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ORIGINAL ARTICLE

Maternal anxiety, depression and sleep disorders before and during pregnancy, and preschool ADHD symptoms in the NINFEA birth cohort study

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Aims. Maternal mental disorders have been associated with the risk of attention-deficit/hyperactivity disorder (ADHD) in children. Within the context of a mother–child cohort, we examined whether maternal anxiety, depression and sleep disorders are associated with pre-school ADHD symptoms.

Methods. The study included 3634 singletons from the Italian NINFEA (Nascita e INFanzia: gli Effetti dell'Ambiente') cohort. Maternal doctor-diagnosed anxiety, depression and sleep disorders before and during pregnancy were assessed from the questionnaires completed during pregnancy and 6 months after delivery. Mothers rated child ADHD symptoms at 4 years of age, according to the Diagnostic and Statistical Manual of Mental Disorders. Hyperactive–impulsive (ADHD-H), inattentive (ADHD-I) and total ADHD scores were analysed in the models adjusted for child's gender, first-born status, maternal age, education, alcohol consumption and smoking during pregnancy.

Results. The total ADHD score at age 4 was associated with maternal lifetime anxiety (17.1% percentage difference in score compared with never; 95% CI 7.3–27.9%), sleep disorders (35.7%; 95% CI 10.7–66.5%) and depression (17.5%; 95% CI 3.2–33.8%). Similar positive associations were observed also for ADHD-H and ADHD-I traits, with slightly attenuated associations between maternal sleep disorders and child ADHD-I score, and maternal depression and both ADHD scores. All the estimates were enhanced when the disorders were active during pregnancy and attenuated for disorders active only during the pre-pregnancy period.

Conclusions. Maternal anxiety, depression and sleep disorders are associated with a relative increase in the number of ADHD-H, ADHD-I and total ADHD symptoms in preschoolers.

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Key words: Attention-deficit/hyperactivity disorder, mental health, prospective study, risk factors.

Introduction

Pregnancy represents a particularly vulnerable period for the onset, recurrence and exacerbation of major mental health conditions, including depression, anxiety and mood disorders (Howard *et al.* 2014). It has been reported that approximately 7–15% of women during pregnancy are affected by mental disorders (Gelaye *et al.* 2016; Van den Bergh *et al.* 2017), whose common symptoms, such as disordered appetite, sleep disturbances and mood swings are often difficult to distinguish from physiological changes occurring during pregnancy, and thus, the reported prevalence is likely underestimated. Sleep disturbances, for example, are among the major symptoms associated with depression, and during pregnancy are considered as both a result of stress and as a stressor *per se* that may contribute to adverse pregnancy outcomes (Palagini *et al.* 2014). Moreover, mental disorders often coexist (Fried *et al.* 2017) increasing the burden of adverse effects on the mother and her child.

A number of studies reported associations of prenatal maternal depression and anxiety with offspring health outcomes, including low birth weight, preterm birth (Grote *et al.* 2010) and respiratory morbidity (van de Loo *et al.* 2016). Also, sleep disorders, such as obstructive sleep apnoea and insomnia have been shown to be associated with pregnancy complications and adverse perinatal outcomes (Bin *et al.* 2016; Felder

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et al. 2017). Furthermore, maternal mental disorders during pregnancy influence the child cognitive, emotional, social and behavioural development increasing the risk of emotional (internalising) and behavioural (externalising) difficulties, such as attention-deficit/hyperactivity disorder (ADHD) (Glover, 2011; Stein *et al.* 2014).

ADHD is a childhood-onset neurodevelopmental disorder characterised by symptoms of inattention, hyperactivity and impulsivity. Its aetiology is multifactorial (Thapar & Cooper, 2016), including an important heritability component (heritability estimates ranging from 75 to 90%) (Goodman & Stevenson, 1989; Thapar *et al.* 1999; Thapar *et al.* 2000; Faraone *et al.* 2005), several environmental risk factors (Thapar & Cooper, 2016) and gene–environment interactions (Nigg *et al.* 2010; Harold *et al.* 2013). Parental expectations of the child's behaviour play an important role in the definition of ADHD and are known to differ among populations (Zwirs *et al.* 2006).

Several studies reported an association of maternal anxiety and depression during pregnancy with an increased risk of ADHD in preschool children, but only a few of them had prospectively collected exposure data (Clavarino *et al.* 2010; Van Batenburg-Eddes *et al.* 2013; Bendiksen *et al.* 2015; Wolford *et al.* 2017). Much of the research was focused on maternal depression and anxiety during pregnancy and less attention has been paid to depression and anxiety occurring before pregnancy.

To take into account the parents' cultural context and different exposure time windows, we aimed at examining maternal diagnoses of anxiety and depression before and during pregnancy in association with inattentive and hyperactivity-impulsivity ADHD traits in 4-year-old offspring in a large mother-child cohort carried out in South Europe (Italy). We also analysed doctor-diagnosed maternal sleep disorders before and during pregnancy, which can both contribute to mental health conditions and be a symptom of other mental disorders (Fried *et al.* 2017). Maternal sleep disorders, to our knowledge, have not been studied before in association with child ADHD.

Methods

Study population

Data were collected from the study 'Nascita e INFanzia: gli Effetti dell'Ambiente' (NINFEA), whose protocol was approved by the Ethical Committee of the San Giovanni

Battista Hospital and CTO/CRF/Maria Adelaide Hospital of Turin. The NINFEA cohort study is an internet-based birth cohort with the aim of investigating prenatal and early life exposures in relation to childhood health and development from a life-course perspective (www.progettoninfea.it) (Richiardi *et al.* 2007).

Approximately 7500 pregnant women who had access to the Internet and enough knowledge of the Italian language to complete online questionnaires were recruited from 2005 until 2016. The women completed the first baseline questionnaire at any time during pregnancy, and the children have been followed-up with additional five questionnaires completed by their mothers 6 months after delivery and when the children turn 1½, 4, 7 and 10 years of age.

