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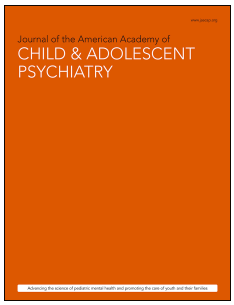

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Claire Reed, MSc, Samuele Cortese, MD, PhD, Henrik Larsson, PhD, Cedric Galera, MD, PhD, Joanne Cotton, PhD, Valerie Brandt, PhD

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Longitudinal Associations Between Physical Health Conditions in Childhood and Attention-Deficit/Hyperactivity Disorder Symptoms at Age 17
RH = ADHD and Physical Health Associations

Claire Reed, MSc, Samuele Cortese, MD, PhD, Henrik Larsson, PhD, Cédric Galéra, MD, PhD, Joanne Cotton, PhD, Valerie Brandt, PhD

Editorial

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Mrs. Reed, Prof. Cortese, and Dr. Brandt are with the University of Southampton, Southampton, United Kingdom. Dr. Cortese is also with Solent NHS Trust, Southampton, United Kingdom; the University of Nottingham, Nottingham, United Kingdom; Hassenfeld Children's Hospital at NYU Langone, New York; and the University Child Study Center, New York. Prof. Larsson is with Karolinska Institute, Stockholm, Sweden, and Örebro University, Örebro, Sweden. Prof. Galéra is with the University of Bordeaux, Bordeaux, France; INSERM, Bordeaux Population Health Center, UMR1219, Bordeaux, France; Centre Hospitalier Perrens, Bordeaux, France; Research Unit on Children's Psychosocial Maladjustment, Montreal, QC, Canada. Dr. Cotton is with the University of Cambridge, Cambridge, United Kingdom.

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Conceptualization: Reed, Cortese, Larsson, Galéra, Cotton, Brandt
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Correspondence to Claire Reed, MSc, University of Southampton, Southampton, United Kingdom; c.l.reed@soton.ac.uk.

ABSTRACT

Objective: While evidence suggests significant cross-sectional relationships between Attention-Deficit/Hyperactivity Disorder (ADHD) and several physical health conditions, less is known about their longitudinal associations. We investigated the cumulative effect of childhood physical health conditions on ADHD symptoms at age 17, controlling for environmental factors, ADHD medication status and ADHD symptoms at age three.

Method: Using Millennium Cohort Study data (Weighted n=8,059), we assessed whether four physical health clusters (sensory, neurological, atopic, and cardio-metabolic) were associated with scores on the ADHD subscale from the Strengths and Difficulties Questionnaire at age 17. Environmental factors were grouped into five cumulative risk indices: prenatal, perinatal, postnatal environment, postnatal maternal wellbeing, and sociodemographic factors. Regression analyses determined whether each physical health cluster was associated with ADHD score while controlling for environmental factors, ADHD medication and earlier symptoms.

Results: Sensory, neurological, and cardio-metabolic clusters were all significantly associated with ADHD symptoms (β range = 0.04-0.09, $p < .001$). The overall model explained 2% of the variance. This rose to 21% ($\Delta R^2 = .06$) after adjusting for confounders. The sensory ($\beta = 0.06$) and neurological ($\beta = 0.06$) clusters remained significant ($R^2 = .21$, $\Delta R^2 = .06$) but the cardio-metabolic cluster was no longer a significant predictor.

Conclusion: Sensory or neurological conditions in childhood were associated with higher ADHD symptoms aged 17 after adjustment of confounders. This was not the case for atopic or cardio-metabolic conditions. These findings have implications for the care of children with sensory/neurological conditions and future research examining ADHD etiopathophysiology.

Key words: ADHD; physical health; environmental factors; ADHD medication

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is characterised by developmentally atypical, pervasive, and impairing symptoms of inattention and/or hyperactivity/impulsivity.[1] ADHD is a complex condition, with many comorbidities often complicating the diagnostic process, symptom management and the quality of life of individuals with ADHD and their families.[2]

There is increasing evidence that ADHD is associated not only with mental health but also with physical conditions. A recent umbrella review[3] encompassing ten meta-analyses on ADHD found significant cross-sectional associations of ADHD with asthma and obesity when considering the most rigorous estimates (adjusted effect sizes). When considering unadjusted effect sizes, there was also convincing or highly suggestive evidence for an association of ADHD with rhinitis and dermatitis.

