Prenatal exposure to anxiolytic and hypnotic medication in relation to behavioral problems in childhood: a population-based cohort study

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ABSTRACT

Benzodiazepines and benzodiazepine-related medications (BBRMs) are anxiolytics and hypnotics acting on γ-amino butyric acid $(GABA)_A$ receptors. BBRMs are assumed to have a low potential for major congenital malformations, but research on more subtle and protracted developing symptoms of these medications is lacking. Therefore, we prospectively investigated the association between BBRM use in pregnancy and long-term effects on child behavior in a large population-based cohort study. The study population consisted of 104 children prenatally exposed to BBRM, 527 children exposed to maternal prenatal anxiety or phobic anxiety symptoms (without exposure to BBRM), and 5609 control children. At child age, 6 years, Oppositional Defiant Disorder (ODD), Aggressive Behavior and Anxiety Problems were assessed by the Child Behavior Checklist (CBCL) reported by the mother and the Teacher Report Form (TRF). Children prenatally exposed to BBRM had higher scores of ODD and aggressive behavior, but not of anxiety. However, these associations were explained by maternal anxiety symptoms during pregnancy. Moreover, prenatal exposure to anxiety (without exposure to BBRM) was associated with increased scores of child ODD, aggressive behavior, and anxiety. In conclusion, the current study demonstrates that prenatal BBRM exposure was not independently associated with ODD and aggressive behavior in childhood when prenatal anxiety symptoms were taken into account.

Keywords: benzodiazepine; benzodiazepine related medications; z-drugs, pregnancy; child behavior; oppositional deviant disorder; aggression.

1. INTRODUCTION

Pregnancy is commonly associated with emotional changes, anxiety, and sleep problems (Goodman et al., 2014; Cai et al., 2013; Mindell et al., 2015). The prevalence of any anxiety disorder during pregnancy varies between 4.4 and 39% (Goodman et al., 2014). Anxiety during pregnancy has been associated with adverse obstetric and neonatal outcomes (Dayan et al., 2002; Hedegaard et al., 1993; van Batenburg-Eddes et al., 2009; Monk et al., 2000). It is important to treat anxiety during pregnancy, but the use of medications in pregnancy could also have potential risks for a mother and her developing child. Therefore, clinicians need to carefully weigh the balance between maternal well-being and child safety in their treatment decisions. This is difficult as information about the potential long-term consequences of anxiolytic and hypnotic medication is limited.

Benzodiazepines and benzodiazepine-related medications (BBRMs) are anxiolytics and hypnotics with the same mechanism of action; they are positive allosteric modulators of the γ-amino butyric acid $(GABA)_A$ receptor. Benzodiazepines may be prescribed in pregnancy to treat anxiety, insomnia, epileptic seizures, hyperemesis gravidarum, eclampsia or the risk of preterm birth (Buhimschi and Weiner, 2009; Baldwin et al., 2013). Further, benzodiazepines are commonly combined with Selective Serotonin Reuptake Inhibitors (SSRIs) in treating comorbid anxiety and depressive disorders (Riska et al., 2014), and for the treatment of excitement and sleep disturbances that frequently occur at the beginning of SSRI treatment. Benzodiazepine-related medications , such as zolpidem, zopiclone and zaleplon (also known as z-drugs) produce fewer anxiolytic and anticonvulsant effects, and they are used to treat insomnia. The prevalence of BBRMs use during pregnancy varies from 1.5-3.9% (Riska et al., 2014; Hanley and Mintzes, 2014). BBRMs are lipophilic, un-ionized compounds that easily penetrate the placental barrier. Newborns can have three to four times higher levels of BBRM in their plasma compared to their mothers (Kanto, 1982; Juric et al., 2009), because maternal serum binding capacity for benzodiazepines is lower during pregnancy and negatively correlated with gestational age (Lee et al., 1982). These high BBRM levels in the fetal circulation may negatively affect offspring development in short and long term.

Several studies have demonstrated associations between prenatal exposure to BBRM and birth and infant outcomes. For example, the risk of major congenital malformations tends to be small (Dolovich et al., 1998; Wikner and Kallen, 2011), but poor neonatal outcomes related to BBRM are more evident (Wikner et al., 2007a; Wang et

al., 2010), and benzodiazepine use in late pregnancy or during labor has been associated with withdrawal symptoms and hypotonia in newborns (Cree et al., 1973; McElhatton, 1994).

Associations of prenatal BBRM exposure with longer-term child outcomes are less clear. Relatively few studies focused on the potential behavioral consequences of prenatal exposure to BBRM (reviewed in El Marroun et al., 2014a). A clinical trial investigated the use of lorazepam as a premedication for Caesarean section and showed that exposed neonates had reduced scores on the Brazelton Neonatal Behavior Assessment Scale (Houghton, 1983). Several studies have reported an association between prenatal exposure to benzodiazepines and short-term effects; such as delays in psychomotor development (Mortensen et al., 2003; Laegreid et al., 1992), social problems, and hearing and speech impairments (Viggedal et al., 1993). Additionally, hyperactivity and attention deficit symptoms in childhood after prenatal exposure to benzodiazepines have been described (Laegreid et al., 1989). No association between prenatal benzodiazepine exposure and child behavior was observed in children whose mothers attempted suicide during pregnancy with high benzodiazepine doses (Gidai et al., 2008a; Gidai et al., 2008b). Likewise, a study investigating teacher-reported child behavior found no differences between children prenatally exposed to benzodiazepine compared to non-exposed children (Stika et al., 1990).

