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Does maternal somatic anxiety in pregnancy predispose children to hyperactivity?

Dr. Blanca Bolea-Alamañac
Assistant Professor, General Systems Division, Centre for Addiction and Mental Health, 80 Workman Way, 6th Floor, Toronto, ON M6J 1H4, Canada.
Email: blanca.bolea@bristol.ac.uk

Dr. Simon JC Davies
Associate Professor, Geriatric Psychiatry Division, Centre for Addiction and Mental Health, 80 Workman Way, 6th Floor, Toronto, ON M6J 1H4, Canada.
T:+1 (416) 535-8501 ext. 39395
Fax: +1 (416) 583-1296
Email: simon.davies@camh.ca

Dr. Jonathan Evans
Consultant Senior Lecturer, Office Room BF12,Oakfield House,Oakfield Grove, Clifton BS8 2BN, Bristol, UK.
Email: j.evans@bristol.ac.uk

Dr. Carol Joinson
Senior Lecturer in Developmental Psychology, School of Social and Community Medicine, University of Bristol, Oakfield House, Oakfield Grove, Clifton, Bristol, BS8 2BN
Email: Carol.Joinson@bristol.ac.uk

Dr. Rebecca Pearson
Lecturer in Psychiatric Epidemiology, Office BF11, Oakfield House, Oakfield Grove, Clifton BS8 2BN, Bristol, UK.
Email address: rebecca.pearson@bristol.ac.uk

Dr. Petros Skapinakis
Division of Psychiatry, University College London, London W1T 7NF, UK
Department of Psychiatry, University of Ioannina School of Medicine, 45110 Ioannina, Greece.
Email: p.skapinakis@gmail.com

Prof. Alan Emond
Professor of Community Child Health, Centre for Child and Adolescent Health, School of Social and Community Medicine,University of Bristol, Office Room BG6a, Oakfield House, Oakfield Grove, Clifton BS8 2BN, Bristol, UK.
Email: alan.emond@bristol.ac.uk

Corresponding author: Dr. Simon JC Davies, Geriatric Psychiatry Division, Centre for Addiction and Mental Health, 80 Workman Way, 6th Floor, Toronto, ON M6J 1H4, Canada.
T: +1(416) 535-8501 ext. 39395
Fax: +1 (416) 5831296
Email: simon.davies@camh.ca

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Dr. Bolea has received speaker fees once from Janssen pharmaceuticals.

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Abstract

Objectives: To explore the association between maternal somatic anxiety in pregnancy and hyperactivity symptoms and ADHD diagnosis in children.

Methods: Data from the Avon Longitudinal Study of Parents and Children cohort (ALSPAC) was used to examine the association between somatic anxiety symptoms in pregnancy measured with five items of the Crown-Crisp Experiential Index, ADHD diagnosis in children at 7.5 and 15 years (obtained with the Development and Well-Being Assessment-DAWBA) and hyperactivity at 4 and 16 years (measured with the Strengths and Difficulties Questionnaire hyperactivity subscale-SDQ).

Results: Maternal somatic anxiety was associated with ADHD diagnosis at age 7.5 [crude OR=1.87 (95% CI =1.21 - 2.91)], adjusted model [OR=1.57 (95% CI =0.99 - 2.48)]. There was no evidence of association with ADHD at 15: crude OR= 2.27 (95% CI = 0.90-5.71), adjusted OR=1.65 (95% CI = 0.63-4.35). An association was found at 4 and 16 with the SDQ hyperactivity subscale: crude OR at 4: 1.70 (95%CI =1.37-2.11), adjusted OR=1.34 (95% CI=1.07-1.69); crude OR at 16: 1.95 (95% CI =1.47-2.58), adjusted OR=1.62 (95%CI= 1.21-2.17).

Conclusion: There was evidence for an association between maternal somatic anxiety in pregnancy and increased hyperactivity symptoms (SDQ) at 4 and 16. There was no association with ADHD diagnosis.

Word count: 200

Keywords: ADHD, hyperactivity, anxiety, depression, pregnancy, ALSPAC.

1-Introduction

Attention Deficit and Hyperactivity Disorder (ADHD) is a common illness. A meta-analysis estimated the prevalence of ADHD in children at around 7.2% (95% CI 6.7-7.8) [1]. ADHD is largely a genetic disorder, with a heritability of 76% based on twin studies [2]. First degree relatives of an individual with ADHD have a two to eight fold increased risk of having the disorder. Genome wide association studies show a variety of genes each producing a modest effect. Candidate genes are linked to dopaminergic, serotoninergic, glutamatergic and cholinergic pathways amongst others [3].

