



HAL
open science

Medical conditions and Attention-Deficit/Hyperactivity Disorder symptoms from early childhood to adolescence

Cedric Galera, Samuele Cortese, Massimiliano Orri, Ophelie Collet, Judith van Der Waerden, Maria Melchior, Michel Boivin, Richard E. Tremblay, Sylvana M. Cote

► To cite this version:

Cedric Galera, Samuele Cortese, Massimiliano Orri, Ophelie Collet, Judith van Der Waerden, et al.. Medical conditions and Attention-Deficit/Hyperactivity Disorder symptoms from early childhood to adolescence. *Molecular Psychiatry*, 2021, 10.1038/s41380-021-01357-x . hal-03467443

HAL Id: hal-03467443

<https://hal.science/hal-03467443v1>

Submitted on 22 Jan 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Medical conditions and Attention-Deficit/Hyperactivity Disorder symptoms from early childhood to adolescence

Authors Cédric Galera*, MD, PhD, (a,b,c,d), Samuele Cortese*, MD, PhD, (e,f,g),
Massimiliano Orri, PhD, (b,h), Ophélie Collet, Msc, (i), Judith van Der Waerden, PhD, (j),
Maria Melchior, PhD, (j), Michel Boivin, PhD, (d,k), Richard Tremblay, PhD, (d,l,m),
Sylvana Côté, PhD, (b,d,m,n)

* Equal contribution

Affiliations:

- (a)** University of Bordeaux, France
- (b)** INSERM, Bordeaux Population Health Center, UMR1219, France
- (c)** Centre Hospitalier Perrens, Bordeaux, France
- (d)** Research Unit on Children's Psychosocial Maladjustment, Montreal, Quebec, Canada
- (e)** University of Southampton, Solent NHS Trust, Southampton, United Kingdom
- (f)** University of Nottingham, United Kingdom
- (g)** Hassenfeld Children's Hospital at NYU Langone, New York, U.S.A.
- (h)** McGill Group for Suicide Studies, Douglas Mental Health University Institute, Department of Psychiatry, McGill University, Montreal, Canada.
- (i)** School of Public Health, University of Montréal, Canada
- (j)** INSERM UMR_S 1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Sorbonne Université, Paris, France
- (k)** School of Psychology, Université Laval, Quebec, Canada
- (l)** Department of Psychology, University of Montreal, Montreal, Quebec, Canada
- (m)** CHU Ste-Justine Research Centre, Montreal, Quebec, Canada
- (n)** University of Montreal, Department of Social and Preventive Medicine, Montreal, Quebec, Canada

Manuscript word count: 4063

Short title: Medical conditions and ADHD across development

Address correspondence to: Cédric Galéra, Bordeaux Population Health Center INSERM U1219, University of Bordeaux, 146 rue Léo Saignat – CS61292, 33076 Bordeaux, France
Email: cedric.galera@u-bordeaux.fr Telephone: +33(0)556561719

ABSTRACT

The comorbidity between physical and mental health conditions is challenging and frequently goes unrecognized in practice. Associations between Attention-Deficit/Hyperactivity Disorder (ADHD) and physical conditions have been reported in youth. However, prior research failed to: 1) address the patterns of associations in early childhood, middle childhood, and adolescence within the same population sample; 2) consider a large set of physical disorders at the same time; 3) take confounders into account. Our goal was to assess the associations between ADHD symptoms and a broad set of physical conditions across developmental periods. This birth cohort study (n= 2057) is the first to explore the associations between ADHD and a wide range of medical conditions by encompassing the whole early development from 5 months to 17 years in the same sample and relying on innovative network analyses. We found significant associations between ADHD symptoms and several physical conditions, some of which were observed in early childhood, middle childhood, and adolescence (e.g., asthma, sleep problems) or were confounded by socioeconomic status **or psychiatric comorbidities** (e.g., body mass index, dental caries). The study calls for an effective integrated care model encompassing mental and general healthcare across the developmental period.

