**Association of maternal use of benzodiazepines and z-hypnotics during pregnancy with motor and communication skills, and ADHD symptoms in preschoolers**

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## Key Points

**Question**: Is the association of prenatal benzodiazepine/z-hypnotic exposure with child developmental risks different according to timing of exposure, duration, or co-exposure with opioids or antidepressants?

**Findings**: In this study, there were a moderate association between benzodiazepine/z-hypnotic exposure in late pregnancy and greater gross motor and communication deficits in children born to women with depressive/anxiety disorders, but not to the extent that the impairment was of clinical relevance. There was no evidence for duration or co-exposure associations on all outcomes.

**Meaning:** These findings show no clinically relevant detrimental risk of prenatal benzodiazepine/z-hypnotic exposure on motor, communication, and ADHD outcomes in preschoolers.

## ABSTRACT

**Importance**: The reproductive safety of benzodiazepine/z-hypnotic exposure on child longer-term developmental risks remains unresolved.

**Objective**: To quantify the association of motor, communication, and ADHD symptoms in pre-schoolers with gestational BZD/z-hypnotic exposure by timing and duration, and co-exposure with opioids or antidepressants.

**Design, Setting, Participants:** Nationwide, population-based Norwegian Mother and Child Cohort Study, recruiting pregnant women in 1999-2008, with children follow-up from 6, 18 and 36 months to 5, 7, 8 years of age. Follow-up of teenagers is ongoing. We included women with depressive/anxiety (n=4195), sleeping (n=5260) or pain-related (n=26631) disorders before and/or during pregnancy.

**Exposures**: Timing analyses: children exposed to benzodiazepines/z-hypnotics in mid (weeks 17-28) or late (> week 29) pregnancy versus those born to non-medicated women. Duration and co-exposure analyses: benzodiazepine/z-hypnotic treatment for multiple 4-week intervals versus one, and co-use of benzodiazepine/z-hypnotic with opioids or antidepressants versus sole benzodiazepines/z-hypnotics.

**Main Outcomes and Measures**: Parent-reported motor and communication skills (Ages-and-Stages Questionnaire) and ADHD symptoms (Conners’ Parent Rating Scale-Revised) at child median age 5.1 years [IQR: 5.0-5.3], as standardized mean scores. We fit general linear propensity score adjusted and marginal structural models. Analyses were stratified by maternal disorder.

**Results**: Of the 41146 eligible pregnancy-child dyads, we included 36086 children (n=18330 boys, n=17756 girls), whereof 283 (0.8%) were prenatally exposed to benzodiazepines/z-hypnotics: 134 (3.2%) in the depressive/anxiety, 60 (1.1%) in the sleeping, and 89 (0.3%) in the pain-related disorder stratum. There was no increased risk for greater ADHD symptoms or fine motor deficits following intrauterine benzodiazepine/z-hypnotic exposure at different timings. Children born to women with depressive/anxiety disorders who took benzodiazepine/z-hypnotic in late pregnancy had greater gross motor (βw: 0.67, 95% CI: 0.21, 1.13) and communication (βw: 0.35, 95% CI: 0.04, 0.65) deficits than unexposed. There was no evidence for substantial duration or co-exposure associations.

**Conclusions and Relevance:** These findings suggest no substantial detrimental risk on child fine motor and ADHD symptoms after prenatal benzodiazepine/z-hypnotic exposure, alone or in combination with opioids or antidepressants. Residual confounding by indication and/or a higher drug dose regimen among women with anxiety/depression may explain the moderate association of gross motor and communication deficits with late pregnancy benzodiazepines/z-hypnotics.

# INTRODUCTION

Up to 15% of pregnant women have an anxiety disorder, often in comorbidity with depression,1, 2 and benzodiazepines are at times required given their anxiolytic and sedative effects.3 Z-hypnotics are benzodiazepine-like drugs that can be used for treatment of insomnia, a common symptom of generalized anxiety.4 During pregnancy, use of benzodiazepines and/or z-hypnotics is in the range 1-4%,5-7 and both medications may interfere with fetal brain maturation given their shared modulating activity on the γ-amino butyric acid (GABA)A receptor.8, 9 Nevertheless, their safety in relation to offspring longer-term outcomes has so far received limited attention.

Associations between prenatal benzodiazepine exposure and fine and gross motor impairment have been observed in toddlers, although the gross motor delay resolved as children grow older.10, 11 Confounding by indication coupled to small sample size and short follow-up, constitute a major drawback of this prior research.10-12 Three recent, more methodologically sound studies13-15 have found no greater risk for lower language competence, externalizing or aggressive behaviors in offspring at 3 and 6 years of age, although a small risk (β: 0.26, 95% CI: 0.00-0.52) of internalizing behaviors was noted following benzodiazepine *in-utero* exposure.13

Both benzodiazepines and z-hypnotics are intermittently used during gestation,5 yet whether early or late exposure, or rather duration of pharmacotherapy, confer different longer-term risks in offspring, remains unresolved. Because use of benzodiazepines and z-hypnotics often concurs with greater co-use of opioid analgesics or antidepressants in pregnancy,16 a better understanding of the association between this co-exposure and child risks is also crucial.

Here we sought to quantify the association of time-varying benzodiazepine/z-hypnotic exposure during pregnancy with child gross and fine motor skills, communication, and attention-deficit/hyperactivity disorder (ADHD) traits by age 5 years. In additional sub-analyses, we aimed to estimate the association of duration of benzodiazepine/z-hypnotic exposure, and co-use of opioid analgesics or antidepressants, with these outcomes. We hypothesized no detrimental risk of benzodiazepine/z-hypnotic exposure in pregnancy on child motor, communication, and ADHD outcomes.

