Exposure to tobacco smoke in utero or during early childhood and risk of hypomania: prospective birth cohort study.

Daniel Mackay, PhD Institute of Health & Wellbeing, University of Glasgow, 1 Lilybank Gardens, G12 8RZ, Glasgow, Scotland, UK.

Jana Anderson, PhD Institute of Health & Wellbeing, University of Glasgow, 1 Lilybank Gardens, G12 8RZ, Glasgow, Scotland, UK.

Jill Pell, MD Institute of Health & Wellbeing, University of Glasgow, 1 Lilybank Gardens, G12 8RZ, Glasgow, Scotland, UK.

Stanley Zammit, PhD Department of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Wales, UK

Daniel J Smith, MD Institute of Health & Wellbeing, University of Glasgow, 1 Lilybank Gardens, G12 8RZ, Glasgow, Scotland, UK.

Corresponding author: Dr Daniel F Mackay (Daniel.Mackay@Glasgow.ac.uk), 1 Lilybank Gardens, Institute of Health and Wellbeing, University of Glasgow, G12 8RZ, Glasgow, Scotland UK. Tel: 0141 330 2567

Abstract

Objectives Using data from a prospective birth cohort, we aimed to test for an association between exposure to tobacco smoke in utero or during early development and the experience of hypomania assessed in young adulthood.

Methods We used data on 2,957 participants from a large birth cohort (Avon Longitudinal Study of Parents and Children, ALSPAC). The primary outcome of interest was hypomania, and the secondary outcome was 'hypomania plus previous psychotic experiences (PE)'. Maternally-reported smoking during pregnancy, paternal smoking and exposure to environmental tobacco smoke (ETS) in childhood were the exposures of interest. Multivariable logistic regression was used and estimates of association were adjusted for socio-economic, lifestyle and obstetric factors.

Results There was weak evidence of an association between exposure to maternal smoking in utero and lifetime hypomania. However, there was a strong association of maternal smoking during pregnancy within the sub-group of individuals with hypomania who had also experienced psychotic symptoms (OR = 3·45, 95%CI 1·49=7·98, P = 0·004). There was no association between paternal smoking, or exposure to ETS during childhood, and hypomania outcomes.

Conclusions Exposure to smoking in utero may be a risk factor for more severe forms of psychopathology on the mood-psychosis spectrum, rather than DSM-defined bipolar disorder.

Key words: Tobacco, Psychoses, Post partum, Nicotine, Bipolar Disorder

1. Introduction

The adverse effects of smoking and exposure to environmental tobacco smoke (ETS) on a range of physical health outcomes are well documented [1 2]. Recent research suggests that exposure to ETS in utero can result in preterm birth, low birth weight and small gestational age [3,4,5] and exposure to smoking in utero has been linked to a range of adverse neuropsychiatric outcomes in offspring [6], including delayed intellectual development [7], neurodevelopmental impairment [8], attention deficit hyperactivity disorder (ADHD) [9], psychotic symptoms [10], schizophrenia [11,12], psychoactive substance use [13], and behavioural and emotional disorders [13].

It is established that nicotine, which easily crosses the placental membrane, can reach high concentrations in the fetal bloodstream, with deleterious effects on brain development [14], neurotransmitter function [15] and cognition [16]. One of the mechanisms of this may be via an action on nicotinic acetylcholine receptors, which influence the development of neural circuits, including those responsible for regulating mood [17]. Nicotine exposure in utero may also increase oxidative stress [18] and can cause epigenetic modifications [19].

To date, only two studies have assessed whether maternal smoking during pregnancy is a risk factor for the development of bipolar disorder (BD) in adulthood, with inconsistent results. In a nested case-control analysis of data from the Child Health and Development Study (CHDS) in the United States, Talati and colleagues compared 79 individuals with bipolar disorder to 632 matched controls [17]. They identified a two-fold increase in risk for BD among offspring who had been exposed to maternal smoking during pregnancy, after adjusting for birth weight, maternal race, maternal alcohol use during pregnancy and maternal psychopathology. More recently, Chudal and colleagues used data from four Finnish population and health registers to compare rates of maternal smoking during pregnancy between 724 individuals with BD and 1419 matched controls [20]. After adjusting for parental psychiatric history, maternal age and maternal educational level, there was no association between maternal smoking during pregnancy and risk of BD.

In the current study, our primary aim was to assess the relationship between exposure to tobacco smoke in utero or during early childhood and risk of hypomania assessed in young adulthood, using prospective data from a large birth cohort. We aimed to extend previous work by adjusting for a range of potential confounders, including mother's age at delivery, maternal education level, maternal social class, marital status, low income, maternal history of depression, exposure to influenza in utero, use of cannabis, alcohol and illicit drugs during pregnancy, offspring sex, birth weight and gestation at delivery. Additionally, we take a broader view of the mood-psychosis

spectrum by assessing the extent to which exposure to tobacco smoke in utero impacts on risk of psychotic experiences in the context of a concurrent history of hypomania.