The primary concern in studies examining prenatal exposure to BBRMs is confounding by indication, which is a specific type of confounding that can occur in observational (non-experimental) pharmacoepidemiological studies of the effects or side effects of medications. As none of the studies described above are experimental, all of the studies were prone to some level of confounding by indication. This type of confounding arises from the fact that individuals who are prescribed or who take a given medication may be inherently different from those individuals who are not treated by medication. Other limitations of the previous studies are that the studies are relatively small, and have a relatively short follow up as most of the studies focused on children younger than 18 months of age. In the current study, we attempted to address these limitations by taking into account maternal anxiety during pregnancy and the child's age of 3 to address confounding by indication and other factors that may confound the association such maternal smoking, drinking and socioeconomic indicators.

Since the long-term effects of prenatal BBRM exposure on childhood behavioral problems are unclear, the goal of this study was to prospectively investigate the association between BBRM (GABAergic anxiolytic and hypnotic medications) use in pregnancy and child behavioral problems in a large cohort study. Based on the studies

described above, we hypothesized that children prenatally exposed to BBRMs will have increased behavioral problems as compared to non-exposed children.

2. METHODS

2.1.Participants

This study was embedded in the Generation R Study, a population-based prospective birth cohort, designed to identify early environmental and genetic causes of growth, development and health during fetal life and childhood (Jaddoe et al., 2012). The Medical Ethics Committee of Erasmus MC in Rotterdam, the Netherlands, has approved the study in accordance with the Declaration of Helsinki of the World Medical Association. Written informed consent was obtained from all the participants.

All pregnant women resident in Rotterdam and whose delivery date was from April 2002 to January 2006 were eligible for enrollment in the study. The present study only included children who participated in the prenatal and postnatal follow-up (n=8101). Of these, 685 (8.5%) were excluded because of unavailable information on maternal medication use. Further, 465 (6.3%) children whose mothers used BBRM but 'not in pregnancy' were excluded, as a spillover effect cannot be ruled out. Information on child emotional and behavioral problems was not obtained in 711 (10.2%) children during follow-up. Finally, 6240 children formed the study population.

2.2. Maternal Use of BBRM and Anxiety during Pregnancy

In this study, we assessed two exposures: (a) BBRM use during pregnancy, and as a contrasting exposure, (b) maternal anxiety symptoms in pregnancy, not treated by benzodiazepines. It is important to contrast long-term child developmental effects of medications used in pregnancy with the common indication of those medications.

In order to optimize ascertainment of medication use, we used two sources of information, which were combined into one exposure variable: (1) self-reports assessed with questionnaires and (2) prescription records from pharmacies. This approach of combining self-reported information and data from prescription records has been described previously (El Marroun et al., 2012; El Marroun et al., 2014b). In each trimester, pregnant women reported whether and when they had used any medications. Using these questionnaires, BBRM exposure and

relatively crude timing (first, second or third trimester) were assessed. To validate the use of filled prescriptions, we asked women for permission to contact their pharmacy. These records provided information on the type of medication, duration, dose and specific timing (Table 1). Any use of BBRM during pregnancy, as assessed by self-reports and prescription records, was defined as exposure. The agreement between self-reports and prescription records (BBRM use versus non-use during pregnancy), measured by Cohen's kappa of the agreement, was fair (κ=0.34).

Of the 104 women who used BBRM during pregnancy, 50 women used them in the first trimester only and 54 women used them in the first and also in one or two additional trimesters. Prescription records were obtained for 67 (64.4%) participants. Information obtained from these pharmacy records is presented in Table 1 for illustrative purposes. According to the prescription records, 81.2 % used BBRMs less than 30 days and doses were therapeutic; there was no case of BBRM use above the maximum daily dose. Using questionnaires, the pregnant women reported the use of brotizolam, clobazam, clonazepam and clorazepate additionally to data from prescription records. Reasons for using BBRMs were not systematically collected (open text fields) and were often left open. Most commonly BBRMs were used because of anxiety and stress symptoms, sleep problems, muscle relaxation, nervousness and panic.

Anxiety and phobic anxiety symptoms were assessed with the Brief Symptom Inventory (BSI) (Derogatis and Melisaratos, 1983) at the 20 weeks of pregnancy. The BSI is a validated questionnaire with 53 items on a 5-point scale, ranging from 0 = 'not at all' to 4 = 'extremely'. We used the anxiety scale with six items and the phobic anxiety scale with five items. According to the Dutch norm data, a score higher than 0.75 indicates clinically relevant anxiety symptoms and a score higher than 0.70 indicates clinically relevant phobic anxiety symptoms (de Beurs, 2004). Based on the reported maternal anxiety symptoms and BBRM use during pregnancy, children were classified into three groups:

(a) Controls – No exposure to BBRM and exposure to a low score of maternal anxiety or phobic anxiety symptoms (n=5609, 89.9%)

(b) Exposed to anxiety – Exposure to clinically relevant anxiety or phobic anxiety symptoms without exposure to benzodiazepines (n=527, 8.4 %)

(c) Exposed to BBRM – Exposure to benzodiazepines or benzodiazepine-related medications during pregnancy (n=104, 1.7%).

