

Adverse family life events during pregnancy and ADHD symptoms in five-year-old offspring

Mina A. Rosenqvist,¹  Arvid Sjölander,¹ Eivind Ystrom,^{2,3,4}  Henrik Larsson,^{1,5} and Ted Reichborn-Kjennerud^{2,6}

¹Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; ²Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway; ³Department of Psychology, University of Oslo, Oslo, Norway; ⁴School of Pharmacy, University of Oslo, Oslo, Norway; ⁵School of Medical Sciences, Örebro University, Örebro, Sweden; ⁶Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Background: Prenatal exposure to maternal adverse life events has been associated with offspring ADHD, but the role of familial confounding is unclear. We aimed to clarify if adverse life events during pregnancy are related to ADHD symptoms in offspring, taking shared familial factors into account. **Method:** Data were collected on 34,751 children (including 6,427 siblings) participating in the population-based Norwegian Mother and Child Cohort Study. During pregnancy, mothers reported whether they had experienced specific life events. We assessed ADHD symptoms in five-year-old children with the Conners' Parent Rating Scale–Revised: short form. We modeled the associations between life events and mean ADHD scores with ordinary linear regression in the full cohort, and with fixed-effect linear regression in sibling comparisons to adjust for familial confounding. **Results:** Children exposed to adverse life events had higher ADHD scores at age 5, with the strongest effect observed for financial problems (mean differences 0.10 [95% CI: 0.09, 0.11] in adjusted model), and the weakest for having lost someone close (0.02 [95% CI 0.01, 0.04] in adjusted model). Comparing exposure-discordant siblings resulted in attenuated estimates that were no longer statistically significant (e.g. mean difference for financial problems -0.03 [95% CI $-0.07, 0.02$]). ADHD scores increased if the mother had experienced the event as painful or difficult, and with the number of events, whereas sibling-comparison analyses resulted in estimates attenuated toward the null. **Conclusions:** These results suggest that the association between adverse life events during pregnancy and offspring ADHD symptoms is largely explained by familial factors. **Keywords:** ADHD; prenatal exposures; delayed effects; adverse life events; antenatal stress; MoBa; the Norwegian Mother and Child Cohort Study.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder, with a prevalence of around 7.2% in children (Thomas, Sanders, Doust, Beller, & Glasziou, 2015). ADHD is characterized by symptoms of inattention, hyperactivity and impulsivity, and is associated with psychosocial impairment, poor academic functioning and psychiatric problems in children and adolescents (Faraone et al., 2015). Twin studies have shown that ADHD is highly heritable, but 10%–40% of the variance in liability is explained by environmental influences (Faraone & Larsson, 2018). In addition, the heritability estimate may include unknown amounts of environmental influences due to gene-environment interaction, and it is important to identify environmental risk factors for ADHD, as these factors may represent targets for prevention.

Prenatal influences have received increasing attention as potential causes of ADHD (Latimer et al., 2012), mainly due to the hypothesis that prenatal

exposures predispose individuals to disorders such as ADHD through fetal programming. Fetal programming refers to a process where factors in the intrauterine environment are hypothesized to influence the normal development of the fetus. Prenatal exposures, such as maternal stress, might permanently influence the structure, physiology and metabolism, causing long-lasting changes that might predispose individuals to later disorders (Barker, 1998). Prenatal stress has been suggested to influence the child's neurodevelopment and later risk of developing ADHD through exposure to high levels of maternal glucocorticoids (stress hormones), through impaired intrauterine blood flow, or through DNA methylation (Barker, Walton, & Cecil, 2018; Van den Bergh, Mulder, Mennes, & Glover, 2005).

Different stressors, such as adverse life events, have been used to measure prenatal and early childhood exposure to stress. In a pioneer study from 1975, Rutter et al. showed that aggregated psychosocial adversity was associated with an increased risk of childhood mental disorders (Rutter, Cox, Tupling, Berger, & Yule, 1975), which has later been supported by several more recent studies (e.g. Bjorkenstam, Bjorkenstam, Jablonska, & Kosidou, 2017; Counts, Nigg, Stawicki, Rappley, & von Eye, 2005). However, in this study, we focus on exposures during the prenatal period in order to explore the

Previously presented at the 6th World Congress on ADHD in Vancouver, Canada, 20–23 April 2017, where it was awarded the Young Scientist Award, and at the 47th Behavior Genetics Annual Meeting, in Oslo, Norway, 28 June–1 July 2017.

Conflict of interest statement: See Acknowledgements for full disclosures.

fetal programming hypothesis. There are several studies showing an association between stressful life events during pregnancy and offspring ADHD (Class et al., 2014; Glover, 2011; Grizenko et al., 2012; Huizink et al., 2007; Kim et al., 2009; Laucht et al., 2000; Li, Olsen, Vestergaard, & Obel, 2010; MacKinnon, Kingsbury, Mahedy, Evans, & Colman, 2018; Motlagh et al., 2010; Park, Cho, Kim et al., 2014; Park, Kim, Kim et al., 2014; Rodriguez & Bohlin, 2005; Ronald, Pennell, & Whitehouse, 2011; Zhu et al., 2015). However, two studies did not find any statistically significant associations between adverse life events during pregnancy and offspring ADHD (Lee, Chang, & Lung, 2006; Rice et al., 2010). Both studies were based on small samples (70 and 205 respectively), which limits the studies' power to detect an association, and might explain why no statistically significant association was found. These differences indicate the need for a meta-analysis on the subject. This discrepancy might also be explained by the variety in measures used, such as bereavement (Class et al., 2014; Li et al., 2010); experiencing an acute disaster (Huizink et al., 2007); self-perceived stress (Grizenko, Shayan, Polotskaia, Ter-Stepanian, & Joobar, 2008; Motlagh et al., 2010; Rice et al., 2010; Rodriguez & Bohlin, 2005; Zhu et al., 2015); and cumulative stress (Laucht et al., 2000; Lee et al., 2006; Ronald et al., 2011). Since no study has compared the effect of different life events, it is unclear if ADHD symptoms in offspring are influenced by prenatal maternal exposure to stressful events in general (i.e. global stress), or if any specific event is particularly influential.

It is important to consider the mother's subjective experience of adverse life events as the same event might be perceived as very stressful for one individual, and not stressful for another. If prenatal stress has a programming effect on the fetus, the effect may be stronger if the mother perceived the event as stressful. The mother's perception of the events has only been considered in five previous studies in relation to offspring ADHD symptoms (Grizenko et al., 2008; MacKinnon et al., 2018; Rice et al., 2010; Rodriguez & Bohlin, 2005; Zhu et al., 2015). Only two of these studies were longitudinal and based on larger samples (MacKinnon et al., 2018; Zhu et al., 2015). MacKinnon et al. (2018) found that prenatal exposure to high levels of stress was consistently associated with high levels of hyperactivity symptoms in 10,184 children followed from age 7 to 16. Zhu et al. (2015) found that severe stress during pregnancy was associated with higher odds of having elevated levels of ADHD symptoms among offspring boys (OR: 2.41, 95% CI: 1.03–5.66) but not girls (OR: 1.33, 95% CI: 0.47–3.83), based on 1,765 four-year-old children.

