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Authors	Maher, Gillian M.;McCarthy, Fergus P.;Khashan, Ali S.
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Hypertensive Disorders of Pregnancy and Behavioural Outcomes in the Offspring: Findings from the Millennium Cohort Study

Gillian M. Maher#[1,2] PhD, Fergus P. McCarthy[1,3] PhD, Ali S. Khashan[1,2] PhD

[1]INFANT Research Centre, Cork, Ireland.

[2]School of Public Health, Western Gateway Building, University College Cork, Cork, Ireland.

[3]Department of Obstetrics and Gynaecology, University College Cork, Cork, Ireland

#Corresponding Author:

Dr. Gillian M. Maher

School of Public Health, 4th floor, Western Gateway Building, Western Road, University College Cork, Cork, Ireland.

Telephone: +353(0)214205523

Email: gillian.maher@ucc.ie

Abstract

Background: The aim of this study was to examine the association between hypertensive disorders of pregnancy (HDP) and behavioural outcomes in offspring at five time-points.

Methods: We used maternal-reported data from the Millennium Cohort Study. Data on HDP were collected when children were 9-months. Data on behavioural outcomes were collected at age 3, 5, 7, 11 and 14years using the Strengths and Difficulties Questionnaire (SDQ). Multivariate logistic regression analysis examined a HDP-behavioural difficulties relationship, using validated SDQ cut-off points. Multilevel models with linear splines examined the association between HDP and repeated measures of SDQ.

Results: 18,274 singleton children were included in the study at baseline, Multivariate logistic regression suggested HDP was not significantly associated with SDQ domain cut-off points at ages 3, 7 and 11years. At age 5years, HDP was associated with a 40% increased odds of behavioural difficulties based on total SDQ(≥17) (OR:1.40, 95% CI:1.03,1.91). HDP was associated with a 43% increased odds of Peer Problem difficulties at age 5 (OR:1.43, 95% CI:1.10,1.86), and a 28% increased odds of Peer Problem difficulties(≥4) at age 14 (OR:1.28, 95% CI:1.02,1.61). In the linear spline model, mean SDQ score was higher at each time-point in those exposed to HDP, although did not always reach statistical significance.

Limitations: Data on different classifications of HDP were unavailable; therefore, we could not examine the effect of gestational hypertension and preeclampsia separately.

Conclusions: While we did not find strong evidence of associations between HDP and behavioural outcomes overall, some associations between HDP and behavioural difficulties did persist at age 5 and 14years.

Keywords: Hypertensive Disorders of Pregnancy, Behavioural Outcomes, Epidemiology, Millennium Cohort Study.

Introduction

Hypertensive disorders of pregnancy (HDP) are among the most common complications of pregnancy, estimated to affect up to 10% of all pregnancies(Umesawa and Kobashi, 2017). They are classified by the International Society for the Study of Hypertension in Pregnancy (ISSHP) as "chronic hypertension", "white-coat hypertension", "masked hypertension", "transient gestational hypertension", "gestational hypertension" and "preeclampsia" (*de novo* or superimposed on chronic hypertension)(Brown et al., 2018). While HDP are a recognised risk factor for maternal morbidity(Rana et al., 2019; Say et al., 2014; Umesawa and Kobashi, 2017; Vogel et al., 2014), they have also been linked to a range of adverse outcomes, such as asthma, allergies and obesity in the offspring(Stokholm et al., 2017; Zheng et al., 2017) . Furthermore, HDP has been linked with several neurodevelopmental outcomes in the offspring, including behavioural outcomes(Dachew et al., 2019; Mann and McDermott, 2011). Some of the potential aetiological pathways linking HDP and neurodevelopment include alterations in neuroanatomical and functional connectivity in the brain of exposed offspring leading to behavioural issues (Figueiró-Filho et al., 2017; Mak et al., 2018; Ratsep et al., 2016), while it also possible that the inflammatory response associated with HDP could play a role given that maternal inflammation is a recognised risk factor for adverse neurodevelopmental outcome(Jiang et al., 2018).

Several studies to date have examined the association between HDP and behavioural outcomes in the offspring(Bohm et al., 2019; Dachew et al., 2019; Glasson et al., 2004; Maher et al., 2020; Polo-Kantola et al., 2014; Robinson et al., 2009a; Wu et al., 2009). However, results have largely been conflicting, potentially due to use of different measures of HDP (for example, medical records vs. self-report), different measures of behavioural outcomes, and varying degrees of adjustment for confounding and ranges in follow-up(Bohm et al., 2019; Glasson et al., 2004; Robinson et al., 2009a). Furthermore, while previous evidence suggests that children

can sometimes transition in or out of the abnormal range for behavioural issues throughout childhood, few studies to date have taken account of repeated measures of behaviour over time when examining a HDP-behavioural outcomes relationship(D'Souza et al., 2019b; Maher et al., 2020). Thus, studies examining the association between HDP and behavioural outcomes, allowing for changes in behaviour over time, are required.