Less is known about the environmental ethiology of ADHD. Exposure to lead, organophosphate pesticides and polychlorinated biphenyls have been identified as possible environmental toxins linked to ADHD [4]. Dietary factors (food colouring, highly sugared foods) and psychosocial adversity (low income, parent-child hostility and severe early deprivation) have been studied as possible contributing ethiological factors [4].

Several prenatal exposures have been associated with ADHD [5]. A study of more than 2000 adults prescribed medication for ADHD found 1.3 fold increase in risk for those born before 37 weeks of gestation and a five fold increase if born before 28 weeks of gestation [6]. Children born small for gestational age are also at an increased risk for ADHD [6]. A number of obstetric adverse events have been found to increase ADHD including pre-eclampsia, induced labour, cord prolapse and threatened pre-term labour [7]. Higher rates of ADHD have been found in individuals with a parental history of alcohol use disorder [8], the risk being higher if the parents had an active diagnosis of alcohol abuse before the birth of the child. Both maternal and paternal smoking during pregnancy have been associated with higher rate of symptoms of ADHD in children (rated by parents) [9], with maternal smoking having a bigger effect [10].

Anxiety disorders are considered the most common of all groups of mental illness. They are more prevalent in women with 1.6 fold increase in risk in average across all ages [11]. The prevalence of anxiety disorders during pregnancy varies according to syndrome: 1.3% to 2% of pregnant women will fulfill criteria for panic disorder and up to 8.5% for generalized anxiety disorder (GAD). Prenatal anxiety is a risk factor for postnatal depression. It is generally accepted that under-diagnosis of anxiety disorders is common during this period [12], first because clinicians are generally more inclined to search for depressive symptoms than anxiety and secondly because increase in anxiety during pregnancy may be considered normal by medical staff.

The fetal programming hypothesis postulates that prenatal external influences may program the child in utero to adapt to the environment at birth. Following on from this concept, some researchers [13] have hypothesized that maternal mental state during pregnancy may program the fetal brain and make the child more prone to certain behaviours; for example, maternal prenatal depression has been linked to behavioural problems in toddlers [14]. Prenatal stress has been associated with increased impulsivity, lower cognitive performance, conduct disorder and hyperactivity symptoms in children [15]. Putative biological pathways have been identified for these effects. Maternal hormones may cross the materno-fetal barrier at certain times during pregnancy. Glucocorticoids and catecholamines can influence the development of dopaminergic neurons, produce neural degeneration in the hippocampus and influence the quantity of glucocorticoid receptors in key brain areas such as the amygdala and the paraventricular nucleus of the hypothalamus

[16]. Studies correlating depression in mothers with basal cortisol levels in children show that infants of depressed mothers have higher serum cortisol concentration than controls [17]. Research in this area has concentrated on depression, stress or on negative life events (such as death of relatives) [18]. A few cohort studies have investigated the association between prenatal maternal anxiety and hyperactivity symptoms in children. Van Batenburg-Eddes and colleagues combined data from two different cohorts to evaluate the relationship between maternal and paternal anxiety during pregnancy and SDQ/CBCL scores in 4 and 3 year olds [19]. Prenatal maternal anxiety in this study was associated with increased risk of attentional symptoms. Leis and colleagues used the Crown Crisp Experiential Index (CCEI) anxiety subscale and SDQ hyperactivity/inattention scores at age 11 reported by mothers and teachers [20]. They found an association when hyperactivity symptoms were evaluated using maternal report only but this association was not maintained after adjusting for confounders. Two studies in the ALSPAC cohort showed an association between the prenatal anxiety measured with the CCEI anxiety subscale and children's inattention and hyperactivity symptoms. The first study measured children's behaviour using the Rutter's index and found significant associations with emotional problems, inattention/hyperactivity and conduct problems at age 4 years [21]. The second study used the same exposure but outcomes were examined using the Strengths and Difficulties Questionnaire (SDQ), an association was found between antenatal exposure to anxiety and behavioural problems in children at 7 years, suggesting a pervasive effect [22]. Most studies have concentrated in exposures with several types of anxiety clustered together or on self-report measures of stress. However, less is known about the relationship between specific maternal symptoms of anxiety during pregnancy and child outcomes.

Somatic anxiety symptoms include physical manifestations of anxiety such as dizziness or shortness of breath, fainting, feeling sick or having indigestion, tingling or prickling sensations in body, arms or legs, and excessive sweating. Somatic anxiety symptoms typically increase during pregnancy and peak before delivery. Maternal somatic anxiety symptoms are relevant because they can be examined easily using scales and questionnaires. Symptoms of somatic anxiety can be considered a proxy for panic as these are included in the DSM-5 definition of the disorder [23].