Experiencing multiple adverse events (i.e. cumulative exposure) might be more stressful for the mother, which would likely increase the risk of offspring ADHD further. Only one prospective study

has explored the effect of cumulative exposure to life events during pregnancy in relation to ADHD (Ronald et al., 2011). In that study, the authors found a significant association between the number of stressful life events during pregnancy and parent reported ADHD symptoms in two-year-old offspring, based on the Child Behavior Checklist (Ronald et al., 2011). However, since it is difficult to assess ADHD symptoms in small children, these findings need to be replicated in older children and with longer follow-up time.

Although life events are usually considered to be external influences by the environment, it has been found that these events are to a varying degree dependent from the individual's own genetically influenced behavior tendencies (Kendler & Baker, 2007). Taken together with the high heritability of ADHD (Faraone & Larsson, 2018), and the fact that individuals with ADHD are more likely to experience adverse life events (Friedrichs, Igl, Larsson, & Larsson, 2012), it is possible that an association between prenatal exposure to life events and offspring ADHD is confounded by genetic factors that are transferred from the mother to the child. *Dependent* events, that is, events that are likely the result of the individual's own behavior (e.g. financial problems or divorce), are more heritable than *independent* events, that is, events that are probably unrelated to the individual's own behavior (e.g. death of a relative) (Kendler & Baker, 2007). Therefore, associations between prenatal exposure to independent life events and ADHD would be less likely confounded by genetic influences. Previous studies on the association between life events during pregnancy and offspring ADHD have failed to distinguish between dependent and independent life events.

In pure observational studies, it is difficult to distinguish direct effects of intrauterine exposures from genetic confounding, which make it difficult to draw causal conclusions. Other designs, such as sibling-comparisons or cross-fostering designs, have been suggested to reduce the amount of confounding (D'Onofrio, Lahey, Turkheimer, & Lichtenstein, 2013). In sibling-comparisons, unmeasured familial confounding shared between siblings is accounted for by comparing the risk of the outcome among exposed individuals and their unexposed sibling. The cross-fostering design involves children born by in vitro fertilization (IVF) with egg donation. Since the mother provides the intrauterine environment but is not genetically related to the child, genetic confounding is excluded by the design. A retrospective sibling-comparison study found that children diagnosed with ADHD had higher odds of being exposed to prenatal stress, compared to their siblings without ADHD (OR: 6.29, 95% CI: 1.45–27.26) (Grizenko et al., 2012). However, a cross-fostering study found a statistically significant association between prenatal stress and ADHD symptoms only among children genetically related to their mothers, but not among

unrelated mother-offspring pairs ($\beta = .163, p = .001$, compared to $\beta = .095, p = .25$) (Rice et al., 2010), indicating that the association may, at least partly, be explained by genetic confounding. Furthermore, in two recent large sibling-comparisons based on the longitudinal Norwegian Mother and Child Cohort Study, emotional distress during pregnancy was not associated with offspring emotional difficulties at 6 and 36 months (Bekkhuis et al., 2017), or with internalizing and externalizing behavior at age 5 (Gjerde et al., 2017) after adjusting for familial confounds. Therefore, it remains uncertain if the association between prenatal exposure to adverse life events and ADHD symptoms in childhood reflects a causal association or if it could be explained by unmeasured genetic confounding.

We aimed to clarify if prenatal exposure to adverse life events within the family is associated with the risk of developing ADHD symptoms in childhood, and if such an association remains when adjusting for familial confounding (genetic and environmental).

Materials and method

Study population

This study uses data from the Norwegian Mother and Child Cohort Study (MoBa; Magnus et al., 2006, 2016). MoBa is an ongoing longitudinal study consisting of 114,247 children (from 112,758 pregnancies) born in Norway 1999–2009. Mothers were approached during pregnancy and 41% gave their written consent to participate in the study. Mothers have been asked to participate in several questionnaires, both during pregnancy and during the child's upbringing. MoBa has also been linked with the Norwegian Medical Birth Register to retrieve information about pregnancy and delivery for study participants. The current study is based on version 9 of the quality assured data files released for research in November 2015. Mothers of 34,751 children (including 6,427 individual siblings from 3,186 families) participated in surveys during pregnancy week 30 and when the child was five-years-old (see Figure 1 for a derivation of the analytical sample).

The establishment and data collection in MoBa have been approved by the Norwegian Data Inspectorate (01/4325) and by the Regional Committee for Medical Research Ethics (S-97045; S-95113). The current study was approved by the Regional Committee for Medical Research Ethics (2014/440).

Measures

During pregnancy week 30, mothers completed a survey to report whether they had experienced any of the following life events during the last 12 months: problems at work or school; financial problems; divorce, separation, or end of a relationship; problems with family, friends or neighbors; serious illness or injury; someone close seriously ill or injured; serious accident, fire or robbery; or loss of someone close, such as a family member or close friend. Mothers also reported how emotionally painful or difficult the experienced events were (categorized as not too bad; painful/difficult; and very painful/difficult, separately for each event).

Prenatal exposure to adverse life events were primarily coded as binary variables (event or no event). We also combined all eight life events into a single binary variable to measure global stress (at least one event or no single event).

The potential influence of mother's perceived level of difficulty was considered by creating a four-level categorical variable for each life event separately, coded as: did not experience the event; experienced the event, but did not perceive it as too bad; perceived the event as painful/difficult; or perceived the event as very painful/difficult.

We investigated the effect of cumulative exposure separately for life events considered as *dependent* (problems at work or school; financial problems; divorce, separation, or end of a relationship; problems with family, friends or neighbors) and *independent* (serious illness or injury; someone close seriously ill or injured; serious accident, fire or robbery; or loss of someone close), based on categorizations used in previous studies (Plomin, Lichtenstein, Pedersen, McClearn, & Nesselrode, 1990; Shakoor et al., 2016; Zavos et al., 2012). All dependent events were given a value of 0 (not having experienced the event) or 1 (experienced the event), which were summarized into a three-level categorical variable, with levels 0, 1, and ≥ 2 events. A variable measuring cumulative exposure to independent life events was created in a similar manner, with levels 0, 1, and ≥ 2 events.

Parent-rated ADHD symptoms at age 5 were assessed using the ADHD Index from the Conners' Parent Rating Scale – Revised: short form (CPRS-R (S)) (Conners, Sitarenios, Parker, & Epstein, 1998). The ADHD Index has been shown to have excellent internal consistency with a Cronbach's alpha of .91 and good validity in predicting ADHD (Kumar & Steer, 2003). The scale consists of 12 statements, where parents are asked to rate to what degree the statements correspond with their child's behavior. The possible responses are: never/seldom (0); sometimes (1); quite often (2); and very often (3). The Cronbach's alpha was .87 in the analytical sample. We calculated a mean score of the 12 items (ranging from 0 to 3) for children with response to at least 80% of the items.

