MATERNAL ANXIETY, DEPRESSION AND SLEEP DISORDERS BEFORE AND DURING PREGNANCY, AND PRESCHOOL ADHD SYMPTOMS IN THE NINFEA BIRTH COHORT STUDY.

Short title: **PRENATAL MATERNAL MENTAL HEALTH AND ADHD IN CHILDREN.**

L. Vizzini[1], M. Popovic[1], D. Zugna[1], B. Vitiello[2], M. Trevisan[1], C. Pizzi[1], F. Rusconi[3], L. Gagliardi[4], F. Merletti[1], L. Richiardi[1]

[1] Cancer Epidemiology Unit, Department of Medical Sciences, University of Turin and CPO-Piemonte

[2] Division of Child and Adolescent Psychiatry, University of Turin, Turin, Italy

[3] Epidemiology Unit, Anna Meyer Children's University Hospital, Florence, Italy

[4] Woman and Child Health Department, Pediatric and Neonatology Division, Ospedale della Versilia, Viareggio, Italy

Corresponding author: Daniela Zugna

Department of Medical Sciences, University of Turin

Via Santena 7, Turin 10126, Italy

Phone: +39 011 6334658 Fax: +39 011 6334664

E-mail: daniela.zugna@unito.it

ABSTRACT

Aims: Maternal mental disorders have been associated with the risk of attention3 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 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 (DSM IV). Hyperactive–impulsive (ADHD-H), Inattentive (ADHD-I) and total ADHD scores were analyzed 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 to never; 95% CI: 7.3% to 27.9%), sleep disorders (35.7%; 95% CI: 10.7% to 66.5%), and depression (17.5%; 95% CI: 3.2% to 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 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.

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

KEYWORDS:

Attention-Deficit/Hyperactivity Disorder, Prospective Study, Risk Factors, Mental Health.

ABBREVIATIONS:

ADHD= Attention-Deficit/Hyperactivity Disorder

ADHD-H= ADHD hyperactive-impulsive trait

ADHD-I= ADHD inattentive trait

DSM IV= Diagnostic and Statistical Manual of Mental Disorders 4th edition

DSM V= Diagnostic and Statistical Manual of Mental Disorders 5th edition

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy

Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

INTRODUCTION

Pregnancy represents a particularly vulnearable 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 apnea and insomnia have been shown to be associated with pregnancy complications and adverse perinatal outcomes (Bin *et al.*, 2016, Felder *et al.*, 2017). Furthermore, maternal mental disorders during pregnancy influence the child cognitive, emotional, social, and behavioral development increasing the risk of child's emotional (internalizing) and behavioral (externalizing) difficulties, such as Attention-deficit/hyperactivity disorder (ADHD) (Glover, 2011, Stein *et al.*, 2014). ADHD is a childhood-onset neurodevelopmental disorder characterized by symptoms of inattention, hyperactivity and impulsivity. Its etiology is multifactorial (Thapar and

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

Cooper, 2016), including an important heritability component (heritability estimates ranging from 75% to 90%) (Goodman and Stevenson, 1989, Thapar *et al.*, 1999, Thapar *et al.*, 2000, Faraone *et al.*, 2005), several environmental risk factors (Thapar and Cooper, 2016), and gene-environment interactions (Nigg *et al.*, 2010, Harold *et al.*, 2013). Parental expectations of the child's behavior 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 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 analyzed 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.

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

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

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

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 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 behavior (mean age at questionnaire completion 4.1 years; SD,

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

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 behavioral 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 and Cooper, 2016), we analyzed 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 at 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

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

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 analyzed 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 analyzed 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 categorized 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

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

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 imputation using chained equations (20 imputed data sets) to replace missing values of both outcomes and all confounding factors (Buuren and 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 less than 2.6%.

Maternal characteristics are reported in **Table 1**, while **Table 2** summarizes the main child characteristics. Mothers were mostly Italian born (96.5%), highly educated

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

(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 analyzed 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% to 27.9%), sleep disorders (35.7%; 95% CI: 10.7% to 66.5%), and depression (17.5%; 95% CI: 3.2% to 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 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

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

pregnancy, 33 (76.7%) had depression and anxiety without sleep disorders, 9 (20.9%) had anxiety and sleep disorders without depression, and only 1 (2.3%) mother had sleep disorders and depression without anxiety. Twelve mothers (0.3%) had all three disorders during pregnancy. Depression more likely co-occur 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).

The associations between 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% to 21.2%) and sleep disorders (22.4%; 95% CI: 1.3% to 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% to 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 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

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

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 uniquely contributed 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 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, 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).

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

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 apnea 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 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.

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).

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

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 hypothalamic-pituitary-adrenal (HPA) 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 and 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 and Ayers, 2015, Thapar and 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.

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

Our study has some limitations that should be considered when interpreting the results. First, the assessment of child's behavioral problems was entirely based on maternal report, and mothers with mental disorders at the time of the completion of the questionnaire might have over-reported 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 behavior (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 hypothesized that the effects of prenatal stress on specific offspring neurodevelopmental outcomes may differ according to the pregnancy

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

trimester (Van den Bergh *et al.*, 2017). We did not analyze 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 unrecognized and rarely diagnosed in Italy before the 90s (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

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

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.

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Conflict of interest The authors declare no competing interests.

Data sharing Anonymized 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.

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

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Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy

Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

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Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy

Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

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Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

TABLES

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		

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

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.

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

1 **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)

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

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	

1

2 ADHD= Attention-Deficit/Hyperactivity Disorder, ADHD-H= ADHD hyperactive-impulsive score,

3 ADHD-I= ADHD inattentive score, >7 means good academic performance.

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

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						

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

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)

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

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

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 % difference in number of symptoms (95% CI) [a]		Model 1 % difference in number of symptoms (95% CI) [a]		Model 2 % 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)

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

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

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it

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)

[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, OR= odds ratio, CI= confidence interval, ADHD-H= ADHD hyperactive-impulsive score, ADHD-I= ADHD inattentive score.

Department of Medical Sciences, University of Turin - Via Santena 7, Turin 10126, Italy
Phone: +39 011 6334658 Fax: +39 011 6334664 E-mail: daniela.zugna@unito.it