2-Aim of study

In a previous study we looked at the relationship between somatic anxiety and attentional outcomes measured with the Test of Everyday Attention in Children (TEA-Ch)[24]. In this study we aim to investigate the relationship between maternal symptoms of somatic anxiety during pregnancy and hyperactivity/inattention in their children ascertained at different ages with two different outcomes, hyperactivity/inattention symptoms and ADHD diagnosis.

3-Sample

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a birth cohort established in 1990 in the former county of Avon (UK). Women living in three health districts in the old county of Avon (UK) with a delivery date between April 1991 and December 1992 were eligible. Expression of interest cards were distributed mostly through antenatal and health care services in this area. Women filled these cards and if

they did not actively opt-out were sent questionnaires within approximately 2 weeks of enrolment. The study recruited 14,541 pregnant women, resulting in 14,775 live births of which 14,701 were alive at 1 year of age. The ALSPAC cohort has been described in detail elsewhere [25]. More detailed information on the ALSPAC study is available on the website: http://www.bristol.ac.uk/alspac which contains details of all the data available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/reserachers/data-access/data-dictionary/). In this study we excluded multiple pregnancies as we could not control for added pobstetric risks in this population.

3.1-Ethics

Ethical approval for the study was obtained from the Local Research Ethics Committees and the study is monitored by the ALSPAC Law and Ethics Committee. Specific details on ethical approval are available at http://www.bristol.ac.uk/alspac/researchers/data-access/ethics/.

4-Measures

4.1-Somatic anxiety

Somatic anxiety symptoms were chosen because they are easy to assess and can be considered a proxy for those experienced in panic disorder, as they appear as constituent panic attack symptoms in DSM-IV and DSM 5 criteria [26,27]. Mothers in ALSPAC completed the Crown-Crisp Experiential Index (Crown and Crisp 1965). Each item had four possible responses: never, not very often, often and very often with scores 0 to 3 respectively. To obtain a valid somatic anxiety measure, data were factor analysed. The five items selected for the somatic anxiety factor were: dizziness or shortness of breath, fainting, feeling sick or having indigestion, tingling or prickling sensations in body, arms or legs, and extra sweating. Information about maternal anxiety was obtained at weeks 18 and 32 of pregnancy. The final measure was a composite of both time points (sum of the scores on each of the symptoms at both time points). The somatic anxiety factor was dichotomized with the top 20% of scorers considered for the case category.

4.2-Hyperactivity

The hyperactivity/inattention subscale from the Strengths and Difficulties Questionnaire (SDQ) was used to measure symptoms of ADHD at age 4 and 16 years assessed by parental report. The SDQ has been widely adopted in epidemiological studies in the UK and continental Europe and has good sensitivity and specificity [28]. Parental ratings in the SDQ have been shown to be reliable [29]**.** The scores on the hyperactivity subscale were dichotomized with a cut-off point at two standard deviations above the mean [30]. Cut off points were the same for boys and girls at age 4 (cut off point at 8) but differed at age 16 (cut off point at 6 for girls and 7 for boys) as the distribution of scores at that age was different in women and men.

4.3-ADHD

Children were assessed at age 7 and 15 using the Development and Well-being Assessment (DAWBA), an instrument specifically designed to obtain diagnostic data based on DSM-IV and ICD-10 criteria [26,31]. It has four components: three interviews (parent, teacher and participant) and a computer assisted rating algorithm based on the information provided in the interviews [32]. Experienced clinicians have access to this information and make a diagnosis based on all evidence. The computer algorithm offers suggestions on diagnosis according to probability. Raters can accept or decline the computer based diagnosis depending on the available data and their clinical judgement. Full DAWBA diagnoses were available for a subset of children of the ALSPAC cohort at age 7.5, of those 5,035 had complete data in all the covariates. Multiband diagnoses were used for children at age 15 (N= 2,891). The DAWBA multiband is a recent development to the original instrument [33]. The basic idea is to use the computer predictions to establish probabilities for a population in a series of percentage levels also known as "bands". In band 0 less than 0.1 % of the population has the diagnosis, in band 1, 0.5%; in band 2, 3%; in band 3, 15%; in band 4, 50% and in band 5, 70%. This is an attempt to produce diagnostic endpoints without the use of a highly skilled rater. The band system is not aimed at clinical use but at obtaining diagnoses in large population surveys. DAWBA categories can be used as categorical variables. The DAWBA multiband has good correlation with diagnostic prevalence at a population level and has proved useful both at assessing risk factors and dose effects. DAWBA bands were used as binary variables by collapsing band 4 and 5 as "high probability of ADHD disorder" and bands 0, 1, 2, and 3 as "low probability of ADHD disorder". This approach was validated by Goodman and colleagues [33].