Information about sex, year of birth, maternal and paternal age at child's birth (categorized into 5-year categories), region of birth, and parity (categorized as nulliparous, 1, 2, 3, or ≥ 4) was retrieved from the Norwegian Medical Birth Register.

Statistical analyses

We assessed the associations between prenatal exposure to adverse life events and ADHD symptoms at age 5 as mean differences in ADHD scores (and corresponding 95% Confidence Intervals, CI) in ordinary linear regression models. Maternal and paternal age at child's birth, region of birth and child's birth year were considered as potential confounding factors and therefore adjusted for in multivariable models. Cluster-robust standard errors were used to account for nonnormality in data and dependence between observations. We analyzed the effect of being exposed to any life event, the influence of mother's perception of the events, and the effect of cumulative exposure to adverse life events (separately for dependent and independent life events) in a similar manner. Two of the events, *serious illness/injury* and *serious accident/fire/robbery*, have been treated as independent events in some studies (Plomin et al., 1990; Shakoor et al., 2016; Zavos et al., 2012), but might also be perceived as self-inflicted and thereby dependent (Bolinskey, Neale, Jacobson, Prescott, & Kendler, 2004; Foley, Neale, & Kendler, 1996). Therefore, we re-categorized these events as dependent in a sensitivity analysis.

To assess whether associations were confounded by unmeasured familial factors, we repeated all analyses in siblings, using fixed-effects linear regression models to assess mean differences in ADHD scores among siblings differentially exposed to life events during pregnancy. Comparing exposure-discordant siblings automatically adjusts for confounding from environmental factors shared by siblings (D'Onofrio et al., 2013; Lahey & D'Onofrio, 2010). Full siblings have the same parents, and in general, comparing full siblings adjusts

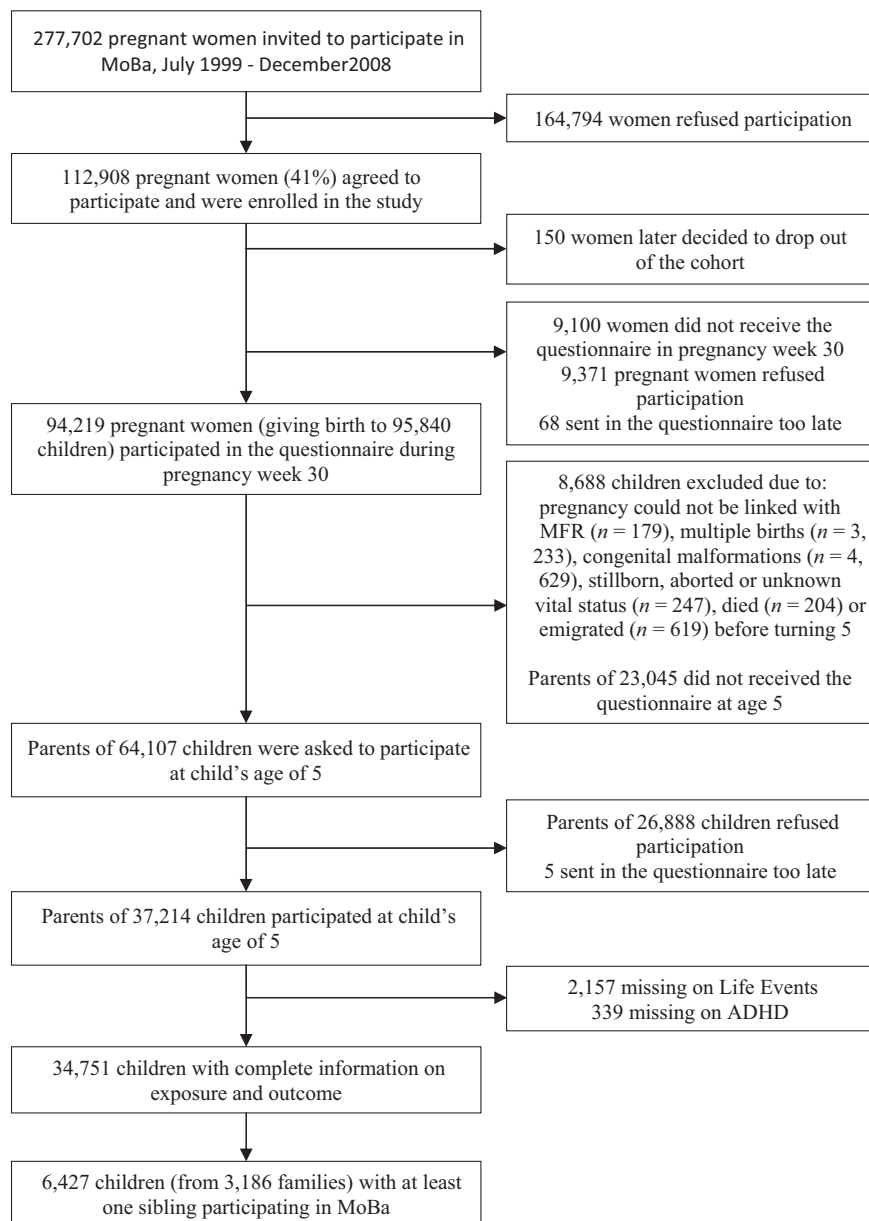


Figure 1 Flow chart of participation in MoBa and derivation of analytical sample. MoBa, the Norwegian Mother and Child Cohort Study; MBR, the Norwegian Medical Birth Register

for all parental genetic effects, and partly for offspring genetic effects (D'Onofrio et al., 2013; Lahey & D'Onofrio, 2010). Furthermore, exposure to maternal experience of adverse life events during pregnancy cannot be influenced by genetic characteristics of the offspring; thus, there is no risk of residual confounding due to offspring-specific genetic factors. For two of the life events (separated/divorced and involved in serious accident/fire/robbery), there was too little variation within sets of siblings for sibling-comparison analyses to be feasible (Table S1). In sibling analyses, we adjusted for maternal age at birth, region of birth parity, and year of birth in multivariate models.

As siblings brought up together likely share more environmental factors the closer they are in age, we repeated the analyses stratifying for the age difference between siblings in a pair (1–2 years vs. 3–5 years) as a sensitivity analysis.

The generalizability of the results from siblings to the entire cohort was assessed by analyzing the associations among all siblings in the cohort as unrelated individuals, using ordinary linear regression with cluster-robust standard errors. We also

performed an attrition analysis where we estimated the associations between baseline characteristics (including exposure to life events) and nonparticipation at age 5 using logistic regression models.