# METHOD

Data from the Norwegian Mother and Child Cohort Study (MoBa) were linked to the Medical Birth Registry of Norway (MBRN) via the women’s personal identification number. MoBa is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health.17, 18 Participants were recruited from all over Norway in 1999-2008 through a postal invitation in connection with a publicly offered routine ultrasound at 17-18 weeks of gestation. Data were gathered prospectively via two prenatal self-administered questionnaires at week 17 (Q1) and 30 (Q3). Follow-up questionnaires on maternal and child health were sent to mothers when the child was 6 months (Q4), 18 months (Q5), 3 years (Q6), 5 (Q7) years, 7 and 8 years of age, and up to teenage.19 Follow-up of children started in 1999 and is still ongoing in teenagers. Fathers-to-be also completed one prenatal questionnaire. The current study is based on version 9 of the quality-assured data files, which include complete follow-up data at child age 5 years. The cohort now includes 114500 children, 95200 mothers and 75200 fathers.17 The participation rate for all invited pregnancies is 41%. Of those agreeing to participate, the response rate is 92-95% (Q3-Q1) to 77% (Q5).18 This study followed the STROBE reporting guideline for cohort studies.

The MoBa study obtained a license from the Norwegian Data Inspectorate and approval from The Regional Committee for Medical Research Ethics. All participants gave written informed consent prior to participation. The MBRN is based on compulsory notification of all live births, stillbirths and induced abortions.20 Figure 1 outlines the exclusion criteria to achieve the final study population.

## Maternal disorders

We included pregnancies within women having an underlying indication for treatment with benzodiazepine/z-hypnotics, i.e. depressive and/or anxiety disorders.3, 21 Because z-hypnotics are used to treat sleeping problems, and benzodiazepine may be co-prescribed for pain management,22 these two indications were additionally considered. In MoBa Q1 and Q319 women were presented a list of previous and/or concurrent illnesses, and could indicate whether they have had i) depression or anxiety or other mental disorders (hereafter, depressive/anxiety disorders since these were the most commonly reported) before and/or during pregnancy; ii) sleeping problems during early pregnancy; iii) long-term or acute pain-related conditions before/during, or only during pregnancy, respectively (Figure 1). In case of comorbidity, women were assigned a primary underlying disorder based on the above hierarchy. We conducted all analyses separately in each maternal disorder stratum. Maternal depressive and anxiety symptom severity was measured via the short versions of The Hopkins Symptom Checklist-25 (SCL-25) at week 17 (5 items, SCL-5) and 30 (8 items, SCL-8).23, 24 More information is provided in the eAppendix in the Supplement.

## Exposures

The Q1, Q3 and Q4 provided information about benzodiazepine and z-hypnotic exposure.19 Women reported the name of the medication taken along with timing of use (6 months before pregnancy and during pregnancy by 4-week intervals). On the basis of the Anatomical Therapeutic Chemical (ATC) classification system,25 benzodiazepines included drugs within the ATC groups N05BA (diazepam, oxazepam, alprazolam), N05CD (nitrazepam, midazolam, flunitrazepam), and N03AE01 (clonazepam). Z-hypnotics included zopiclone and zolpidem (N05CF). Due to similar mechanisms of actions, benzodiazepines and Z-hypnotics were studied as one group and separate classes.

To explore the temporal sequence between measurement of depressive/anxiety symptoms and drug use, we defined the primary exposure windows as early (weeks 0-16), mid (weeks 17-28) and late (week 29-delivery) pregnancy (eFigure 1). Length of benzodiazepine and z-hypnotic exposure was defined according to whether a single or multiple 4-week intervals were checked in the questionnaires. Women were classified as exposed if they reported use of benzodiazepine and/or z-hypnotic during these periods. We defined co-exposure with an opioid (ATC N02A), or an antidepressant (ATC N06A), as reported co-use of benzodiazepine/z-hypnotics during gestation. In the latter, the reference group consisted of pregnancies exposed to benzodiazepine/z-hypnotics but not to opioids or antidepressants during pregnancy. The timing analyses were conducted separately, in each maternal disorder stratum; the duration and co-exposure analyses were solely performed in women with depressive/anxiety disorders.

## Outcomes

Child outcomes were parent-reported via completion of widely-used, validated diagnostic measures of child developmental and behavior: the “Ages and Stages Questionnaire” (ASQ) and the Conners Parent Rating Scale-Revised (CPRS-R).26-28 MoBa included selected ASQ items representing the ‘gross motor’, ‘fine motor’ and ‘communication’ developmental domains (six items per domain). Mothers were asked to rate whether each item reflected their child’s motor skills and ability to understand and tell. Child ADHD traits of ‘inattention’ and ‘hyperactivity/impulsivity’ were measured by twelve CPRS-R items. Mothers were asked to rate whether each item reflected their child’s behavior in the last six months. The ASQ and CPRS-R items and related scoring are described in eFigure 2. For each domain within the scales, mean scores were calculated and standardized. Higher z-scores indicated greater endorsement of each domain (e.g., greater fine motor deficit). In the current study, the internal consistency was 0.9 for the CPRS-R, and 0.6-0.7 for the ASQ domains.

## Covariates

We identified a sufficient set of confounders with the aid of directed acyclic graphs and subject knowledge.29 These were: maternal folate intake, parity, marital status, as ascertained from the MBRN; Body Mass Index (BMI), gross yearly income, , smoking and alcohol use in pregnancy, maternal and paternal education, as reported in the MoBa questionnaires; self-reported co-medication with opioid analgesics, acetaminophen, nonsteroidal anti-inflammatory drugs, other psychotropics (i.e., antipsychotics, antiepileptics, antidepressants), and sedating antihistamines; severity of maternal depressive and anxiety symptoms in pregnancy as measured by the SCL-5/8 in MoBa; Life Time History of Major Depression (LTH of MD), measured via five key depressive symptoms closely corresponding to the DSM-III criteria for lifetime major depression;30 presence and painfulness of maternal adverse life events close to the pregnancy period, as measured in Q3; and an obstetric comorbidity index, based on MBRN records.31

Postnatal and other parental factors were taken into account under alternate model specifications in the timing analysis (eTable 1). Further information on covariates and the above factors is provided in the eAppendix in the Supplement.