4.4-Covariates

Table 1 and **2** illustrate the distribution of exposures, outcomes and covariates in the SDQ sample at age 4 years and DAWBA 7.5 years respectively. Child, maternal and sociodemographic variables were added to the model. Child factors included gender, birthweight (cut off at <2.5 kg) and gestational age (cut off point <37 weeks of gestation). Mother related covariates included maternal age (cut off >=18 years), maternal use of alcohol (cut off point at >1 glass of alcohol a week), maternal smoking (cut off point at any cigarette smoked) and maternal education (cut off between obtaining O levels and achieving A levels). Paternal support was measured by the answer to the items "was your partner supportive during pregnancy?" and "was your partner affective during pregnancy?". Several sociodemographic factors were incorporated to the model: crowding index (number of people living in the household divided by the number of rooms; cut off at 1 person/room), social class [(United Kingdom Office of Populations, Censuses and Surveys classification, cut off between category 3M "skilled manual occupation" and 3N "skilled non manual occupation"[34]], having financial difficulties (yes/no) and having difficulties buying things for the baby (yes/no). This last covariate was extracted from the Family Adversity Index (FAI), an ALSPAC specific measure derived from a series of questions about family welfare gathered during pregnancy [35]. Life events were assessed via maternal questionnaires using a survey of 42 questions based on previous scales and designed specifically for ALSPAC [36] with a cut off at the top 15%. This variable was also weighted to include the impact these events had on the mother and not just their presence or absence. This variable also included obstetric events such as eclampsia and hyperemesis which may overlap with symptoms of somatic anxiety.

[Table 1 and 2]

5-Statistical Methods

5.1-Confirmatory Factor Analysis

Confirmatory Factor Analysis (CFA) of the Crown Crisp Experiential Index yielded two separate factors: one that could be characterized as “depression” and another one defined as “somatic anxiety”. The latter included the following items: “troubled by dizziness or shortness of breath”, “felt as though you may faint, feel sick or have indigestion”, “tingling or prickling sensations in body, arms or legs” and “extra sweating”. The procedure used to obtain these two factors has been described elsewhere [37]. **Table 3** shows the distribution of each item of the CCEI included in the somatic anxiety factor in the mothers sample at 18 weeks of pregnancy (N=11029).

[Table 3]

5.2-Logistic Regression

A logistic regression model was fitted using somatic anxiety as exposure and SDQ hyperactivity sub scores and DAWBA ADHD diagnoses separately as outcomes. Bias due to missing data was dealt with using Multiple Imputation with Chained Equations (MICE) [38]. This method is a specific subtype of multiple imputation in which variables with missing data are regressed conditionally on all the other variables. 50 imputations in 10 cycles were calculated for the SDQ data at age 4 and the DAWBA at age 7.5, 100 imputations for DAWBA at 15 and 150 for SDQ at 16 years.

6-Results

6.1-Hyperactivity/inattention. 5,697 children had complete data at age 4 and 3,605 at age 16. The results of the regression model for maternal somatic anxiety and hyperactivity symptoms at ages 4 and 16 are illustrated in **Table 4**. There was evidence for an association between maternal somatic anxiety and hyperactivity with an OR of 1.70 (1.37-2.11), $p<0.001$ in the unadjusted model and an OR of 1.34 (1.07-1.69), $p=0.011$ in the fully adjusted model. This association persisted at the 16 year old time point, with an OR of 1.95 (1.47-2.58), $p<0.001$ in the unadjusted model and an OR of 1.62 (1.21-2.17), $p<0.001$ in the fully adjusted model.

[Table 4]

6.2-ADHD. Of the 5,035 children with complete data in the somatic anxiety exposure, DAWBA, and covariates at age 7.5 years, only 42 met criteria for a diagnosis of combined ADHD, another 42 for inattentive subtype and 11 for hyperactive subtype. Data were not analysed per subtype as the number of participants in each category was too small. Instead a binary variable ADHD/ Not ADHD was created. There was an association with somatic anxiety in the unadjusted analysis OR=1.87 (1.21-2.91), $p=0.007$ but it attenuated in the adjusted analysis OR=1.57 (0.99-2.48), $p=0.055$. Using the DAWBA multiband data at age 15 years, no association was found either in the unadjusted or fully adjusted models:

unadjusted OR=2.27 (0.90-5.71), p=0.082, adjusted OR=1.65 (0.63-4.35), p=0.311. **Table 5** summarizes these results.