Stata Statistical Software: Release 14 (StataCorp. 2014. College Station, TX: StataCorp LP) were used for all analyses.

Results

Table 1 presents descriptive statistics of study participants. The mean ADHD symptom score (range: 0–3) was 0.36 (*SD*: 0.38; median: 0.25; interquartile range: 0.08–0.50), and children prenatally exposed to at least one life event had higher scores than unexposed children (mean score 0.40, *SD*: 0.39, compared to 0.32, *SD*: 0.35). The most common events were having problems at work (26.6%) and conflicts with friends/family (19.1%) (Table S1).

Table 1 Descriptive characteristics of study participants in relation to prenatal exposure to any life events in the family

Characteristic	Total (n = 34,751) n (%)	Exposed to any life event (n = 19,493) n (%)	Unexposed (n = 15,258) n (%)
ADHD score at age 5, mean (SD)	0.36 (0.38)	0.40 (0.39)	0.32 (0.35)
Sex			
Boy	17,575 (50.6)	9,850 (50.5)	7,725 (50.6)
Girl	17,176 (49.4)	9,643 (49.5)	7,533 (49.4)
Year of birth			
2004	6,058 (17.4)	3,490 (17.9)	2,568 (16.8)
2005	6,736 (19.4)	3,811 (19.6)	2,925 (19.2)
2006	7,782 (22.4)	4,348 (22.3)	3,434 (22.5)
2007	6,764 (19.5)	3,800 (19.5)	2,964 (19.4)
2008	5,847 (16.8)	3,207 (16.5)	2,640 (17.3)
2009	1,564 (4.5)	837 (4.3)	727 (4.8)
Maternal age at child's birth			
≤19 years	138 (0.4)	102 (0.5)	36 (0.2)
20–24 years	2,603 (7.5)	1,701 (8.7)	902 (5.9)
25–29 years	11,229 (32.3)	6,353 (32.6)	4,876 (32)
30–34 years	14,234 (41)	7,709 (39.5)	6,525 (42.8)
35–39 years	5,789 (16.7)	3,186 (16.3)	2,603 (17.1)
≥40 years	758 (2.2)	442 (2.3)	316 (2.1)
Paternal age at child's birth			
≤19 years	48 (0.1)	35 (0.2)	13 (0.1)
20–24 years	1,087 (3.1)	759 (3.9)	328 (2.2)
25–29 years	7,495 (21.6)	4,321 (22.2)	3,174 (20.8)
30–34 years	13,922 (40.2)	7,628 (39.2)	6,294 (41.3)
35–39 years	8,607 (24.8)	4,683 (24.1)	3,924 (25.8)
40–44 years	2,560 (7.4)	1,439 (7.4)	1,121 (7.4)
45–49 years	709 (2)	420 (2.2)	289 (1.9)
≥50 years	242 (0.7)	150 (0.8)	92 (0.6)
Parity			
Nulliparous	16,515 (47.5)	9,505 (48.8)	7,010 (45.9)
1	12,207 (35.1)	6,651 (34.1)	5,556 (36.4)
2	4,802 (13.8)	2,639 (13.5)	2,163 (14.2)
3	962 (2.8)	531 (2.7)	431 (2.8)
≥4	265 (0.8)	167 (0.9)	98 (0.6)
Region of birth			
South/east	19,223 (55.4)	10,955 (56.3)	8,268 (54.3)
West	8,559 (24.7)	4,638 (23.8)	3,921 (25.7)
Middle	4,967 (14.3)	2,747 (14.1)	2,220 (14.6)
North	1,936 (5.6)	1,110 (5.7)	826 (5.4)

Results from fully adjusted linear regression models comparing ADHD scores among exposed and unexposed are presented in Figure 2 (see Table S2 for results from both crude and adjusted models). Being exposed to any life event during pregnancy was associated with a mean increase of 0.07 (95% CI: 0.07, 0.08) in the ADHD score. All life events were associated with higher ADHD scores, with the strongest effect observed for *separated/divorced* (mean difference in ADHD score 0.11, 95% CI: 0.06, 0.15), *financial problems* (0.10, 95% CI: 0.09, 0.11), and *serious accident/fire/robbery* (0.10, 95% CI: 0.04, 0.15). The weakest effects were observed for *lost someone close* (mean difference 0.02, 95% CI: 0.01, 0.04) and *someone close seriously ill/injured* (0.04, 95% CI: 0.03, 0.05). Comparing exposure-discordant siblings resulted in attenuated estimates where most events were associated with a mean difference of -0.03 to 0.03 in ADHD scores, although with wider confidence intervals compared to ordinary linear regression analyses (Figure 2; Table S2). Furthermore, there were no longer any clear

differences between specific life events. For instance, the mean difference for being exposed to any life event was -0.01 (95% CI: -0.03 , 0.01), -0.03 (95% CI -0.07 , 0.02) for *financial problems*, and -0.01 (95% CI: -0.05 , 0.02) for *lost someone close* in adjusted models.

For most life events, mean ADHD scores increased the more painful/difficult the mothers rated the event (Table S3). For instance, *financial problems* were associated with an increase of 0.08 (95% CI: 0.07, 0.09) in mean ADHD score if the mother rated the event as not too painful; 0.14 (95% CI: 0.11, 0.17) if rated as painful; and 0.20 (95% CI: 0.14, 0.26) if rated as very painful, in adjusted models. No such clear pattern was found for the events *seriously ill/injured* and *someone close seriously ill/injured*. Comparing siblings resulted in estimates that were attenuated toward null and less precise (i.e. the 95% confidence intervals for the associations were wider compared with results from population-level analyses). Furthermore, there were no longer any clear patterns with regard to how painful mothers

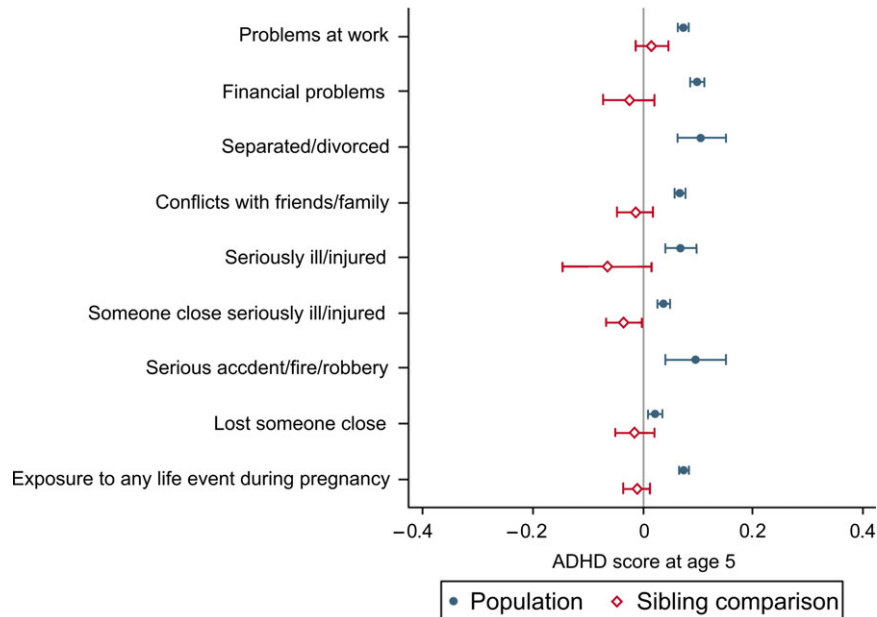


Figure 2 Associations between prenatal exposure to adverse life events and mean ADHD scores at age 5, shown as beta-values (with 95% confidence intervals) from fully adjusted models, separately for analyses on population level and from sibling comparisons