2.3. Childhood emotional and behavioral problems

Child emotional and behavioral problems were reported by the mother using Child Behavior Checklist for ages 1½ to 5 (CBCL 1½ -5) when the children were 6 years old. As the majority (60%) of the children were younger than 6 years old at the time of CBCL assessment (37 % were 6 years old and 3 % of the children were 7 years old), we used the CBCL 1½ -5 version for all children during this assessment wave to enhance comparability across all children, as recommended in the ASEBA manual (Achenbach, 2000). Previously, our research group showed that the Cronbach's alphas for all scales were the same in 6 year-old children and in children older than 6 years, indicating that problems were also reliably measured in children older than 6 years of age (Basten et al., 2016).

Additionally, the Teacher Report Form (TRF) was assessed at age 6½ years. Both questionnaires contain items about behavioral, social and emotional problems that are scored on a 3-point scale (Achenbach, 2000). The CBCL and the TRF have two types of scales: scales oriented to Diagnostic and Statistical Manual of Mental Disorders (DSM) and empirically based syndrome scales. The Oppositional Defiant Disorder (ODD) and the Anxiety Problems subscales are consistent with diagnostic categories of the DSM, 4th edition (American Psychiatric Association, 1994). The Aggressive Behavior scale is an empirically derived syndrome scale. For example, teachers and parents reported on whether the child is defiant, disobedient or has temper tantrums (ODD); whether the child clings to adults, is nervous or too anxious (Anxiety); or whether the child destroys things, hits others or has explosive or unpredictable behavior (Aggressive Behavior). The CBCL and the TRF are standardized instruments to assess child emotional and behavioral problems; the Dutch versions of these checklists are reliable and well validated (Tick et al., 2007). The syndromes subscales had a good fit in 23 international studies (Ivanova et al., 2010).

2.4. Covariates

Demographic information, including maternal and paternal age, ethnicity, educational level and family income was based on self-report. Maternal ethnicity was defined according to the classification of Statistics Netherlands and

categorized into Dutch, non-Dutch Western and non-Dutch non-Western, based on the country of birth of their parents (Statistics Netherlands, 2004). Family income, defined by the monthly income of the household, was defined as less than € 1200 (below social security level), € 1200-2000 (modal income) and more than € 2000 (higher than modal). Maternal smoking and alcohol drinking habits were obtained by questionnaires in each trimester and categorized into: 'no', 'until the pregnancy was known' and 'continued during pregnancy'. Information on maternal SSRI use, like maternal BBRM use during pregnancy, was collected with questionnaires in each trimester and prescription records and was included as an important confounding factor (Wikner et al., 2007b). Information on other psychotropic medication (such as tricyclic antidepressants, antipsychotic, antiepileptic or other sleep medication) was assessed as well. Information on other psychiatric symptoms in the prenatal period was also collected using the BSI (Derogatis and Melisaratos, 1983) at 20 weeks, which includes the following scales: total psychopathology symptoms (global severity index, GSI), anxiety, phobic anxiety, depressive symptoms, hostility, interpersonal sensitivity, obsessive-compulsive symptoms, paranoid ideation, psychoticism and somatization. At the child's age of 3 years, we used a shortened version of the BSI and only assessed depressive symptoms, anxiety, interpersonal sensitivity and hostility.. Child characteristics including gender, birth weight, gestational age and Apgar score were measured at physical examination at birth and were obtained from midwife and hospital registries.

2.5. Statistical Analyses

We used analysis of variance (ANOVA) with Bonferroni-corrected post-hoc tests for parametric continuous variables, Kruskal-Wallis tests for non-parametric continuous variables and χ^2 statistics for categorical variables to compare the descriptive characteristics of the two exposure groups compared to the control group. Demographic variables and psychopathology scores during pregnancy and at the child's of age 3 years were compared. Additionally, we compared the characteristics of the BBRM exposed and the anxiety exposed children using two samples t-test for the continuous outcome and χ^2-test for the categorical outcome.

The main analyses were performed using linear regression analyses to examine the relationship of prenatal BBRM exposure or maternal anxiety with child ODD symptoms. The predictor variable was the exposure group (control, exposed to anxiety, exposed to BBRM) and the outcome was ODD symptoms score. For the predictor, we used dummy variables with the controls being the reference group. We used the continuous score for ODD symptoms rather than the clinical cut-off to study the continuum of symptoms in the general population and to

increase the power of our analyses. To test the specificity of the association, we studied the relation between prenatal BBRM use and childhood anxiety symptoms using the same models. Additional regression analyses were performed with the Aggressive Behavior scale of the CBCL and TRF. Furthermore, the generalized estimating equation (GEE) was used to analyze the same association combining the ratings of the mothers and the teachers. The GEE procedure adjusts for within-subject correlation, provides more precise effect estimates and reduces the error derived from multiple comparisons (Rothman, 2008). It was not our aim to test for differences between two informants or a possible age trend in child behavioral problems.

Main models were adjusted for child age and gender, maternal age, socioeconomic status, smoking and drinking habits during pregnancy. Model 2 was adjusted for SSRI use in pregnancy to test whether the results were driven by prenatal SSRI exposure. Based on the change-in-estimate methods (Mickey and Greenland, 1989) maternal education, ethnicity, paternal age, Apgar score and birth order were not included as they did not affect the association. Likewise, gestational age and birth weight did not affect the association. In the analyses, we did not adjust for the use of other psychoactive medications, as the numbers of these medications were very low in the total study sample ($n<10$). To deal with confounding by indication in the last step, we adjusted models for the scale of maternal prenatal anxiety symptoms (Model 3). We reported Betas (B), their 95% confidence intervals, and the p-values. B represents the adjusted increase or decrease of outcome score as measured by the CBCL or the TRF in the exposed versus the unexposed group. Finally, in sensitivity analyses, we further adjusted the models for anxiety symptoms measured when the child was 3 years.