[Table 5]

6.3-Missing data

At 4 years old, the variable most frequently missing was socioeconomic status, followed by birthweight, crowding and the exposure variable (somatic anxiety). As the cohort grew older the outcome (SDQ hyperactivity subscale) was the most commonly missed variable followed by crowding and socioeconomic status. Social status was the most frequent missing variable in the DAWBA data at age 7.5, followed by birthweight and crowding. Ultimately, the patterns of missing data did not differ between the two outcomes. The population with missing SDQ scores had higher odds of maternal depression, were of lower socioeconomic status, smoked more frequently and reported less support from partners during pregnancy. This is consistent with current literature about attrition in large cohorts, which describes loss of follow up in lower socioeconomic status and in women with mental health diagnoses. There was no evidence for a difference between observed and missing populations at 4 years, probably because attrition was smaller at that age. At age 16, the loss of follow up was more pronounced with evidence for differences in all socioeconomic markers. However, the results after imputation did not vary from the adjusted models in the complete case set (see **tables 4 and 5**).

6.4-Association between somatic anxiety and depression

Symptoms of somatic anxiety appear in panic disorder which is also associated with depression. To elucidate if these symptoms produced an effect per se or only when associated with depression we performed a sensitivity analyses controlling for the depression factor. At age 16 years unadjusted analysis showed an OR of 1.41 (p=0.025, 95% CI 1.04-1.92) while in adjusted analyses with all covariates including depression the OR was (p=0.066, 95% CI 0.98-1.82). At age 4 the OR was 1.22 (p=0.087, 95% CI 0.97-1.55) for the unadjusted analysis and 1.11 for the fully adjusted analysis (p=0.382, 95% CI 0.87-1.42). Similar non-significant results were obtained when examining ADHD diagnosis as an outcome with an OR at 7 years of 1.54 unadjusted (p=0.074, 95% CI 0.95-2.48) and 1.42 fully adjusted (p=0.160, 95% CI 0.86-2.33) and at 15 y with an OR of 1.42 (p=0.446, 95% CI 0.57-3.56) unadjusted and of 1.57 (p=0.382, 95% CI 0.55-4.56).

7-Discussion

This large prospective study found some evidence for an association between maternal somatic anxiety and hyperactivity symptoms measured with the SDQ at age 4 which persisted to age 16 years. There was little evidence for an association between maternal somatic anxiety and ADHD diagnosis. This might be explained by the small number of children with a diagnosis of ADHD in the sample and by the accumulation of missing data in those with ADHD compared to non-cases. If there was a specific mechanism of harm for children with accumulated adversity (lack of parental support, low socioeconomic status, aggregation of negative life events, etc.) this would not be evident even after a relatively complex imputation procedure for missing data.

Published evidence for an association of maternal anxiety during pregnancy and hyperactivity in children is mixed. Most research has concentrated on stress paradigms based on negative life events, focusing on the quality or quantity of those events and not on the particular symptoms the women experienced. Van Batenburg and colleagues considered attentional outcomes using the CCEI as exposure, and found an association between both measures [19]. However, they used the traditional anxiety subscale of the CCEI which included items that in factor analyses cluster with depression. O'Connor found an association only for boys at age 4 and for boys and girls at age 7 [22]. Further studies in children aged 10-11 did not find an association (Leis, Heron, Stuart, & Mendelson, 2014). However, they again used the CCEI anxiety subscale following the same paradigm as Van Batenburg. The problem with this approach is that both anxiety and depression symptoms and personality characteristics were included as exposure, so the purported "anxiety subscale" of the CCEI was potentially measuring accumulated burden of illness as shown by a number of symptoms not specific to a particular construct. Furthermore, the possible role of certain somatic anxiety symptoms as markers of risk would be overlooked.