perceived the event (Table S3). For instance, *financial problems* were associated with an increase of -0.03 (95% CI: $-0.08, 0.02$) in ADHD score if the mother rated the event as not too painful; 0.00 (95% CI: $-0.11, 0.11$) if rated as painful; and -0.07 (95% CI: $-0.26, 0.11$) if rated as very painful, in adjusted models.

Figure 3 presents the association between cumulative exposure to adverse life events and ADHD scores at age 5, separately for dependent and independent life events. Exposure to multiple events resulted in increasing ADHD scores both for dependent and independent events, but with stronger associations for dependent events (e.g. exposure to ≥ 2 dependent events was associated with an increase of 0.14 [95% CI: $0.12, 0.15$] in the mean ADHD score, compared with an increase of 0.06 [95% CI: $0.04, 0.08$] among those exposed to ≥ 2 independent events in fully adjusted models; see Table S4 for full results). When exposure-discordant siblings were compared, there were no longer any differences between exposed and unexposed children, with estimates close to null, although less precise (Figure 3; Table S4). Treating *seriously ill/injured* and *serious accident* as dependent events, instead of independent, did not change the results (Table S5).

Analyzing siblings born 1–2 years apart separately from siblings born 3–5 years apart mainly resulted in similar estimates (Table S6). Analyzing siblings as unrelated individuals resulted in similar estimates as when the entire cohort was analyzed (Table S7). Results from attrition analysis showed that higher parental age, parity, geographic region, and experience of some adverse life events during pregnancy of the child (financial problems; divorce/separation;

conflicts with friends or family; and being involved in a serious accident) were associated with nonparticipation at the child's age of 5 (Table S8).

Discussion

In this large prospective population-based cohort study, prenatal maternal exposure to adverse life events was associated with higher levels of ADHD symptoms at age 5. However, familial confounding seemed to explain most of these associations.

At population level, the associations with ADHD symptoms increased if the mother had experienced the event as painful, which likely reflects how stressful the event was, whereas no such association was found when adjusting for familial confounding. This suggests that the associations were not driven by high maternal stress levels during pregnancy, but rather by familial factors. Moreover, cumulative exposure to adverse events was associated with ADHD symptoms in a dose-response like fashion. However, these associations were attenuated toward the null in sibling-comparison analyses, again indicating that unmeasured familial factors confounded the associations.

Dependent life events are more heritable than independent life events (Kendler & Baker, 2007), and thereby also more likely influenced by the individual's personality traits or genetic predisposition to ADHD. In this study, associations between adverse life events in the family during pregnancy and ADHD symptoms in offspring seemed to be stronger for dependent events (such as financial problems and separation/divorce), and weaker for independent events (e.g. bereavement and injury/

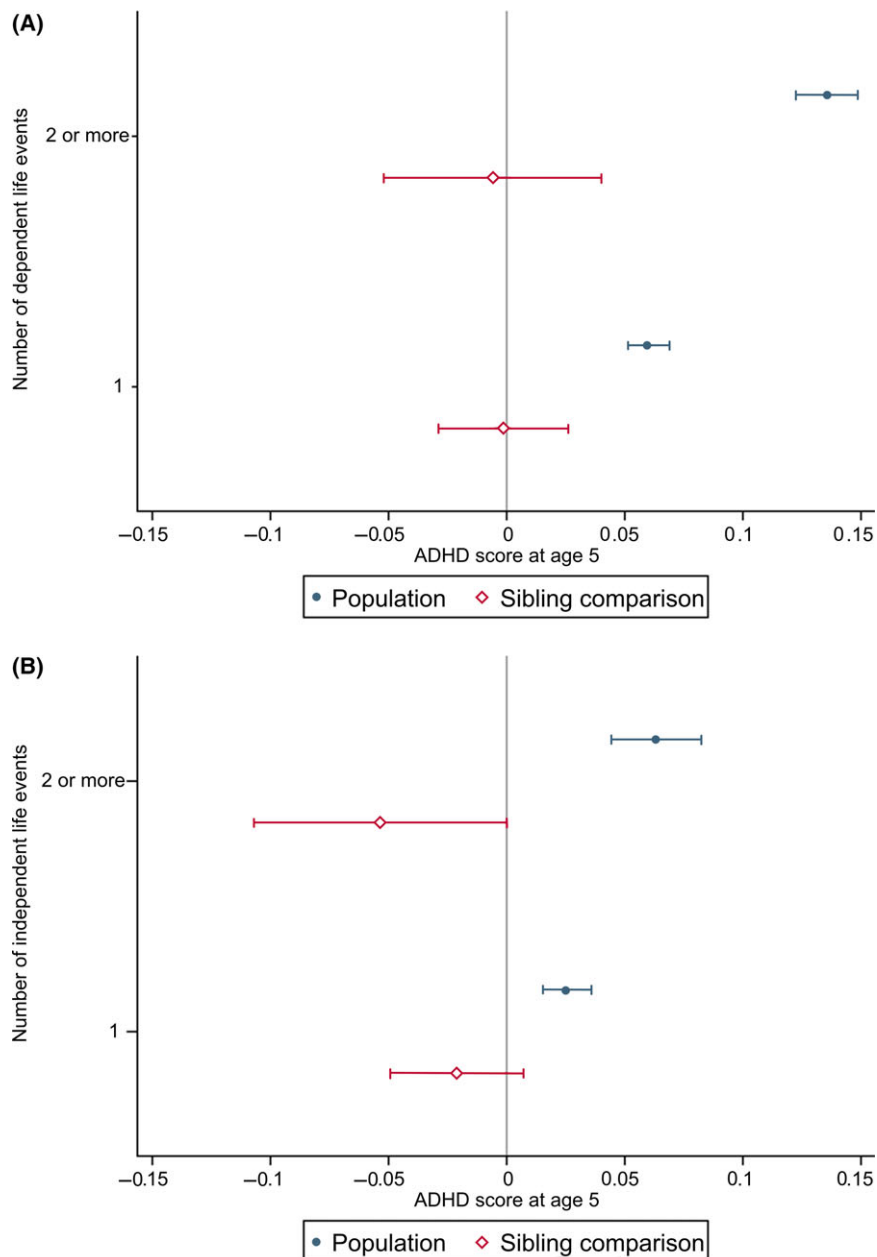


Figure 3 Associations between cumulative exposure to (A) dependent and (B) independent adverse life events during pregnancy and ADHD scores at age 5, shown as beta-values (with 95% confidence intervals) from fully adjusted models, separately for analyses on population level and from sibling comparisons

illness in someone close), indicating the presence of genetic confounding. Moreover, results from the sibling-comparison analyses consistently showed no association between prenatal exposure to adverse life events and ADHD symptoms in offspring. Therefore, these findings indicate that associations found in previous studies may have been confounded by unmeasured genetic or environmental influences.