Key words Medical and psychiatric comorbidity / Attention Deficit Hyperactivity Disorder / Epidemiology / Childhood / Adolescence

TEXT

INTRODUCTION

An increasing body of research points to a significant association between mental and medical disorders(1,2). The pathways underpinning the link between mental and medical conditions are complex and potentially bidirectional. Medical conditions may contribute to symptoms of mental disorders (e.g., hypothyroidism leading to depressive symptoms)(3), while negative outcomes associated with mental disorders may increase the risk for medical conditions (e.g., increased risk of sexually transmitted infections in bipolar disorder)(4). It is also possible that mental and medical disorders share common risk factors, including, among others, common genetic vulnerability, early trauma, chronic stress, inflammatory or autoimmune response, and socioeconomic factors (e.g., low income and poor educational attainment)(5,6). Gaining insights into these associations has important implications for the daily clinical management of patients with both mental and medical conditions.

Here we focus on the link between several medical conditions and the most common neurodevelopmental disorder, namely Attention-Deficit/Hyperactivity Disorder (ADHD)(7,8). ADHD is associated with substantial personal burden and societal costs(9,10). In addition to well established comorbidity with other mental disorders (e.g. anxiety)(11), there is meta-analytic evidence, mostly based on cross-sectional studies, of a significant association between ADHD and several medical/physical conditions, including sleep alterations(12), obesity(13,14), metabolic conditions (15), asthma(16), and atopic diseases(17).

However, prior research on the association between ADHD and medical conditions can be expanded in several ways. First, most of the available evidence is restricted to specific developmental periods (i.e., childhood or adolescence), thus not capturing the developmental patterns from early childhood to adolescence (18). Understanding the links between ADHD and medical conditions across development is crucial to optimize the clinical management of patients affected by the double burden of ADHD and medical conditions (19,20).

Furthermore, most previous studies linking ADHD to medical disorders did not provide a comprehensive view of the interrelationships between ADHD and several medical disorders, rather tending to focus on individual disorders (13,16). This is crucial to plan comprehensive management strategies of ADHD patients with more than one medical condition. Finally,

possible confounding factors, especially socioeconomic status and sex, have not systematically been taken into account in previous studies(21).

To fill these gaps, the present study aimed to assess the associations between ADHD symptoms and a broad set of medical conditions in early childhood, middle childhood and adolescence, using a large birth cohort prospectively followed up for 17 years, and controlling for confounding by socioeconomic status and sex.

METHODS

Participants and procedure

We draw on data from the Quebec Longitudinal Study of Child Development (QLSCD), which was approved by the St. Justine Hospital Research Center ethics committees and the Quebec Statistics Institute, Canada. Data were collected by the Quebec Statistics Institute(22).

Participants selected from the Quebec Birth Registry were stratified on living area/birth rate. Families were included in the QLSCD if the pregnancy lasted 24-42 weeks and the mother could speak English or French. Follow-up was conducted yearly during childhood (up to 12 years) and biyearly during adolescence (up to 17 years of age). Data were collected by trained interviewers through structured interviews. Results of the assessment from previous waves were not communicated to the interviewers in subsequent assessments. All questionnaires are available at <https://www.jesuisjeserai.stat.gouv.qc.ca/>. Written informed consent was obtained from all the participants at each wave. The initial population-based sample comprised 2120 infants representative of children born in the Canadian Province of Quebec between October 1997 and July 1998, with the exception of Northern Quebec, Cree territory, Inuit territory, and Native Reserves (2.2% of all births). Details about representativeness have been published elsewhere(22). Participants with available ADHD scores were retained for the analyses, which were conducted during three distinct periods of development: 1) Early childhood (5 months-5 years); 2) Middle childhood (6-12 years); 3) Adolescence (13-17 years).