From a public health perspective, symptoms of somatic anxiety are easy to identify as valid instruments for the detection of anxiety during pregnancy exist [39]. In contrast with other symptoms of mental health distress, symptoms of anxiety are non-stigmatizing and can be screened by medical staff without requiring further training. Intervention programs can then be developed. Clinicians can then prescribe either pharmacological or psychological treatment in pregnancy to prevent further harm to the future child. There is evidence that anxiolytic medications may have differential effects on somatic symptoms compared to psychological symptoms of anxiety [40]. For example, lower doses of pregabalin were effective in the treatment of psychological symptoms of anxiety but not somatic anxiety symptoms [41]. This has implications for the treatment of anxiety during pregnancy. A large nationwide prescription study did not find an increase in congenital malformations in children of women exposed to anxiolytic drugs compared to non-exposed women [42]; this knowledge should facilitate pharmacological treatment of these symptoms in a clinical setting. Several psychological interventions have been evaluated to improve maternal wellbeing during pregnancy. Family- nurse partnerships, where a nurse supports the mother up to two years after delivery have shown positive results in some countries but not others [43,44]. A systematic review of psychological preventative interventions for distress in pregnancy found a small effect for women at risk of social adversity and for women already reporting high levels of anxiety at baseline [45]. The interventions evaluated were heterogeneous (mentoring, psychoeducation, group support, music therapy, mindfulness, self-help, relaxation techniques and acupuncture), as well as the populations studied which may limit the generalizability of these results. Perhaps a single intervention is not as important as the creation of service hubs oriented to prenatal and perinatal care where parents can access a number of resources including group support, individual and family therapy and nursing/medical input. This concept has been extensively studied for the prevention of postpartum depression [46] and could easily include the treatment of anxiety in the perinatal period. This study highlights the importance of maternal psychological wellbeing during pregnancy. Most prenatal programs concentrate on obstetric risk, nutritional input and early assessment of depression, considering anxiety as part of the problem in the framework of integrative care will increase the effectivity of these interventions and may reduce future risks to mother and child.

7.1-Limitations

This study has several limitations. Missing data analyses showed that women-child dyads in the higher levels of adversity were more likely to drop out of the cohort than affluent families. A complex MICE model was computed to compensate for this; however, missing data models can only attempt to reproduce the population, so it is possible that an additive effect exists for the high adversity- high somatic anxiety mothers that was not captured in our sample. We did not control for maternal depression. The focus of interest in this paper was how specific symptoms affected children later on and not whether these were attributable to specifically to anxiety or depression. It is possible that these symptoms concur with depression, generalized anxiety or panic disorder. This follows the current trend towards dimensionality in psychiatric epidemiology [47-49], the idea being that symptoms per se could be used as markers of future risk regardless of specific diagnoses. Sensitivity analyses performed regressing the somatic factor while controlling for depressive symptoms reinforced the fact that somatic anxiety symptoms may express its effect as part of depression, this would imply that is depression and not anxiety having an effect in future ADHD symptomatology. This being the case, the role of somatic anxiety symptoms as indicators of risk would still persist and be relevant for screening.

An effort was made to account for all known confounders; however, residual confounding is still possible. For instance, information about medication during pregnancy was scarce in this cohort and it was not included in the model. In general, women are rarely treated with psychotropic medication “de novo” during pregnancy but they may continue previous prescriptions. At the time of conclusion of this study ALSPAC data was not linked with primary care data or prescription data so it was not possible to obtain an accurate picture of psychotropic prescribing during pregnancy. We did not have information regarding maternal or paternal ADHD status, so genetic risk could not be disentangled from environmental risks. It is relevant that ADHD is indeed an inheritable illness and this genetic risk could not be assessed with the methods and data presented in this paper. Additive effects of several variables should also be considered; for example, there is some evidence that prenatal maternal anxiety and depression may increase the risk of binge drinking in pregnancy which in turn will increase the risk of behavioural problems in the child later on [50]. In the sample of 16 year olds, we did not control for a diagnosis of ADHD at 4 years. Our exposure was prenatal and therefore both children at 4 and at 16 had been exposed, we considered a previous diagnosis not relevant for the hypothesis that this effect persists up to the late teenage years.

Reporter bias cannot be ruled out— perhaps anxious mothers report more hyperactive behaviours in their children. Research carried out on parental reports of SDQ suggests that parents are reliable raters [29]; however, the specific effect of parental mental state at the moment of report cannot be completely excluded.

There is also the possibility of overlap between symptoms of hyperemesis and somatic anxiety. We performed subsequent analyses on somatic anxiety after delivery that showed that maternal report of somatic anxiety was consistent before prenatal and postnatal time points which appears to rule out this overlap but brings to the forefront the possibility of a continuous effect of prenatal and postnatal somatic anxiety on child’s behaviour. Maternal

anxiety in early childhood has been associated with both internalizing and externalizing behaviours [51]. The child may model behaviours from their parents that may lead to hyperactivity. On the other hand, many post-natal events may attenuate or increase the effect of prenatal exposure. Care by other relatives such as grandparents and partners, adequate stimulation, post-natal maternal support and schooling may diminish the consequences of exposure.

8-Conclusions

Our results point at a possible relationship between prenatal somatic anxiety and with hyperactivity/inattention symptoms in the child, which may persist until adolescence. Maternal prenatal somatic anxiety may not increase the risk of an ADHD diagnosis in the child but might be a contributing factor. More research is needed to elucidate the specific impact of somatic anxiety symptoms during pregnancy in the future child, particularly in those families where multiple risk factors accumulate.