Our findings are in line with the cross-fostering study by Rice et al. (2010), but not with the retrospective sibling comparison by Grizenko et al. (2012). Both studies were based on small sample sizes (474 and 142 respectively), which is reflected by the wide confidence intervals in the study by Grizenko et al. (OR for the association between prenatal stress and

offspring ADHD: 6.29, 95% CI 1.45–27.26). Furthermore, the association found in the study by Grizenko et al. might be explained by recall bias since exposure was retrospectively assessed in the study, and mothers' reports might therefore be influenced by whether their children expressed ADHD symptoms. Our findings are also similar to the results from two previous studies based on MoBa, where maternal distress (anxiety or depression) during pregnancy was associated with behavior problems in offspring at a population level, but not in sibling-comparison analyses (Bekkhuis et al., 2017; Gjerde et al., 2017). We expand further on these results by specifically assessing the effect of stressful life events on ADHD symptoms.

To our knowledge, this is the first study examining prenatal exposure to several specific life events in relation to ADHD symptoms, where both the mother's subjective experience of the events and exposure to multiple events has been taken into account. The study was based on a large longitudinal cohort. Comparing siblings allowed us to adjust for unmeasured genetic and environmental influences shared between siblings in a family.

Some limitations should be kept in mind when interpreting the results from this study. Self-selection due to low participation could have introduced bias. Selection into the cohort has been shown to influence prevalence estimates for several pregnancy-related exposures and outcomes, but not the association between these exposures and outcomes (Nilsen et al., 2009). Findings from a recent study suggest that participants in MoBa are representative for the general population with regard to ADHD, even though participants in MoBa have lower prevalence rates of diagnosed ADHD (Oerbeck et al., 2017). Participants in MoBa also have higher socioeconomic position than the general population (Magnus et al., 2006; Nilsen et al., 2009), and a recent Norwegian study found that families with lower socioeconomic position more frequently experience negative life events (Bøe, Serlachius, Sivertsen, Petrie, & Hysing, 2018). Since, early childhood exposure to financial difficulties has been associated with ADHD even after adjusting for familial factors (Larsson, Sariaslan, Langstrom, D'Onofrio, & Lichtenstein, 2014), future studies are needed to investigate associations with adverse life events specifically among families with lower socioeconomic position to assess the generalizability of our findings. Due to the young age of study participants, and in order to increase statistical power, we relied on parent-rated ADHD symptoms instead of clinical diagnoses. However, several studies have suggested that ADHD can be viewed as a dimensional scale of symptoms (Faraone et al., 2006; Larsson, Anckarsater, Rastam, Chang, & Lichtenstein, 2012). Not all families were invited to participate in the 5-year follow-up since some children had turned six by the time the questionnaire was finalized. This resulted in a smaller sample for this study, but is unlikely to influence the association between prenatal exposure to life events and ADHD symptoms. On the other hand, it might influence the generalizability of our findings since our attrition analysis showed that parental age, parity, geographic region, and exposure to some adverse events were associated with nonparticipation at age 5. Moreover, there are some challenges related to studying adverse life events. Several of these events are likely related, and it could be difficult to disentangle them. Some mothers might have experienced the events before pregnancy as the experience of events was not restricted to pregnancy, but to the last 12 months. Also, the categorization of events as dependent and independent is not always

straightforward. For instance, being involved in a serious accident might be an independent event for some individuals, and for others it might be influenced by risk-seeking behavior and impulsiveness. However, our sensitivity analysis where we re-categorized two events did not change the results. Pregnancy could be considered a stressful event in itself, which we had no specific information about. Comparing exposure-discordant siblings implies a selection of siblings that are likely to differ regarding nonshared causes of the exposure as well, including random measurement error, which could result in a dilution of true associations (Frisell, Öberg, Kujala, & Sjölander, 2012). Lastly, sibling comparisons were not possible for some events since there was too little variation between siblings, which hampers the interpretation about causal associations for these events.

Conclusion

These findings show that the association between adverse life events during pregnancy and ADHD symptoms in offspring seems to be explained by familial factors, such as shared genetic influences. These findings do not support the hypothesis that prenatal stress causes offspring ADHD through a programming effect and future research should focus on exploring other prenatal influences that might be causally related to ADHD. Studies investigating the influence of adverse life events in the family should focus on early childhood exposures, where the role of familial confounding is still unclear. These findings have some clinical implications; pregnant women experiencing adverse events should receive the necessary support, but they do not need to worry that the stress from experiencing such an event would influence their child's risk of ADHD.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1. Prenatal exposure to adverse life events: distribution, discordant siblings, and sibling correlations.

Table S2. Associations between prenatal exposure to adverse life events and ADHD scores at age five.

Table S3. Associations between prenatal exposure to adverse life events, taking mother's perceived level of difficulty into account, and ADHD scores at age five.

Table S4. Associations between cumulative exposure to dependent and independent adverse life events and ADHD scores at age five.

Table S5. Associations between cumulative exposure to dependent and independent adverse life events and ADHD scores at age five.

Table S6. Associations between prenatal exposure to adverse life events and ADHD scores at age five, shown

separately for siblings born 1–2 years apart and for siblings born 3–5 years apart.

Table S7. Associations between prenatal exposure to adverse life events and ADHD scores at age five among all siblings participating in MoBa, analyzed as unrelated individuals.

Table S8. Associations between descriptive characteristics (including prenatal exposure to adverse life events) and non-participation at age 5.

Acknowledgements

The authors are grateful to all the participating families in Norway who take part in the ongoing Norwegian Mother and Child Cohort Study. The Norwegian Mother and Child Cohort Study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research, NIH/NIEHS (contract no N01-ES-75558), NIH/NINDS (grant no.1 UO1 NS 047537-01

and grant no.2 UO1 NS 047537-06A1). M.R. was supported by a grant from the Swedish Research Council for Health, Working Life and Welfare (FORTE grant number 2015-00075). E.Y. is funded by the Norwegian Research Council (grant no. 231105). Funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. H.L. reports grants from Shire and has served as a speaker for Eli-Lilly and Shire. The remaining authors have declared that they have no competing or potential conflicts of interest.