## Statistical analysis

*Timing of exposure analysis*

To estimate associations by timing of exposure, we fit marginal structural models (MSM) with two time points to account for i) time-varying benzodiazepine/z-hypnotic exposure; ii) time-varying confounders (i.e, depressive and anxiety symptoms in pregnancy, comedication with opioids, antidepressants, sedatives antihistamines, acetaminophen); iii) loss to follow-up.32, 33 We estimated the probability of benzodiazepine/z-hypnotic treatment using a pooled logistic regression in which the outcome was current treatment with an benzodiazepine/z-hypnotic in mid or late pregnancy, and covariates were maternal baseline factors, time-varying and time-fixed confounders, and benzodiazepine/z-hypnotic history treatment in gestational weeks 0-16 (see Model 1, eTable 1). We also calculated the probability of remaining in the study given maternal baseline covariates, and then derived stabilized inverse probability of treatment (IPTW) and censoring (IPCW) weight for each pregnancy at each time point. Generalized linear model with robust standard errors were fit applying the IPTW, as well as the composite IPTW\*IPCW. To further examine confounding by indication, we conducted separate analyses for each maternal disorder stratum. Analyses by medication class were also performed.

*Duration and co-exposure analysis*

Because women in the depressive/anxiety disorder stratum were those most often co-exposed with an opioid or antidepressant, and treated for longer periods, we determined duration and co-exposure associations solely in this stratum by fitting crude and propensity score (PS) adjusted generalized linear models with robust standard errors. Logistic regression models were first fit to estimate the probability of ‘exposure’ to: benzodiazepine/z-hypnotic in i) two or more intervals during pregnancy, relative to one interval; ii) co-use of an opioid or antidepressant during pregnancy relative to benzodiazepine/z-hypnotic alone, given a modified set of sufficient confounders (see eAppendix).

The crude and adjusted beta coefficients with 95% CI represent the standardized mean difference in the developmental outcomes between children according to the various exposure definitions. Power analysis for the various exposure windows is outlined in eTables 2-3. The study had enough statistical power to detect clinically relevant effect sizes (d >1.00) or smaller in most analytical scenarios.

*Missing data and multiple imputation*

Up to 16.5% of the pregnancies had missing values in at least one of the sufficient confounders. Under the assumption that data were missing at random, we imputed incomplete data via multiple imputation (cf. eAppendix for more detail).34-36

*Sensitivity analyses*

We conducted a number of sensitivity analyses to assess the robustness of our findings, as described in the eAppendix in the Supplement. To verify the validity of the outcome measures, we evaluated the strength of the following associations: i) maternal and paternal ADHD traits with child’s ADHD traits on the CPRS-R; ii) child diagnosis of language or motor delay/clumsy at age 5 with communication or motor skills on the ASQ, respectively. We employed as negative control children born to women who took benzodiazepine/z-hypnotics in the six month period before, but not during pregnancy. We conducted probabilistic bias analyses to correct for exposure misclassification, unmeasured confounding, and random error by specifying trapezoidal distributions of the bias parameters (cf. eAppendix).37, 38 To address the role of chance, we re-estimated the association measures of the main analyses with the corresponding 99% CI. All statistical analyses were performed by using STATA version 15.

# RESULTS

The study population comprised 36086 pregnancy-child dyads within 32799 mothers (Figure 1). Relative to women who remained into the study, those lost to follow-up between birth and 5 years postpartum more often had unfavourable correlates (e.g., lower education and income, more severe antenatal depressive symptoms, smokers in pregnancy). Use of benzodiazepine/hypnotics in gestation was not associated with loss to follow-up.

Depressive/anxiety disorders and sleeping problems constituted the primary maternal disorder for 11.6% (n=4195) and 14.6% (n=5260) of the pregnancies, and pain-related disorders were so for the remainder (73.8%, n=26631). Of the women with depressive/anxiety disorders, the majority reported depression before/during pregnancy, either alone (n=2437) or in comorbidity with anxiety and/or other mental illnesses (n=1057). Anxiety or other mental illness alone was reported by 435 and 220 women, respectively. Baseline characteristics of the sample by benzodiazepine/z-hypnotic exposure during pregnancy, overall and by maternal primary disorder, are shown in Table 1 and eTable 4, respectively. The distribution of missing data on confounders by exposure status in pregnancy are depicted in eFigures 3-5. The median gestational weeks when the two prenatal questionnaires were completed were 16.9 [Interquartile range (IQR): 15.4-18.7] and 30.1 [IQR: 29.0-31.4].

Gestational exposure to any benzodiazepine/z-hypnotic occurred in 283 pregnancies (0.8%). Benzodiazepine-anxiolytics (n=147, 0.4%; mainly diazepam and oxazepam) and z-hypnotics (n=133, 0.4%; mainly zopiclone) were the most common exposures. The highest proportion of pharmacotherapy, co-exposure with opioids or antidepressants, and longer treatment duration, was within women with depressive/anxiety disorders (eTables 2-3).