2. Methods

2.1 Description of cohort and study sample

The ALSPAC birth cohort is comprised of all live births in the County of Avon, UK, with expected due dates between April 1991 and December 1992. The initial cohort comprised 14,062 live births, with 13,998 alive at one year (http://www.bristol.ac.uk/alspac/, accessed 19th March 2016). The ALSPAC website contains details of all data available in the data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/, accessed March 19th 2016). Ethical approval for this study was obtained from the ALSPAC Ethics and Law Committee and Local Research Ethics Committees.

From birth, parents completed regular questionnaires about all aspects of their child's health and development. From age 7, children attended assessment centres for tests and interviews annually. To date, ALSPAC data have been used in a wide range of studies in mental health [21 22]. In this study, we assess data on the 2,957 ALSPAC participants who completed an assessment of the primary outcome of interest, namely lifetime experience of hypomania, at age 22-23.

2.1.1 Sample selection

From the original ALSPAC cohort, 9,359 young adults were invited to complete the *"Your Life Now (at age 21+)"* assessments, which included the Hypomania Checklist (HCL-32) questionnaire. Participants could choose from paper or online versions. A total of 3,447 participants returned the questionnaire (36.8% response rate), including 2,957 with complete answers (representing our study sample).

2.2 Outcome measures

2.2.1 Primary outcome: lifetime hypomania assessed in young adulthood

Hypomania was defined using the HCL-32, assessed when participants were aged 22-23 years. The HCL-32 is a self-completed questionnaire for lifetime experience of manic features [23]. It asks individuals to consider a time when they were in a "high or hyper" state and respond to a number of statements about their emotions, thoughts and behaviours at this time. Examples of the 32 symptom statements are: "*I think faster*"; "*I make more jokes or puns when I am talking*"; and "*I take more risks in my daily life*". The HCL-32 also asks about the duration of episodes and any impact on family, social and work life [24 25]. Although initially developed as a screening instrument for use in people diagnosed with depressive disorders, it is also a sensitive screening tool for bipolar disorder type II within non-clinical settings, including samples of young adults [26 27].

We defined lifetime history of hypomania in line with previous approaches for studies of this nature, namely: a score of 14 or more out of 32 hypomanic features; *plus* at least one response of either "negative consequences" or "negative plus positive consequences"; *plus* a report that these mood changes caused a reaction in others; *plus* a duration of "2-3 days" or more. Overall, this definition of hypomania, which includes severity, impairment and duration criteria, is much more conservative than other studies using the HCL-32, which have tended to use only the threshold score of 14 for caseness [27 28]. We chose a duration criterion of 2-3 days or more because the 4 day threshold within DSM excludes many individuals with bipolar disorder type II [29 30] and because two days is the modal duration of hypomania for individuals with bipolar II disorder [31 32] Based on previous work in non-clinical samples, we expected that between 5-10% of respondents might satisfy our criteria for hypomania [26 33]

2.2.2 Secondary outcome: hypomania with previous psychotic experiences (PE)

'Hypomania plus previous PE' was also studied as an outcome. PE were assessed using the semi-structured Psychosis-Like Symptoms interview (PLIKSi) administered at ages 12 and 18 [34]. The PLIKSi consists of 12 core questions covering hallucinations (visual and auditory); delusions (delusions of being spied on, persecution, thoughts being read, reference, control, grandiose ability and other unspecified delusions); and experiences of thought interference (thought broadcasting, insertion and withdrawal) over the past 6 months. Clinical cross-questioning and probing was used to establish the presence of symptoms, and coding of all items followed the glossary definitions and rating rules for SCAN (Schedule for Clinical Assessment in Neuropsychiatry). PE were coded as present if one or more of the experiences was rated as 'suspected or definitely present' by a trained psychologist. Unclear responses after probing were always 'rated down', and symptoms only rated

as definite when a credible example was provided. In our analysis we included only symptoms that could not be directly attributed to falling asleep/waking or to fever and were reported either in the PLIKSi at age 12 or in the PLIKSi at age 18 [35 36].

2.3 Exposures of interest: maternal smoking during pregnancy, paternal smoking during pregnancy and exposure to ETS in early childhood.

Exposure to smoking in utero throughout pregnancy was based on maternal responses to specific questions asking about number of cigarettes smoked. This was assessed at three time points: 8 weeks gestation, 18 weeks gestation, and 8 weeks post-partum. Paternal smoking during pregnancy was assessed at 8 weeks gestation. Exposure to ETS in early childhood was defined as active maternal and/or paternal smoking at 1 year 9 months since birth, 2 years 9 months and 3 years 11 months since birth.

2.4 Confounding variables

We identified *a priori* several potential maternal/paternal, socioeconomic and offspring confounding variables based on previous literature in this area: mother's age at delivery, maternal education level, maternal social class, marital status, low income, maternal history of depression, exposure to influenza, use of cannabis, alcohol and illicit drugs during pregnancy, offspring sex, birth weight and gestation at delivery [10, 11].

2.5 Statistical analyses

Median and interquartile ranges were used to summarise continuous variables, and count and percentages for categorical variables. P-values were obtained using the Kruskal-Wallis and Chi-squared test, and chi square for trend was used for ordinal variables (social class). Univariate and multivariable logistic regression analyses were used to calculate odds ratios (OR) and 95% confidence intervals (95% CI) for hypomania as the dependent variable and with maternal smoking during pregnancy, paternal smoking during pregnancy and exposure to ETS in early childhood as the indpendent variables. Multivariable logistic regressions were adjusted for mother's age at delivery, maternal education level, maternal social class, marital status, low income, maternal history of depression, exposure to influenza, use of cannabis, alcohol and hard drugs during pregnancy; offspring sex, birth weight and gestation at delivery.