Using data from the Millennium Cohort Study, we aimed to examine the association between HDP and behavioural outcomes using the Strengths and Difficulties Questionnaire (SDQ) at ages 3, 5, 7, 11, and 14 years using validated cut-off points, while also taking account of repeated measures of SDQ in order to allow for change in SDQ score over time.

Methods

Study Population

The Millennium Cohort Study (MCS) is a nationally representative longitudinal study of children born between 2000 and 2002, and living in 398 areas in England, Scotland, Wales and Northern Ireland. The first sweep of data collection took place when children were around 9 months of age (MCS1). Follow-ups have currently been conducted at ages 3 years (MCS2), 5 years (MCS3), 7 years (MCS4), 11 years (MCS5) and 14 years (MCS6)(Connelly and Platt, 2014). Ethical approval was obtained from an NHS Research Ethics Committee (MREC), and informed consent was obtained from parents, as well as from the children themselves as they grow up(Connelly and Platt, 2014).

Sampling Frame

The MCS used stratified cluster sampling by UK country (England, Wales, Scotland and Northern Ireland), and electoral ward. Eligible children were identified using government child benefit records. While child benefit has almost universal coverage, exceptions include families whose residency status is temporary or uncertain, for example, members of foreign armed forces or asylum seekers. Certain subgroups of the population, such as children living in disadvantaged areas, children of ethnic minority backgrounds and children growing up in the smaller nations of the UK were intentionally oversampled to ensure that typically hard to reach populations are adequately represented. Cohort members remained eligible for inclusion if they remained living in the United Kingdom (UK) at the time of sampling. The total population at baseline (MCS1) was 18,552 families (18,827 children)(Connelly and Platt, 2014; Plewis, 2007). This reduced to 15,590 families at MCS2, 15,246 at MCS3, 13,857 at MCS4, 13,287 at MCS5, and 11,726 at MCS6(Connelly and Platt, 2014).

Exposure

Hypertensive Disorders of Pregnancy: Data on HDP were obtained when children were around 9 months old (MCS1) through a face-to-face computer assisted personal interview. The child's mother was asked the following question: "Did you have any illnesses or other problems during your pregnancy that required medical attention or treatment?" If the answer to this question was yes, she was instructed to choose all that apply from a list of illnesses. The list included "Raised blood pressure, eclampsia/preeclampsia or toxaemia". If she ticked this box, then a diagnosis of HDP was assumed.

Outcome

Strengths and Difficulties Questionnaire (SDQ)

The SDQ was developed as a screening tool to assess emotional and behavioural problems in children and young people between 2 and 17 years old. It consists of a 25-item questionnaire with five subscales: emotional, conduct, hyperactivity, peer problems and prosocial behaviours(Goodman, 1997). Data were collected using parent-administered SDQ when children were aged 3 years (MCS2), 5 years (MCS3), and 7 years (MCS4), 11 years (MCS5) and 14 years (MCS6).

The main respondent (which was usually the mother) answered "not true", "somewhat true", and "certainly true" to a series of questions, with 'somewhat true' always scored as 1, and the scoring of 'not true' and 'certainly true' varying with the item (full scoring procedures are available online: https://www.sdqscore.org). Scores for each domain range from 0-10, with lower scores indicating more positive outcomes, with the exception of prosocial behaviour which is reversed scored (i.e. higher scores indicate more positive outcomes). Using validated cut-offs, similar to other childhood behavioural outcome studies conducted on Millennium Cohort participants(Goodman, 1997; Heikkilä et al., 2011; Kelly et al., 2009), SDQ cut-off

points for behavioural difficulties were defined as follows: total SDQ≥17, emotional≥5, conduct≥4, hyperactivity≥7, peer problems≥4 and prosocial behaviour≤4.

Confounding Variables

In the main analysis, we included only covariates in our model, which we believe to be associated with the exposure and outcome, and have excluded any variables that might be potential mediators of the association. Therefore, we controlled for the following potential confounders, all of which were measured at MCS1: maternal age, maternal education, maternal smoking status, maternal alcohol consumption during pregnancy, pre-pregnancy body mass index (BMI), household income, infant sex, parity and ethnic origin.