*Associations by timing of exposure*

Child developmental outcomes were assessed by a median age of of 5.1 years [IQR: 5.0-5.3]. Benzodiazepines/z-hypnotics exposure at different timings in pregnancy did not pose any increased risk for greater ADHD traits or fine motor deficits in offspring (Table 2). Children of mothers with depressive/anxiety disorders exposed to benzodiazepines/z-hypnotics in late pregnancy, had greater gross (weighted β (βw): 0.67, 95% CI: 0.21 to 1.13) motor deficits than unexposed in the time window. This association was only present among boys (βw: 0.91; 95% CI: 0.47 to 1.35; cf. eAppendix), and was observed for benzodiazepine and z-hypnotic monotherapy exposure. A small size association was also present between benzodiazepine/z-hypnotic in late pregnancy and greater communication deficits (βw: 0.35, 95% CI: 0.04 to 0.65), mainly driven by z-hypnotic exposure (Tables 2-3). The above associations were not evident in the sleeping and pain-related disorder strata, but rather an inverse association was observed in these strata between benzodiazepine/z-hypnotic exposure and child motor skills (Table 2). The characteristics of the estimated weights are described in eTable 5. Adjusting for loss to follow-up did not materially change the main results (eTable 6).

*Associations by duration of exposure, and co-exposure with opioids or antidepressants*

Children of mothers with depressive/anxiety disorders who took benzodiazepine/z-hypnotics in multiple 4-week intervals did not present a substantial increased risk for adverse developmental outcomes, relative to a sole interval exposed (Table 4). Likewise, co-exposure with an opioid or an antidepressant did not pose any additional risk for the various developmental outcomes than benzodiazepine/z-hypnotic alone.

*Associations in sensitivity analyses*

Our outcome measures were consistently and strongly associated with known predictors or parents’ report of child medical diagnoses. The negative control was not associated with the various child outcomes, except with greater ADHD traits in offspring (eTables 7-8). Results of the sensitivity and probabilistic bias analyses, described in the eAppendix in the Supplement, showed that our association measures were generally robust.

# DISCUSSION

This study reports novel evidence on the association between benzodiazepine/z-hypnotic exposure during pregnancy and motor and communication skills, and ADHD symptoms in preschoolers. After accounting for time-varying depressive and anxiety symptoms in pregnancy and maternal underlying disorder, we found no substantial increased risk for greater ADHD traits or fine motor deficits in offspring exposed to benzodiazepine/z-hypnotic medications at different timings in gestation. Although the role of chance, unmeasured factors, and residual confounding by maternal disease severity cannot be ruled out, children of mothers with depressive/anxiety disorders taking benzodiazepine or z-hypnotic in late gestation, presented a greater risk for gross motor and communication deficits by age 5 years compared with unexposed, but not to the extent that the impairment was of clinical relevance.

The association of child ADHD and inherent traits with maternal use of benzodiazepine/z-hypnotics is an under researched topic.12 Laegreid et al.39 described hyperactivity and attention deficit symptoms in children regularly exposed to benzodiazepine *in-utero*. Yet, such risk could not be substantiated by more recent research, including the current study.13, 14 Our null association between prenatal benzodiazepine/z-hypnotic use and greater ADHD traits in offspring was consistently observed across the various maternal disorder strata. On individual drug class level, the negligible association that emerged specifically for benzodiazepine exposure was likely a chance finding, or an overestimation of the true drug effect, due to the failure to correct for exposure misclassification and unmeasured confounding by maternal personality traits, and/or familial genetic risk.

Our observed risk for greater gross motor deficits following late pregnancy benzodiazepine/z-hypnotic exposure was evident solely among children of mothers with depressive/anxiety disorders, for both drug classes, and specific to boys. In absolute terms, we would expect four to six children to have greater gross motor deficits for every 100 women treated with benzodiazepine or z-hypnotics in late gestation (assuming a 1% prevalence of the outcome among the unexposed).40, 41 However, the present difference in motor proficiency was below clinically relevant cutoff points,42 even after accounting for important parental contributors. Although correction for exposure misclassification and unmeasured confounding by maternal personality traits could slightly inflate the difference in motor proficiency between benzodiazepine/z-hypnotic exposed and unexposed children, this difference would still be below the threshold for a gross motor impairment.42 Several factors can explain the lack of finding replication in similarly exposed children born to women with sleeping or pain-related disorders: residual confounding by maternal psychiatric disease, greater cortisol level and stress in women with depressive/anxiety disorders at the end of gestation, but also a higher drug dosage regimen in these women.43-45 Even though prior studies on the topic are scarce,10, 11 the interplay between higher drug dosage and sex-specific developmental pathways cannot be ruled out.46

Disentangling timing from duration or cumulative dose effects is challenging. Unlike prior research,10, 15 our results do not support the notion that prolonged benzodiazepine/z-hypnotic treatment poses considerable detrimental risks on child motor or communication development relative to shorter-term use.10 Our borderline association with fine motor deficits was negligible, with an upper bound below clinically relevant cut-off for impairment. Although chance finding are possible, our duration and timing results, coupled to biological reserach,47 can provide some hints about possible mechanisms of developmental alteration by in-utero exposure to benzodiazepine/z-hypnotics, as well as its potential interplay with negative perinatal outcomes such as newborn floppiness, on child motor skills at later age.46, 48

Albeit with some amount of uncertainty, we did not observe strong co-exposure effects on all the investigated child outcomes, relative to sole benzodiazepine/z-hypnotic use in gestation. Recent research has indeed shown that the risk posed by prenatal antidepressant on child motor development and ADHD is small in magnitude,49, 50 and most likely attributable to confounding by indication and other unmeasured factors. Our inverse association between benzodiazepine/z-hypnotic-opioid co-exposure on child gross motor deficits was an unexpected finding, possibly due to chance and small sample size.