Correspondence

Mina A. Rosenqvist, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Box 281, 17177 Stockholm, Sweden; Email: mina.rosenqvist@ki.se

Key points

- Prenatal exposure to maternal adverse life events has been associated with offspring ADHD, but the role of familial confounding is unclear.
- In this large prospective population-based cohort study, prenatal maternal exposure to adverse life events was not associated with higher levels of ADHD symptoms at age 5 when adjusting for familial confounding such as shared genetic influences.
- Pregnant women do not need to worry that the stress from experiencing such an event would influence their child's risk of ADHD.

References

- Barker, D.J.P. (1998). In utero programming of chronic disease. *Clinical Science*, 95, 115–128.
- Barker, E.D., Walton, E., & Cecil, C.A.M. (2018). Annual Research Review: DNA methylation as a mediator in the association between risk exposure and child and adolescent psychopathology. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 59, 303–322.
- Bekkhuis, M., Lee, Y., Nordhagen, R., Magnus, P., Samuelsen, S.O., & Borge, A.I.H. (2017). Re-examining the link between prenatal maternal anxiety and child emotional difficulties, using a sibling design. *International Journal of Epidemiology*, 47, 156–165.
- Bjorkenstam, E., Bjorkenstam, C., Jablonska, B., & Kosidou, K. (2017). Cumulative exposure to childhood adversity, and treated attention deficit/hyperactivity disorder: A cohort study of 543 650 adolescents and young adults in Sweden. *Psychological Medicine*, 48, 498–507.
- Bøe, T., Serlachius, A.S., Sivertsen, B., Petrie, K.J., & Hysing, M. (2018). Cumulative effects of negative life events and family stress on children's mental health: The Bergen Child Study. *Social Psychiatry and Psychiatric Epidemiology*, 53, 1–9.
- Bolinskey, P.K., Neale, M.C., Jacobson, K.C., Prescott, C.A., & Kendler, K.S. (2004). Sources of individual differences in stressful life event exposure in male and female twins. *Twin Research*, 7, 33–38.
- Class, Q.A., Abel, K.M., Khashan, A.S., Rickert, M.E., Dalman, C., Larsson, H., ... & D'Onofrio, B.M. (2014). Offspring psychopathology following preconception, prenatal and postnatal maternal bereavement stress. *Psychological Medicine*, 44, 71–84.
- Conners, C.K., Sitarenios, G., Parker, J.D., & Epstein, J.N. (1998). The revised Conners' Parent Rating Scale (CPRS-R): Factor structure, reliability, and criterion validity. *Journal of Abnormal Child Psychology*, 26, 257–268.
- Counts, C.A., Nigg, J.T., Stawicki, J.A., Rappley, M.D., & vonEye, A. (2005). Family adversity in DSM-IV ADHD combined and inattentive subtypes and associated disruptive behavior problems. *Journal of the American Academy of Child and Adolescent Psychiatry*, 44, 690–698.
- D'Onofrio, B.M., Lahey, B.B., Turkheimer, E., & Lichtenstein, P. (2013). Critical need for family-based, quasi-experimental designs in integrating genetic and social science research. *American Journal of Public Health*, 103, S46–S55.
- Faraone, S.V., Asherson, P., Banaschewski, T., Biederman, J., Buitelaar, J.K., Ramos-Quiroga, J.A., ... & Franke, B. (2015). Attention-deficit/hyperactivity disorder. *Nature Reviews Disease Primers*, 1, 15020.
- Faraone, S.V., Biederman, J., Doyle, A., Murray, K., Petty, C., Adamson, J.J., & Seidman, L. (2006). Neuropsychological studies of late onset and subthreshold diagnoses of adult attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 60, 1081–1087.
- Faraone, S.V., & Larsson, H. (2018). Genetics of attention deficit hyperactivity disorder. *Molecular Psychiatry*. [Epub ahead of print]. <https://doi.org/10.1038/s41380-018-0070-0>.
- Foley, D., Neale, M., & Kendler, K. (1996). A longitudinal study of stressful life events assessed at interview with an epidemiological sample of adult twins: The basis of