Another recent birth cohort study[4] (n = 2057) assessed cross-sectional associations between ADHD symptoms and a large number of physical conditions at different time points during development, from five months to 17 years. Some of the associations between ADHD symptoms and several physical conditions were consistently found in early childhood, middle childhood, and adolescence (e.g., asthma, sleep problems), while others were present only at one time point, or were confounded by socioeconomic status or psychiatric comorbidities (e.g., body mass index, dental caries). It is possible that either ADHD contributes to the increased risk for physical conditions, or that, vice versa, physical conditions increase the risk of ADHD or that common underlying factors contribute to both.[5]

However, while the bulk of the studies on the links between ADHD and physical conditions have addressed cross-sectional associations, longitudinal associations shedding light on the direction of the relationship have been less explored and have focused on single physical conditions, e.g., obesity/increased body mass index.[6]

To address these limitations, the present study used a large-scale population-representative sample to examine the hypothesis that a cumulative number of physical health conditions across child development are associated with ADHD symptoms in adolescence.

When assessing this relationship, it is important to control for two important confounders: 1) environmental factors associated with an increased risk of ADHD. In this regard, there is meta-analytic evidence that ADHD is more common in children whose mothers smoked during pregnancy or suffered pre-eclampsia.[7] Other risk factors include low birth weight and prematurity[8], and several indicators of socioeconomic disadvantage such as low family income, single parent households and low maternal education.[9] 2) medications for ADHD that may impact on a number of physiologic systems,- for instance, stimulants can negatively affect (at least at the beginning of the treatment) weight [10] and sleep.[11]

To gain insight into the longitudinal relationship between physical conditions and ADHD symptom development, we explored whether a cumulative number of physical disorders in childhood predicted ADHD symptoms at age 17, controlling for cumulative environmental risk, ADHD medication use and ADHD symptoms reported at age three.

METHOD

Sample

We used data from the Millennium Cohort Study (MCS), a longitudinal study that collected information from over 19,000 UK families with children born between 2000 and 2002. To date, seven waves of data have been collected, at ages 9 months and 3, 5, 7, 11, 14, and 17 years, respectively. In this study, as in previous research[12], only the first sibling of each family was included (4.9% excluded) to prevent confounding effects of family membership. Participants were also excluded if data relating to their biological mother were unavailable (5.1%) or all physical health predictor variables were missing (1.1%). As in previous longitudinal analyses[13], only participants with non-missing outcome data at age 17 were included in the analysis.

The number of participating families varied between waves, and households sampled from disadvantaged areas were more likely to withdraw.[14] As such, standardised weights were applied to ensure the sample was representative of the UK population and to account for attrition rates. Weights were calculated by multiplying the wave one sample design weights by the non-response weights of each wave. As data in this study were taken from all waves, weights from the most recent data sweep were applied. Descriptive statistics for all weighted variables in the current sample for the study (n=8059) are reported in Tables 1 and 2. This study was approved by the Ethics committee of University of [anonymised], in addition to the informed consent procedures obtained in the MCS.[15] Parents gave written informed consent to the open use of the anonymised dataset.

Measures

Outcome measure – parent-reported ADHD symptoms

The parent-reported hyperactivity/inattention subscale of the Strengths and Difficulties Questionnaire (SDQ[16]), measured at age 17, was used as a continuous dependent variable. The subscale hyperactivity/inattention is composed of five items ("restless, overactive, cannot stay still for long", "constantly fidgeting or squirming", "easily distracted, concentration wanders", "thinks things out before acting", "good attention span, sees tasks through to the end"). The SDQ items are rated from 0 to 2 points (0= never, 1= sometime true, 2= certainly true- or reverse coded for positive statements). Scores on the hyperactivity/inattention subscale range between 0 and 10, with a higher score indicating more ADHD symptoms. The SDQ has been found to be a valid measure with the hyperactivity/inattention subscale predicting ADHD diagnosis[17] with a Cronbach's alpha of 0.88, indicating good reliability. In the current sample, SDQ scores are significantly correlated ($p < .001$) across all six waves (ages 3-17 years) in which they are reported.

ADHD was diagnosed in a subset of children, with n = 174 children having an ADHD diagnosis by age 17. The main analysis was replicated with diagnosed ADHD as the outcome variable to test robustness of the results. We found that adolescents with an ADHD diagnosis at age 17 had a significantly higher hyperactivity / inattention SDQ score (M = 5.09) than adolescents without an ADHD diagnosis (M = 2.38; $t(8386) = 16.31$, $p < .001$, $d = 1.25$).