Several limitations need mentioning. Maternal disorders were self-reported, and anxiety was listed only in the prenatal questionnaire at week 17. Depressive and anxiety symptoms were not measured at baseline, but only at two time points in pregnancy; however information about LTH of MD was utilized in the generation of the stabilized weights. Non-differential exposure misclassification could be an additional concern, which could have led to an underestimation of the true drug effects. Information on dosage is not available in MoBa, which challenges to tease apart timing from duration/cumulative dose effects. Our outcome measures were parent-reported; however their internal consistency was generally satisfactory and they were strongly associated with known predictors and medical diagnosis of child impairment. Although the risk of outcome misclassification cannot be ruled out, this was probably non-differential, and the depression-distortion bias had a negligible impact on our effect estimates. The MoBa study has a low response rate (41%), with a possible self-selection of the healthiest women.25 Although association measures have been shown to be valid in MoBa in relation to immediate birth outcomes,59 the impact of selection bias on longer-term child outcomes, and thus on our results, cannot be excluded. Our small sample size precluded duration and co-exposure analyses in the sleeping and pain-related disorder strata, and limited our detectable effect sizes. The findings of this study may not be generalizable to populations of pregnant women outside Norway.

# CONCLUSIONS

We found no substantial increased risk for greater ADHD traits or fine motor deficits in offspring exposed to benzodiazepine/z-hypnotic medications at different timings in gestation or for longer duration. Children born to women with depressive/anxiety disorders who took benzodiazepine and/or z-hypnotic late in pregnancy had greater gross motor and communication deficits compared with the unexposed, but not to the extent that the impairment was of clinical relevance. These associations may be attributable to residual confounding by maternal psychiatric disease, and/or to a higher dose drug effect in these women, which calls for future dose effect studies. Prenatal co-exposure with an opioid or an antidepressant did not pose any additional detrimental risk on child developmental outcomes at preschool-age, relative to sole benzodiazepines/z-hypnotics.

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#### Figure Title

Figure 1:Flowchart to achieve the final study population

#### Figure Legends

Conditions of exclusion may overlap. MBRN=Medical Birth Registry of Norway; Q=questionnaire; GW=gestational week.

aQ1 is the first MoBa questionnaire completed around gestational week 17. Completion of Q1 implied enrolment into the study.

bMissing informationon all ‘Age and Stage Questionnaire’ subscales and on the ‘Conner’s Parent Rating Scale’.

cIt indicates 1299 twin and 14 triplet pregnancies.

dIncludes long-term (i.e., arthritis, sciatica, fibromyalgia, headache, migraine) pain-related conditions before and/or during pregnancy, and acute pain-related conditions (i.e., pelvic girdle, back, groin, muscle/joint pains) during pregnancy.

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The authors report no conflicts of interest in this work. HN is a member of several non-profit organizations: She is a board member of the Norwegian Pharmaceutical Society, member of the scientific board of the European Network of Teratology Information Services, chair of the Pregnancy Special Interest Group (SIG), International Society of Pharmacoepidemiology (ISPE) and member of the Executive committee, European Drug Utilization Group (EuroDURG). She serves as independent expert, member of the Pharmacovigilance Risk Assessment Committee (PRAC), European Medicines Agency (EMA). AL is currently Head of Steering Committee of the Norwegian Society for Pharmacoepidemiology, which is a non-profit organization for pharmacoepidemiologists in Norway.

AL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. AL, affiliated at the PharmacoEpidemiology and Drug Safety Research Group, Department of Pharmacy, & PharmaTox Strategic Research Initiative, Faculty of Mathematics and Natural Sciences, University of Oslo, Norway conducted and is responsible for the data analysis.