As preterm birth and small for gestational age (SGA) may be potential mediators or potential confounders of the association between HDP and SDQ, interaction terms were used to examine the association between HDP and total SDQ cut-off in those born at term/preterm, and non-SGA/SGA in separate analyses. Additionally, we stratified results by level of deprivation in a sensitivity analysis and further controlled for maternal depression/mental illness during pregnancy in a separate analysis. See eMethods 1 for description of confounders.

Statistical Analysis

Data were analysed using Stata/MP 14.2. Survey commands were used, and estimates were weighted to account for the stratified cluster sample design and analyses covering the whole of the UK. Multivariate logistic regression analysis estimated odds ratios (OR) and 95% confidence intervals (CI) for HDP and behavioural difficulties using SDQ cut-off points at ages 3, 5 and 7, 11 and 14 years. Model 1 represented the crude model. Model 2 represented the confounder-adjusted analysis.

Repeated Measures Analysis: As the SDQ was measured at five time points (ages 3, 5 and 7, 11 and 14 years), multilevel modelling with linear splines (placing 'knot points' at age 5 and 7, 11 and 14 years) was used to take account of repeated measures over time. Multilevel models address the issue of correlations between measurements from the same individual over time as they take non-independence of repeated measures on the same individual into account(Howe et al., 2016; O'Keeffe et al., 2018). The multilevel approach can also estimate the SDQ trajectory for all participants regardless of the number and timing of their measurements, and take non-linearity in the trajectory into account(Tilling et al., 2011). We modelled trajectories for HDP-SDQ score on a continuous scale, with random effects at two levels: measurement occasion and individual, with the starting point centred at age 3 (when SDQ was first measured) in all models. Similar to above, model 1 represented the crude model and model 2 represented the confounder-adjusted analysis. Bonferroni correction was used when a result was statistically significant to adjust for multiple tests.

Sensitivity Analysis: An interaction term was used to examine the association between HDP and total SDQ cut-off in children born at term (i.e. ≥37 weeks' gestation) and children born preterm (i.e. <37 weeks' gestation) compared to non-exposure to HDP, in children born at ≥37 weeks' gestation. Additionally, an interaction term examining a HDP-total SDQ cut-off relationship by non-SGA/SGA was used. SGA was defined as birthweight <10th percentile for gestational age and sex of child and based on maternal-reporting of child's birthweight, gestational age and sex. We examined the association between HDP and total SDQ cut-off, stratified by level of deprivation. Deprivation decile scores were calculated from home postcodes using the 2004 overall Indices of Multiple Deprivation (IMD)(Ministry of Housing; Communities and Local Government). A binary variable was created to represent children living in areas of highest deprivation (deciles 1–5) and lowest deprivation (deciles 6–10). We repeated the main adjusted analyses examining HDP and total SDQ cut-off, among participants

selected based on having complete exposure, outcome and covariate data. As teachers also reported on the SDQ at ages 7 and 11 years only, we examined the association between HDP and teacher-reported total SDQ cut-off at ages 7 and 11 years to assess the potential for reporter bias. Finally, we performed additional analyses examining HDP and total SDQ cut-off while further controlling for maternal depression/mental illness during pregnancy.

Results

A total of 18,274 singleton mother-child pairs with data on HDP were included in the current study (eFigure 1). Mother and child characteristics are outlined in Table 1. Of the study cohort, 7.12% (n=1,301) had a diagnosis of HDP, while the mean SDQ score was higher among those exposed to HDP compared to those unexposed, at each time point.

HDP and SDQ (ages 3, 5, 7, 11 and 14 years)

Logistic regression: Adjusted results in Table 2 suggested that HDP was not significantly associated with any of the SDQ cut-off points at ages, 3, 7 and 11 years. At age 5 years, adjusted results suggested that HDP was associated with a 40% increase in odds of having behavioural difficulties based on total SDQ score (OR: 1.40, 95% CI: 1.03, 1.91), and a 43% increased odds of having Peer Problem difficulties (OR: 1.43, 95% CI: 1.10, 1.86). However, only the estimate for Peer Problem difficulties remained statistically significant after Bonferroni correction (i.e. result was still significant at (0.05/5) $p<0.01$).

The adjusted OR for the association between HDP and Emotional difficulties was 1.26 (95% CI: 0.92, 1.73), HDP-Conduct difficulties: 0.94 (95% CI: 0.72, 1.23), HDP-Hyperactivity difficulties: 1.23 (95% CI: 0.96, 1.57) and HDP-Prosocial Behaviour difficulties: 1.09 (95% CI: 0.64, 1.85) at age 5 years, however, these did not reach statistical significance.