Measures

ADHD symptoms

Behavioral ratings of ADHD symptoms (inattention, hyperactivity and impulsivity) were obtained from the person most knowledgeable about the child (at the age of 1.5, 2.5, 3.5, 4.5, and 5 years; the mothers in >98% of the cases), from teacher reports (6, 7, 8, 10, and 12 years), and from participants' self-reports (13, 15 and 17 years). Symptom ratings of behavior until age 13 years were adapted from the Social Behavior Questionnaire, created for the Canadian National Longitudinal Study of Children and Youth(23). It includes items from the Child Behavior Checklist(24), the Ontario Child Health Study Scales(25), and the Preschool Behavior Questionnaire(26). Behavioral ratings at ages 15 and 17 years were made via the Mental Health and Social Inadaptation Assessment for Adolescents(27). Inattention items included the following: *Cannot concentrate, cannot pay attention for long; Is inattentive; and Easily distracted, difficulty pursuing any activity*. Hyperactivity/impulsivity items comprised: *Can't sit still, is restless or hyperactive; Impulsive, acts without thinking; and Difficulty waiting his/her/your turn in games/activities*. These items correspond to the items of Criterion A of the DSM-5 criteria for ADHD and reflect those used in other standardized measures of childhood behavioral problems such as the Strengths and Difficulties Questionnaire(28). These measures have been extensively used in ADHD research as proxies of ADHD categorical diagnosis, particularly in epidemiological samples from the general population, and are in line with a view of ADHD as a quantitative trait, supported by recent genetic findings(29–32). Items were rated on a frequency scale (never/not true = 0, sometimes/somewhat true = 1, often/very true = 2). At each wave, scores were summed and divided by the number of items and then rescaled to range from 0 to 10. We averaged the behavioral scores over the waves of each age period, consistently with prior studies, thus obtaining a single *ADHD symptoms* score for each developmental period(33). Alpha scores for ADHD symptoms were 0.70 for early childhood ratings (1.5–5 years), 0.86 for middle childhood ratings (6–12 years), and 0.73 for adolescent ratings (13–17 years), respectively.

Medical conditions

Data on medical conditions were reported by the person most knowledgeable (PMK) about the child/adolescent at all waves (the mother in 98% of cases). The study collected the following diagnoses: asthma, dental caries, diabetes, eczema, epilepsy, food or digestive

allergies, hypercholesterolemia, hypertension, migraine, injuries, acute infections, body mass index (BMI), burn, poisoning, bruxism, night terrors, snoring, symptoms of restless legs syndrome (RLS), sleepwalking, and sleep duration.

Data on asthma, dental caries, diabetes, eczema, epilepsy, and food or digestive allergies corresponded to the cumulative frequency across periods and was coded as yes versus no, based on the PMK's report of a diagnosis made by a physician. The other variables correspond to the frequency for each index period and were coded as follows: hypercholesterolemia (yes versus no, based on physician's diagnostic report); hypertension (yes versus no, based on physician's diagnostic report); migraine (yes versus no, based on physician's diagnostic report); injuries [any versus none, based on report of accidental injuries requiring medical assessment (bicycle or scooter collision while riding/fall/sport injury/mouth or teeth injury)]; acute infections (gastrointestinal, otitis, bronchitis, pneumonia, pharyngitis, laryngitis, flu) (≥ 2 versus < 2 , based on report of number of infections per data collection wave and averaged over each period); BMI (standardized) ($\geq 1SD$ versus $< 1SD$, based on reported weights and sizes); burn (any versus none, based on report of burn requiring medical assessment); poisoning (any versus none, based on report of poisoning requiring medical assessment); bruxism (frequent/always versus sometimes/never, based on report of teeth-grinding during the night); night terrors (frequent/always versus sometimes/never, based on report of night terrors); snoring (frequent/always versus sometimes/never, based on report of snoring or noisy breathing when sleeping); symptoms of RLS (yes versus no, based on report of unpleasant sensations in legs at bedtime that make subject move); sleepwalking (yes versus no, based on report of somnambulism or sleepwalking); and sleep duration per night (short versus non-short (early childhood < 10 hours; childhood < 9 hours 30 minutes; adolescence < 8 hours), based on report of mean number of hours slept per night). The waves in which each of these conditions were assessed as well as their time frame are reported in the Supplement (**eTable 1**). For age at onset of medical conditions see eTable 2.