**Table 1:** Cohort characteristics by exposure to BZD/z-hypnotics during pregnancy (n=36086)

| **Characteristics** | **BZD/z-hypnotic exposure during pregnancy**† | |
| --- | --- | --- |
|  | **No** | **Yes** |
|  | **n=35803** | **n=283** |
| ***Maternal sociodemographics and life-style*** |  | |
| **Age (years); mean ± sd** | 30.6±4.4 | 31.7±4.4 |
| **BMI at conception; mean ± sd** | 24.0±4.2 | 23.8±4.2 |
| **Primiparous; n (%)** | 16952 (47.4) | 143 (50.5) |
| **Married/Cohabiting; n (%)** | 34571 (96.6) | 258 (91.2) |
| **Educational level;a n (%)** |  |  |
| University/College | 25646 (71.6) | 211 (74.6) |
| Lower than University/College | 10004 (27.9) | 71 (25.1) |
| **Gross yearly income;b n (%)** |  |  |
| Average | 26347 (73.6) | 204 (72.1) |
| Low | 4011 (11.2) | 33 (11.7) |
| High | 4515 (12.6) | 38 (13.4) |
| **Smoking status (yes) at week 30; n (%)** | 1634 (4.6) | 34 (12.0) |
| **Alcohol use in pregnancy; n (%)** |  |  |
| No/very limited use | 31628 (88.3) | 222 (78.5) |
| Medium use | 3354 (9.4) | 46 (16.3) |
| Weekly use | 298 (0.8) | 12 (4.2) |
| **Folate intakec (yes); n (%)** | 31499 (88.0) | 250 (88.3) |
| ***Maternal health*** |  |  |
| **Comorbidity index; z-score ± sd** | 0.02±1.01 | 0.35±1.24 |
| **LTH of MDd (yes);n (%)** | 2236 (6.3) | 54 (19.1) |
| **Depressive/anxiety symptoms during pregnancy; z-score ± sd** |  |  |
| SCL-5 at week 17 | -0.01±0.99 | 0.91±1.81 |
| SCL-8 at week 30 | -0.01±0.99 | 0.93±1.71 |
| **Emotional stability trait (range 1-5);e mean ± sd** | 2.7±0.53 | 2.9±0.51 |
| **Life-time adverse event at baseline;f n (%)** |  |  |
| None or at least one event but not painful | 21967 (61.4) | 110 (38.9) |
| At least one event, painful | 8165 (22.8) | 94 (33.2) |
| At least one event, very painful | 4141 (11.6) | 66 (23.3) |
| **Co-medication in pregnancy (yes);n (%)** |  |  |
| Antidepressants | 361 (1.0) | 55 (19.4) |
| Antipsychotics | 284 (0.8) | 17 (5.7) |
| Opioid analgesics | 707 (2.0) | 35 (12.4) |
| Antiepileptic drugs | 133 (0.4) | 6 (2.1) |
| NSAIDs | 2369 (6.6) | 41 (14.5) |
| Acetaminophen | 17571 (49.1) | 197 (69.6) |
| Sedating antihistamines | 193 (0.5) | 30 (10.6) |
| **Illicit substance use(yes);g n (%)** | 202 (0.6) | 14 (5.0) |
| ***Child’s and postpartum characteristics*** | |  |
| **Breastfeeding months up to child’s age 6 months; mean ± sd** | 5.7±2.5 | 5.5±2.5 |
| **Infant gender (male); n (%)** | 18185 (50.8) | 145 (51.2) |
| **Any malformation (yes); n (%)** | 1745 (4.9) | 13 (4.6) |
| **Premature birth (yes); n (%)** | 1617 (4.5) | 17 (6.0) |
| **Nursery/daycare attendance; n (%)** |  |  |
| Never between 1-5 years of age | 5229 (14.6) | 50 (17.7) |
| Any time between 1-5 years of age | 25710 (71.8) | 198 (70.0) |
| Always between 1-5 years of age | 4864 (13.6) | 35 (12.4) |
| **Number of postnatal maternal adverse events;h mean ± sd** |  |  |
| Between 0-3 years postpartum | 0.59**±**0.95 | 0.86**±**1.12 |
| Between 4-5 years postpartum | 0.81**±**1.06 | 1.28**±**1.38 |
| **Postnatal depressive/anxiety symptoms; z-score ± sd** |  |  |
| SCL-8 average between 0.5-5 year postpartum | -0.01**±**0.99 | 0.81**±**1.45 |
| SCL-8 specifically at 5 years postpartum | -0.01**±**1.00 | 0.53**±**1.33 |
| **Maternal ADHD symptoms at 3 year postpartum; n (%)** |  |  |
| None | 26399 (73.7) | 190 (67.1) |
| Mild | 2272 (6.4) | 32 (11.3) |
| Moderate to severe | 350 (1.0) | 8 (2.8) |
| **Parents positive involvement with children; z-score ± sd** | 0.00 (1.00) | -0.06 (1.09) |
| ***Paternal characteristics*** |  |  |
| **Age (years); n (%)** |  |  |
| < 25 | 1255 (3.5) | 5 (1.8) |
| 25-39 | 30786 (86.0) | 227 (80.2) |
| 40-49 | 3422 (9.6) | 43 (15.2) |
| > 49 | 257 (0.7) | 3 (1.1) |
| **Educational level; n (%)** |  |  |
| University/College | 19189 (53.6) | 147 (51.9) |
| Lower than University/College | 16370 (45.7) | 132 (46.6) |
| **Sleeping problems (yes);n (%)** | 1739 (4.9) | 23 (8.1) |
| **Mental illness (yes);n (%)** | 390 (1.1) | 4 (1.4) |
| **Paternal ADHD symptom at time of pregnancy; n (%)** |  |  |
| None | 13660 (38.2) | 101 (35.7) |
| Mild | 2201 (6.2) | 22 (7.8) |
| Moderate to severe | 258 (0.7) | 3 (1.1) |

Abbreviations: BDZ=benzodiazepines; BMI=body mass index; SCL-5 and SCL-8=short version (5- and 8-item) of The Hopkins Symptom Checklist; NSAID=non-steroidal anti-inflammatory drugs; LTH of MD=Lite time history of Major Depression; ADHD=Attention Deficit Hyperactive Disorder.

†Numbers may not add up to total due to missing values, ranging from 0.4-0.7% (maternal/paternal education), to 1.5-1.9% (BMI, alcohol habits), and 2.1-2.7% (LTH of MD, smoking status and income). For the prenatal SCL-5/8 missing values were 2.8% and 4.6%, and for perinatal history of adverse events they were 4.9%. Information on maternal and paternal ADHD, and parenting, was available for 30-65% of the study population because the instruments were only present in later versions of the MoBa questionnaire. The father questionnaire was available for 30326 mother-child dyads (84%).

aOngoing or completed educational level. bAverage: 14800 to 49900 USD; low: ≤ 14800 USD; high: ≥ 50000 USD. cFolate before and/or during first trimester. dDefined as Kendlers Life time major depression scale score of 3 or more simultaneous depressive symptoms of duration of more than 2 weeks. eAs measured by the International Personality Item Pool (IPIP) Big-Five Factor Markers. fAdverse life events in the perinatal period, i.e. from 7 months before pregnancy to week 30 of pregnancy. gBefore and/or during pregnancy. hNumber of adverse life events in the early and late postnatal period, with no severity specification.