In a secondary analysis, multinomial logistic regression was used to calculate the OR and 95% CI for exposure to maternal smoking in utero, paternal smoking in utero and childhood exposure to ETS using hypomania with and without previous lifetime experience PE as the dependent variable. This regression analysis also adjusted for the confounders listed above. Missing data was imputed using imputation by chained equations using the "ice" module in Stata. Twenty five data sets were created and then analysed.

3. Results

3.1 Baseline characteristics

Overall, 220 (7·4%) of respondents satisfied criteria for hypomania and the remaining participants were classified as a 'no hypomania' comparison group (table 1). The median HCL-32 score was 19 (IQR 16-23) in the hypomania group and 15 (IQR 11-19) in the 'no hypomania' group (p<0·001). Table 1 shows that the two groups did not differ in terms of most of the potential confounding variables, although the hypomania group were more likely to be male (41·8% versus 34·8%, p=0·035), and to have a mother who was aged under 30 (70·3% versus 59·0%, p=0·001).

3.2 Smoking during pregnancy, paternal smoking, exposure to ETS and risk of hypomania

There was weak evidence of an association between exposure to maternal smoking in utero and lifetime hypomania assessed in young adulthood: 21·2% of mothers in the hypomania group reported smoking throughout pregnancy, compared to 16·1% in the comparison group (P = 0·06; table 1). Exposure to paternal smoking in pregnancy and ETS in early childhood had no effect on lifetime hypomania (P = 0·340 and P = 0·264 respectively; table 1). Univariate logistic regression of lifetime hypomania with the three smoking exposure variables found no evidence of an association (table 3). This also remained the case after adjusting for confounding factors but there was some attenuation in the effect of maternal smoking, with odds ratio falling from 1·35 to 1·29 after adjustment (table 3).

3.3 Smoking during pregnancy, paternal smoking and exposure to ETS and risk of 'hypomania with PE'

In a secondary analysis, we tested for an association between in utero maternal smoking, parental smoking in pregnancy and ETS exposure in childhood and lifetime hypomania with and without previous experience of PE, relative to controls with no history of either hypomania or PE. The three

groups were similar in terms of most confounding factors but there was strong evidence of a difference in the proportion of mothers who reported smoking during pregnancy (32·6% in the 'hypomania plus PE' group, 16·4% in the 'hypomania, no PE' group, and 13·9% in the control group; P = 0·002) (table 2).

There was no association between paternal smoking during pregnancy (P = 0·571) and between ETS exposure in early childhood with risk of hypomania with PE (P = 0·446). The effect of maternal age differed across the three groups (P = 0·004), as did exposure to gestational influenza (P = 0·025) (table 3).

We tested the above association further using multinomial logistic regression, with the control group as the base group (table 4) and 'hypomania no PE' and 'hypomania plus PE' as the groups of primary interest. There was no association between the 'hypomania no PE' group with any of the three smoking exposure variables. However, for the 'hypomania plus PE' group, the effect of maternal smoking in utero was significant in both univariate and multivariable analyses (multivariate OR = 3·45, 95%CI 1·49 7·98, P = 0·004).

4. Discussion

Although we did not find strong evidence of an association between maternal smoking during pregnancy and hypomania in offspring, there was an association with 'hypomania plus previous PE', suggesting that maternal smoking during pregnancy may be a risk factor for more severe forms of psychopathology occurring along the mood-psychosis spectrum. We did not find any association between paternal smoking or exposure to ETS during childhood and any of the hypomania outcomes.

It should be noted that our outcomes of interest (hypomania as defined by the HCL-32 and 'hypomania plus previous PEs') are not formal ICD-10 or DSM5 diagnoses but rather they are psychopathological constructs which permit an assessment of the impact of exposures on psychiatric phenotypes which cross the mood-psychosis spectrum. This is clearly a limitation if the primary interest is strictly-defined bipolar disorder (as in ICD-10 or DSM5), but this approach has merit because it is consistent with with recent proposals, such as those within the Research Domain Criteria (RDoC), to move beyond restrictive categories of arbitrarily-defined disorder towards an assessment of psychiatric outcomes which cross traditional diagnostic boundaries; in this case, the mood-psychosis spectrum [43,44].

Previous findings with regard to strictly-defined BD in this area are inconsistent. Talati and colleagues identified a two-fold increase in risk for BD among offspring exposed to maternal smoking in utero [17] whereas Chudal and colleagues found no association [20]. Although both studies used a formal diagnosis of BD (rather than hypomania) as the primary outcome, neither took account of as wide a range of potential confounders as we have been able to do in our study, notably exposure to influenza during pregnancy and exposure to alcohol and drug use during pregnancy. Further, the BD outcomes in the two previous studies were not sub-divided into BD with and without lifetime experience of psychotic features.