For this study, we used the NINFEA database version 11.2017. The outcome was assessed at the age of 4 years where the response rate of the questionnaire is 77% (Pizzi, 2016). A total of 3634 singletons who at the time of the data download had completed the assessment at age 4 years, were included in the study.

Explanatory variables

Maternal mental disorder data were collected with a questionnaire completed during pregnancy (mean gestational age at completion 26.3 weeks, standard deviation (SD) 9.5) in which women were asked to answer a checklist of chronic conditions ever diagnosed by a doctor. The full checklist consisting of 30 different maternal chronic conditions is available online at the study website (Progetto Ninfea, 2005). We selected from the checklist the following maternal mental disorders: (i) diagnosis of depression, (ii) diagnosis of anxiety and (iii) diagnosis of sleep disorders. For each reported condition, participants were further asked to report whether the condition was present only before pregnancy, only during pregnancy or in both periods. Information on the third-trimester exposures was retrieved from the questionnaire completed 6 months after delivery.

We defined three exposure time windows: (i) lifetime diagnosis – a disorder ever diagnosed by a doctor, (ii) pre-pregnancy exposure – a previous diagnosis of a disorder that was not active during the index pregnancy and (iii) during pregnancy exposure – a disorder active during the index pregnancy.

The definitions of sleep disorders were based on any doctor-diagnosed a sleep disorder, as information on specific Diagnostic and Statistical Manual of Mental Disorders (DSM V) (American Psychiatric Association, 2013) subcategories was not available in the NINFEA cohort. In addition, for sleep disorders during pregnancy, we did not consider the third trimester of pregnancy in order to avoid exposure misclassification due to deterioration in sleep quality across pregnancy (Polo-Kantola *et al.* 2017).

Potential confounders were chosen *a priori* and included maternal age at delivery (<30; 30–34; 35+ years), maternal educational level (university degree *vs.* lower level), maternal smoking during pregnancy (ever *vs.* never smoking), maternal alcohol consumption during the first trimester of pregnancy (at least 1 drink/day *vs.* <=6 drinks/week), gender of the child and first-born status.

Outcome variables

When the child turned 4 years, mothers were asked to respond to a list of questions regarding the child's behaviour (mean age at questionnaire completion 4.1 years; SD, 0.2 years). This list is based on the criteria for ADHD diagnosis of the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) (American Psychiatric Association, 1994) that provides a standard assessment of inattentive and hyperactive–impulsive symptoms prior to 7 years of age (Tandon *et al.* 2009). The DSM IV questionnaire consists of 18 dichotomous (yes/no) items that are used to define two behavioural subscales: (i) inattentive score (ADHD-I) and (ii) hyperactive–impulsive score (ADHD-H).

For a clinical diagnosis, the two traits would have to be confirmed in two settings, e.g. at home and at school, showing evidence of interference on social and academic functioning, but for research purposes, we based our outcome definition only on the mothers' report.

As from a population perspective, ADHD can be seen as a continuously distributed risk dimension (Larsson *et al.* 2012; Thapar & Cooper, 2016), we analysed ADHD symptoms as continuous scores. One of the nine items of the inattentive sub-scale ('Often has trouble keeping attention on tasks or play activities') was not included in the NINFEA questionnaire until a later update of the follow-up questionnaires, and, therefore, we considered only eight items for the ADHD-I score.

Given the association of ADHD with Intelligence Quotient (IQ), intellectual disability (Dykens, 2000) and low long-term academic outcomes (Polderman *et al.* 2010; Washbrook *et al.* 2013), we used data from the NINFEA assessment at age 7 years (mean age 7.1 years; SD 0.2 years) in which mothers were asked to indicate their children's final grades in mathematics and reading/writing in the first year of the primary school. We considered that a positive association between ADHD scores reported at age 4-years and lower academic performance at school age would indicate that maternally reported ADHD scores are reliable and valid measures of children's cognitive impairments related to ADHD. Information from the assessment at age 7 years was available for 1392 children who were born before November 2010 and thus met the age criterion for the assessment at age 7 years. The primary school in Italy uses a grading system that ranges from 1 (impossible to assess) to 10 (excellent). We coded the child's academic achievement in mathematics and reading/writing as low (equal or less of 7) and high (8–10).

Statistical methods

The total ADHD, ADHD-H and ADHD-I scores were treated as continuous variables and analysed using linear regression models. The number of symptoms was log-transformed [log (y + 1)] to satisfy the assumption of normality. After the transformation, visual inspection and tests based on kurtosis and skewness indicated a normal distribution. Model estimates are reported as percentage differences in the number of symptoms (Törnqvist *et al.* 1985). We specified two adjustment models: (i) adjustment for child's gender, first-born status, mother's age and educational level, and (ii) additional adjustment for maternal smoking and alcohol use during pregnancy. Maternal anxiety, depression and sleep disorders were analysed separately and in the following time windows: (i) lifetime diagnosis, (ii) pre-pregnancy only and (iii) during pregnancy.

To take into account comorbidities between the three disorders, we additionally analysed the total number of disorders experienced during pregnancy. We categorised the exposed subjects in the following groups: (i) mothers who never had a diagnosis of any of the three disorders (reference), (ii) mothers with a history of at least one of the disorders before pregnancy but not during pregnancy, (iii) mothers with only one of the disorders during pregnancy, (iv) mothers with the two disorders during pregnancy and (v) mothers with all the three disorders during pregnancy. Finally, to explore the relative importance and contribution of each of the disorders to ADHD symptoms we specified a model where all the three disorders were mutually adjusted (i.e. all variables included in the same model).