Covariates

All variables, **except psychiatric comorbidities**, were measured when the child was 5 months of age: sex of child (male versus female); socioeconomic status, assessed with five aggregate items regarding parental educational level, parental occupation, and annual gross income (range, -3 to 3, centered at 0, with higher scores indicating higher socioeconomic status); family dysfunction score, assessed with 7 items (e.g., Do not get along well together) from the McMaster Family Assessment (34) administered to mother and scores range from 0 to 10, with higher scores indicating lower family functioning; maternal and paternal depression, assessed using short version of the Center for Epidemiological Study Depression Scale (35) with scores ranging from 0 to 10, with higher scores indicating higher depressive symptoms; maternal and paternal anti-sociality, assessed with binary questions on five different conduct problems based on DSM-IV criteria for conduct disorder and antisocial personality disorder (scores range from 0 to 5, with higher scores indicating more antisocial behaviors); low birth weight (<2500g versus > or = 2500g), maternal and paternal age at birth (in years), no intact family (single or blended versus others), and immigrant mother (mother born outside Canada versus born in Canada). **Behavioral/psychiatric comorbidities were measured with the same tools as ADHD symptoms (23-27). They included problems of anxiety, emotional problems and oppositional behaviors in early and middle childhood; and problems of anxiety, depression, and conduct disorder in adolescence.**

Data Analyses

Analyses aimed to:

1. Visually represent the associations (networks) between ADHD symptoms and a set of medical conditions in specific developmental periods using graph theory approaches, where each condition is represented by nodes and their links by edges. This approach is suitable to show how several conditions cluster together in networks and the strength of these associations. We estimated partial correlation networks to explore the shared variance among ADHD symptoms and medical conditions. Partial correlation networks assess unique relations among a large set of variables. We estimated the Mixed Graphical Models (MGMs)(36) for the medical conditions and ADHD symptoms (R software package, mgm). We used LASSO regularization regression to identify the most relevant edges among the large number of pairwise associations. The LASSO penalty parameter was selected using the

Extended Bayesian Information Criterion (EBIC) for which the tuning parameter lambda was set to 0. Accuracy and stability were assessed by 100 non-parametric bootstraps of the edge weights(37) and displaying the proportion of non-zero estimates (R package, bootnet). We used the node strength centrality index to assess the strength of internode connections.

2. Estimate the unadjusted associations between medical conditions and ADHD symptoms **(outcome)**, via linear regressions and expressed as β and Cohen's d (standardized mean differences).

3. Quantify the adjusted associations between medical conditions and ADHD symptoms by developmental period. To further assess the association between medical conditions and ADHD symptoms, we conducted multivariate modeling for each medical condition, taking sex of the youth and family socioeconomic status at each period into account. We used linear regression models to estimate the associations of medical problems and ADHD symptoms (outcome) at each period. Medical variables and covariates with missing data were imputed (multiple imputation on 40 data sets for multivariate analyses and 1 data set for network analyses) based on ADHD symptoms, medical conditions and key variables (sex of child, low birth weight, maternal age at birth, family socioeconomic status, immigrant status, not intact family) (R package, mice). A change-in-estimate (CIE) > 10% between unadjusted and adjusted association was indicative of a confounding effect of adjustment variables (38).

We also conducted **sensitivity analyses** to test the robustness of the findings by 1) **adjusting on psychiatric comorbidities including problems of anxiety (early childhood, middle childhood, adolescence), emotional problems (early childhood, middle childhood), oppositional behaviors (early childhood, middle childhood), depression (adolescence), and conduct disorder (adolescence)**; 2) adjusting (beyond sex of child and family socioeconomic status) for the following additional variables identified as confounders in previous systematic reviews of the relationships between ADHD and two common medical conditions (i.e. asthma/obesity): low birth weight, maternal age at birth, immigrant status, and lack of intact family(13,16); **3) conducting the analyses on the samples with complete cases** (i.e. without imputed data).

RESULTS

Sample characteristics

The initial sample at recruitment and the three samples used in the present study (early childhood, middle childhood, and adolescent samples) included 2120, 2057, 1631, and 1548 participants, respectively. There were no significant differences between the three study samples and the initial sample regarding main family and individual characteristics, except for mother's immigrant status, with immigrant mothers less likely to participate in follow-up (**Table 1**).