Gestational influenza, one of the confounders considered in our study, may be a risk factor for more severe forms of BD [37,38,39]. The association with BD type II or hypomania has not been extensively investigated, although in our recent analysis of the ALSPAC cohort we found a weak association between gestational influenza and hypomania which did not survive adjustment for confounding factors [40].

Our findings suggest that exposure to maternal smoking in utero may be a risk factor for more severe forms of BD characterised by both manic and psychotic features (such as BD type I), rather than non-psychotic forms of BD (such as BD type II). This is consistent with previous work which has identified maternal smoking during pregnancy as a risk factor for psychosis-like symptoms [10] and schizophrenia [11] in offspring. Very recently, Niemelä and colleagues reported that maternal smoking during pregnancy (indexed by cotinine level) was associated with an increased odds of schizophrenia in offspring (OR = 3·41, 95% CI 1·86–6·24) and that this association was not explained by maternal age, parental psychiatric disorder or socioeconomic status [41].

4.1 Strengths and limitations

The ALSPAC birth cohort is a large, well-characterised and representative sample from the UK and, relative to previous work, our study has the advantage of a prospective design and a relatively large sample size [21,22]. Our study also fills an important gap in the literature between clinical and population samples by assessing features of hypomania within a non-clinical cohort of young adults. This could be considered to represent an advance on previous reports because the level of detail available within the ALSPAC cohort permits a wider range of confounding factors to be taken into account.

However, we acknowledge some limitations. Participant attrition has been an issue in studies using more recent outcome measures within ALSPAC and potentially a source of bias. It is, however, possible that the effect sizes we have observed might be underestimates because offspring with bipolar features were more likely to not return their questionnaires. Our outcome measure, the HCL-32, may be subject to reporting bias because it relies on self-report in areas such as risk-taking, sexual activity and alcohol use. However, this instrument is well validated as a screening tool for bipolar disorder type II. [26,27] It is also possible that respondents completed the HCL-32 with reference to a period of intoxication with recreational drugs, even though the opening statement specifically asks that they consider "a period when [they] were in a high state, *not related to recreational drug use".* There have not yet been sensitivity and specificity tests of the HCL-32 as a categorical measure which includes both duration and impact on functioning as criteria but it is likely that by including these features we improve sensitivity for a diagnosis of hypomania (previous methods have tended to focus solely on a threshold score on the HCL-32, usually 14 out of 32). [24,25,42]

Other potential limitations relate to the self-reported nature of smoking by mothers: it is clearly possible that some mothers may have smoked during pregnancy but did not report this when asked. Further, there was a lack of information available on psychiatric comorbidity and substance abuse, although with a sample aged 22 this may not be important given that they will have not yet been assessed from a diagnostic perspective

5.0 Conclusions

Overall, within a birth cohort followed up into early adulthood, we found that maternal smoking during pregnancy (but not paternal smoking or exposure to ETS in childhood) was associated with increased risk of hypomania only in the context of a concomitant history of PE. Maternal smoking during pregnancy, paternal smoking and exposure to ETS in childhood were all not associated with increased risk of hypomania without previous PE. This suggests that maternal smoking during pregnancy may be a risk factor for more severe forms of psychopathology rather than simply hypomania. Future work should explore associations between exposure to smoking in utero and dimensional aspects of psychopathology across affective and psychotic disorders, rather than with catergorical diagnoses defined solely by formal diagnostic systems such as ICD-10 and DSM5 [43,44].

Acknowledgements

We are extremely grateful to all the families who took part in this study and the midwives for their help in recruiting them. The whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. The ALSPAC is funded by the UK Medical Research Council, the Wellcome Trust and the University of Bristol provide core support. This specific analysis was funded by a Strategic Start-Up Grant from the University of Glasgow to DJS. DJS is supported by a Lister Institute Prize Fellowship.

Disclosures

None. The authors report no conflicts of interest.

Table 1. Maternal, pregnancy and offspring characteristics by presence or absence of hypomania in young adulthood.

	Hypomania N=220	No hypomania N=2,737	P value
Maternal characteristics			
	N, %	N, %	
Age at delivery			
Age<=30	147 (70.3)	1,537 (59.0)	0.001
Age>30	62 (29.7)	1,069 (41.0)	
Missing	11	131	
Highest educational level			
Degree or above	41 (19.8)	544 (21.4)	0.588
Other qualification	166 (80.2)	1,997 (78.6)	
Missing	196	13	
Social class			
I	21 (11.4)	191 (8.5)	0.473
II	60 (32.4)	825 (36.6)	
III	78 (42.2)	939 (41.7)	
IV	14 (7.6)	131 (5.8)	
V	9 (4.9)	144 (6.4)	
VI	3 (1.6)	23 (1.0)	
Missing	35	484	
Maternal depression			
Yes	16 (7.9)	156 (6.1)	0.313
No	186 (92.1)	2,387 (93.9)	
Missing	18	194	
Housing tenure			
Council tenant	10 (4.9)	132 (5.2)	0.830
Other tenure	196 (95.1)	2,407 (94.8)	
Missing	14	198	
Marital status			
Single	37 (18.1)	380 (14.8)	0.212
Married	168 (81.9)	2,186 (85.2)	
Missing	15	171	
Income Support			
No income support	189 (94.0)	2,397 (95.7)	0.259
Income support	12 (6.0)	17 (4.3)	
Missing			
Pregnancy characteristics			
	Median (IQR)	Median (IQR)	
Gestation at delivery	40 (39-41)	40 (39-41)	0.770
Missing	11	131	
	N (%)	N (%)	
Gestational influenza			
Yes	46 (24.9)	469 (20.1)	0.121
No	139 (75.1)	1,865 (79.9)	
Missing	35	403	