At age 14 years, adjusted results suggested that HDP was associated with a 28% increased odds of having Peer Problem difficulties (OR: 1.28, 95% CI: 1.02, 1.61). However, the estimate for Peer Problem difficulties was no longer statistically significant after Bonferroni correction. HDP was not significantly associated with total SDQ cut-off (OR: 0.94, 95% CI: 0.70, 1.27), Emotional (OR: 1.19, 95% CI: 0.93, 1.53) Conduct (OR: 0.99, 95% CI: 0.73, 1.33), Hyperactivity (OR: 1.13, 95% CI: 0.83, 1.53) or Prosocial Behaviour (OR: 0.89, 95% CI: 0.58, 1.37) in the adjusted models at age 14 years.

Repeated Measures Analysis: Adjusted mean trajectories of SDQ from age 3 to 14 years comparing those exposed and unexposed to HDP are shown in Fig. 1. Adjusted results suggested that children exposed to HDP had a higher mean SDQ score compared to the unexposed group at age 3 years (mean difference: -0.62, 95% CI: -0.33, -0.90). SDQ mean scores increased by 3.47 (95% CI: -1.78, 8.73) in the unexposed group from age 3 to 5 years, with a slower increase in the exposed group (mean difference: 0.13, 95% CI: -0.16, 0.42). From age 5 to 7 years, SDQ scores increased again in both groups, with a slower rate of increase in the exposed group (mean difference: 0.11, 95% CI: -0.18, 0.38). From age 7 to 11 years, SDQ mean scores decreased by -4.95 (95% CI: -12.11, 2.21) in the unexposed group, with a slower decrease in the exposed group (mean difference: -0.24, 95% CI: -0.55, 0.09). Finally, from age 11 to 14 years, SDQ mean scores decreased by -1.51 (95% CI: -8.29, 5.26) in the unexposed group, with a faster decrease in the exposed group (mean difference: 0.04, 95% CI: -0.29, 0.37). (Fig. 1 and Table 3).

Sensitivity Analysis: The adjusted effect estimates for HDP and total SDQ cut-off were higher among those born preterm compared to those born at term at ages 3, 7, 11 and 14 years. However, these did not reach statistical significance, potentially due to small numbers of children with behavioural difficulties who were exposed to HDP and born preterm. At age 5, the OR among those exposed to HDP and born at term was 1.46 (95% CI: 1.05, 2.05), while this was reduced 1.32 (95% CI: 0.60, 2.89) among those exposed to HDP and born preterm (eTable 1 in the Supplement).

Adjusted estimates suggested a significant association between HDP and total SDQ cut-off among those not born SGA at ages 3 years (OR: 1.32, 95% CI: 1.01, 1.73) and 5 years only (OR: 1.48, 95% CI: 1.07, 2.05). No significant associations between HDP and total SDQ cut-off were observed in those born SGA, potentially due to small numbers of cases exposed to HDP and born SGA (eTable 2 in the Supplement).

Similar to our main findings, adjusted estimates suggested a significant association between HDP and total SDQ cut-off at age 5 years only among those in the highest deprivation deciles (OR: 1.53, 95% CI: 1.03, 2.28). However, this spanned the null value among those in the lowest deprivation deciles (OR: 1.34, 95% CI: 0.65, 2.75) at age 5 years (eTable 3 in the Supplement). Adjusted associations of HDP and total SDQ cut-off, among participants selected based on having complete exposure, outcome and covariate data were not significantly different to our main findings, however the OR at age 5 years increased to 1.85 (95% CI: 1.14, 3.01) (eTable 4). The OR examining the association between HDP and teacher-reported total SDQ cut-off at ages 7 and 11 years was 1.40 (95% CI: 0.97, 2.02) and 0.90 (95% CI: 0.54, 1.47) respectively (eTable 5). Finally, results of analyses including maternal depression/mental illness during pregnancy as a potential confounder were similar to our main findings (eTable 6).

Discussion

This study aimed to examine the association between HDP and behavioral outcomes (using the SDQ) at age 3, 5, 7, 11 and 14 years using validated cut-off points, while also taking account of repeated measures of SDQ to allow for change in behavioural score over time. These analyses have yielded two principal findings.