**Table 2**: Associations of timing of BZD/z-hypnotic exposure in pregnancy with child outcomes by maternal underlying disorder

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Maternal disorder strata** | | | | | | | |
|  |  | **Depressive/anxiety disorders**  **n=4195** | |  | **Sleeping problems**  **n=5260** | |  | **Pain-related disorders**  **n=26631** | |
| **BZD/z-hypnotic** | **na** | **Crude**  **β (95% CI)** | **Weightedb,c**  **β (95% CI)** | **na** | **Crude**  **β (95% CI)** | **Weightedb,c**  **β (95% CI)** | **na** | **Crude**  **β (95% CI)** | **Weightedb,c**  **β (95% CI)** |
| **ASQ, gross motor skills** | | | | | | | | | |
| Exposed,  midpregnancy | 55 | 0.03  (-0.25, 0.31) | -0.19  (-0.55, 0.18) | 19 | -0.39  (-0.51, -0.26) | -0.30  (-0.52, -0.09) | 23 | 0.21  (-0.28, 0.71) | 0.15  (-0.70, 1.01) |
| Exposed,  late pregnancy | 50 | 0.28  (-0.06, 0.62) | 0.67  (0.21, 1.13) | 17 | -0.28  (-0.60, 0.05) | -0.19  (-0.56, 0.18) | 24 | -0.14  (-0.44, 0.16) | -0.06  (-0.67, 0.56) |
| **ASQ, fine motor skills** | | | | | | | | | |
| Exposed,  midpregnancy | 55 | 0.02  (-0.46, 0.50) | 0.04  (-0.44, 0.51) | 19 | -0.07  (-0.48, 0.33) | -0.22  (-0.69, 0.25) | 24 | 0.11  (-0.28, 0.49) | 0.06  (-0.32, 0.45) |
| Exposed,  late pregnancy | 49 | 0.55  (-0.11, 1.22) | 0.52  (-0.11, 1.16) | 17 | -0.11  (-0.51, 0.29) | 0.08  (-0.58, 0.73) | 25 | -0.32  (-0.51, -0.12) | **-**0.45  (-0.69, -0.21) |
| **ASQ, communication skills** | | | | | | | | | |
| Exposed,  midpregnancy | 54 | 0.16  (-0.12, 0.44) | -0.11  (-0.40, 0.19) | 17 | 0.06  (-0.30, 0.43) | 0.21  (-0.28, 0.69) | 25 | -0.14  (-0.47, 0.19) | -0.17  (-0.57, 0.23) |
| Exposed,  late pregnancy | 47 | 0.26  (-0.05, 0.58) | 0.35  (0.04, 0.65) | 16 | -0.10  (-0.45, 0.25) | -0.26  (-0.62, 0.10) | 24 | -0.14  (-0.41, 0.14) | -0.06  (-0.46, 0.33) |
| **CPRS-R, ADHD traits** | | | | | | | | | |
| Exposed,  midpregnancy | 54 | 0.20  (-0.13, 0.52) | -0.04  (-0.36, 0.28) | 19 | 0.23  (-0.29, 0.76) | 0.13  (-0.34, 0.59) | 24 | -0.17  (-0.46, 0.12) | -0.14  (-0.58, 0.31) |
| Exposed,  late pregnancy | 50 | 0.22  (-0.08, 0.52) | 0.08  (-0.19, 0.35) | 17 | -0.07  (-0.64, 0.51) | 0.01  (-0.48, 0.50) | 26 | -0.00  (-0.65, 0.65) | 0.02  (-0.61, 0.66) |

Abbreviations: BDZ=benzodiazepines; ASQ=Ages and Stages Questionnaire; CPRS-R= Conners Parent Rating Scale-Revised; ADHD= attention-deficit/hyperactivity disorder.

aThe number of exposed pregnancies may differ across the specific outcomes, depending on whether these individual measures were reported by mothers.

bThe reference group consists of unexposed pregnancies in the corresponding time window.

cWeighted estimates with stabilized inverse probability of treatment weighting (constructed at each time point using baseline covariates, time-varying and time-fixed confounding factors, and BZD/z-hypnotic history treatment).

**Table 3:** Associations by class of medication exposure on child outcomes in the depressive/anxiety disorder stratum (n=4183)a

|  | **n**b | **Crude modelsc**  **β (95% CI)** | **Weighted modelsc,d**  **β (95% CI)** |
| --- | --- | --- | --- |
| **BZD monotherapy** |  |  |  |
| **ASQ, gross motor skills** |  |  | |
| Exposed, midpregnancy | 28 | -0.14 (-0.43, 0.15) | -0.47 (-0.78, -0.17) |
| Exposed, late pregnancy | 23 | 0.10 (-0.27, 0.48) | 0.80 (0.12, 1.48) |
| **ASQ, fine motor skills** |  |  |  |
| Exposed, midpregnancy | 28 | 0.07 (-0.37, 0.50) | -0.30 (-0.76, 0.15) |
| Exposed, late pregnancy | 22 | 0.19 (-0.26, 0.63) | 0.74 (-0.12, 1.60) |
| **ASQ, communication skills** |  |  |  |
| Exposed, midpregnancy | 28 | 0.10 (-0.20, 0.41) | -0.15 (-0.43, 0.13) |
| Exposed, late pregnancy | 23 | -0.02 (-0.32, 0.29) | 0.06 (-0.16, 0.27) |
| **CPRS-R, ADHD traits** |  |  |  |
| Exposed, midpregnancy | 27 | 0.05 (-0.45, 0.55) | -0.24 (-0.63, 0.15) |
| Exposed, late pregnancy | 23 | 0.21 (-0.24, 0.66) | 0.29 (0.02, 0.57) |
| **Z-hypnotic monotherapy** |  |  |  |
| **ASQ, gross motor skills** |  |  |  |
| Exposed, midpregnancy | 22 | 0.21 (-0.35, 0.77) | 0.03 (-0.74, 0.80) |
| Exposed, late pregnancy | 24 | 0.54 (-0.05, 1.13) | 0.93 (0.28, 1.58) |
| **ASQ, fine motor skills** |  |  |  |
| Exposed, midpregnancy | 22 | 0.54 (-0.02, 1.10) | 0.32 (-0.68, 1.32) |
| Exposed, late pregnancy | 24 | 0.78 (0.19, 1.37) | 0.58 (-0.44, 1.59) |
| **ASQ, communication skills** |  |  |  |
| Exposed, midpregnancy | 21 | 0.19 (-0.31, 0.70) | -0.27 (-0.76, 0.23) |
| Exposed, late pregnancy | 21 | 0.44 (-0.08, 0.97) | 0.49 (-0.01, 0.98) |
| **CPRS-R, ADHD traits** |  |  |  |
| Exposed, midpregnancy | 21 | 0.24 (-0.24, 0.72) | 0.11 (-0.45, 0.67) |
| Exposed, late pregnancy | 24 | 0.20 (-0.23, 0.63) | -0.10 (-0.49, 0.29) |