Networks of medical conditions and ADHD symptoms by developmental period

Figure 1 shows the networks of medical conditions and ADHD symptoms for the three age periods (early childhood, middle childhood, and adolescence). Coherently, medical conditions formed communities in the network structure, particularly regarding atopic, sleep and infection problems. In early childhood, ADHD symptoms were associated with bruxism, sleepwalking, RLS, injuries, acute infections, asthma, higher BMI, dental caries, and short sleep duration (regularized edge weights equal to 0.24, 0.22, 0.21, 0.20, 0.17, 0.14, 0.08, 0.07, and 0.04, respectively). In middle childhood, ADHD symptoms were associated with RLS, higher BMI, dental caries, food and digestive allergies, sleepwalking, and asthma (regularized edge weights equal to 0.20, 0.11, 0.11, 0.10, 0.10, and 0.09, respectively). In adolescence, ADHD symptoms were associated with RLS, short sleep duration, acute infections, dental caries, injuries, and asthma (regularized edge weights equal to 0.13, 0.09, 0.08, 0.08, 0.07, and 0.06, respectively). Non-parametric bootstraps on edge weight are shown in **eFigures 1a, 1b, 1c**. All regularized edge weights are provided in **eFigures 2a, 2b, 2c**. The node strength centrality indices for the variables of the network are shown in **eFigure 3**.

Unadjusted associations

Table 2 reports the unadjusted associations between the medical conditions and ADHD symptoms across the three developmental periods. Whilst ADHD was significantly associated with some medical conditions consistently **in the three** developmental periods (e.g.

asthma/RLS), other associations were significant only at specific time points (e.g. link between ADHD and BMI, significant only in early childhood and middle childhood).

Adjusted associations between medical conditions and ADHD symptoms by developmental period

Table 3 reports univariate and multivariate associations between medical conditions and ADHD symptoms by developmental period adjusted for sex and SES. In early childhood, ADHD symptoms were significantly and positively related to a higher risk of numerous conditions including asthma, higher BMI, epilepsy, dental caries, acute infections, injuries, and sleep problems (i.e. night terrors/bruxism/sleepwalking/snoring/RLS/short sleep duration). The reduction in the strength of associations after adjustment suggested a confounding role of sex and SES with asthma (CIE=25.7%), BMI (CIE=38.5%), epilepsy (CIE=12.7%), dental caries (CIE=66.7%), injuries (CIE=10.2%), sleepwalking (CIE=19.6%), snoring (CIE=14.2%) and RLS (CIE=10.5%). In middle childhood, ADHD symptoms significantly increased the likelihood to present asthma, food and digestive allergies, higher BMI, dental caries, and sleep problems (i.e. night terrors/sleepwalking/RLS). The reduction in the strength of associations after adjustment suggested a confounding role of sex and SES with asthma (CIE=47.5%), BMI (CIE=35.7%), dental caries (CIE=66.6%), night terrors (CIE=35.7%), sleepwalking (CIE=15%), and RLS (CIE=31.6%). In adolescence, ADHD symptoms were significantly and positively related to a higher risk of asthma, dental caries, acute infections, injuries, poisoning, RLS, and short sleep duration. The association with dental caries was confounded by adjustment variables (CIE=16.7%).

Sensitivity analyses

Results of sensitivity analyses regarding psychiatric comorbidities are shown in eTable 3. In early childhood the reduction in the strength of associations after adjustment suggested a confounding role of anxiety with asthma (CIE=31.4%), epilepsy (CIE=15.7%), dental caries (CIE=42.9%), acute infections (CIE=68.8%), injuries (CIE=12.2%), night terrors (CIE=51.1%), bruxism (CIE=34.9%), sleepwalking (CIE=29.5%), snoring (CIE=30.6%), RLS (CIE=61.4%) and short sleep duration (CIE=61.1%). It also showed a confounding role of emotional problems with asthma (CIE=20.0%), epilepsy (CIE=17.0%), dental caries (CIE=23.8%), acute infections

(CIE=43.8%), injuries (CIE=14.3%), night terrors (CIE=27.2%), bruxism (CIE=23.8%), sleepwalking (CIE=18.0%), snoring (CIE=14.3%), RLS (CIE=35.0%) and short sleep duration (CIE=11.1%). Additionally, we found a confounding role of oppositional behaviors with asthma (CIE=34.3%), BMI (CIE=46.1%), epilepsy (CIE=46.4%), dental caries (CIE=14.3%), acute infections (CIE=40.6%), injuries (CIE=40.8%), night terrors (CIE=53.4%), bruxism (CIE=49.2%), sleepwalking (CIE=45.9%), snoring (CIE=55.1%), RLS (CIE=50.9%), and short sleep duration (CIE=77.8%).