Predictors - Physical Health Conditions

At each wave of data collection (age 9 months to 17 years), parents were asked about their child's physical health. This information was gathered in several ways, including asking whether they had ever seen a health care professional about any problems and, if yes, asking to give details. Parents were also asked about specific diagnoses (e.g., 'has -child's name- ever had asthma?'). Hospital admissions were also recorded along with the reason for admission, such as convulsions, fits or epilepsy. We created variables to identify whether each child had ever experienced the condition. Physical conditions where a diagnosis could be given repeatedly and on a temporary basis, such as infection or diarrhoea, were excluded.

We grouped the physical conditions into four clusters, according to similar physiological mechanisms, reflecting their grouping in the ICD-11, as well as existing empirical evidence.[18-23] a) Sensory cluster (eyesight problems and hearing problems), b) Atopic cluster (eczema, asthma, and hay fever), c) Neurological cluster (fits and epilepsy, sleeping problems, stutter, movement problems and other neurological disorders), d) Cardio-metabolic cluster (obesity [at wave 7 only to exclude the natural weight fluctuations of young children], diabetes, and any reported heart or circulation condition including congenital heart disease). Cohort members' cumulative physical risk was therefore indicated by the number of conditions they had ever had in each cluster.

Control Variables - Cumulative Risk Indices (CRIs) and age three SDQ score.

Informed by previous evidence (Table 1), 20 environmental risk factors for ADHD were identified and controlled for within the available MCS data.[24] Data were collected during interviews with parents at the first data sweep (age 9 months). Individual risk factors were classified as either 'high risk' or 'low risk' (e.g., caesarean section yes/ no). Continuous variables were assigned a cut-off with reference to previous literature (Table 1). Risk factors were grouped and totalled to create five cumulative risk indices (CRIs) as follows: 1) *Prenatal risk index*, including maternal pre-pregnancy BMI, blood pressure problems in pregnancy, maternal diabetes and smoking during pregnancy, 2) *Perinatal risk index*, including birth weight, gestation, delivery method, and pregnancy lie/presentation, 3) *Postnatal risk (environment) index*, including maternal age, number of parents in the household, maternal education, and breastfeeding, 4) *Postnatal risk (maternal wellbeing) index*, including maternal distress, maternal depression/anxiety, and maternal attachment. Maternal distress was assessed using a 9-item short form version[25] of the Rutter Malaise Inventory.[26] The highest loading items in the first principal factor were used to create the 9-item scale measuring psychological distress. Mothers were asked a series of questions requiring a yes/no response such as "Do you often feel miserable or depressed?" High risk maternal distress was indicated by a score of ≥ 4[27] and psychometric properties are reported to be good.[28] A diagnosis of depression and/or anxiety was also included in the maternal wellbeing index, along with maternal attachment measured using a 6-item modified version of the Condon Maternal Attachment Questionnaire.[29] In this scale, mothers are asked about their feelings in different situations such as when they are caring for or having to leave their baby. Responses were recoded to ensure all items followed the same 1-5 scale which was then summed to give a total score out of 30. In line with previous literature,[30] high risk was categorised as the 25% of scores with the lowest attachment. 5)

Socioeconomic status and demographic risk index including sex, ethnicity, household income, housing tenure and overcrowding.

To account for ADHD symptoms experienced at a younger age, SDQ score reported by parents at age three was added as an additional predictor.

ADHD medication

Only at wave six, when cohort members were 14, parents were asked if their child was taking any prescribed medication for ADHD. A list of possible medications was given, including both stimulants and non-stimulants and medication, and the variable was coded as yes if parents indicated their child was taking any medication on the list.

Statistical Analysis

Stepwise, multiple regression analysis was conducted using IBM SPSS Statistics for Windows (Version 28.0, Chicago, Illinois) to analyse the relationship between the physical health clusters and ADHD symptoms at age 17 before and after controlling for cumulative environmental risk, ADHD medication and age three SDQ score. SDQ scores on the hyperactivity/inattention subscale at age 17 were entered as the dependent variable in all four regression models. The predictors entered into each model were as follows: Model 1- physical health clusters; model 2- physical health clusters and cumulative risk indices; model 3- physical health clusters, cumulative risk indices and ADHD medication; model 4- physical health clusters, cumulative risk indices, ADHD medication and SDQ score at age three. Variance inflation factor values did not indicate multicollinearity for any of the variables. To ensure correct temporal ordering of the regression model, physical health diagnoses from all timepoints were used to predict ADHD symptoms and diagnosis at age 17. However, to confirm robustness of the findings when accounting for earlier ADHD symptoms, we included in the main analysis a fourth

regression model with SDQ score at age three as an additional predictor. To show further robustness of the results, model 3 was repeated as a binary logistic regression with ADHD diagnosis (yes/no) as the outcome.