Illicit drug use during pregnancy			
Yes	1 (0.5)	10 (0.39)	0.838
No	205 (99.5)	2,542 (99.6)	
Missing	14	185	
Cannabis use during pregnancy			
Yes	7 (3.5)	81 (3.3)	0.868
No	194 (96.5)	2,399 (96.7)	
Missing			
Alcohol use during pregnancy			
Yes	146 (70.9)	1,800 (70.4)	0.878
No	60 (29.1)	758 (29.6)	
Missing	14	179	
Offspring characteristics			
	Median (IQR)	Median (IQR)	
Age (years)	21.9 (21.5-22.4)	22.01 (21.5-22.4)	0.617
Missing	2	24	
	N (%)	N (%)	
Sex			
Female	128 (58.2)	1786 (65.3)	0.035
Male	92 (41.8)	951 (34.8)	
Missing N=0			
Child Ethnicity			
White	193 (96.5)	2,423 (96.3)	0.866
Non-white	7 (3.5)	94 (3.7)	
Missing	20	220	
	Median (IQR)	Median (IQR)	
Birth weight (g)	3,380 (3,100-3,720)	3,460 (3,120-3,760)	0.120
Missing	14	162	
	Median (IQR)	Median (IQR)	
HCL_32 score	19 (16-23)	15 (11-19)	0.001
Missing N=0			
Smoking Exposure			
Maternal smoking during pregnancy T1,T2,T3			
Yes	44 (21.2)	419 (16.1)	
No	164 (78.9)	2,181 (83.9)	0.060
Missing	12	137	
Paternal smoking during pregnancy			
Yes	30 (22.7)	317 (19.3)	
No	102 (77.3)	1,325 (80.7)	0.340
Missing	220	1,095	
ETS exposure in early childhood			
Yes	68 (46.9)	875 (48.3)	
No	77 (53.1)	937 (51.7)	0.264
Missing	75	925	

Table 2. Maternal, pregnancy and offspring characteristics: hypomania with and without PE, versus controls.

	Hypomania plus PE N=45	Hypomania, no PE N=150	Controls (N=2,088)	P value
Maternal characteristics				
	N (%)	N (%)	N (%)	
Age at delivery				
Age<=30	31 (72.1)	100 (70.9)	1,162 (58.7)	0.004
Age>30	12 (27.9)	41 (29.1)	819 (41.3)	
Missing	2	9	107	
Highest educational level				
	N (%)	N (%)	N (%)	
Degree or above	9 (20.9)	28 (20.1)	434 (22.4)	0.813
Other qualification	34 (79.1)	111 (79.9)	1,506 (77.6)	
Missing	2	11	148	
Social class				
I	3 (7.3)	15 (12.2)	152 (8.75)	
II	14 (34.2)	42 (34.2)	651 (37.5)	
III	16 (39.0)	50 (40.7)	722 (41.5)	
IV	4 (9.8)	9 (7.3)	97 (5.6)	
V	3 (7.3)	6 (4.9)	105 (6.0)	
VI	1 (2.4)	1 (0.8)	11 (0.6)	0.794
Missing	4	27	350	
Maternal depression				
Yes	4 (9.8)	9 (6.5)	107 (5.5)	0.458
No	37 (90.2)	129 (93.5)	1,835 (94.5)	
Missing	4	12	146	
Housing tenure				
Council house	3 (7.0)	6 (4.3)	75 (3.9)	
Other tenure	40 (93.0)	133 (95.7)	1,863 (96.1)	0.572
Missing	2	11	150	
Marital status				
Single	9 (20.9)	22 (15.8)	278 (14.2)	0.409
Married	34 (79.0)	117 (84.2)	1,682 (85.8)	
Missing	2	11	128	
Income support				
No	1,838 (96.1)	131 (95.6)	39 (90.7)	0.206
Yes	75 (3.9)	6 (4.4)	4 (9.3)	
Missing	2	13	175	
Pregnancy characteristics				
	Median (IQR)	Median (IQR)	Median (IQR)	0.514
Gestation at delivery	40 (39-41)	40 (39-41)	40 (39-41)	
Missing	2	9	107	