In middle childhood, the reduction in the strength of associations after adjustment suggested a confounding role of anxiety with BMI (CIE=33.3%), and RLS (CIE=12.3%). We also found evidence of a confounding role of emotional problems with asthma (CIE=40.0%), food or digestive allergies (CIE=73.5%), BMI (CIE=100%), dental caries (CIE=17.9%), night terrors (CIE=20.5%), sleepwalking (CIE=12.5%), and RLS (CIE=19.3%). We also found a confounding role of oppositional behaviors with asthma (CIE=32.5%), food or digestive allergies (CIE=63.3%), BMI (CIE=97.6%), dental caries (CIE=53.8%), night terrors (CIE=91.1%), sleepwalking (CIE=55.0%), and RLS (CIE=43.9%).

In adolescence, the reduction in the strength of associations after adjustment suggested a confounding role of anxiety for acute infections (CIE=48.3%), poisoning (CIE=35.6%), and short sleep duration (CIE=59.3%). Additionally, there was evidence of a confounding role of depression for acute infections (CIE=34.5%), poisoning (CIE=61.3%), and short sleep duration (63.0%). Finally, a confounding role of conduct problems for asthma (CIE=65.2%), dental caries (CIE=58.3%), injuries (CIE=29.2%), RLS (CIE=16.3%), and short sleep duration (CIE=29.6%) was detected. The rest of sensitivity analyses showed the same pattern of results (eTable 4, and eTable 5).

DISCUSSION

Main results and comparison with the literature

This study is the first to our knowledge to explore the associations between ADHD and a wide range of medical conditions by encompassing the whole early development from 5 months to 17 years in the same sample. We found significant associations between ADHD symptoms and several medical conditions. Of note, several of these associations started from

early childhood. Specifically, we confirm the link with asthma supported by meta-analytic evidence from cross-sectional(16) and longitudinal studies(17) and found significant adjusted associations in early childhood.

In line with a large body of literature, sleep problems were related to ADHD. Interestingly RLS symptoms were significantly associated with ADHD symptoms **(both unadjusted and adjusted associations) in each** developmental period. This extends previous evidence based on studies focused on specific age groups(39). In addition, a significant adjusted association in early childhood was found for symptoms of other sleep disorders, including night terrors, bruxism, snoring, and sleepwalking (the latter persisting in childhood). Short sleep duration was significantly associated with ADHD in adolescence. Overall, our results related to sleep problems highlight the need to focus on specific disorders, rather than on “sleep problems” as a generic construct.

A significant adjusted association in early childhood was also found for epilepsy, in line with current recommendations to screen for ADHD in children with epilepsy(40). However, whilst these recent recommendations suggest screening for ADHD from 6 years of age, we found that the adjusted association was significant only in early childhood.

We also found a significant adjusted association between ADHD symptoms and injuries, during early childhood and adolescence, in line with previous meta-analytic evidence by Ruiz-Goikoetxea et al.(41) pointing to a significantly higher risk of unintentional physical injuries in individuals with ADHD. Likewise, the significant association with poisoning that we found in adolescents, **reduced to non-significance by psychiatric comorbidities**, adds to previous meta-analytic findings based on aggregated data that showed a significant association but without a significant age effect from childhood to adolescence.

We also found a significant association between ADHD symptoms and acute infections in early childhood and adolescence, **which was reduced and became non-significant after adjustment on psychiatric comorbidities**. This topic of research has received little attention so far, but overall corroborates initial findings suggesting an association between the etiology of ADHD and infectious agents such as viruses and Group A beta-hemolytic streptococcus(42).