To avoid a bias of complete case analysis, we accounted for missing information of the covariates by using multiple imputation methods. The determinants and outcomes were not imputed. The proportion of missing data for this study sample varied between 0.2 and 17.7%, with the exception of maternal anxiety symptoms at 36 months (37.7%). We reported pooled effect estimates of five imputed datasets. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), 21.0 (IBM, Armonk, New York, USA).

2.6. Sample Size Calculation

We performed calculations to estimate the size of the exposed groups required to detect small effect sizes; according to Cohen small effect size is 0.10-0.30 (Cohen, 1992). Assuming the significance criterion $\alpha=0.05$, 80% power and

a ratio of 1:54 (exposed to benzodiazepine: controls), 128 children exposed to benzodiazepines would enable detection of the effect size of 0.25. This condition was satisfied in the combined report of our analysis, but using maternal report only, the effect size of 0.32 could be detected; and similarly using teachers report only, the effect size of 0.36 could be detected. Likewise, taking into account the same criteria for α and power, and a ratio 1:11 (exposed to anxiety: controls), 137 children exposed to anxiety would enable detection of the effect size of 0.25; this was fulfilled in all parts of our analysis including this exposure group.

3. RESULTS

3.1. Demographics

Psychopathology characteristics are displayed in Table 2; it shows that on average the control group scores the lowest on all psychopathology variables and the group with clinically relevant anxiety and phobic anxiety has the highest average score of other psychopathology. Overall the correlation coefficients of the different BSI subscales varied between 0.39 and 0.76.

Demographic characteristics of this sample are presented in Table 3. Mothers with anxiety were younger, more often of non-Dutch origin, less educated, had lower household income, and smoked more often during pregnancy than the control group. Fathers of children from this group were younger than fathers from the control group. Compared with the control group, mothers taking BBRMs during pregnancy were less educated, had a lower household income, and smoked more often during pregnancy. SSRIs were used by 63 pregnant women in the study sample; in the control group 33 SSRI users were present, in the group exposed to anxiety 10 women used SSRIs and in the group that used BBRMs in pregnancy 20 women also used SSRIs.

Next, we compared the BBRM-exposed group with the anxiety-exposed group. Mothers taking BBRMs were significantly older (t=-3.77, p<0.001), more likely to be of Dutch origin (χ^2=19.62, p<0.001), had higher household income (χ^2=7.50, p<0.023), smoked more (χ^2=7.72, p=0.021) and drank more alcohol during pregnancy (χ^2=14.90, p=0.002). Furthermore, mothers taking BBRMs had significantly less prenatal anxiety symptoms (t=8.88, p<0.001) and phobic anxiety symptoms (t=3.34, p=0.001). Importantly, they did not differ in anxiety scores at the child's age of 3 years (t=-0.02, p=0.984).

3.2. Child ODD and Aggressive Behavior

In Table 3, we report the associations between prenatal exposure to BBRMs and ODD, represented by beta and its 95% confidence interval. The betas represent the difference in CBCL/TRF scores between exposed and unexposed children. Children exposed to BBRM in pregnancy were more likely to have higher ODD scores than the control group. The ODD score were higher according to maternal report (B=0.77, 95% CI: 0.27-1.27, p=0.003), and teacher report (B=0.47, 95% CI: 0.05-0.90, p=0.030). Consequently, the combined reports, analyzed using GEE, also showed a positive association between prenatal BBRM exposure and ODD scores in childhood (B=0.66, 95% CI: 0.25-1.06, p=0.001), which remained significant after adjustment for prenatal SSRI exposure (B=0.48, 95% CI: 0.09-0.87, p=0.017). However, when the model was adjusted for maternal anxiety symptoms this association was no longer statistically significant (B=0.32, 95% CI:-0.08-0.73, p=0.120).

Children exposed to maternal anxiety that was not treated by benzodiazepines showed increased mother-reported (B=0.51, 95% CI 0.27-0.74, p<0.001) by not teacher-reported (B=0.05, 95% CI:-0.16-0.24, p=0.661) ODD symptoms in childhood. When we combined the maternal and teacher reports to increase the number of observations, the GEE model showed significantly higher ODD symptoms in childhood exposed to BBRMs (B=0.30, 95% CI: 0.12-0.49, p=0.001). When we additionally adjusted this model for prenatal SSRI exposure the effect estimate remained statistically significant (B=0.29, 95% CI: 0.11-0.48, p=0.002).

In addition to ODD symptoms, we tested the association between prenatal BBRM exposure and childhood score at the Aggressive Behavior scale. Prenatal BBRM exposure was associated with increased symptoms of aggressive behavior in childhood (B=1.77, 95% CI: 0.59-2.95, p=0.003). Both teacher-reported (B=1.36, 95% CI: 0.15-2.58, p=0.028) and also the combined GEE model (B=1.64, 95% CI: 0.60-2.68, p=0.002) showed that children prenatally exposed to BBRM had significantly higher scores of aggressive behavior. Further, adjustment for prenatal SSRI exposure did not change this (B=1.15, 95% CI: 0.17-2.13, p=0.022). However, after additional adjustment for maternal anxiety symptoms the effect was not statistically significantly different (B=0.75, 95% CI:-0.28-1.77, p=0.154).