First, HDP was not significantly associated with any of the SDQ domain cut-off points at ages, 3, 7 and 11 years. At age 5 years, children exposed to HDP had a 40% increased odds of having behavioural difficulties based on total SDQ score. Additionally, children exposed to HDP had a 43% increased odds of having Peer Problem difficulties at age 5, and an almost 30% increased odds of having Peer Problem difficulties at age 14 years. However, only the estimate for Peer Problem difficulties at age 5 years remained statistically significant after Bonferroni correction. Therefore while our results support the notion that behavioural difficulties are not always stable throughout childhood as children can sometimes transition in or out of cut-offs points for behavioural difficulties(D'Souza et al., 2019a), it is also possible that the associations observed here are a chance finding.

Second, the repeated measures analysis suggested that those exposed to HDP had a higher mean SDQ score at each time point (ages 3, 5, 7, 11 and 14 years) compared to those unexposed to HDP, although did not always reach statistical significance. From ages 3 to 5 years and 5 to 7 years, we observed an increase in mean score in both unexposed and exposed groups, with a slower rate of increase in the exposed group. From ages 7 to 11 years and 11 to 14 years, mean scores decreased in both groups, with a slower decrease in the exposed group between 7 and 11 years, and a faster decrease in the exposed group between 11 and 14 years.

Comparison with other studies

Similar to our findings, Dachew and colleagues did not find an association between preeclampsia and/or gestational hypertension and parent-reported SDQ at age 11 years based

on data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a prospective birth cohort study based in Southwest England(Dachew et al., 2019). In addition to this, using data from a nationally representative study of children living in Ireland, we have previously shown that preeclampsia was not significantly associated with parent-reported SDQ at ages 3 and 7-8 years, while exposure to preeclampsia was associated with Emotional and Hyperactive domains of the SDQ at age 5 years(Maher et al., 2020). However, as quality data on gestational hypertension was not available, the analysis was limited to preeclampsia-SDQ only(Maher et al., 2020). A previous study by Robinson et al. used the Child Behaviour Checklist (CBCL) to assess behaviour and suggested a positive association with gestational hypertension, but not with preeclampsia, from ages 8-14 years only(Robinson et al., 2009b). The authors did not find an association at ages 2 and 5 years however, proposing that lower demands on younger children to self-regulate behaviour, may result in parents being less likely to view and rate their child's behavior as unusual or problematic at a younger age(Eisenberg et al., 1997; Robinson et al., 2009b).

While few studies to date have taken repeated measures of SDQ into account when examining a HDP-SDQ relationship, we have previously shown that exposure to preeclampsia was associated with a higher mean SDQ score at ages 3, 5 and 7 years compared to those unexposed to preeclampsia in our Irish based study(Maher et al., 2020). Although in contrast to the current study, the trajectory of SDQ decreased between ages 3 and 5, and increased between 5 and 7 years. This discrepancy may partly be explained by varying definitions of exposures used (i.e. raised blood pressure or eclampsia/preeclampsia in the current study, and preeclampsia only in the previous study)(Maher et al., 2020).

Strengths and Limitations

This study has several limitations. First, as data on HDP was based on maternal reporting, it is therefore subject to recall bias. However, pregnancy-associated hypertension (including preeclampsia or gestational hypertension) has previously been shown to have a sensitivity of 60%, specificity of 95%, positive predictive value of 64%, and negative predictive value of 94%, from three to six years after pregnancy(Carter et al., 2015). Data on HDP was collected 9-months post-delivery in the current study and is therefore likely to be more accurate than data collected three to six years after pregnancy. Second, data on different classifications of HDP were unavailable; therefore, we could not examine the effect of gestational hypertension and preeclampsia separately. This led to a limited comparability with other studies, which often focus on one specific hypertensive disorder. Third, our outcome data collected through the SDQ relied on the subjective evaluation of the child's parents, though the scale has been widely used and found to be valid and reliable screening tool to assess behavioural difficulties in children and young people(Goodman, 2001). Fourth, there is a potential for selection bias as the sample size included 18,552 families in MCS1, and was reduced to 11,726 at MCS6. However, the multilevel approach allowed us to estimate the SDQ trajectory for all participants regardless of the number and timing of their measurements, and results from analyses with and without selection on complete exposure, outcome and confounder data were similar, indicating a low likelihood of selection driven by missing data. Nonetheless, as previous evidence suggests that children with behavioural disorders are more prone to loss to follow-up, this may have biased our results towards the null(Wolke et al., 2009). Fifth, as with all observational research, residual confounding including confounding due to shared genetics cannot be ruled out in observational studies. Sixth, the small number of children exposed to HDP among those categorised as having behavioural difficulties (particularly in the Prosocial Behaviour domain) may have limited statistical power. Finally, we were unable to explore the potential role of

antihypertensive medication data in the development of behavioural difficulties, nor could we take into account severity of HDP, since this data was not available.