Among the **others** non-significant associations after adjustment, notable was the one between BMI and ADHD. This result may initially appear at odds with meta-analytic evidence by Cortese et al.(13) showing a significant association between obesity and ADHD in childhood,

as well as in adulthood. However, whilst the meta-analysis by Cortese et al. focused on obesity as a categorical diagnosis, we focused on BMI and there may be non-linear relationship between BMI and ADHD symptoms. Furthermore, only some of the studies included in the meta-analysis of adjusted odds ratios accounted for the variables we adjusted for, i.e., sex, SES **or psychiatric comorbidities**. Importantly, in our study, most associations were slightly confounded by relevant co-variates, suggesting the relative independence of the link between medical conditions and ADHD symptoms. However the strengths of the associations between BMI and ADHD, as well as dental caries and ADHD, were reduced and became non-significant after adjustment **on sex, SES, or psychiatric comorbidities**, suggesting a stronger confounding role of **these** covariates.

Interpretation

The mechanisms and reasons underlying the significant associations that we found are likely complex and multifactorial. Common genetic alterations may contribute to some of these associations. For instance, the association between RLS and ADHD symptoms may involve a shared dopamine dysfunction, possibly implicating iron(39). Genetic determinants (i.e., alterations in BTBD9 gene) might underpin this common pathophysiology. More generally, the actual findings regarding the polygenic score prediction of complex phenotypes, such as ADHD, underline the highly polygenic and pleiotropic nature of these predictions (6). Inflammatory mechanisms are also likely to contribute to some of the associations by acting as mediators or as common risk factors. The allergic inflammation that characterizes asthma could increase the level of circulating cytokines, which in turn might impact some areas of the prefrontal cortex and neurotransmitter systems implicated in ADHD(43). Similarly, allergic mechanisms related to sleep alterations may contribute, at least partially, to ADHD symptoms(44). Infections themselves trigger modulations of immunity which could share common pathways with ADHD, as illustrated by the Pediatric Autoimmune Neuropsychiatric Disorders associated with streptococcal infections (42,45). With respect to epilepsy, the association with ADHD appears complex and might involve various mechanisms ranging from common genetic factors to the iatrogenic effects of anti-epileptics(46). Beyond the biological correlates, ADHD symptoms may themselves be at play in the relationship with certain medical conditions. Cardinal features such as poor attention and impulsivity, as well as comorbid neuropsychological characteristics including executive dysfunction or risk-taking, make individuals more vulnerable to accidental injuries(41). Emotional impulsivity

may also lead to dysregulated eating patterns with subsequent weight gain. However, ADHD and weight dysregulation/obesity might share common biological risk factors, including genetic variants and dopaminergic dysfunctions in the brain(13). Disorganization and difficulties to maintain routines may also contribute to jeopardize oral hygiene practices, and ADHD medications may impact salivary function and appetite(47), which in turn may heighten the risk of dental caries. Of note, some associations were significantly reduced after adjusting for sex, SES, **or psychiatric comorbidities**. Therefore, confounding by sex, SES and/or **psychiatric comorbidities** may be an alternative hypothesis for the interpretation in some instances (e.g., ADHD/dental caries; ADHD/BMI).

Strengths and limitations

This study has several strengths. First, it relies on a large and unique population-based sample followed from early childhood until adolescence. Second, it considers a wide range of medical conditions. Third, it takes relevant confounders into account. It also has some limitations. First, behavioral and medical assessments were based on participants' reports rather than on clinical and objective assessments. However, participants often report the diagnoses made by their own doctors and the symptom-based scales we used have shown satisfactory psychometric properties(26). Second, changes in raters over time with respect to ADHD symptoms could produce an instability bias. However, the assessments for each developmental period were conducted by well-informed respondents with respect to individuals' behaviors. Parents provided information about the early-childhood period, which is considered appropriate. Teachers provided information about children's symptoms in middle childhood, as they are the best placed to identify departures from behavioral normality at this age(48). The adolescent period was informed by self-reports, which have been shown to be relevant to evaluate behavioral symptoms although they may lead to under-reporting and thus to more conservative results(49,50). Third, the study sample was subject to attrition. However, there were no significant differences in key variables when compared with the initial sample, except for the mother's immigrant status. Fourth, we could not explore causality behind the studied associations because of the absence of temporal precedence in the modeling of ADHD and medical conditions. Fifth, although we explored a wide range of medical conditions, the investigation was not exhaustive (for instance, sleep apnea was not assessed) and was limited by low statistical power for rare conditions in this general population sample. Sixth, we did not address the effects of ADHD medication. However,