RESULTS

Weighted frequencies of physical health clusters and cumulative risk indices are reported in Table 2. As clusters were formed based on physiological similarity, they consisted of differing numbers of conditions and proportional frequencies. For example, the cardio-metabolic cluster consisted of three conditions with obesity markedly more prevalent than the other two disorders, whereas the sensory cluster consisted of two conditions with similar frequencies. In total, 91 children (1%) were taking ADHD medication and the average SDQ score at age 17 was 2.64 (*SD* = 2.34). Skewness and kurtosis were found to be within the normal range.

Model 1 (physical health clusters only) was overall significant ($F(4,5411) = 29.37$, $p < .001$) and explained 2% of the variance. As individual predictors, the sensory ($\beta = 0.08$, $p < .001$), neurological ($\beta = 0.10$, $p < .001$) and cardio-metabolic ($\beta = 0.04$, $p < .001$) clusters all significantly predicted ADHD symptoms at age 17. Model 2 (physical health clusters + CRIs) was also statistically significant ($F(9,5406) = 61.59$, $p < .001$) with 10% of the variance explained ($R^2_{adj} = .09$, $\Delta R^2 = .07$). Again, the sensory ($\beta = 0.08$, $p < .001$) and neurological ($\beta = 0.09$, $p < .001$) clusters were significantly associated with ADHD symptoms but the cardio-metabolic cluster was no longer a significant predictor. This remained unchanged in model 3 ($F(10,5405) = 96.37$, $p < .001$) with only the sensory ($\beta = 0.07$, $p < .001$) and neurological ($\beta = 0.09$, $p < .001$) clusters significantly predicting ADHD symptoms at age 17. Overall, model 3 explained 15% of the variance ($R^2_{adj} = .15$, $\Delta R^2 = .06$). Model 4 was again overall significant ($F(11,5404) = 129.27$, $p < .001$). The model explained 21% of the variance ($R^2_{adj} = .21$, $\Delta R^2 = .06$) with the sensory ($\beta = 0.06$, $p < .001$) and neurological cluster ($\beta = 0.06$, $p < .001$)

significantly predicting age 17 ADHD symptoms. The atopic cluster was not a significant predictor in any of the four regression models. The CRIs all significantly predicted ADHD symptoms in both model 2 and model 3 (β range = 0.03-0.18). In model 4, all CRIs significantly predicted ADHD symptoms except perinatal factors. A summary of the regression statistics can be found in Table 3. The mean SDQ score for each cumulative number of conditions in each cluster are shown in Figure 1.

A binary logistic regression with ADHD diagnosis as the outcome variable showed that the sensory cluster significantly predicted ADHD diagnosis, (b = 0.27, p = .020, OR = 1.31 (95% CI: 1.04, 1.65)).

The neurological cluster also significantly predicted ADHD diagnosis, (b = 0.66, p < .001, OR = 1.94 (95% CI: 1.48, 2.53)). Each additional neurological condition almost doubled the odds of an ADHD diagnosis.

DISCUSSION

This is the first study that analyzed the longitudinal association between a broad range of physical conditions in childhood and ADHD symptoms at age 17, controlling for cumulative environmental risk factors for ADHD, ADHD medication status and earlier ADHD symptoms. The sensory and neurological clusters were both significant predictors of hyperactivity/ inattention symptoms at age 17 and remained so after controlling for confounders. Moreover, the odds of having an ADHD diagnosis at age 17 was almost twice as likely when adolescents had predating neurological issues. The atopic cluster was not a significant predictor in any of the regression models and, after controlling for environmental risk and ADHD medication, the cardio-metabolic cluster was also not a significant predictor.