Compared to the control group, children prenatally exposed to maternal anxiety had higher scores of aggressive behavior as reported by the mother (B=1.44, 95% CI: 0.89-1.99, p<0.001). However, the teacher report showed no significant difference in aggressive behavior (B=0.09, 95% CI:-0.48-0.66, p=0.753). According to

combined GEE model, children prenatally exposed to anxiety had significantly higher scores of childhood aggressive behavior (B=0.86, 95% CI: 0.37-1.34, p=0.001).

3.3. Child Anxiety Problems

BBRM-exposed children had higher mother-reported but not teacher-reported anxiety scores (Table 3). However, after taking into account prenatal SSRI exposure, the association did not remain statistically significant.

Interestingly, children exposed to maternal anxiety, not treated by benzodiazepines, were more likely to have higher anxiety scores. Results derived from maternal report (B=0.97, 95% CI: 0.76-1.19, p<0.001) were consistent with results derived from the teacher report (B=0.21, 95% CI: 0.05-0.37, p=0.009). The relation between prenatal exposure to maternal anxiety and childhood anxiety symptoms remained statistically significant when combining maternal and teacher report using the GEE model (B=0.66, 95% CI: 0.46-0.85, p<0.001). These associations remained the same when taking into account prenatal SSRI exposure.

3.4. Maternal anxiety at the child's age of 3 years

Prenatal anxiety and anxiety symptoms at the child's age of 3 years were moderately correlated (r=0.33). Anxiety symptoms at the child's age of 3 years were significantly associated with childhood outcomes, and when taking anxiety the child's age of 3 into account it explained part of the associations of maternal anxiety during pregnancy with childhood ODD and aggressive behavior, but the association of maternal anxiety during pregnancy with childhood anxiety remained present.

4. DISCUSSION

In this large population-based cohort study, we found that children, born to mothers who had a prescription or reported use of BBRMs in pregnancy had higher scores of ODD and aggressive behavior. However, after adjusting the model for the maternal anxiety symptoms, the observed associations were no longer significant. On the other hand, maternal anxiety or phobic anxiety during pregnancy, not treated by benzodiazepines, was associated with increased scores of child ODD, aggressive behavior, and child anxiety.

The prevalence of prenatal BBRM use in our cohort was 1.5% (n=114 among 7416 mothers with available data of medication use in pregnancy). This prevalence is similar to the prevalence of 1.5% reported in a recent Norwegian study (Riska et al., 2014) but was lower than the prevalence of 3.9% in the USA (Hanley and Mintzes, 2014). Interestingly, in our study sample, only 3 pregnant women used benzodiazepine related medications (0.04%), which is much lower than the prevalence of 4.7% in Taiwan (Wang et al., 2010). Additionally, in our study, the pharmacy records show that 81.2% of the mothers used BBRM according to recommendations, less than 30 days. The agreement between pharmacy records and questionnaires measured by stringent Cohen's kappa was fair; kappa was likely driven by the low percentage of users compared to non-users (Shrout et al., 1987). Or it may be that women who used BBRMs for short periods were not sure whether it was before or after they knew they were pregnant. It is also possible that women did not take their medication even though they BBRMs were prescribed and they filled their prescriptions in the pharmacy. Additionally, it may be possible that women indeed reported using BBRMs, but obtained medications from other pharmacies; in these cases, this information would not be present in the prescription record. These explanations could all have contributed to the fair agreement between self-reported and prescription BBRM use.

Little is known about possible long-term consequences of prenatal BBRM exposure and child behavior. Prenatal exposure to benzodiazepines has been associated with a delay in development and attention-deficit and hyperactivity symptoms (Laegreid et al., 1989; Viggedal et al., 1993), but has not been associated with children's school behavior (Stika et al., 1990). In the current study, the associations of prenatal BBRM exposure with childhood ODD symptoms and aggressive behavior were confounded by maternal anxiety during pregnancy. Interestingly, women who used BBRMs in pregnancy had much lower anxiety scores and only 22.1% had clinically relevant anxiety or phobic anxiety symptoms. Lower anxiety scores in the BBRM-using women could be due to using BBRMs for other reasons than anxiety, such as insomnia and muscle spasms or it could be due to the fact that their anxiety was managed with BBRMs.

Further, this study shows that maternal anxiety symptoms during pregnancy are associated with negative child internalizing and externalizing problems. This association may be biased by maternal report, however, the association, albeit less strong, is also observed when the teacher reports about child emotional and behavioral problems. Several mechanisms could underlie this association. First, it is very likely that common genetic or

epigenetic factors affecting both maternal anxiety and child development explain our finding. For example, a recent study showed that prenatal stress was related to epigenetic changes (DNA methylation) of the glucocorticoid receptor gene, a receptor that plays a role in the hypothalamus–pituitary–adrenal (HPA) axis (Ostlund et al., 2016). Further, research suggests that maternal distress during pregnancy leads to an elevated maternal HPA-axis activity, which causes an increased release of glucocorticoids that in turn negatively affect fetal development (reviewed in Huizink et al., 2004; reviewed in Van den Bergh et al., 2005) and an impaired uterine blood flow resulting in a lack of oxygen has also been proposed as a potential mechanism (reviewed in Van den Bergh et al., 2005). Second, our results showed that women with high levels of anxiety symptoms also experienced other psychological problems, which may influence our findings. Third, it is possible that the observed relation could reflect group differences in parenting styles or other unmeasured confounding family factors, and residual confounding may still be present. For example, it has been shown that harsh parental discipline is related to anxiety in children (Mackenbach et al., 2014).