Abbreviations: BDZ=benzodiazepines; ASQ=Ages and Stages Questionnaire; CPRS-R= Conners Parent Rating Scale-Revised; ADHD= attention-deficit/hyperactivity disorder.

a12 pregnancies were excluded because of co-use of BZD and z-hypnotics.

bThe number of exposed pregnancies may differ across the specific outcomes, depending on whether these individual measures were reported by mothers. Overall, there were 68 and 50 pregnancies exposed to BZD monotherapy and z-hypnotic monotherapy at any time in pregnancy, respectively.

cThe reference group consists of unexposed pregnancies in the corresponding time window.

dWeighted estimates with stabilized inverse probability of treatment weighting (constructed at each time point using baseline covariates, time-varying and time-fixed confounding factors, and BZD or z-hypnotic history treatment).

**Table 4:** Association ofprolonged BZD/z-hypnotic use and co-exposure with an opioid or antidepressant on child developmental outcomes in the depressive/anxiety disorder stratuma

|  | **n**b | **Crude models**  **β (95% CI)** | **PS adjusted models**  **β (95% CI)** |
| --- | --- | --- | --- |
| **Length of BZD/z-hypnotic exposure** | | | |
| **ASQ, gross motor skills** |  |  |  |
| Exposed, 1 interval | 82 | Reference | Reference |
| Exposed, ≥ 2 intervals | 52 | 0.05 (-0.31, 0.40) | -0.05 (-0.44, 0.34) |
| **ASQ, fine motor skills** |  |  |  |
| Exposed, 1 interval | 81 | Reference | Reference |
| Exposed, ≥ 2 intervals | 52 | 0.33 (-0.03, 0.69) | 0.38 (-0.04, 0.80) |
| **ASQ, communication skills** |  |  |  |
| Exposed, 1 interval | 79 | Reference | Reference |
| Exposed, ≥ 2 intervals | 50 | 0.17 (-0.21, 0.54) | 0.15 (-0.21, 0.51) |
| **CPRS-R, ADHD traits** |  |  |  |
| Exposed, 1 interval | 81 | Reference | Reference |
| Exposed, ≥ 2 intervals | 51 | 0.27 (-0.11, 0.64) | 0.35 (-0.11, 0.81) |
| **Co-exposure to BZD/z-hypnotic and opioid** | | | |
| **ASQ, gross motor skills** |  |  |  |
| Exposed, BZD/z-hypnotic | 115 | Reference | Reference |
| Co-exposed, with opioid | 19 | **-**0.49 (-0.75, -0.24) | -0.47 (-0.82, -0.11) |
| **ASQ, fine motor skills** |  |  |  |
| Exposed, BZD/z-hypnotic | 114 | Reference | Reference |
| Co-exposed, with opioid | 19 | -0.17 (-0.57, 0.23) | -0.23 (-0.71, 0.24) |
| **ASQ, communication skills** |  |  |  |
| Exposed, BZD/z-hypnotic | 110 | Reference | Reference |
| Co-exposed, with opioid | 19 | 0.29 (-0.14, 0.72) | 0.29 (-0.24, 0.83) |
| **CPRS-R, ADHD traits** |  |  |  |
| Exposed, BZD/z-hypnotic | 114 | Reference | Reference |
| Co-exposed, BZD/z-hypnotic-opioid | 18 | -0.18 (-0.58, 0.23) | -0.30 (-0.83, 0.22) |
| **Co-exposure to BZD/z-hypnotic and antidepressant** | | | |
| **ASQ, gross motor skills** |  |  |  |
| Exposed, BZD/z-hypnotic | 82 | Reference | Reference |
| Co-exposed, with antidepressant | 52 | 0.20 (-0.14, 0.55) | 0.18 (-0.18, 0.54) |
| **ASQ, fine motor skills** |  |  |  |
| Exposed, BZD/z-hypnotic | 81 | Reference | Reference |
| Co-exposed, with antidepressant | 52 | 0.10 (-0.25, 0.46) | 0.06 (-0.34, 0.46) |
| **ASQ, communication skills** |  |  |  |
| Exposed, BZD/z-hypnotic | 78 | Reference | Reference |
| Co-exposed, with antidepressant | 51 | 0.29 (-0.09, 0.67) | 0.27 (-0.16, 0.69) |
| **CPRS-R, ADHD traits** |  |  |  |
| Exposed, BZD/z-hypnotic | 80 | Reference | Reference |
| Co-exposed, with antidepressant | 52 | 0.21 (-0.15, 0.57) | 0.23 (-0.16, 0.62) |

Abbreviations: BDZ=benzodiazepines; ASQ=Ages and Stages Questionnaire; CPRS-R= Conners Parent Rating Scale-Revised; ADHD= attention-deficit/hyperactivity disorder; PS=Propensity score.

aOverall, there were 52 pregnancies exposed in ≥ 2 intervals versus 82 exposed in 1 interval only. There were 19 pregnancies co-exposed to BZD/z-hypnotics and opioids, versus 115 exposed to BZD/z-hypnotics only. There were 52 pregnancies co-exposed to BZD/z-hypnotics and antidepressants, versus 82 exposed to BZD/z-hypnotics only.

bThe number of exposed pregnancies may differ across the specific outcomes, depending on whether these individual measures were reported by mothers.