- individual variation in event exposure. *Psychological Medicine*, 26, 1239–1252.
- Friedrichs, B., Igl, W., Larsson, H., & Larsson, J.-O. (2012). Coexisting psychiatric problems and stressful life events in adults with symptoms of ADHD—a large Swedish population-based study of twins. *Journal of Attention Disorders*, 16, 13–22.
- Frisell, T., Öberg, S., Kuja-Halkola, R., & Sjölander, A. (2012). Sibling comparison designs: Bias from non-shared confounders and measurement error. *Epidemiology*, 23, 713–720.
- Gjerde, L.C., Eilertsen, E.M., Reichborn-Kjennerud, T., McAdams, T.A., Zachrisson, H.D., Zambrana, I.M., ... & Ystrom, E. (2017). Maternal perinatal and concurrent depressive symptoms and child behavior problems: A sibling comparison study. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 58, 779–786.
- Glover, V. (2011). Annual Research Review: Prenatal stress and the origins of psychopathology: An evolutionary perspective. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 52, 356–367.
- Grizenko, N., Fortier, M.E., Zadorozny, C., Thakur, G., Schmitz, N., Duval, R., & Joober, R. (2012). Maternal stress during pregnancy, ADHD symptomatology in children and genotype: Gene-environment interaction. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*, 21, 9–15.
- Grizenko, N., Shayan, Y.R., Polotskaia, A., Ter-Stepanian, M., & Joober, R. (2008). Relation of maternal stress during pregnancy to symptom severity and response to treatment in children with ADHD. *Journal of Psychiatry and Neuroscience*, 33, 10–16.
- Huizink, A.C., Dick, D.M., Sihvola, E., Pulkkinen, L., Rose, R.J., & Kaprio, J. (2007). Chernobyl exposure as stressor during pregnancy and behaviour in adolescent offspring. *Acta Psychiatrica Scandinavica*, 116, 438–446.
- Kendler, K.S., & Baker, J.H. (2007). Genetic influences on measures of the environment: A systematic review. *Psychological Medicine*, 37, 615–626.
- Kim, H.-W., Cho, S.-C., Kim, B.-N., Kim, J.-W., Shin, M.-S., & Kim, Y. (2009). Perinatal and familial risk factors are associated with full syndrome and subthreshold attention-deficit hyperactivity disorder in a Korean community sample. *Psychiatry Investigation*, 6, 278–285.
- Kumar, G., & Steer, R.A. (2003). Factorial validity of the Conners' Parent Rating Scale-revised: Short form with psychiatric outpatients. *Journal of Personality Assessment*, 80, 252–259.
- Lahey, B.B., & D'Onofrio, B.M. (2010). All in the family: Comparing siblings to test causal hypotheses regarding environmental influences on behavior. *Current Directions in Psychological Science*, 19, 319–323.
- Larsson, H., Anckarsater, H., Rastam, M., Chang, Z., & Lichtenstein, P. (2012). Childhood attention-deficit hyperactivity disorder as an extreme of a continuous trait: A quantitative genetic study of 8,500 twin pairs. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 53, 73–80.
- Larsson, H., Sariaslan, A., Langstrom, N., D'Onofrio, B., & Lichtenstein, P. (2014). Family income in early childhood and subsequent attention deficit/hyperactivity disorder: A quasi-experimental study. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 55, 428–435.
- Latimer, K., Wilson, P., Kemp, J., Thompson, L., Sim, F., Gillberg, C., ... & Minnis, H. (2012). Disruptive behaviour disorders: A systematic review of environmental antenatal and early years risk factors. *Child: Care, Health and Development*, 38, 611–628.
- Laucht, M., Esser, G., Baving, L., Gerhold, M., Hoesch, I., Ihle, W., ... & Weindrich, D. (2000). Behavioral sequelae of perinatal insults and early family adversity at 8 years of age. *Journal of the American Academy of Child and Adolescent Psychiatry*, 39, 1229–1237.
- Lee, C.Y., Chang, Y.Y., & Lung, F.W. (2006). The marriage-related risk factors during maternal pregnancy in children with attention-deficit hyperactivity disorder. *Child: Care, Health and Development*, 32, 205–212.
- Li, J., Olsen, J., Vestergaard, M., & Obel, C. (2010). Attention-deficit/hyperactivity disorder in the offspring following prenatal maternal bereavement: A nationwide follow-up study in Denmark. *European Child and Adolescent Psychiatry*, 19, 747–753.
- MacKinnon, N., Kingsbury, M., Mahedy, L., Evans, J., & Colman, I. (2018). The association between prenatal stress and externalizing symptoms in childhood: Evidence from the Avon Longitudinal Study of Parents and Children. *Biological Psychiatry*, 83, 100–108.
- Magnus, P., Birke, C., Vejrup, K., Haugan, A., Alsaker, E., Daltveit, A.K., ... & Stoltenberg, C. (2016). Cohort profile update: The Norwegian mother and child cohort study (MoBa). *International Journal of Epidemiology*, 45, 382–388.
- Magnus, P., Irgens, L.M., Haug, K., Nystad, W., Skjaerven, R., Stoltenberg, C., & MoBa Study Group (2006). Cohort profile: The Norwegian mother and child cohort study (MoBa). *International Journal of Epidemiology*, 35, 1146–1150.
- Motlagh, M.G., Katsovich, L., Thompson, N., Lin, H., Kim, Y.-S., Scahill, L., ... & Leckman, J.F. (2010). Severe psychosocial stress and heavy cigarette smoking during pregnancy: An examination of the pre- and perinatal risk factors associated with ADHD and Tourette syndrome. *European Child and Adolescent Psychiatry*, 19, 755–764.
- Nilsen, R.M., Vollset, S.E., Gjessing, H.K., Skjaerven, R., Melve, K.K., Schreuder, P., ... & Magnus, P. (2009). Self-selection and bias in a large prospective pregnancy cohort in Norway. *Paediatric and Perinatal Epidemiology*, 23, 597–608.
- Oerbeck, B., Overgaard, K.R., Aspenes, S.T., Pripp, A.H., Mordre, M., Aase, H., ... & Zeiner, P. (2017). ADHD, comorbid disorders and psychosocial functioning: How representative is a child cohort study? Findings from a national patient registry. *BMC Psychiatry*, 17, 23.
- Park, S., Cho, S.-C., Kim, J.-W., Shin, M.-S., Yoo, H.-J., Oh, S.M., ... & Kim, B.-N. (2014). Differential perinatal risk factors in children with attention-deficit/hyperactivity disorder by subtype. *Psychiatry Research*, 219, 609–616.
- Park, S., Kim, B.-N., Kim, J.-W., Shin, M.-S., Yoo, H.-J., Lee, J., & Cho, S.-C. (2014). Associations between maternal stress during pregnancy and offspring internalizing and externalizing problems in childhood. *International Journal of Mental Health Systems*, 8, 44.
- Plomin, R., Lichtenstein, P., Pedersen, N.L., McClearn, G.E., & Nesselroade, J.R. (1990). Genetic influence on life events during the last half of the life span. *Psychology and Aging*, 5, 25.
- Rice, F., Harold, G.T., Boivin, J., van denBree, M., Hay, D.F., & Thapar, A. (2010). The links between prenatal stress and offspring development and psychopathology: Disentangling environmental and inherited influences. *Psychological Medicine*, 40, 335–345.
- Rodriguez, A., & Bohlin, G. (2005). Are maternal smoking and stress during pregnancy related to ADHD symptoms in children? *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 46, 246–254.
- Ronald, A., Pennell, C.E., & Whitehouse, A.J. (2011). Prenatal maternal stress associated with ADHD and autistic traits in early childhood. *Frontiers in Psychology*, 1, 223.
- Rutter, M., Cox, A., Tupling, C., Berger, M., & Yule, W. (1975). Attainment and adjustment in two geographical areas. I—The prevalence of psychiatric disorder. *British Journal of Psychiatry*, 126, 493–509.
- Shakoor, S., Zavos, H.M., Haworth, C.M., McGuire, P., Cardno, A.G., Freeman, D., & Ronald, A. (2016). Association between

- stressful life events and psychotic experiences in adolescence: Evidence for gene-environment correlations. *The British Journal of Psychiatry*, 208, 532–538.
- Thomas, R., Sanders, S., Doust, J., Beller, E., & Glasziou, P. (2015). Prevalence of attention-deficit/hyperactivity disorder: A systematic review and meta-analysis. *Pediatrics*, 135, e994–e1001.
- Van den Bergh, B.R., Mulder, E.J., Mennes, M., & Glover, V. (2005). Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: Links and possible mechanisms. A review. *Neuroscience and Biobehavioral Reviews*, 29, 237–258.
- Zavos, H., Wong, C.C., Barclay, N.L., Keers, R., Mill, J., Rijsdijk, F.V., ... & Eley, T.C. (2012). Anxiety sensitivity in adolescence and young adulthood: The role of stressful life events, 5HTTLPR and their interaction. *Depression and Anxiety*, 29, 400–408.
- Zhu, P., Hao, J.-H., Tao, R.-X., Huang, K., Jiang, X.-M., Zhu, Y.-D., & Tao, F.-B. (2015). Sex-specific and time-dependent effects of prenatal stress on the early behavioral symptoms of ADHD: A longitudinal study in China. *European Child and Adolescent Psychiatry*, 24, 1139–1147.

Accepted for publication: 10 September 2018