates of frequencies can be biased due to selective participation, exposure–outcome associations have not previously differed between MoBa participants and the general population [44]. Gustavson et al. demonstrated using Monte Carlo simulation studies that association estimates are generally quite robust against selective participation even when the frequency estimates are biased [45, 46].

In conclusion, our results indicate that prenatal exposures to BZDs influence internalizing problems in children. Exposure to BZD- anxiolytic or z-hypnotic medications was not associated with increased externalizing problems. Exposure to BZD-anxiolytics, however, was associated with increased internalizing problems in the child, lasting up to 3 years of age. These findings could not be explained by shared familial confounding, reported indication for use, or other measured confounding factors, but residual unmeasured confounding cannot be ruled out.

Acknowledgments

We are grateful to all the participating families in Norway who take part in this ongoing cohort study.

Author Contributions

Conceptualization: Ragnhild E. Brandlistuen, Eivind Ystrom, Sonia Hernandez-Diaz, Svetlana Skurtveit, Randi Selmer, Marte Handal, Hedvig Nordeng.

Data curation: Ragnhild E. Brandlistuen, Eivind Ystrom.

Formal analysis: Ragnhild E. Brandlistuen, Eivind Ystrom, Hedvig Nordeng.

Funding acquisition: Ragnhild E. Brandlistuen.

Methodology: Ragnhild E. Brandlistuen, Eivind Ystrom, Sonia Hernandez-Diaz, Randi Selmer, Marte Handal, Hedvig Nordeng.

Project administration: Ragnhild E. Brandlistuen, Hedvig Nordeng.

Supervision: Eivind Ystrom, Hedvig Nordeng.

Writing – original draft: Ragnhild E. Brandlistuen, Eivind Ystrom, Sonia Hernandez-Diaz, Svetlana Skurtveit, Randi Selmer, Marte Handal, Hedvig Nordeng.

Writing – review & editing: Ragnhild E. Brandlistuen, Eivind Ystrom, Sonia Hernandez-Diaz, Svetlana Skurtveit, Randi Selmer, Marte Handal, Hedvig Nordeng.

References

1. Vesga-Lopez O, Blanco C, Keyes K, Olfson M, Grant BF, Hasin DS. Psychiatric disorders in pregnant and postpartum women in the United States. Archives of general psychiatry. 2008; 65(7):805–15. https://doi.org/10.1001/archpsyc.65.7.805 PMID: 18606953;
2. Rubertsson C, Hellstrom J, Cross M, Sydsjo G. Anxiety in early pregnancy: prevalence and contributing factors. Arch Womens Ment Health. 2014; 17(3):221–8. https://doi.org/10.1007/s00737-013-0409-0 PMID: 24442712.

3. Riska BS, Skurtveit S, Furu K, Engeland A, Handal M. Dispensing of benzodiazepines and benzodiazepine-related drugs to pregnant women: a population-based cohort study. Eur J Clin Pharmacol. 2014; 70(11):1367–74. https://doi.org/10.1007/s00228-014-1744-4 PMID: 25204310.

4. Okun ML, Ebert R, Saini B. A review of sleep-promoting medications used in pregnancy. American journal of obstetrics and gynecology. 2015; 212(4):428–41. https://doi.org/10.1016/j.ajog.2014.10.1106 PMID: 25448509.

5. Mandelli M, Morselli PL, Nordin S, Pardi G, Principi N, Sereni F, et al. Placental transfer to diazepam and its disposition in the newborn. Clin Pharmacol Ther. 1975; 17(5):564–72. PMID: 1126114.

6. Olney JW, Wozniak DF, Farber NB, Jevtovic-Todorovic V, Bittigau P, Ikonomidou C. The enigma of fetal alcohol neurotoxicity. Annals of medicine. 2002; 34(2):109–19. PMID: 12108574.

7. Gai N, Grimm VE. The effect of prenatal exposure to diazepam on aspects of postnatal development and behavior in rats. Psychopharmacology (Berl). 1982; 78(3):225–9. PMID: 6818579.

8. Kellogg CK. Benzodiazepines: influence on the developing brain. Prog Brain Res. 1988; 73:207–28. https://doi.org/10.1016/S0079-6123(08)60506-3 PMID: 2843947.

9. Kellogg CK, Chisholm J, Simmons RD, Ison JR, Miller RK. Neural and behavioral consequences of prenatal exposure to diazepam. Monogr Neural Sci. 1983; 9:119–29. PMID: 6684207.

10. Kellogg C, Tervo D, Ison J, Parisi T, Miller RK. Prenatal exposure to diazepam alters behavioral development in rats. Science. 1980; 207(4427):205–7. PMID: 7350658.

11. Schlimp M, Rasseier H, Abriel H, Youmbi M, Baumann JB, Lichtensteiger W. Diazepam effects on the fetus. Neurotoxicology. 1989; 10(3):501–16. PMID: 2560534.

12. Laegreid L, Hagberg G, Lundberg A. The effect of benzodiazepines on the fetus and the newborn. Neuropediatrics. 1992; 23(1):18–23. https://doi.org/10.1055/s-2008-1071305 PMID: 1348849.