This study also contains several strengths. First, we used data from a nationally representative longitudinal study of children living in the UK. Second, as SDQ was measured at five time points, we conducted repeated measures analysis using multilevel modelling with linear splines. This allowed us to estimate the SDQ trajectory for all participants (regardless of the number and timing of their measurements), while also taking non-linearity in the SDQ trajectory into account(Tilling et al., 2011). Third, we controlled for a wide range of confounding factors, including maternal age, maternal education, maternal smoking status, maternal alcohol consumption during pregnancy, pre-pregnancy BMI, household income, infant sex, parity and ethnic origin, while preterm birth and SGA were included in sensitivity analyses as they could be considered as mediators or potential confounders. Fourth, the reported prevalence of HDP in the current study of 7.12% was similar to that of the national estimate of HDP for 2000-2001, reducing the possibility of misclassification of the exposure(Bohm et al., 2019).

Conclusion

While we did not find strong evidence of associations between exposure to HDP and behavioural outcomes overall, exposure to HDP was associated with an increased likelihood of behavioural difficulties based on total SDQ at age 5, and Peer Problem difficulties at ages 5 and 14 years. Further research, using larger sample sizes, is needed to replicate these findings, and should consider severity and different classifications of HDP when examining a HDP-behavioural outcome relationship.

Author Statement

Authors GMM and ASK designed the study and wrote the protocol. Author GMM managed the literature searches and analyses. Author GMM undertook the statistical analysis, and author GMM wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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Conflict of Interest

No conflicts of interest, including financial interest.

Table 1: Perinatal and Sociodemographic Characteristics Related to Hypertensive Disorder of Pregnancy and Childhood Behavioural Outcomes among Millennium Cohort Study Participants

Characteristic	No HDP	HDP
Total Population, N (%)	16,973 (92.88)	1,301 (7.12)
Infant Sex, n (%)		
Male	8,741 (51.50)	662 (50.88)
Female	8,232 (48.50)	639 (49.12)
Parity, n (%)		
First born child	6,977 (41.11)	707 (54.34)
Maternal age, years, mean (SD)	28.27 (5.94)	28.38 (6.01)
Maternal Education completed, n (%)		
Less than O level	3,366 (19.83)	191 (14.68)
O level	7,445 (43.86)	615 (47.27)
A level	1,563 (9.21)	133 (10.22)
Diploma or above	4,054 (23.88)	331 (25.44)
Other/unknown	545 (3.21)	31 (2.38)
Maternal smoking status, n (%)		
Non-smoker	10,835 (63.84)	888 (68.26)
Quit during pregnancy	2,127 (12.53)	192 (14.76)
Smoked during pregnancy	4,004 (23.59)	221 (16.99)
Maternal alcohol consumption during pregnancy, n (%)		
No	12,006 (70.89)	983 (75.56)
Yes	4,931 (29.11)	318 (24.44)
Maternal pre-pregnancy BMI, n (%)		
Underweight	964 (5.68)	44 (3.38)
Normal weight	10,203 (60.11)	616 (47.35)
Overweight	3,026 (17.83)	319 (24.52)
Obese	1,235 (7.28)	209 (16.06)
Unknown	1,545 (9.10)	113 (8.69)
Household income, n (%)		
Lowest quintile	4,312 (25.41)	268 (20.60)
Second quintile	3,837 (22.61)	265 (20.37)
Third quintile	3,180 (18.74)	270 (20.75)
Fourth quintile	2,899 (17.08)	272 (20.91)
Highest quintile	2,684 (15.81)	225 (17.29)
Ethnic origin, n (%)		
White	13922 (82.16)	1140 (87.69)
Other ethnic origin	3022 (17.84)	160 (12.31)
Gestational age, n (%)		
<37 weeks	1,033 (6.09)	207 (15.91)
37 weeks	911 (5.37)	96 (7.38)
38 weeks	2,266 (13.35)	224 (17.22)
39 weeks	3,595 (21.18)	267 (20.52)
40 weeks	4,810 (28.34)	293 (22.52)
>40 weeks	4,141 (24.40)	203 (15.60)
Unknown	217 (1.27)	11 (0.85)
Small for gestational age, n (%)	1599 (9.42)	141 (10.84)
Total SDQ: Maternal-reported (age 3 years), mean (SD)	9.55 (5.29)	10.02 (5.32)
Total SDQ: Maternal-reported (age 5 years), mean (SD)	7.30 (4.99)	7.68 (5.12)
Total SDQ: Maternal-reported (age 7 years), mean (SD)	7.43 (5.42)	7.85 (5.60)
Total SDQ: Maternal-reported (age 11 years), mean (SD)	7.41 (5.67)	8.11 (5.93)
Total SDQ: Maternal-reported (age 14 years), mean (SD)	8.11 (5.94)	8.59 (6.12)

Data refer to the n (%) or mean and standard deviation (SD) where appropriate.
Abbreviations: HDP, hypertensive disorders of pregnancy; BMI, body mass index; SDQ, Strengths and Difficulties Questionnaire; SD, standard deviation.