Associations of the number of symptoms on the two ADHD subscales with the academic outcomes in mathematics and reading/writing were estimated using logistic regression models adjusted for maternal depression, anxiety and sleep disorders, maternal age and education, child's gender and first-born status. As information on academic outcomes was missing for 9.2% of our sample, we performed multivariate multiple imputations using chained equations (20 imputed data sets) to replace missing values of both outcomes and all confounding factors (Buuren & Groothuis-Oudshoorn, 2011). Statistical analyses were

performed using R software version 3.3.1 (R Core Team, 2016).

Results

The study included 3634 children with the completed assessment at 4 years of age. Children lost to follow-up at age 4 were not significantly different from those included in the study in all the baseline characteristics, including being first-born, maternal age, maternal education and smoking during pregnancy (all p-values > 0.05). The percentage of missing data for maternal and child characteristics was <2.6%.

Maternal characteristics are reported in Table 1, while Table 2 summarises the main child characteristics. Mothers were mostly Italian born (96.5%), highly educated (63.5%) and were aged on average 33.6 (SD 4.2) years at delivery. In our sample, 3.8% of mothers reported a diagnosis of depression, 8.9% anxiety and 1.7% sleep disorders. In total, 402 (11.1%) mothers had at least one of the analysed mental disorders. At 4 years of age, children had a mean total ADHD score of 3.6 (SD 3.0), a mean ADHD-H score of 2.4 (SD 2.1) and a mean ADHD-I score of 1.2 (SD 1.5). The associations of the confounding variables with ADHD-H and ADHD-I are reported in Table S1.

The total ADHD score was associated with maternal lifetime diagnosis of anxiety (ever *vs.* never: 17.1%; 95% CI 7.3–27.9%), sleep disorders (35.7%; 95% CI 10.7–66.5%), and depression (17.5%; 95% CI 3.2–33.8%).

The associations between maternal mental disorders and child ADHD-H and ADHD-I scores at 4 years of age are reported in Table 3. Both maternal anxiety and sleep disorders were associated with an increase in ADHD-H score. A positive association, though weaker in magnitude, was observed also between maternal depression and ADHD-H score. The direction of the effects was similar also for ADHD-I, although the association of maternal sleep disorders with ADHD-I was somewhat weaker. All the estimates were higher when the disorders were active during pregnancy, for both ADHD traits, and were diminished or annulled for disorders active only during the pre-pregnancy period.

Of the 135 (3.7%) mothers with a history of at least one disorder before but not during pregnancy, 84 (62.2%) had anxiety, 12 (8.9%) sleep disorders and 39 (28.9%) depression. Of the 212 (5.8%) mothers with only one disorder active during pregnancy, 172 (81.1%) had anxiety, 19 (9.0%) sleep disorders and 21 (9.9%) depression. Among the 42 (1.2%) mothers with two disorders active during pregnancy, 33 (76.7%) had depression and anxiety without sleep disorders, nine (20.9%) had anxiety and sleep disorders without depression, and only one (2.3%) mother had sleep disorders and depression without anxiety. Twelve mothers (0.3%) had all three disorders during pregnancy. Depression more likely co-occurs with anxiety and sleep disorders and there is also a large overlap between anxiety and sleep disorders (all chi-square test p-values < 0.05).

Table 1. *Maternal characteristics (n = 3634)*

Variable	*N*	(%)
Country of birth		
Italy	3505	(96.5)
Other country	129	(3.5)
Age at childbirth (years)		
<30	681	(18.7)
30–34	1575	(43.3)
35+	1378	(37.9)
Maternal education[a]		
Low	1322	(36.5)
High	2299	(63.5)
Missing	13	
Smoking during pregnancy		
No	3352	(92.4)
Yes	277	(7.6)
Missing	5	
Alcohol consumption during the first trimester of pregnancy		
≤6 drinks/week	3315	(93.6)
at least 1 drink/day	225	(6.4)
Missing	94	
Anxiety		
Never	3311	(91.1)
Lifetime diagnosis	323	(8.9)
Pre-pregnancy	91	(2.5)
During pregnancy	232	(6.4)
Depression		
Never	3490	(96.2)
Lifetime diagnosis	139	(3.8)
Pre-pregnancy	70	(1.9)
During pregnancy	69	(1.9)
Missing	5	
Sleep disorders		
Never	3567	(98.3)
Lifetime diagnosis	61	(1.7)
Pre-pregnancy	20	(0.6)
During pregnancy[b]	41	(1.1)
Missing	6	
Anxiety and/or depression and/or sleep disorders before or during pregnancy		
Never	3225	(88.9)
At least one condition	402	(11.1)
Missing	7	

[a]High – University degree, Low – other.
[b]Sleep disorders during pregnancy do not include the third trimester exposures.

Table 2. *Child characteristics*

Variable	*N*	(%)
Child characteristics at birth and 4 years (n = 3634)		
Gender		
Boys	1854	(51.0)
Girl	1780	(49.0)
First born		
No	944	(26.1)
Yes	2677	(73.9)
Missing	13	
Gestational age (weeks)		
37+	3493	(96.2)
<37	139	(3.8)
Missing	2	
ADHD-H number of symptoms		
0	830	(23.4)
1	612	(17.2)
2	650	(18.3)
3	513	(14.4)
4	378	(10.6)
5	257	(7.2)
6	158	(4.4)
7	84	(2.4)
8	48	(1.4)
9	21	(0.6)
Missing	83	
ADHD-I number of symptoms		
0	1448	(40.9)
1	897	(25.3)
2	596	(16.8)
3	316	(8.9)
4	138	(3.9)
5	77	(2.2)
6	47	(1.3)
7	17	(0.5)
8	5	(0.1)
Missing	93	
Child characteristics at 7 years (n = 1392)		
Academic score in reading/writing		
>7	1011	(80.0)
≤7	253	(20.0)
Missing	128	
Academic score in mathematics		
>7	1035	(81.7)
≤7	232	(18.3)
Missing	125	

ADHD, Attention-deficit/hyperactivity disorder; ADHD-H, = ADHD hyperactive–impulsive score; ADHD-I, ADHD inattentive score, >7 means good academic performance.