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Table 1. Distribution of child, maternal related and sociodemographic covariates in the 4 y SDQ sample (N=5697).

SDQ hyperactivity/inattention subscale (parental report) at 4 years					
Remainder(<2 stand. Dev from mean)			High scorers (>2 stand.dev from mean)		Total
	N	%	N	%	N %
Gender					
Male	2,695	47.3	287	5.0	2,982 52.3
Female	2,561	45.0	154	2.7	2,715 47.7
Birthweight					
>2.5 kg	5,111	89.7	421	7.4	5,532 97.1
<=2.5 kg	145	2.5	20	0.4	165 2.9
Gestational age					
>=37 weeks	5,065	88.9	418	7.3	5,483 96.2
<37 weeks	191	3.4	23	0.4	214 3.8
Maternal somatic anxiety					
Remainder	4,220	74.1	311	5.5	4,531 79.5
Top 20%	1,036	18.2	130	2.3	1,166 20.5
Maternal age					
>=18	5,204	91.3	434	7.6	5,638 99
<18	52	0.9	7	0.1	59 1.0
Alcohol use during pregnancy (glass/week)					
<=1	5,173	90.8	435	7.6	5,608 98.4
>1	83	1.5	6	0.1	89 1.6
Smoking during pregnancy					
No	4,571	80.2	354	6.2	4,925 86.4
Yes	685	12.0	87	1.5	772 13.6
Maternal education					

=>A levels 55.7	2,876	50.5	300	5.3	3,176
<=O levels 44.3	2,380	41.8	141	2.5	2,521
Crowding index					
<=1 82.0	4,340	76.2	329	5.8	4,669
>1 18.0	916	16.1	112	2.0	1,028
Social status*					
>=3M 83.9	4,419	77.6	362	6.4	4,781
<=3N 16.1	837	14.7	79	1.4	916
Difficulties buying things for the baby					
No 80.0	4,265	74.9	295	5.2	4,560
Yes 20.0	991	17.4	146	2.6	1,137
Life events					
Remainder 85.7	4,538	79.7	343	6.0	4,881
Top 15% 14.3	718	12.6	98	1.7	816
Financial difficulties					
No 93.2	4,925	86.4	382	6.7	5,307
Yes 6.8	331	5.8	59	1.0	390
Partner was supportive during pregnancy					
Yes 91.4	4,833	84.8	374	6.6	5,207
No 8.6	423	7.4	67	1.2	490
Partner was affective during pregnancy					
Yes 89.6	4,756	83.5	350	6.1	5,106
No 10.4	500	8.8	91	1.6	591

*Social status cut off between category 3M “skilled manual occupation” and 3N “skilled non manual occupation”.

Table 2. Distribution of child, maternal related and sociodemographic covariates in the 7.5 y DAWBA sample (N=5035).

DAWBA DSM-IV clinical diagnosis at 7.5 years: any ADHD disorder						
	No	%	Yes	%	Total	%
Gender						
Male	2,519	50	80	1.6	2,599	51.6
Female	2,421	48.1	15	0.3	2,436	48.4
Birthweight						
>2.5 kg	4,799	95.3	89	1.8	4,888	97.1
<=2.5 kg	141	2.8	6	0.1	147	2.9
Gestational age						
>=37 weeks	4,753	94.4	84	1.7	4,837	96.1
<37 weeks	187	3.7	11	0.2	198	3.9
Maternal somatic anxiety						
Remainder	3,964	78.7	65	1.3	4,029	80
Top 20%	976	19.4	30	0.6	1,006	20
Alcohol during pregnancy						
<1 glass of alcohol a week	4,871	96.7	90	1.8	4,961	98.5
>=1 glass of alcohol a week	69	1.4	5	0.1	74	1.5
Smoking during pregnancy						
No	4,344	86.3	76	1.5	4,420	87.8
Yes	596	11.8	19	0.4	615	12.2
Maternal education						
O levels or less	2,651	52.7	53	1.1	2,704	53.7
A levels or more	2,289	45.5	42	0.8	2,331	46.3
Crowding index						
<=1	4,103	81.5	75	1.5	4,178	83

>1	837	16.6	20	0.4	857
17					
Social status*					
>=3M	4,199	83.4	79	1.6	4,278
85					
<=3N	741	14.7	16	0.3	757
15					
Difficulties buying things for the baby					
No	4,011	79.7	60	1.2	4,071
80.9					
Yes	929	18.5	35	0.7	964
19.1					
Financial problems					
No	4,651	92.4	82	1.6	4,733
94					
Yes	289	5.7	13	0.3	302
6					
Life events					
Remainder	4,256	84.5	78	1.5	4,334
86.1					
Top 15%	684	13.6	17	0.3	701
13.9					
Partner was supportive during pregnancy					
Yes	4,534	90	81	1.6	4,615
91.7					
No	406	8.1	14	0.3	420
8.3					
Partner was affectionate during pregnancy					
Yes	4,439	88.2	77	1.5	4,516
89.7					
No	501	10	18	0.4	519
10.3					

*Social status cut off between category 3M “skilled manual occupation” and 3N “skilled non manual occupation”.