Gestational influenza				
Yes	14 (34.2)	30 (24.0)	342 (19.0)	0.025
No	27 (65.9)	95 (76.0)	1,454 (81.0)	
Missing	4	25	292	
	N (%)	N (%)	N (%)	
Illicit drug use during pregnancy				
Yes	0 (0.0)	0	4 (0.21)	
No	42 (100.0)	139 (100.0)	1,943 (99.8)	0.830
Missing	3	11	141	
Cannabis use during pregnancy				
Yes	1 (2.4)	5 (3.7)	63 (3.3)	
No	40 (97.6)	130 (96.3)	1,835 (96.7)	0.923
Missing	4	15	190	
Alcohol use during pregnancy				
Female	32 (76.2)	101 (72.7)	1,402 (72.0)	
Male	10 (23.8)	38 (27.3)	546 (28.0)	0.824
Missing	3	11	140	
Offspring Characteristics				
Age (years)	21.9 (21.5-22.4)	22.01 (21.5-22.4)	21.9 (21.5-22.4)	0.963
Missing	2	0	14	
	Median (IQR)	Median (IQR)	Median (IQR)	0.181
Birth weight	3,390 (3,180-3,620)	3,370 (3,080-3,700)	3,460 (3,140-3,740)	
Missing	3	11	129	
	N(%)	N(%)	N(%)	
Sex				
Female	29 (64.4)	84 (56.0)	1,328 (63.6)	
Male	16 (35.6)	66 (44.0)	760 (36.4)	0.173
Missing = 0				
	Median (IQR)	Median (IQR)	Median (IQR)	0.001
HCL_32 score	20 (18-23)	19 (16-22)	15 (11-19)	
Smoking Exposure				
Maternal smoking during pregnancy (T1,T2,T3)				
Yes	14 (32.6)	23 (16.4)	274 (13.9)	
No	29 (67.4)	117 83.6)	1,704 (86.2)	0.002
Missing	2	10	110	
Paternal smoking during pregnancy				
Yes	7 (23.3)	19 (21.1)	230 (17.9)	
No	23 (76.7)	71 (78.9)	1,055 (82.1)	0.571
Missing	15	60	803	
ETS exposure in early childhood				
Yes	17 (50.0)	50 (51.0)	623 (45.0)	

No	17 (50.0)	48 (49.0)	761 (55.0)	0.446
Missing	11	52	704	

Table 3 Exposure to maternal smoking, paternal smoking or ETS during childhood and hypomania binary dependent variable (multiple imputation results).

	Hypomania	
Univariable		
	OR 95% CI	**P value**
Maternal smoking	1.35 (0.88, 2.09)	0.170
Paternal smoking	1.19 (0.62, 2.29)	0.591
Exposure to ETS during childhood	0.92 (0.50, 1.70)	0.793
Multivariable		
Maternal smoking	1.29 (0.83, 2.00)	0.259
Paternal smoking	1.24 (0.64, 2.43)	0.435
Exposure to ETS during childhood	0.91 (0.48, 1.72)	0.762

Multivariable model is adjusted for high maternal age, maternal education (degree), maternal social class, maternal depression, offspring sex, marital status, income support recipient, gestational influenza, estimated gestational age, cannabis use during pregnancy, alcohol use during pregnancy and low birthweight. OR = odds ratio

Table 4 Exposure to maternal smoking, paternal smoking or ETS during childhood and hypomania with and without previous PE (multiple imputation results)

	Hypomania without PE		**Hypomania with PE**	
Univariable				
	OR 95% CI	**P value**	**OR 95% CI**	**P value**
Maternal smoking	1.06 (0.64, 1.76)	0.810	3.31 (1.50, 7.27)	0.003
Paternal smoking	1.31 (0.62, 2.79)	0.480	0.82 (0.28, 2.39)	0.721
Exposure to ETS during childhood	0.94 (0.46, 1.91)	0.862	0.78 (0.26, 2.31)	0.657
Multivariable				
Maternal smoking	1.00 (0.59, 1.68)	0.989	3.45 (1.49, 7.98)	0.004
Paternal smoking	1.41 (0.64, 3.09)	0.383	0.83 (0.26, 2.65)	0.758
Exposure to ETS during childhood	0.95 (0.45, 1.99)	0.884	0.68 (0.22, 2.13)	0.511

PE = psychotic experiences. Multivariable model is adjusted for high maternal age, maternal education (degree), maternal social class, maternal depression, offspring sex, marital status, income support recipient, gestational influenza, estimated gestational age, cannabis use during pregnancy, alcohol use during pregnancy and low birthweight. OR = odds ratio

References

1. Mackay D, Haw S, Ayres JG, Fischbacher C, Pell JP. Smoke-free legislation and hospitalizations for childhood asthma. New England Journal of Medicine. 2010 Sep 16;363(12):1139-45.

2. Pell, JP, Haw S, Cobbe S, et al. Smoke-free legislation and hospitalizations for acute coronary syndrome. New England Journal of Medicine. 2008 Jul 31;359(5):482-91.

3. Mackay DF, Nelson SM, Haw SJ, Pell JP. Impact of Scotland's smoke-free legislation on pregnancy complications: retrospective cohort study. PLoS Med. 2012 Mar 6;9(3):e1001175.

4. Been JV, Nurmatov UB, Cox B, Nawrot TS, van Schayck CP, Sheikh A. Effect of smoke-free legislation on perinatal and child health: a systematic review and meta-analysis. The Lancet. 2014 May 9;383(9928):1549-60.

5. Cox B, Martens E, Nemery B, Vangronsveld J, Nawrot TS. Impact of a stepwise introduction of smoke-free legislation on the rate of preterm births: analysis of routinely collected birth data. Bmj. 2013 Feb 14;346:f441.