The associations between the number of maternal mental disorders during pregnancy and child ADHD-H and ADHD-I scores at 4 years of age are presented in Table 4. Both ADHD-H score and, to a lesser extent, ADHD-I score showed a relative increase with increasing the number of disorders active during pregnancy. When all the three conditions were included in the same model (i.e. mutually adjusted) lifetime anxiety (11.2%; 95% CI 2.1–21.2%) and sleep disorders (22.4%; 95% CI 1.3–48.1%), but not depression (2.5%; 95% CI −9.7 to 16.4%), remained associated with ADHD-H, while only maternal anxiety was associated with offspring ADHD-I (anxiety: 8.6%; 95% CI 0.7–17.1%; depression: 3.4%; 95% CI −7.6 to 15.6%; sleep disorders 9.5%; 95% CI −7.1 to 29.1%).

Associations between child's ADHD at age of 4 years and their academic achievement at the end of the first year of primary school are reported in Table 5. ADHD-I score was negatively associated with academic performance at age 7 years, while no association was found with the ADHD-H score.

Discussion

Our study found positive associations of maternal lifetime anxiety, depression and sleep disorders with offspring ADHD symptoms at 4 years of age. Although the magnitude of the effects and the width of the confidence intervals varied, the associations were quite consistent for both inattentive and hyperactive–impulsive ADHD subscales. Notably, all the associations were stronger when the disorders were actively symptomatic during pregnancy, and there was an evident increase in the number of ADHD symptoms with increasing the number of disorders active during pregnancy. All the associations were largely attenuated if the disorders were present only during the pre-pregnancy period. Anxiety and sleep disorders contributed uniquely to the ADHD-H symptoms in the mutually adjusted model, while only maternal anxiety contributed to the ADHD-I symptoms. Finally, the ADHD-I score, but not the ADHD-H score, at 4 years of age was associated with lower scores in reading/writing and mathematics.

Our findings are generally consistent with those reported by previous longitudinal birth cohort studies, but with slightly stronger effects of maternal mental disorders during pregnancy on offspring ADHD. In the Norwegian MoBa cohort, an increase in maternal prenatal distress score was associated with an increase in the number of ADHD-H, but not with ADHD-I symptoms (Bendiksen *et al.* 2015). The authors explained that the lack of the association with ADHD-I may be due to lack of power, as only a few children had a clinically significant ADHD-I. Consistently, the PREDO cohort study found an increase in ADHD symptoms in 3–6-year-old children born to mothers with depressive symptoms during pregnancy (Wolford *et al.* 2017). Furthermore,

Table 3. *Associations between maternal mental disorders and children's ADHD-H and ADHD-I scores at 4 years of age (n = 3634)*

	Unadjusted		Model 1		Model 2	
	% difference in number of symptoms (95% CI)[a]		% difference in number of symptoms (95% CI)[a]		% difference in number of symptoms (95% CI)[a]	
ADHD-H						
Anxiety						
Never	0	(Ref)	0	(Ref)	0	(Ref)
Lifetime diagnosis	16.8	(8.0–26.2)	14.6	(6.1–23.8)	13.5	(4.8–22.8)
Pre-pregnancy	2.3	(−11.1–17.7)	0.7	(−12.4–15.6)	1.2	(−12.0–16.4)
During pregnancy	23.2	(12.5–34.9)	20.9	(10.4–33.3)	19.2	(8.6–31.0)
Sleep disorder						
Never	0	(Ref)	0	(Ref)	0	(Ref)
Lifetime diagnosis	30.3	(9.3–55.4)	32.1	(10.7–57.6)	29.8	(8.1–55.9)
Pre-pregnancy	11.0	(−18.1–50.4)	11.9	(−17.0–50.8)	12.6	(−17.2–53.0)
During pregnancy	41.2	(13.9–75.1)	44.2	(16.0–79.2)	40.3	(11.8–76.1)
Depression						
Never	0	(Ref)	0	(Ref)	0	(Ref)
Lifetime diagnosis	15.1	(2.6–29.1)	12.8	(0.6–26.5)	11.9	(−0.5–25.8)
Pre-pregnancy	15.3	(−1.7–35.3)	11.3	(−5.2–30.7)	10.5	(−6.0–30.0)
During pregnancy	14.8	(−2.3–35.0)	14.3	(−2.7–34.1)	13.4	(−4.0–33.9)
ADHD-I						
Anxiety						
Never	0	(Ref)	0	(Ref)	0	(Ref)
Lifetime diagnosis	12.9	(5.4–20.9)	11.8	(4.5–19.6)	11.3	(3.8–19.3)
Pre-pregnancy	8.3	(−4.3–22.6)	8.0	(−4.4–22.0)	8.7	(−3.9–23.0)
During pregnancy	14.8	(5.9–24.3)	13.4	(4.7–22.7)	12.4	(3.5–22.1)
Sleep disorder						
Never	0	(Ref)	0	(Ref)	0	(Ref)
Lifetime diagnosis	15.9	(−0.4–34.9)	18.5	(1.9–37.9)	15.4	(−1.5–35.1)
Pre-pregnancy	6.5	(−18.6–39.3)	5.5	(−18.9–37.2)	3.6	(−20.9–35.6)
During pregnancy	20.6	(0.4–44.8)	25.5	(4.4–50.9)	22.0	(0.5–48.1)
Depression						
Never	0	(Ref)	0	(Ref)	0	(Ref)
Lifetime diagnosis	11.8	(1.0–23.8)	11.9	(1.2–23.8)	10.0	(−0.8–22.0)
Pre-pregnancy	11.7	(−3.1–28.7)	10.5	(−4.1–27.4)	8.7	(−5.8–25.5)
During pregnancy	11.9	(−3.0–29.1)	13.3	(−1.6–30.5)	11.4	(−3.8–29.0)

CI, confidence interval, Model 1: Adjusted for maternal age and education, child gender and first-born status, Model 2: Adjusted as Model 1 and additionally adjusted for maternal smoking and alcohol use during pregnancy; ADHD-H, ADHD hyperactive–impulsive score; ADHD-I, ADHD inattentive score.