Table 3. Distribution of the five somatic anxiety items in the complete population of ALSPAC women with data at 18 weeks of pregnancy (N=11029).

Dizziness or breathlessness		
Never	4,453	40.4%
Not v. often	4,593	41.7%
Often	1,648	14.9%
Very often	333	3%
Feeling faint		
Never	5,424	49.2%
Not v. often	4,274	38.8%
Often	1,088	9.9%
Very often	243	2.2%
Nausea or indigestion		
Never	2,605	23.6%
Not v. often	4,663	42.3%
Often	2,698	24.5%
Very often	1,063	9.6%
Tingling or prickling sensations		
Never	7,924	71.8%
Not v often	2,036	18.5%
Often	855	7.8%
Very often	214	1.9%
Extra sweating or heart flutters		
Never	7,758	70.3%
Not v. often	2,527	22.9%
Often	643	5.8%
Very often	101	0.9%

Table 4 Odds ratios and 95% confidence intervals for the association between maternal somatic anxiety in pregnancy and offspring hyperactivity at 4 and 16 years. SDQ= Strengths and Difficulties Questionnaire.

VARIABLES	Unadjusted model	Adjusted 1: maternal factors	Adjusted 2: child factors	Adjusted 3: sociodemographic factors	Fully adjusted imputed model
SDQ hyperactivity 4 years					
Odds ratio	1.70	1.63	1.63	1.34	1.38
95% confidence interval	(1.37-2.11)	(1.31-2.02)	(1.31-2.03)	(1.07-1.69)	(1.15-1.66)
N	5,697	5,697	5,697	5,697	9,501
p	<0.001	<0.001	<0.001	<0.001	0.011
SDQ hyperactivity 16 years					
Odds ratio	1.95	1.91	1.91	1.62	1.79
95% confidence interval	(1.47 - 2.58)	(1.44 - 2.53)	(1.44 - 2.54)	(1.21 - 2.17)	(1.41 - 2.28)
N	3,605	3,605	3,605	3,605	14,692
p	<0.001	<0.001	<0.001	<0.001	<0.001

Adjusted 1: Maternal age, maternal education, smoking and alcohol intake during pregnancy. **Adjusted 2**: Further adjusted for gender of child, birthweight and gestational age. **Adjusted 3**: Further adjusted for difficulties buying items for the baby, life events, social status, crowding index, financial difficulties, partner support and partner affection.

Table 5. Odds ratios and 95% confidence intervals for the association between maternal somatic anxiety in pregnancy and offspring hyperactivity assessed with DAWBA at 7.5 and 15 years (multiband). DAWBA=Development and Well-Being Assessment.

VARIABLES	Unadjusted model	Adjusted 1: maternal factors	Adjusted 2: child factors	Adjusted 3: sociodemographic factors	Fully adjusted imputed model
Any ADHD diagnosis 7.5 y (n=95)					
Odds ratio	1.87	1.84	1.81	1.57	1.45
95% confidence interval	(1.21 - 2.91)	(1.19 - 2.87)	(1.16 - 2.83)	(0.99 - 2.48)	(1.00 - 2.11)
N	5,035	5,035	5,035	5,035	8,091
p	0.007	0.006	0.009	0.055	0.048
Any ADHD diagnosis 15 y.(n=26)					
Odds ratio	2.27	2.26	2.16	1.65	1.22
95% confidence interval	(0.90 - 5.71)	(0.89 - 5.70)	(0.85 - 5.48)	(0.63 - 4.35)	(0.59 - 2.50)
N	2,891	2,891	2,891	2,891	20,751
p	0.082	0.085	0.105	0.311	0.596

Adjusted 1: Maternal age, maternal education, smoking and alcohol intake during pregnancy. **Adjusted 2**: Further adjusted for gender of child, birthweight and gestational age. **Adjusted 3**: Further adjusted for difficulties buying items for the baby, life events, social status, crowding index, financial difficulties, partner support and partner affection.