6. Abbott, L.C. and U.H. Winzer-Serhan, *Smoking during pregnancy: lessons learned from epidemiological studies and experimental studies using animal models.* Critical Reviews in Toxicology, 2012. **42**(4): p. 279-303.

7. Naeye, R.L., Peters, E.C., *Mental development of children whose mothers smoked during pregnancy.* Obstet. Gynecol., 1984. **64**(5): p. 601-607.

8. Olds, D.L., Henderson C.R., Tatelbaum, R., *Intellectual impairment in children of women who smoke cigarettes during pregnancy.* Pediatrics, 1994. **93**(2): p. 221-227.

9. Thapar, A., Fowler, T., Rice, F., Scourfield, J., van den Bree, M.,Thomas, H., et al., *Maternal Smoking During Pregnancy and Attention Deficit Hyperactivity Disorder Symptoms in Offspring.* American Journal of Psychiatry, 2003. **160**(11): p. 1985-1989.

10. Zammit, S., Thomas, K., Thompson, A., Horwood, J., Menezes, P., Gunnell, D., et al., *Maternal tobacco, cannabis and alcohol use during pregnancy and risk of adolescent psychotic symptoms in offspring.* British Journal of Psychiatry, 2009. **195**(4): p. 294-300.

11. Stathopoulou, A., I.N. Beratis, and S. Beratis, *Prenatal tobacco smoke exposure, risk of schizophrenia, and severity of positive/negative symptoms.* Schizophrenia Research, 2013. **148**(1–3): p. 105-110.

12. Niemelä S, Sourander A, Surcel HM, Hinkka-Yli-Salomäki S, McKeague IW, Cheslack-Postava K, et al., *Prenatal Nicotine Exposure and Risk of Schizophrenia Among Offspring in a National Birth Cohort.* American Journal of Psychiatry. **0**(0): p. appi.ajp.2016.15060800.

13. Ekblad, M., Gissle, M.,Lehtonen, L., Korkeila, J. *Prenatal smoking exposure and the risk of psychiatric morbidity into young adulthood.* Archives of General Psychiatry, 2010. **67**(8): p. 841-849.

14. Ekblad, M., J. Korkeila, and L. Lehtonen, *Smoking during pregnancy affects foetal brain development.* Acta Paediatrica, 2015. **104**(1): p. 12-18.

15. Dwyer, J.B., R.S. Broide, and F.M. Leslie, *Nicotine and brain development.* Birth Defects Research Part C: Embryo Today: Reviews, 2008. **84**(1): p. 30-44.

16. Clifford, A., L. Lang, and R. Chen, *Effects of maternal cigarette smoking during pregnancy on cognitive parameters of children and young adults: A literature review.* Neurotoxicology and Teratology, 2012. **34**(6): p. 560-570.

17. Talati, A., Bao,Y., Kaufman, J.,Schaefer, C.A.,Brown, A.S ., *Maternal Smoking During Pregnancy and Bipolar Disorder in Offspring.* American Journal of Psychiatry, 2013. **170**(10): p. 1178-1185.

18. Fraga, D.B., Deroza, P.F., Ghediim, F.V., Steckert, A.V., De Luca, R.D., Silverio, A., et al., *Prenatal exposure to cigarette smoke causes persistent changes in the oxidative balance and in DNA structural integrity in rats submitted to the animal model of schizophrenia.* Journal of Psychiatric Research. **45**(11): p. 1497-1503.

19. Lee K W, Richmond,R., Hu P, French L, Shin J, Bourdon C, et al, *Prenatal exposure to maternal cigarette smoking and DNA methylation: epigenome-wide association in a discovery sample of adolescents and replication in an independent cohort at birth through 17 years of age.* Environ Health Perspect, 2015. **123**: p. 193-199.

20. Chudal, R., Brown, A S, Gissler, M, Suominen, A, Sourander, A *Is maternal smoking during pregnancy associated with bipolar disorder in offspring?* Journal of Affective Disorders, 2015. **171**: p. 132-136.

21. Fraser, A., Macdonald-Wallis C., Tilling, K., Boyd, A., Golding, J., Smith, G.D et al., *Cohort profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort.* International journal of epidemiology, 2013.

22. Niarchou, M., S. Zammit, and G. Lewis, *The Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort as a resource for studying psychopathology in childhood and adolescence: a summary of findings for depression and psychosis.* Social Psychiatry and Psychiatric Epidemiology, 2015. **50**(7): p. 1017-1027.

23. Angst J, Adolfsson R, Benazzi F, Gamma A, Hantouche E, Meyer TD, et al., *The HCL-32: towards a self-assessment tool for hypomanic symptoms in outpatients.* Journal of Affective Disorders, 2005. **88**(2): p. 217-233.

24. Carvalho AF, Takwoingi Y, Sales PM, Soczynska JK, Köhler CA, Freitas TH., et al., *Screening for bipolar spectrum disorders: A comprehensive meta-analysis of accuracy studies.* Journal of affective disorders, 2015. **172**: p. 337-346.