[a]Negative values indicate a relative decrease in the number of ADHD sub-scale symptoms.

a positive association between maternal anxiety during pregnancy and persistent attention problems in children was found in the Australian MUSP cohort (Clavarino *et al.* 2010), and antenatal maternal anxiety and depression were associated with an increased risk of child inattention at 3 years of age in the UK ALSPAC and Dutch Generation R cohorts (Van Batenburg-Eddes *et al.* 2013).

To our knowledge, this is the first study reporting an association between maternal sleep disorders and offspring ADHD. We observed that doctor-diagnosed maternal sleep disorders, especially if active during pregnancy, are strongly associated with offspring ADHD. These associations were evident particularly for the ADHD-H trait, where the observed difference was independent of maternal comorbid depression and anxiety. Maternal insomnia and sleep apnoea have been associated with preterm birth (Felder *et al.* 2017) and pregnancy complications, including gestational diabetes and hypertension (Bazalakova, 2017; Bourjeily *et al.* 2017). Chronic sleep deprivation is also known to be related to stress system activation that may influence adverse pregnancy outcomes (Palagini *et al.* 2014). It should be noted that we

Table 4. *Associations of the Number of Comorbid maternal mental Disorders with children's ADHD-H and ADHD-I scores at 4 years of age (n = 3634)*

	Unadjusted		Model 1		Model 2	
	% difference in number of symptoms (95% CI)[a]		% difference in number of symptoms (95% CI)[a]		% difference in number of symptoms (95% CI)[a]	
ADHD-H						
Diagnosis of anxiety, sleep disorders or depression						
Never	0	(Ref)	0	(Ref)	0	(Ref)
History of at least one disorder before but not during pregnancy	1.5	(−9.6–13.9)	−1.2	(−12.0–10.8)	−1.1	(−12.0–11.2)
One disorder in pregnancy	19.2	(8.4–31.1)	17.9	(7.3–29.5)	14.3	(3.7–26.1)
Two disorders in pregnancy	35.1	(10.3–65.4)	29.3	(5.7–58.2)	31.9	(6.4–63.6)
Three disorders in pregnancy	29.3	(−13.1–92.6)	34.2	(−9.2–98.6)	34.7	(−8.9–99.3)
ADHD-I						
Diagnosis of anxiety, sleep disorders or depression						
Never	0	(Ref)	0	(Ref)	0	(Ref)
History of at least one disorder before pregnancy, but not in pregnancy	7.8	(−2.7–19.6)	6.5	(−3.9–18.0)	6.3	(−4.2–17.9)
One disorder in pregnancy	12.3	(3.3–22.1)	12.4	(3.5–22.1)	10.7	(1.6–20.6)
Two disorders in pregnancy	20.2	(0.5–43.8)	16.8	(−2.2–39.6)	14.7	(−5.0–38.6)
Three disorders in pregnancy	12.1	(−20.0–57.0)	17.0	(−15.9–62.8)	17.5	(−15.5–63.4)

CI, confidence interval, Model 1: Adjusted for maternal age and education, child gender and first-born status, Model 2: Adjusted as Model 1 and additionally adjusted for maternal smoking and alcohol use during pregnancy; ADHD-H, ADHD hyperactive–impulsive score; ADHD-I, ADHD inattentive score.
[a]Negative values indicate a relative decrease in the number of ADHD sub-scale symptoms.

assessed only doctor-diagnosed disorders and, therefore, the effect of less severe sleep disturbances, which have much higher prevalence in general population and among pregnant women, requires future research. However, our findings suggest the importance of the sleep disorders assessment in women of reproductive age.

Table 5. *Associations between ADHD scores at age 4 and poor academic performance in reading/writing and mathematics at age 7 (n = 1392)*

	Mathematics		Reading/writing	
	OR (95% CI)[a]		OR (95% CI)[a]	
ADHD-H				
Unit of increase	1.04	(0.97–1.11)	1.03	(0.96–1.10)
ADHD-I				
Unit of increase	1.17	(1.06–1.29)	1.20	(1.09–1.31)

OR, odds ratio; CI, confidence interval; ADHD-H, ADHD hyperactive–impulsive score; ADHD-I, ADHD inattentive score.
[a]Results from logistic regression analyses adjusted for maternal anxiety, depression or sleep disorders before and during pregnancy, maternal age and education, child gender and first-born status.

In our analyses, we took into account several important confounding factors, and the associations we found between these confounders and ADHD-H and ADHD-I were consistent with previous research (Sayal *et al.* 2014; Arnett *et al.* 2015; Obel *et al.* 2016), providing indirect support to the validity of our research setting. Preterm birth is a potential mediator of the association between maternal mental health and neurodevelopmental problems (McCoy *et al.* 2014), and was thus not considered as a potential confounder in our study. However, further controlling for gestational age as a continuous variable or restricting analysis to children born at term did not change the results more than marginally (data not shown).