Children with more sensory conditions had higher hyperactivity and inattention symptoms at age 17. This is in line with previous studies showing that both eyesight and hearing problems

increase the risk of ADHD[31-33]. Our findings build on this known association between ADHD and eyesight/ hearing problems by showing that the likelihood of hyperactivity and inattention symptoms increases as the number of sensory conditions increases. DeCarlo and colleagues[33] proposed that sensory disorders place a large demand on executive functioning. Sensory problems may deplete executive functioning skills, leading to a reduced ability to successfully perform tasks known to be impaired in ADHD, such as those requiring organisation and concentration. It follows, therefore, that an increased number of sensory conditions may exacerbate inattention or hyperactivity symptoms in people who may already struggle with executive functioning.

This raises the question, which should be explored in future research, of whether hearing and eyesight problems magnify existing symptoms, mimic ADHD symptoms that may otherwise not be present, or whether ADHD and sensory problems may share neurobiological underpinnings.[34]. Our findings suggest that, to maintain quality of life, people with sensory disorders may need support with symptoms beyond those primarily associated with their health condition, because people with high levels of ADHD symptoms often experience a poorer quality of life, even if they do not meet the criteria for a diagnosis of ADHD.[35]

A higher number of neurological conditions during development also significantly predicted ADHD symptoms at age 17 when controlling for risk factors, medication and earlier ADHD symptoms. This is in line with previous studies reporting associations between ADHD and individual neurological conditions, such as stutter [36] and epilepsy.[37] Sleep problems, stutter and epilepsy are all known to individually predict ADHD, as well as each other.[21] Our results expand this knowledge by showing that a cumulation of neurological conditions further increases the likelihood of experiencing ADHD symptoms and an ADHD diagnosis later on in adolescence.

Previous literature has suggested this relationship may be bi-directional[38] as ADHD and conditions such as epilepsy may have shared risk factors or a shared neurobiological origin, with each predicting an increased risk of the other. Previous studies have found a shared genetic association between ADHD and neurological conditions, such as epilepsy[39] and sleep problems.[40] It is possible that some genetic variants affect several neurological, as well as mental conditions, increasing polygenic risk.[41]

Neurological conditions such as epilepsy are also known to impact executive functioning networks[42] which may modulate ADHD symptom expression. Executive functions involve the frontal cortex[43] which is associated with both epilepsy and ADHD.[39] Alterations in executive functioning networks which are associated with ADHD and neurological conditions may offer another explanation of the cormorbidity between the conditions.

Contrary to previous research,[44] atopic disorders were not significantly associated with higher ADHD symptoms. This result was surprising considering the wealth of evidence to support an association between atopic conditions and ADHD. Both eczema and hay fever had frequencies higher than expected and notably higher than other conditions (42.3% and 30.8% respectively). It may be that these conditions were over-reported in the sample, which influenced the results. Future research utilising clinical diagnoses rather than parent-reported physical conditions may reduce measurement error and shed light on the association between cumulative atopic conditions and ADHD symptoms. Another possible explanation for our findings is that individual conditions predict ADHD symptoms but that an accumulation of conditions does not increase the likelihood further.

This may also be the case for cardio-metabolic disorders as the cardio-metabolic cluster also produced different results to the sensory and neurological clusters. The cumulative effect of cardio-metabolic conditions significantly predicted ADHD symptoms in the first regression model but not when controlling for environmental risk or ADHD medication. Previous research

has reported an increased likelihood of developing diabetes in young people with ADHD, even after controlling for medication and demographic factors[45]. Our findings suggest that this relationship may not be bidirectional as cardiometabolic conditions did not predict an increase in hyperactivity/inattention symptoms. Rather than an accumulation of cardiometabolic conditions being associated with an increase in hyperactivity/inattention symptoms, it may be that environmental factors, or even other ADHD-related features such as impulsive decision making, are driving this relationship. These findings add weight to the complexity of the association between physical health and ADHD, demonstrating the influence of environmental risk on this relationship. For cardio-metabolic conditions at least, an individual's environment may play a larger part in determining the nature of the relationship.

All cumulative risk indices were themselves significantly associated with ADHD symptoms at age 17. The postnatal mother environment and SES/demographics indices had the largest effect size, and both consisted of environmental factors which are considered to reflect mainly psychosocial rather than biological influences compared to the other indices. For example, gestation and birth weight are irreversible factors which affect a child's biology at a fixed point in time, potentially with long term consequences. Factors affecting the whole household, such as income or housing tenure, have a greater effect on a child's physical environment but are also subject to greater fluctuation and their influence may vary depending on changes over time. This suggests further investigation is warranted to explore how different environmental factors affect the relationship between cumulative physical conditions and ADHD.