25. Court H, Forty L, Jones L, Gordon-Smith K, Jones I, Craddock N, et al., *Improving the psychometric utility of the hypomania checklist (HCL-32): A Rasch analysis approach.* Journal of Affective Disorders, 2014. **152–154**: p. 448-453.

26. Meyer TD, Hammelstein P, Nilsson LG, Skeppar P, Adolfsson R, Angst J, *The Hypomania Checklist (HCL-32): its factorial structure and association to indices of impairment in German and Swedish nonclinical samples.* Comprehensive psychiatry, 2007. **48**(1): p. 79-87.

27. Meyer, T.D., Schrader, J., Ridley, M., Lex, C., *The Hypomania Checklist (HCL) — Systematic review of its properties to screen for bipolar disorders.* Comprehensive Psychiatry, 2014. **55**(5): p. 1310-1321.

28. Hardoy MC, C.M., Cadeddu M, Murru A, Dell'Osso B, Morosini PL, Calabrese JR., *Validation of the Italian version of the "Mood Disorder Questionnaire" for the screening of bipolar disorders.* Clinical Practice and Epidemiology in Mental Health, 2005. **1**(8).

29. Goldberg JF, Perlis RH, Bowden CL, Thase ME, Miklowitz DJ, Marangell LB, et al., *Manic Symptoms During Depressive Episodes in 1,380 Patients With Bipolar Disorder: Findings From the STEP-BD.* American Journal of Psychiatry, 2009. **166**(2): p. 173-181.

30. Pini S, de Queiroz V, Pagnin D, Pezawas L, Angst J, Cassano GB, et al., *Prevalence and burden of bipolar disorders in European countries.* European Neuropsychopharmacology, 2005. **15**(4): p. 425-434.

31. Benazzi, F., *Is four days the minimum duration of hypomania in bipolar II disorder?* European Archives of Psychiatry and Clinical Neuroscience., 2001. **251**: p. 32-34.

32. Angst, J., Cassano G., *The mood spectrum: improving the diagnosis of bipolar disorder.* Bipolar Disorders, 2005. **7**(supplement 4): p. 4-12.

33. Holtmann, M., Pörtner, F., Duketis, E., Flechtner, H-H., Angst, J., Lehmkuhl, G., *Validation of the Hypomania Checklist (HCL-32) in a nonclinical sample of German adolescents.* Journal of Adolescence, 2009. **32**(5): p. 1075-1088.

34. Zammit S, Odd D, Horwood J, Thompson A, Thomas K, Menezes P, et al., *Investigating whether adverse prenatal and perinatal events are associated with non-clinical psychotic symptoms at age 12 years in the ALSPAC birth cohort.* Psychological Medicine, 2009. **39**(9): p. 1457-67.

35. Zammit S, Odd D, Horwood J, Thompson A, Thomas K, Menezes P, et al., *Psychotic Experiences and Psychotic Disorders at Age 18 in Relation to Psychotic Experiences at Age 12 in a Longitudinal Population-Based Cohort Study.* American Journal of Psychiatry, 2013. **170**(7): p. 742-750.

36. Thompson A, Horwood J, Salvi G, Thomas K, Duffy L, Gunnell D., et al., *IQ and non-clinical psychotic symptoms in 12-year-olds: results from the ALSPAC birth cohort*. Vol. 193. 2008. 185-191.

37. Simanek, AM., Meier, HCS *Association between prenatal exposure to maternal infection and offspring mood disorders: a review of the literature* Curr. Probl. Pediatr. Adolesc. Health Care, 45 (2015), pp. 325–364.

38. Parboosing R, Bao Y, Shen L, Schaefer CA, Brown AS, *Gestational influenza and bipolar disorder in adult offspring* JAMA Psychiatry, 70 (2013), pp. 677–685

39. Canetta SE, Bao Y, Ennis FA, Cruz J, Terajima M, Shen L. et al *Serological documentation of maternal influenza exposure and bipolar disorder in adult offspring* Am. J. Psychiatry, 171 (2014), pp. 557–563

40. Anderson JJ, Hoath S, Zammit S, Meyer TD, Pell JP, Mackay D et al *Gestational influenza and risk of hypomania in young adulthood: prospective birth cohort study.* Journal of affective disorders. 2016 Aug 31;200:182-8.

41. Niemelä S, Sourander A, Surcel HM, Hinkka-Yli-Salomäki S, McKeague IW, Cheslack-Postava K et al., *Prenatal Nicotine Exposure and Risk of Schizophrenia Among Offspring in a National Birth Cohort.* American Journal of Psychiatry. **0**(0): p. appi.ajp.2016.15060800

42. Vieta E, Sanchez-Moreno J, Bulbena A, Chamorro L, Ramos JL, Artal J, et al., *Cross validation with the mood disorder questionnaire (MDQ) of an instrument for the detection of hypomania in Spanish: The 32 item hypomania symptom check list (HCL-32).* Journal of Affective Disorders, 2007. **101**(1-3): p. 43-55

43. Cuthbert, BT. , Insel Toward the fufuture of psychiatric diagnosis:the seven pillars of RDoC BMC Med 2013:11(1):126

44. Insel, T The NIMH research domain criteria(EDoC) project: precision medicine for psychiatry. Am J Psychiatry 2014; 171(4):395-7