In spite of the strengths of our study, such as the prospective cohort design, the long duration of follow-up, exposure information from two sources, the assessment of child problems by two informants and the ability to take into account many confounding factors (such as maternal smoking and drinking during pregnancy), some limitations should be discussed. First, the number of children exposed to BBRM was relatively small, which limits the power, and therefore we were not able to study the BBRM-type, dose-dependent, or trimester-specific effects. However, as BBRMs all involve the GABAergic system, type-specific effects would be unlikely. Second, we did not have any information regarding the indication of BBRM use. BBRMs are prescribed for anxiety, but also for insomnia; insomnia is the first indication for benzodiazepines, the only indication for benzodiazepine related medications, and the most likely indication for short-term use. Still, insomnia and anxiety are usually comorbid. Third, we did not obtain DSM clinical diagnoses; we had measures of maternal anxiety and child behavioral problems on a continuous scale. However, the instruments used were well validated (Derogatis and Melisaratos, 1983; Tick et al., 2007). Another limitation is that maternal psychopathology was measured only once in mid-pregnancy and could not be directly linked to BBRM treatment. Ideally, it should be measured multiple times during pregnancy, but usually, this is not feasible in epidemiological settings. Further, we based the categorization only on anxiety, phobic anxiety and BBRM use during pregnancy, and thus cannot rule out that the control group comprises women with other psychiatric disorders. However, the data does show that in the control group the average psychopathology scores are

low (Table 2). Finally, confounding by indication remains the primary limitation of pharmaco-epidemiological studies.

Primary prevention of anxiety in women of childbearing age is an important goal and can improve the health of both mother and child. Further, proper management of anxiety during pregnancy should have priority as our results show that prenatal anxiety may have long-term consequences on child development. Decision-making regarding pharmacological treatment of anxiety and insomnia in pregnancy should be driven by scientific evidence from studies investigating prenatal BBRM exposure and diverse child outcomes. Based on the clinical guidelines, monotherapy should be preferred and tailored to the individual aiming to provide optimal treatment of the disorder in the pregnant mother and to minimize exposure of medications and their metabolites in the fetus (Bulletins--Obstetrics, 2008).

In conclusion, this large cohort study with long-term follow-up suggests that prenatal anxiety is associated with ODD, aggressive behavior and anxiety symptoms in offspring. Prenatal exposure to moderate use of BBRMs was not independently associated with ODD and aggressive behavior in childhood when prenatal anxiety symptoms were taken into account. Studies on prenatal exposure to psychiatric medications and child outcomes should always attempt to address confounding, in particular confounding by indication and to carefully assess maternal psychopathology.

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CONFLICT OF INTEREST

F.C. Verhulst is head of the Department of Child and Adolescent Psychiatry at Erasmus MC, which publishes the Achenbach System of Empirically Based Assessment (ASEBA) and from which the department receives remuneration. All other authors declare no competing financial interest in relation to the work described.

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Table 1

Table 1 Information on benzodiazepines and benzodiazepine-related medication from prescription records

Type of medication		*Used doses*			*Duration of treatment* [a]			*Use in DDDs* [b]		
Name	Number of patients used it [c]	Mean dose (mg)	Min. dose (mg)	Max. dose (mg)	Mean duration (days)	Min. (days)	Max. (days)	DDD (mg)	Total dosage use in DDDs	Dosage use in DDDs per patient
Benzodiazepines										
Alprazolam	2	0.9	0.25	1.5	17.5	6	29	1.0	45.0	22.5
Bromazepam	2	10.5	9.0	12.0	127	49	205	10.0	290.1	145.1
Diazepam	21	7.7	2.0	20.0	16.9	1	101	10.0	222.0	11.1
Lorazepam	3	1.7	1.0	2.0	86.3	85	87	2.5	173.2	57.7
Oxazepam	14	14.6	5.0	50.0	18.9	2	54	50.0	74.5	5.3
Lormetazepam	4	2.0	1.0	4.0	17	5	30	1.0	178.0	44.5
Midazolam	1	7.5	-	-	287	-	-	15.0	143.5	143.5
Nitrazepam	1	5.0	-	-	1	-	-	5.0	1.0	1.0
Temazepam	18	12.2	10.0	20.0	11.2	1	30	20.0	126.0	7.0
Benzodiazepine related medication										
Zolpidem	2	10.0	10.0	10.0	6.5	3	10	10.0	13.0	6.5
Zopiclone	1	7.5	-	-	1	-	-	7.5	1.0	1.0

[a] Duration of treatment represents use of medications between two defined dates: conception date=last menstrual period+7 days, and birth date. Only one woman used midazolam during whole pregnancy. According to data from prescription records, 81.2% of children were prenatally exposed to benzodiazepines or benzodiazepine-related medications (z-drugs) less than 30 days (four weeks), as it is recommended.

[b] DDD=Defined daily dose; a statistical measure of medication consumption defined by World Health Organization (WHO).

[c] Number of patients who used benzodiazepines in pregnancy and had the prescription records was 67, but 2 patients used two different benzodiazepines; therefore the sum of patients in this table is 69.