Table 2: Association between Hypertensive Disorders of Pregnancy and Domains of the Strengths and Difficulties Questionnaire at ages 3, 5, 7, 11 and 14 years among Millennium Cohort Study Participants

Exposure to HDP (age 3 years)	**Exposed Cases: HDP+SDQ cut-off**	**Model 1[a] OR (95% CI)**	**Model 2[b] OR (95% CI)**
Total SDQ (cut-off ≥17)	115	1.14 (0.90, 1.44)	1.25 (0.97, 1.61)
Emotional	48	1.22 (0.86, 1.73)	1.34 (0.93, 1.93)
Conduct	358	1.00 (0.86, 1.18)	1.07 (0.91, 1.27)
Hyperactivity	181	1.18 (0.97, 1.45)	1.20 (0.98, 1.49)
Peer Problems	128	1.00 (0.79, 1.25)	0.99 (0.79, 1.25)
Prosocial Behaviour	99	1.02 (0.75, 1.38)	1.12 (0.82, 1.53)
Exposure to HDP (age 5 years)			
Total SDQ (cut-off ≥17)	72	1.33 (0.99, 1.79)	1.40 (1.03, 1.91)
Emotional	66	1.24 (0.91, 1.69)	1.26 (0.92, 1.73)
Conduct	91	0.85 (0.66, 1.09)	0.94 (0.72, 1.23)
Hyperactivity	128	1.20 (0.95, 1.52)	1.23 (0.96, 1.57)
Peer Problems	105	1.46 (1.13, 1.88)	1.43 (1.10, 1.86)
Prosocial Behaviour	23	1.06 (0.64, 1.77)	1.09 (0.64, 1.85)
Exposure to HDP (age 7 years)			
Total SDQ (cut-off ≥17)	66	0.96 (0.72, 1.29)	0.95 (0.69, 1.29)
Emotional	82	1.18 (0.89, 1.56)	1.13 (0.85, 1.50)
Conduct	87	0.89 (0.68, 1.17)	0.89 (0.67, 1.18)
Hyperactivity	150	1.22 (0.98, 1.53)	1.22 (0.97, 1.55)
Peer Problems	87	0.97 (0.74, 1.28)	0.93 (0.69, 1.25)
Prosocial Behaviour	22	1.23 (0.73, 2.09)	1.23 (0.71, 2.12)
Exposure to HDP (age 11 years)			
Total SDQ (cut-off ≥17)	79	1.14 (0.85, 1.51)	1.06 (0.78, 1.43)
Emotional	124	1.25 (0.99, 1.59)	1.22 (0.96, 1.57)
Conduct	79	0.93 (0.71, 1.23)	0.89 (0.67, 1.19)
Hyperactivity	120	1.30 (1.01, 1.66)	1.24 (0.95, 1.61)
Peer Problems	118	1.23 (0.96, 1.58)	1.13 (0.87, 1.46)
Prosocial Behaviour	14	0.83 (0.42, 1.62)	0.73 (0.37, 1.45)
Exposure to HDP (age 14 years)			
Total SDQ (cut-off ≥17)	77	0.97 (0.73, 1.29)	0.94 (0.70, 1.27)
Emotional	125	1.17 (0.92, 1.49)	1.19 (0.93, 1.53)
Conduct	82	1.01 (0.76, 1.35)	0.99 (0.73, 1.33)
Hyperactivity	84	1.15 (0.86, 1.53)	1.13 (0.83, 1.53)
Peer Problems	160	1.35 (1.08, 1.68)	1.28 (1.02, 1.61)
Prosocial Behaviour	36	0.94 (0.62, 1.42)	0.89 (0.58, 1.37)

[a]Crude analysis.
[b]Adjusted for maternal age, maternal education, maternal smoking status, maternal alcohol consumption during pregnancy, pre-pregnancy BMI, household income, infant sex, parity and ethnic origin.
Abbreviations: HDP, hypertensive disorders of pregnancy; OR, odds ratio; 95% CI, 95% confidence interval; SDQ, Strengths and Difficulties Questionnaire.