13. Gillberg C. "Floppy infant syndrome" and maternal diazepam. Lancet. 1977; 2(8031): 244. PMID: 69847.

14. McElhatton PR. The effects of benzodiazepine use during pregnancy and lactation. Reprod Toxicol. 1994; 8(6):461–75. PMID: 7881198.

15. Rementeria JL, Bhatt K. Withdrawal symptoms in neonates from intrauterine exposure to diazepam. J Pediatr. 1977; 90(1):123–6. PMID: 830876.

16. Gidaj I, Acs N, Banhidy F, Czeizel AE. A study of the effects of large doses of medazepam used for self-poisoning in 10 pregnant women on fetal development. Toxicol Ind Health. 2008; 24(1–2):61–8. https://doi.org/10.1177/0748233708089016 PMID: 18818182.

17. Viggdal G, Hageberg BS, Laegreid L, Aronsson M. Mental development in late infancy after prenatal exposure to benzodiazepines—a prospective study. Journal of child psychology and psychiatry, and allied disciplines. 1993; 34(3):295–305. PMID: 8463369.

18. Stika L, Elisova K, Honzakova L, Hrochova H, Plechatova H, Strnadova J, et al. Effects of drug administration in pregnancy on children’s school behaviour. Pharm Weekbl Sci. 1990; 12(6):252–5. PMID: 1982564.

19. El Marroun H, White T, Verhulst FC, Tiemeier H. Maternal use of antidepressant or anxiolytic medication during pregnancy and childhood neurodevelopmental outcomes: a systematic review. Eur Child Adolesc Psychiatry. 2014; 23(10):973–92. https://doi.org/10.1007/s00787-014-0558-3 PMID: 24863148.

20. Kordas K, Park A. European birth cohorts offer insights on environmental factors affecting human development and health. International journal of epidemiology. 2015; 44(3):731–4. https://doi.org/10.1093/ije/dyv132 PMID: 26232419.
27. Petty CR, Rosenbaum JF, Hirshfeld-Becker DR, Henin A, Hubley S, LaCasse S, et al. The child behavior checklist broad-band scales predict subsequent psychopathology: A 5-year follow-up. J Anxiety Disord. 2008; 22(3):532–9. https://doi.org/10.1016/j.janxdis.2007.04.003 PMID: 17521868

28. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999; 10(1):37–48. Epub 1999/01/15. PMID: 9888278.

29. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC medical research methodology. 2008; 8:70. Epub 2008/11/01. https://doi.org/10.1186/1471-2288-8-70 PMID: 18973665;

30. Textor J, Hardt J, Knuppel S. DAGitty A Graphical Tool for Analyzing Causal Diagrams. Epidemiology. 2011; 22(5):745–746. PMID: 21811114

31. Strand BH, Dalgaard OS, Tambs K, Rognerud M. Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). Nordic journal of psychiatry. 2003; 57(2):113–8. Epub 2003/05/15. https://doi.org/10.1080/08039480310000932 PMID: 12745773.

32. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. The lifetime history of major depression in women. Reliability of diagnosis and heritability. Archives of general psychiatry. 1993; 50(11):863–70. PMID: 8215812.

33. Brandlstuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. International journal of epidemiology, 2013; 42 (6):1702–13. https://doi.org/10.1093/ije/dyt183 PMID: 24163279

34. Mortensen JT, Olsen J, Larsen H, Bendsen J, Obel C, Sorensen HT. Psychomotor development in late infancy after prenatal exposure to benzodiazepines—a prospective study. Neuropediatrics. 1992; 23(2):60–7. PMID: 1351263.

35. D’Onofrio BM, Lahey BB, Turkheimer E, Lichtenstein P. Critical need for family-based, quasi-experimental designs in integrating genetic and social science research. American journal of public health. 2013; 103 Suppl 1:S46–55. https://doi.org/10.2105/AJPH.2013.301252 PMID: 23927516;

36. Sjölander A, Frissell T, Kuja-Halkola R, Öberg S, Zetterqvist J. Carryover Effects in Sibling Comparison Designs. Epidemiology. 2016; 27(6):852–8. https://doi.org/10.1097/EDE.000000000000541 PMID: 27488059

37. Frissell T, Oberg S, Kuja-Halkola R, Sjölander A. Sibling comparison designs: bias from non-shared founders and measurement error. Epidemiology. 2012; 23(5):713–20. PMID: 22781362.

38. Skurtveit S, Selmer R, Tverdal A, Furu K, Nystrøm W, Handal M. Drug exposure: inclusion of dispensed drugs before pregnancy may lead to underestimation of risk associations. J Clin Epidemiol. 2013; 66 (9):964–72. https://doi.org/10.1016/j.jclinepi.2013.02.011 PMID: 23800534.

39. Gustavson K, Borren I. Bias in the study of prediction of change: a Monte Carlo simulation study of the effects of selective attrition and inappropriate modeling of regression toward the mean. BMC medical research methodology. 2014; 14:133. Epub 2014/12/19. https://doi.org/10.1186/1471-2288-14-133 PMID: 25519494;

40. Gustavson K, von Soest T, Karevold E, Roysamb E. Attrition and generalizability in longitudinal studies: findings from a 15-year population-based study and a Monte Carlo simulation study. BMC Public Health. 2012; 12:918. Epub 2012/10/31. https://doi.org/10.1186/1471-2458-12-918 PMID: 23107281.