Although the specific mechanism involved in the associations between maternal mental disorders and offspring attention and/or hyperactivity/impulsivity problems are still unclear, several possible explanations have been suggested. First, maternal mental disorders could act by activating the HPA (hypothalamic–pituitary–adrenal) axis, which, through an excessive increase

in cortisol levels, might compromise fetal brain development (Van den Bergh *et al.* 2005; Beijers *et al.* 2014; Glover, 2015). In addition, the observed relationship could also be due to confounding by shared familial characteristics, such as genetics (Thapar & Cooper, 2016), as well as residual confounding by socioeconomic status (Foulon *et al.* 2015) and/or lifestyle (Sayal *et al.* 2014; Rijlaarsdam *et al.* 2017). Finally, mental disorders are generally persistent and could affect parenting style and mother–child attachment during postnatal period (Harold *et al.* 2013; Webb & Ayers, 2015; Thapar & Cooper, 2016) – factors that are known to be associated with later ADHD symptoms (Storebo *et al.* 2016).

The main strength of the NINFEA study is that the exposure information was collected prospectively during pregnancy. To the best of our knowledge, this is the first study on prenatal risk factors for ADHD in the Italian population, and thus, serves as a replication of findings from other populations (Zwirs *et al.* 2006). Our findings provide further evidence that maternal anxiety and depression contribute to the onset of offspring ADHD symptoms and extend the existing evidence also to maternal sleep disorders. We were able to evaluate two distinct ADHD subscales and most of the observed associations were evident both for inattentive and for hyperactive–impulsive trait. Finally, the follow-up at 7 years of age on the academic performance supports the clinical significance of the ADHD-I phenotype.

Our study has some limitations that should be considered when interpreting the results. First, the assessment of child's behavioural problems was entirely based on maternal report, and mothers with mental disorders at the time of the completion of the questionnaire might have overreported child ADHD symptoms (Najman *et al.* 2000). However, the observed associations were qualitatively similar for depression, anxiety and sleep disorders, and it is unlikely that the misreporting of child symptoms would have been driven in the same direction by these three disorders. Moreover, empirical evidence suggests a weak association between maternal mental health and differential reporting of offspring ADHD symptoms. In particular, a study on ADHD children showed that parental ADHD status does not affect maternal reporting of ADHD symptoms in their children (Faraone *et al.* 2003).

Considering that in the NINFEA cohort ADHD score and the academic achievement were assessed prospectively 3 years apart, and that the reported grades at school are not likely to be affected by maternal perception of her own child, our finding of a lower academic achievement among children with ADHD-I further supports the validity of the ADHD assessment in our cohort. Similarly, a previous study reported a lower academic achievement among children with an inattentive trait, but not among those with hyperactive behaviour (Polderman *et al.* 2011). These associations have been consistently replicated in large sample size studies with information on several potential confounding factors, including intelligence, family income and comorbidities (Polderman *et al.* 2010).

As different functions and structures of the brain develop in different periods of gestation, it has been hypothesised that the effects of prenatal stress on specific offspring neurodevelopmental outcomes may differ according to the pregnancy trimester (Van den Bergh *et al.* 2017). We did not analyse single trimester exposures as the prevalence of these disorders during pregnancy is rather low (e.g. depression prevalence is 2%), and the stratified analyses would have limited power. However, in this study, we used doctor-diagnosed mental disorders capturing, therefore, more serious and chronic conditions that generally do not pass in short time periods, such as pregnancy trimester.

Another limitation of our study is the lack of information on maternal ADHD diagnosis that potentially could act as a confounding factor. It should be noted that ADHD was unrecognised and rarely diagnosed in Italy before the 1990s (Gallucci *et al.* 1993), and therefore, difficult to be assessed in most of the mothers participating in the NINFEA cohort. However, given the relatively low ADHD prevalence in general population (Simon *et al.* 2009) compared with anxiety, depression and sleep disorders, and the relatively strong associations that we found, it is unlikely that confounding by maternal ADHD could entirely explain the findings of our study.

Finally, participants of the NINFEA cohort, like those of many other cohort studies, are a selected population with relatively high education and socioeconomic status. However, it has been extensively shown that, although this selective participation might affect prevalence estimates, it does not imply distorted estimates of association in cohort studies (Pizzi *et al.* 2012; Rothman *et al.* 2013).

Conclusions

Our findings indicate that antenatal maternal mental disorders, in particular depression, anxiety and sleep disorders, are associated with higher scores of inattentive and hyperactive–impulsive symptoms in their children at age 4 years and that these associations are stronger if the disorders are active during pregnancy. Antenatal preventive strategies focused on identification and reduction of mental disorders may be important for improving child psychological development.

Supplementary material

The supplementary material for this article can be found at https://doi.org/10.1017/S2045796018000185.

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Conflict of interest

The authors declare no competing interests.

Availability of data and materials

Anonymised data are available upon request to qualified researchers who meet the criteria for access to confidential data for the purpose of academic, non-commercial research, as required by the authors' IRB. Data on exposure and outcome variables are available upon request by contacting lorenzo.richiardi@unito.it

References

Arnett AB, Pennington BF, Willcutt EG, DeFries JC, Olson RK (2015). Sex differences in ADHD symptom severity. *Journal of Child Psychology and Psychiatry* **56**, 632–639.

Association American Psychiatric (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. DSM IV. American Psychiatric Association: Washington, DC.

Association American Psychiatric (2013). *Diagnostic and Statistical Manual of Mental Disorders*, 5th edn. DSM V. American Psychiatric Association: Washington, DC.

Bazalakova M (2017). Sleep disorders in pregnancy. *Seminars in Neurology* **37**, 661–668.

Beijers R, Buitelaar JK, de Weerth C (2014). Mechanisms underlying the effects of prenatal psychosocial stress on child outcomes: beyond the HPA axis. *European Child and Adolescent Psychiatry* **23**, 943–956.