Table 3: Repeated Measures Analysis Examining the Association between Hypertensive Disorders of Pregnancy and Total Strengths and Difficulties Questionnaire Score at ages 3, 5, 7, 11 and 14 years among Millennium Cohort Study Participants			
Model 1[a]	**Mean trajectory (95% CI) (No HDP)**	**Mean trajectory (95% CI) (HDP)**	**Mean difference in trajectory (95% CI) comparing no HDP to HDP**
Age 3 SDQ	9.69 (9.61, 9.77)	10.12 (9.82, 10.41)	-0.43 (-0.12, -0.73)
Change SDQ Age 5	-2.25 (-2.33, -2.17)	-2.35 (-2.63, -2.07)	0.10 (-0.19, 0.38)
Change SDQ Age 7	0.17 (0.09, 0.25)	0.13 (-0.14, 0.39)	0.04 (-0.24, 0.32)
Change SDQ Age 11	0.17 (0.08, 0.26)	0.46 (0.15, 0.77)	-0.29 (-0.61, 0.03)
Change SDQ Age 14	0.53 (0.43, 0.62)	0.45 (0.13, 0.77)	0.08 (-0.26, 0.40)
Age 14 SDQ	8.31 (8.19, 8.42)	8.81 (8.40, 9.22)	-0.50 (-0.07, -0.93)
Model 2[b]			
Age SDQ3	13.21 (8.77, 17.65)	13.83 (9.38, 18.28)	-0.62 (-0.33, -0.90)
Change SDQ Age 5	3.47 (-1.78, 8.73)	3.34 (-1.92, 8.61)	0.13 (-0.16, 0.42)
Change SDQ Age 7	1.40 (-3.72, 6.53)	1.29 (-3.83, 6.43)	0.11 (-0.18, 0.38)
Change SDQ Age 11	-4.95 (-12.11, 2.21)	-4.71 (-11.88, 2.45)	-0.24 (-0.55, 0.09)
Change SDQ Age 14	-1.51 (-8.29, 5.26)	-1.55 (-8.34, 5.23)	0.04 (-0.29, 0.37)
Age 14 SDQ	11.62 (4.95, 18.30)	12.20 (5.51, 18.90)	-0.58 (-0.17, -0.98)

[a]Crude analysis.

[b]Adjusted for maternal age, maternal education, maternal smoking status, maternal alcohol consumption during pregnancy, pre-pregnancy BMI, household income, infant sex, parity and ethnic origin.

Abbreviations: HDP, hypertensive disorders of pregnancy; 95% CI, 95% confidence interval; SDQ, Strengths and Difficulties Questionnaire.

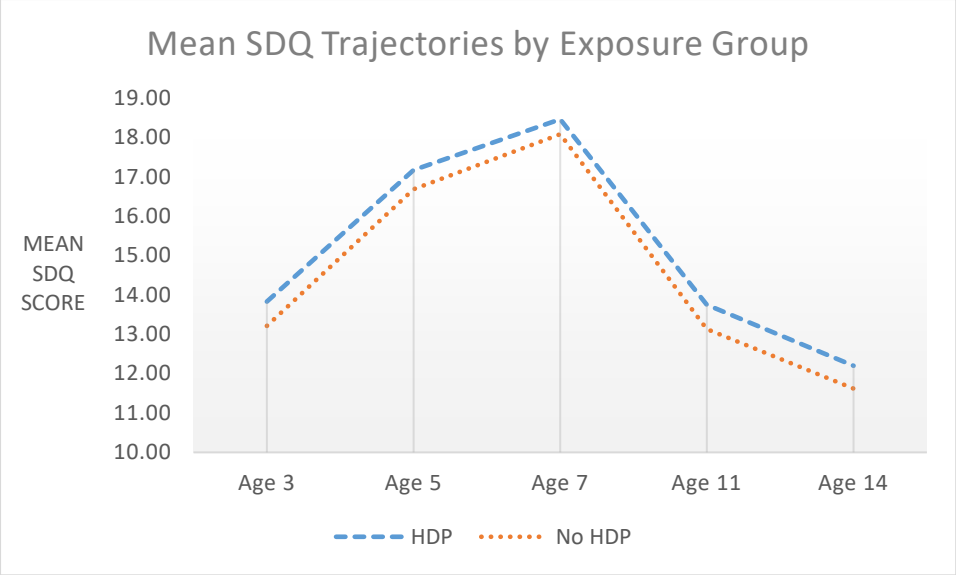


Fig. 1 Predicted trajectory of mean SDQ scores in sweeps 2-6 (adjusted model)

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