This study has several strengths. It used a large sample, weighted to represent the general population. Data were obtained longitudinally, allowing analysis of environmental risk before the age of three as a predictor of ADHD symptoms in later adolescence. It is also the first study to control for both environmental risk and medication use while examining the cumulative effect of several physical health conditions. The results further our insight into the

pathophysiology of ADHD and point to associations that may eventually inform clinical practice in terms of implemetation of additional support programes. A key area for future research would be to explore the effects of early treatment and support for physical conditions on later development of ADHD symptoms. However, when considering their possible clinical implications, our findings should be interpreted with caution. Although the SDQ differentiated well between children with and without an ADHD diagnosis, it is not a screening instrument for ADHD. The sensitivity analyses that we conducted with ADHD diagnosis are limited by only a subset of children having been evaluated for ADHD, therefore, our figures are likely underestimated. However, the consistency of the results in our sensitivity analysis indicates that our findings may extend to cases with a categorical diagnosis. There are some additional limitations to consider. First, the analyses were restricted by the amount and variety of physical health and environmental data available. Second, this study only looked at physical health as a predictor of ADHD symptoms and did not explore the reverse relationship nor the possibility of a bi-directional association. Third, due to a lack of data, it was not possible to analyse the effect of parental history of ADHD or physical health. ADHD is known to be highly heritable[46] as are many physical health conditions. Therefore, it is likely that a parent's health and neurodiversity may impact both ADHD symptoms and physical health of their child as well as the home environment.

In summary, this study found a significant relationship between a number of cumulative physical disorders diagnosed during childhood and ADHD symptoms in adolescence. The results indicate that sensory disorders and neurological disorders predicted ADHD symptoms even when relevant environmental risk is controlled for, suggesting possible biological commonalities including genetic association.

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Table 1. Weighted Frequencies of Sample Demographics and Other Environmental Risk Factors (N=8,059)

	High Risk Criteria	High Risk N (%)
SES and demographics		
Sex[47]	Male	4016 (49.8)
Ethnicity[48]	Any ethnicity other than white	968 (12)
Household income[49]	Below 60% median poverty indicator	2502 (31.1)
Household crowding[12]	Fewer rooms than people (excluding bathrooms)	743 (9.2)
Housing Tenure[50]	Social housing or renting from local authority	1825 (22.7)
Prenatal factors		
Maternal pre-pregnancy BMI[51]	>24.9	2089 (25.9)
Antenatal blood pressure[7]	Mother diagnosed with Pre-eclampsia/ Hypertension	561 (7)
Maternal diabetes diagnosis[7]	Mother has Diabetes diagnosis	159 (2)
Smoking in pregnancy[52],[53]	Mother smoked 1 or more cigarettes during pregnancy	1716 (21.3)
Perinatal factors		
Birthweight [8]	<2.5kg	502 (6.2)
Gestation [8],[54]	<37 weeks gestation (premature)	663 (8.2)
Delivery[7]	Caesarean section	1584 (19.7)
Presentation/lie[7]	Breech presentation/ other abnormal lie	452 (5.6)
Postnatal environmental factors		
Maternal age[55]	≤19 years	671 (8.3)
Number of parents in household[49]	1 parent living in household	1270 (15.8)
Mother's education[56],[57]	Mother educated to <NVQ[c] level 3 (2 A-levels)	4847 (60.1)
Breastfeeding[58]	No breastfeeding	2480 (30.8)
Postnatal maternal wellbeing factors		
Maternal distress[59],[27]	<4 on Rutter Malaise Inventory	358 (4.4)
Maternal mental health diagnosis[60]	Depression/anxiety diagnosis	2008 (24.9)
Maternal attachment[61],[30]	>22 on Condon Maternal Attachment Scale	1870 (23.2)

Note: SES = socioeconomic status; BMI = Body Mass Index; NVQ = National Vocational Qualifications

Table 2. Weighted Frequencies of Individual and Clustered Physical Health Conditions, and Cumulative Risk Indices (N=8,059)