Table 2

Table 2 Psychopathology characteristics of the study population [a]

Variable	*Control group* (n=5609)	*Exposed to anxiety* (n=527)	p-value [b]	*Exposed to benzodiazepines* (n=104)	p-value [b]
Maternal characteristics					
Symptoms of psychopathology					
In the prenatal period, mean (se), IQR					
Total problems score (global severity index)	0.18 (0.0027), 0.19	0.95 (0.0231), 0.71	<0.001	0.54 (0.0698), 0.67	<0.001
Anxiety [c]	0.15 (0.0028), 0.17	1.21 (0.0252), 0.67	<0.001	0.61 (0.0885), 0.67	<0.001
Phobic anxiety	0.04 (0.0016), 0.00	0.65 (0.0286), 0.80	<0.001	0.38 (0.0830), 0.40	<0.001
Depressive symptoms	0.12 (0.0038), 0.17	0.95 (0.0362), 1.17	<0.001	0.49 (0.0785), 0.67	<0.001
Hostility	0.22 (0.0043), 0.40	0.86 (0.0299), 0.80	<0.001	0.47 (0.0668), 0.60	<0.001
Interpersonal sensitivity	0.17 (0.0043), 0.25	0.92 (0.0353), 1.00	<0.001	0.54 (0.0743), 0.75	<0.001
Obsessive-compulsive	0.36 (0.0056), 0.60	1.23 (0.0336), 1.15	<0.001	0.75 (0.0892), 0.80	<0.001
Paranoid Ideation	0.14 (0.0043), 0.20	0.92 (0.0383), 1.20	<0.001	0.45 (0.0763), 0.60	<0.001
Psychoticism	0.08 (0.0027), 0.00	0.65 (0.0280), 0.80	<0.001	0.34 (0.0642), 0.40	<0.001
Somatization	0.30 (0.0049), 0.43	1.01 (0.0282), 0.86	<0.001	0.67 (0.0824), 0.71	<0.001
Symptoms of psychopathology					
At 3 years, mean (se), IQR					
Anxiety [c]	0.15 (0.0043), 0.17	0.41 (0.0334), 0.67	<0.001	0.42 (0.0778), 0.67	<0.001
Depressive symptoms	0.11 (0.0043), 0.17	0.37 (0.0382), 0.50	<0.001	0.22 (0.0543), 0.33	0.161
Hostility	0.16 (0.0041), 0.20	0.34 (0.0273), 0.40	<0.001	0.25 (0.0508), 0.20	0.015
Interpersonal sensitivity	0.12 (0.0046), 0.25	0.42 (0.0372), 0.50	<0.001	0.22 (0.0528), 0.25	0.185

[a] Control group: no benzodiazepine use, a low score on anxiety and phobic anxiety symptoms scales during pregnancy; Exposed to anxiety: children exposed to clinically relevant anxiety or phobic anxiety symptoms during pregnancy; Exposed to benzodiazepines: children exposed to benzodiazepines or benzodiazepine-related medications in pregnancy.

[b] p-values were derived from Kruskal–Wallis tests for non-parametric continuous variables comparing means between the control group as a reference, and the group exposed to anxiety or the group exposed to benzodiazepines.

[c] All descriptive parameters were computed using non-imputed original data and presented here for the descriptive purpose of the psychopathology of the study population. Maternal prenatal anxiety symptoms were used in further analyses and therefore this variable was imputed using the multiple imputations method. This resulted in pooled means and standard errors from five datasets per group: control group 0.18 (0.0031), exposed to anxiety 1.21 (0.0251) and exposed to benzodiazepines 0.62 (0.0747).

IQR: Interquartile range

Table 3

Table 2 Descriptive statistics of the study population [a]

Variable	*Control group* (n=5609)	*Exposed to anxiety* (n=527)	p-value [b]	*Exposed to benzodiazepines* (n=104)	p-value [b]
Maternal characteristics					
Age at inclusion, years: mean (s.e.), IQR	30.41 (0.0661), 6.29	28.71 (0.2506), 8.99	<0.001	31.04 (0.5641), 7.27	0.207
Ethnicity, %					
Dutch	55.8	31.8	<0.001	52.9	0.602
Non-Dutch Western	8.8	8.9		11.5	
Non-Dutch non Western	35.4	59.3		35.6	
Education, %					
Primary education	9.0	17.1	<0.001	18.5	<0.001
Secondary education	42.9	52.8		46.9	
Higher education	48.1	30.1		34.6	
Household income, %					
Less than € 1200	18.2	38.7	<0.001	26.9	0.016
€ 1200-2000	17.8	26.9		23.7	
More than € 2000	64.0	34.4		49.4	
Smoking habits, %					
Never smoked in pregnancy	76.1	65.2	<0.001	51.3	<0.001
Smoked in early pregnancy	8.8	9.6		10.8	
Smoked throughout pregnancy [c]	15.1	25.2		37.9	
Drinking habits, %					
Never drank in pregnancy	44.6	53.5	0.001	37.7	0.072
Drank in early pregnancy	13.6	11.3		22.7	
Drank occasionally in pregnancy	33.3	29.5		28.7	
Drank frequently in pregnancy [d]	8.4	5.7		10.9	
SSRI use in pregnancy, %					
Used in pregnancy	0.6	1.9	0.001	19.2	<0.001
Paternal characteristics					
Age at inclusion, years: mean (s.e.), IQR	33.28 (0.0807), 6.56	32.06 (0.3224), 9.33	<0.001	33.58 (0.5684), 6.29	0.652
Child characteristics					
Gender of child, %					
Boys	49.9	49.9	0.986	39.4	0.035
Girls	50.1	50.1		60.6	
Gestational age at birth, weeks: mean (s.e.), IQR	39.83 (0.0244), 1.86	39.87 (0.0742), 1.86	0.663	39.45 (0.2328), 2.00	0.037
Birth weight, grams: mean (s.e.), IQR	3419.94 (7.61), 690	3361.36 (23.72), 620	0.024	3317.88 (67.87) 825	0.091
Apgar 1 min, mean (s.e.), IQR	8.58 (0.0160), 1	8.52 (0.0570), 1	0.227	8.57 (0.1250), 0	0.962
Birth order, %					
1st	57.1	61.3	0.049	56.3	0.121
2nd	30.7	25.6		25.2	
≥3rd	12.2	13.2		18.4	