Bendiksen B, Aase H, Diep LM, Svensson E, Friis S, Zeiner P (2015). The associations between pre- and postnatal maternal symptoms of distress and preschooler's symptoms of ADHD, oppositional defiant disorder, conduct disorder, and anxiety. *Journal of Attention Disorders*.

Bin YS, Cistulli PA, Ford JB (2016). Population-based study of sleep apnea in pregnancy and maternal and infant outcomes. *Journal of Clinical Sleep Medicine* **12**, 871–877.

Bourjeily G, Danilack VA, Bublitz MH, Lipkind H, Muri J, Caldwell D, Tong I, Rosene-Montella K (2017). Obstructive sleep apnea in pregnancy is associated with adverse maternal outcomes: a national cohort. *Sleep Medicine* **38**, 50–57.

Buuren S, Groothuis-Oudshoorn K (2011). Mice: multivariate imputation by chained equations in R. *Journal of Statistical Software* **45**, 1–67.

Clavarino AM, Mamun AA, O'Callaghan M, Aird R, Bor W, O'Callaghan F, Williams GM, Marrington S, Najman JM, Alati R (2010). Maternal anxiety and attention problems in children at 5 and 14 years. *Journal of Attention Disorders* **13**, 658–667.

Dykens EM (2000). Psychopathology in children with intellectual disability. *Journal of Child Psychology and Psychiatry* **41**, 407–417.

Faraone SV, Monuteaux MC, Biederman J, Cohan SL, Mick E (2003). Does parental ADHD bias maternal reports of ADHD symptoms in children? *Journal of Consulting and Clinical Psychology* **71**, 168–175.

Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, Sklar P (2005). Molecular genetics of attention-deficit/hyperactivity disorder. *Biological Psychiatry* **57**, 1313–1323.

Felder JN, Baer RJ, Rand L, Jelliffe-Pawlowski LL, Prather AA (2017). Sleep disorder diagnosis during pregnancy and risk of preterm birth. *Obstetrics and Gynecology* **130**, 573–581.

Foulon S, Pingault JB, Larroque B, Melchior M, Falissard B, Cote SM (2015). Developmental predictors of inattention-hyperactivity from pregnancy to early childhood. *PLoS ONE* **10**, e0125996.

Fried EI, van Borkulo CD, Cramer AO, Boschloo L, Schoevers RA, Borsboom D (2017). Mental disorders as networks of problems: a review of recent insights. *Social Psychiatry and Psychiatric Epidemiology* **52**, 1–10.

Gallucci F, Bird HR, Berardi C, Gallai V, Pfanner P, Weinberg A (1993). Symptoms of attention-deficit hyperactivity disorder in an Italian school sample: findings of a pilot study. *Journal of the American Academy of Child & Adolescent Psychiatry* **32**, 1051–1058.

Gelaye B, Rondon MB, Araya R, Williams MA (2016). Epidemiology of maternal depression, risk factors, and child outcomes in low-income and middle-income countries. *The Lancet. Psychiatry* **3**, 973–982.

Glover V (2011). Annual research review: prenatal stress and the origins of psychopathology: an evolutionary perspective. *Journal of Child Psychology and Psychiatry* **52**, 356–367.

Glover V (2015). Prenatal stress and its effects on the fetus and the child: possible underlying biological mechanisms. *Advances in Neurobiology* **10**, 269–283.

Goodman R, Stevenson J (1989). A twin study of hyperactivity--II. The aetiological role of genes, family relationships and perinatal adversity. *Journal of Child Psychology and Psychiatry* **30**, 691–709.

Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ (2010). A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. *Archives of General Psychiatry* **67**, 1012–1024.

Harold GT, Leve LD, Barrett D, Elam K, Neiderhiser JM, Natsuaki MN, Shaw DS, Reiss D, Thapar A (2013). Biological and rearing mother influences on child ADHD symptoms: revisiting the developmental interface between nature and nurture. *Journal of Child Psychology and Psychiatry* **54**, 1038–1046.

Howard LM, Molyneaux E, Dennis CL, Rochat T, Stein A, Milgrom J (2014). Non-psychotic mental disorders in the perinatal period. *Lancet* **384**, 1775–1788.

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* **53**, 73–80.

McCoy BM, Rickert ME, Class QA, Larsson H, Lichtenstein P, D'Onofrio BM (2014). Mediators of the association between parental severe mental illness and offspring neurodevelopmental problems. *Annals of Epidemiology* **24**, 629–634, 634 e1.

Najman JM, Williams GM, Nikles J, Spence S, Bor W, O'Callaghan M, Le Brocque R, Andersen MJ (2000). Mothers' mental illness and child behavior problems: cause-effect association or observation bias? *Journal of the American Academy of Child & Adolescent Psychiatry* **39**, 592–602.

Nigg J, Nikolas M, Burt SA (2010). Measured gene-by-environment interaction in relation to attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry* **49**, 863–873.

Obel C, Zhu JL, Olsen J, Breining S, Li J, Gronborg TK, Gissler M, Rutter M (2016). The risk of attention deficit hyperactivity disorder in children exposed to maternal smoking during pregnancy – a re-examination using a sibling design. *Journal of Child Psychology and Psychiatry* **57**, 532–537.

Palagini L, Gemignani A, Banti S, Manconi M, Mauri M, Riemann D (2014). Chronic sleep loss during pregnancy as a determinant of stress: impact on pregnancy outcome. *Sleep Medicine* **15**, 853–859.

Pizzi C (2016). Technical Report: Follow-up response rates https://www.progettoninfea.it/attachments/39).

Pizzi C, De Stavola BL, Pearce N, Lazzarato F, Ghiotti P, Merletti F, Richiardi L (2012). Selection bias and patterns of confounding in cohort studies: the case of the NINFEA web-based birth cohort. *Journal of Epidemiology and Community Health* **66**, 976–981.