		Number of Conditions N(%)			
	N (%)	**0**	**1**	**2**	**3**
Sensory cluster		5051 (62.7)	2515 (31.2)	493 (6.1)	
Eyesight problems	1802 (22.4)				
Hearing problems	1700 (21.1)				
Atopic cluster		3271 (40.6)	2790 (34.6)	1477 (18.3)	508 (6.3)
Asthma	1375 (17.1)				
Eczema	3411 (42.3)				
Hay fever	2482 (30.8)				
Neurological cluster		6851 (85)	1093 (13.6)	109 (1.4)	6 (0.1)
Movement problems	452 (5.6)				
Neurological disorders	41 (0.5)				
Sleeping problems	82 (1)				
Stutter	261 (3.2)				
Fits or Epilepsy	491 (6.1)				
Cardio-metabolic cluster		5983 (74.2)	2052 (25.5)	24 (0.3)	
Diabetes	22 (0.3)				
Obesity age 17	2031 (25.2)				
Cardiovascular disorders	47 (0.6)				

	Number of Environmental Risk Factors N(%)					
Cumulative Risk Indices	**0**	**1**	**2**	**3**	**4**	**5**
Prenatal factors	4336 (53.8)	2983 (37)	682 (8.5)	53 (0.7)	5 (0.1)	
Perinatal factors	5747 (71.3)	1596 (19.8)	556 (6.9)	148 (1.8)	13 (0.2)	
Postnatal environmental factors	2707 (33.6)	2535 (31.5)	1917 (23.8)	701 (8.7)	199 (2.5)	
Postnatal maternal wellbeing factors	4625 (57.4)	2719 (33.7)	622 (7.7)	90 (1.1)		
Socioeconomic status and demographics	2229 (27.7)	3175 (39.4)	1431 (17.8)	901 (11.2)	298 (3.7)	24 (0.3)

Table 3. Regression Statistics for all Models with Strengths and Difficulties Questionnaire (SDQ) Score at Age 17 as the Outcome Variable

	R^2	R^2 change	B	β	95% CI LL	95% CI UL
Model 1	.02	.02				
Constant			2.10**		2.00	2.20
Clusters						
Sensory			0.31**	0.09	0.22	0.41
Neurological			0.50**	0.09	0.36	0.64
Atopic			0.05	0.02	-0.02	0.11
Cardio-metabolic			0.17**	0.04	0.04	0.31
Model 2	.09	.07				
Constant			1.27**		1.15	1.39
Clusters						
Sensory			0.28**	0.08	0.19	0.37
Neurological			0.44**	0.08	0.38	0.64
Atopic			0.04	0.02	-0.03	0.09
Cardio-metabolic			0.04	0.01	-0.08	0.16
CRIs						
Prenatal risk			0.22**	0.07	0.14	0.30
Perinatal risk			0.09*	0.03	0.01	0.16
Mother environment			0.26**	0.12	0.26	0.38
Mother wellbeing			0.18**	0.05	0.15	0.31
SES and demographics			0.40**	0.18	0.31	0.42
Model 3	.15	.06				
Constant			1.34**		1.23	1.46
Clusters						
Sensory			0.28**	0.08	0.17	0.34
Neurological			0.40**	0.08	0.35	0.60
Atopic			0.02	0.01	-0.05	0.07

Cardio-metabolic			0.05	0.01	-0.06	0.17
CRIs						
Prenatal risk			0.19**	0.06	0.11	0.27
Perinatal risk			0.08*	0.03	0.01	0.15
Mother environment			0.23**	0.10	0.24	0.36
Mother wellbeing			0.14**	0.04	0.11	0.27
SES and demographics			0.36**	0.16	0.27	0.38
ADHD medication			4.86**	0.24	4.35	5.27
Model 4	.21	.06				
Constant			0.70**		0.56	0.84
Clusters						
Sensory			0.22**	0.06	0.13	0.31
Neurological			0.32**	0.06	0.20	0.45
Atopic			0.01	0.00	-0.05	0.07
Cardio-metabolic			0.01	0.00	-0.11	0.13
CRIs						
Prenatal risk			0.16**	0.05	0.08	0.24
Perinatal risk			0.07	0.02	-0.01	0.14
Mother environment			0.16**	0.07	0.10	0.22
Mother wellbeing			0.08*	0.02	0.001	0.16
SES and demographics			0.27**	0.12	0.21	0.32
ADHD Medication			4.39**	0.22	3.91	4.87
SDQ score at age three			0.25**	0.25	0.22	0.27

Note: ADHD = attention-deficit/hyperactivity disorder; CRIs = Cumulative Risk Indices; SES = Socioeconomic Status;

* $p < .05$; ** $p < .001$

Figure 1. Weighted Mean Strengths and Difficulties Questionnaire (SDQ) Scores for Cumulative Numbers of Conditions in Each Physical Health Cluster