[a] Control group: no benzodiazepine use, low score on anxiety and phobic anxiety symptoms scales during pregnancy; Exposed to anxiety: children exposed to clinically relevant anxiety or phobic anxiety symptoms during pregnancy; Exposed to benzodiazepines: children exposed to benzodiazepines or benzodiazepine-related medications in pregnancy.

[b] P-values are derived from ANOVAs with Bonferonni-corrected posthoc tests for parametric continuous variables, Kruskal–Wallis tests for non-parametric continuous variables and χ^2-tests for categorical variables with control group as the comparison group.

[c] Smoking ten or more cigarettes per day fluctuated between 2.3 and 10.6% throughout pregnancy, with the highest percentage in the first trimester.

[d] Drinking more than one drink per day varied between 0.4 and 5.4% throughout pregnancy, with the highest percentage in the first trimester.

[e] At the time of psychopathology measurement 22.1% of pregnant women from the group exposed to benzodiazepines had clinically relevant anxiety or phobic anxiety symptoms.

IQR: Interquartile range

Table 4

Table 4 Prenatal exposure to benzodiazepines or maternal anxiety and behavioral and emotional problems in childhood

		Maternal report			*Teacher's report*			*Combined reports*		
		N	B (95%CI)	p-value	N	B (95%CI)	p-value	N[a]	B (95%CI)	p-value
Childhood ODD										
Control group	Reference	4449	Reference	Reference	3163	Reference	Reference	5191	Reference	Reference
Exposed to benzodiazepines	Model 1[b]	79	0.77 (0.27,1.27)	0.003	62	0.47 (0.05,0.90)	0.030	96	0.66 (0.25,1.06)	0.001
	Model 2[c]		0.54 (0.02,1.06)	0.041		0.37 (0.07,0.81)	0.095		0.48 (0.09,0.87)	0.017
	Model 3[d]		0.23 (-0.30,0.76)	0.393		0.37 (-0.07,0.82)	0.099		0.32 (-0.08, 0.73)	0.120
Exposed to anxiety	Model 1[b]	405	0.51(0.27,0.74)	<0.001	311	0.05 (-0.16,0.24)	0.661	488	0.30 (0.12,0.49)	0.001
	Model 2[c]		0.49 (0.26,0.73)	<0.001		0.04 (-0.16,0.24)	0.685		0.29 (0.11,0.48)	0.002
Childhood Anxiety										
Control group	Reference	4474	Reference	Reference	3161	Reference	Reference	5197	Reference	Reference
Exposed to benzodiazepines	Model 1[b]	79	0.51 (0.05,0.98)	0.031	62	0.22 (-0.11,0.56)	0.188	96	0.41 (0.05,0.76)	0.025
	Model 2[c]		0.35 (-0.13,0.83)	0.156		0.10 (-0.25,0.44)	0.574		0.25 (-0.07,0.58)	0.130
	Model 3[d]		NA	NA		NA	NA		NA	NA
Exposed to anxiety	Model 1[b]	409	0.97 (0.76,1.19)	<0.001	311	0.21 (0.05,0.37)	0.009	490	0.66 (0.46,0.85)	<0.001
	Model 2[c]		0.96 (0.75,1.12)	<0.001		0.21 (0.05,0.36)	0.010		0.65 (0.46,0.84)	<0.001

Models were constructed using linear regression or generalized estimating equation, linear model. Betas represent the increase or decrease for oppositional defiant disorder (ODD) or anxiety symptoms as measured with the Child Behavior Checklist (maternal report) and Teacher's Report Form.

Control group: no benzodiazepine use, low score on anxiety and phobic anxiety symptoms scales during pregnancy; Exposed to benzodiazepines: children exposed to benzodiazepines or benzodiazepine-related medications during pregnancy; Exposed to anxiety: children exposed to clinically relevant anxiety or phobic anxiety symptoms during pregnancy. Models were constructed with the control group as a reference group.

[a] N represented the number of children included in the analysis. In the total report, which is derived by generalized estimating equation, the number of observations for ODD was 7612 in reference group, 716 in group exposed to anxiety and phobic anxiety, and 141 in group exposed to benzodiazepines, in total 8469 observations; the number of observations for anxiety symptoms was 7635 in control group, 720 in group exposed to anxiety and phobic anxiety, and 141 in group exposed to benzodiazepines, in total 8496 observations.

[b] Model 1 was adjusted for child age and gender, maternal age, socioeconomic status, smoking and drinking habits during pregnancy;

[c] Model 2 additionally adjusted for use of Selective Serotonin Reuptake Inhibitors during pregnancy;

[d] Model 3 was additionally adjusted for the level of maternal anxiety symptoms during pregnancy.

NA: Not applicable