Polderman TJ, Boomsma DI, Bartels M, Verhulst FC, Huizink AC (2010). A systematic review of prospective studies on attention problems and academic achievement. *Acta Psychiatrica Scandinavica* **122**, 271–284.

Polderman TJ, Huizink AC, Verhulst FC, van Beijsterveldt CE, Boomsma DI, Bartels M (2011). A genetic study on attention problems and academic skills: results of a longitudinal study in twins. *Journal of the Canadian Academy of Child & Adolescent Psychiatry* **20**, 22–34.

Polo-Kantola P, Aukia L, Karlsson H, Karlsson L, Paavonen EJ (2017). Sleep quality during pregnancy: associations with depressive and anxiety symptoms. *Acta Obstetricia et Gynecologica Scandinavica* **96**, 198–206.

Progetto Ninfea (2005). Questionario 1, Scheda: Anamnesi generale http://www.progettoninfea.it/inspector/q1_11_anamnesi_generale/fields?klass=Q1%3A%3AGeneralCaseHistory.

R Core Team (2016). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing. R Core Team: Vienna, Austria. Retrieved from https://www.R-project.org/.

Richiardi L, Baussano I, Vizzini L, Douwes J, Pearce N, Merletti F, Cohort N (2007). Feasibility of recruiting a birth cohort through the internet: the experience of the NINFEA cohort. *European Journal of Epidemiology* **22**, 831–837.

Rijlaarsdam J, Cecil CA, Walton E, Mesirow MS, Relton CL, Gaunt TR, McArdle W, Barker ED (2017). Prenatal unhealthy diet, insulin-like growth factor 2 gene (IGF2) methylation, and attention deficit hyperactivity disorder symptoms in youth with early-onset conduct problems. *Journal of Child Psychology and Psychiatry* **58**, 19–27.

Rothman KJ, Gallacher JE, Hatch EE (2013). Why representativeness should be avoided. *International Journal of Epidemiology* **42**, 1012–1014.

Sayal K, Heron J, Draper E, Alati R, Lewis SJ, Fraser R, Barrow M, Golding J, Emond A, Davey Smith G, Gray R (2014). Prenatal exposure to binge pattern of alcohol consumption: mental health and learning outcomes at age 11. *European Child and Adolescent Psychiatry* **23**, 891–899.

Simon V, Czobor P, Balint S, Meszaros A, Bitter I (2009). Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. *The British Journal of Psychiatry* **194**, 204–211.

Stein A, Pearson RM, Goodman SH, Rapa E, Rahman A, McCallum M, Howard LM, Pariante CM (2014). Effects of perinatal mental disorders on the fetus and child. *Lancet* **384**, 1800–1819.

Storebo OJ, Rasmussen PD, Simonsen E (2016). Association between insecure attachment and ADHD: environmental mediating factors. *Journal of Attention Disorders* **20**, 187–196.

Tandon M, Si X, Belden A, Luby J (2009). Attention-deficit/hyperactivity disorder in preschool children: an investigation of validation based on visual attention performance. *Journal of Child and Adolescent Psychopharmacology* **19**, 137–146.

Thapar A, Cooper M (2016). Attention deficit hyperactivity disorder. *Lancet* **387**, 1240–1250.

Thapar A, Holmes J, Poulton K, Harrington R (1999). Genetic basis of attention deficit and hyperactivity. *The British Journal of Psychiatry* **174**, 105–111.

Thapar A, Harrington R, Ross K, McGuffin P (2000). Does the definition of ADHD affect heritability? *Journal of the American Academy of Child & Adolescent Psychiatry* **39**, 1528–1536.

Törnqvist L, Vartia P, Vartia YO (1985). How should relative changes be measured? *The American Statistician* **39**, 43–46.

Van Batenburg-Eddes T, Brion MJ, Henrichs J, Jaddoe VW, Hofman A, Verhulst FC, Lawlor DA, Davey Smith G, Tiemeier H (2013). Parental depressive and anxiety symptoms during pregnancy and attention problems in children: a cross-cohort consistency study. *Journal of Child Psychology and Psychiatry* **54**, 591–600.

van de Loo KF, van Gelder MM, Roukema J, Roeleveld N, Merkus PJ, Verhaak CM (2016). Prenatal maternal psychological stress and childhood asthma and wheezing: a meta-analysis. *European Respiratory Journal* **47**, 133–146.

Van den Bergh BR, Mulder EJ, 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.

Van den Bergh BRH, van den Heuvel MI, Lahti M, Braeken M, de Rooij SR, Entringer S, Hoyer D, Roseboom T, Raikkonen K, King S, Schwab M (2017). Prenatal developmental origins of behavior and mental health: the influence of maternal stress in pregnancy. *Neuroscience and Biobehavioral Reviews*.

Washbrook E, Propper C, Sayal K (2013). Pre-school hyperactivity/attention problems and educational outcomes in adolescence: prospective longitudinal study. *The British Journal of Psychiatry* **203**, 265–271.

Webb R, Ayers S (2015). Cognitive biases in processing infant emotion by women with depression, anxiety and post-traumatic stress disorder in pregnancy or after birth: a systematic review. *Cognition & Emotion* **29**, 1278–1294.

Wolford E, Lahti M, Tuovinen S, Lahti J, Lipsanen J, Savolainen K, Heinonen K, Hamalainen E, Kajantie E, Pesonen AK, Villa PM, Laivuori H, Reynolds RM, Raikkonen K (2017). Maternal depressive symptoms during and after pregnancy are associated with attention-deficit/hyperactivity disorder symptoms in their 3- to 6-year-old children. *PLoS ONE* **12**, e0190248.

Zwirs BW, Burger H, Buitelaar JK, Schulpen TW (2006). Ethnic differences in parental detection of externalizing disorders. *European Child and Adolescent Psychiatry* **15**, 418–426.