stimulant medications might have an impact on the association between ADHD symptoms and somatic conditions, particularly with BMI (stimulants are associated with decreased appetite) and sleep problems (stimulants are associated with sleep delay)(51). Future studies should specifically focus on these issues. Finally, as basically all of the included medical conditions may have a variable age at onset but because most of them can start very early in life (first or second year) and can have a variable persistence in life across patients, likely due to a plethora of genetic and non-genetic factors, we could not further model the time-varying nature of the medical conditions we assessed.

Implications

Whether the correlations between medical conditions and ADHD are causal, which directions characterize them, and whether they are consequences of the same underlying factors or are mere correlations reflecting confounding, remain to be understood. Different pathways and heterogeneous mechanisms might contribute to the links between medical conditions and ADHD and vary as a function of each specific condition. It is crucial to further study these underlying mechanisms since they could open avenues for improving ADHD management early on with beneficial long-term effects. The high level of comorbidity between ADHD and medical conditions pleads for a better awareness among clinicians who work with children and adolescents. Physical health specialists (e.g., pediatricians/general practitioners) should be aware of and trained in the frequent co-occurrence of ADHD with asthma, sleep problems, overweight, and dental caries, i.e. the most prevalent medical conditions during childhood and adolescence, and where possible screen for them. For instance, repeated unintentional injuries may prompt trauma surgeons to refer their patient for a psychiatric assessment and ADHD treatment when appropriate. Mental health specialists in turn should be able to consider medical issues and refer to medical physicians, especially when ADHD symptoms are subsequent or aggravated by a medical concern (e.g., sleep disorder). Of note, our results showing significant associations during early childhood point to the need for early screening, when prevention and early treatment strategies may be more effective. This has important implications for service organization and delivery, pointing to the need for an effective integrated care model encompassing mental and general healthcare.

Conclusions

This study shows that medical concerns and ADHD symptoms are significantly intertwined from early developmental stages onwards until adolescence, and mostly beyond the influence

of confounders. It is important to gain insights into the longitudinal links, mediating and moderating effects, and the causal mechanisms underpinning these associations because of their relevance for improving the treatment of the physical and mental health conditions that co-occur in childhood and adolescence.

Acknowledgements

M Boivin and R Tremblay report holding a Canada Research Chair in Child Development funded by the CIHR. S Côté reports being a research fellow of the Fonds de Recherche du Québec. R Tremblay reports being funded by the Canadian Institute of Advanced Research. All other authors declare no competing interests. S Cortese reports funding from the National Institute of Health Research (NIHR)

Contributors

C Galera and S Cortese contributed to the literature search, data analysis, data interpretation, and writing. M Orri, J van Der Waerden, and M Melchior, contributed to the data interpretation and writing. Ophélie Collet contributed to the data analysis, data interpretation and writing. M Boivin, S Côté, and R Tremblay contributed to the study design, data collection, data interpretation and writing. S Côté had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding/Support

The larger Québec Longitudinal Study of Child Development was supported by the Québec Government's Ministry of Health, Ministry of Education, and Ministry of Family Affairs, The Lucie and André Chagnon Foundation, the Robert-Sauvé Research Institute of Health and Safety at Work, and the Québec Statistics Institute. Additional funding was received from the Fonds de Recherche du Québec–Santé, the Fonds de Recherche du Québec–Société et Culture, Canada's Social Science and Humanities Research Council, the Canadian Institutes of Health Research, the St. Justine Research Center, and the French National Research Agency (ANR).

Role of the funder/support

Québec Statistics Institute collected data. The sponsors had no role in the design and conduct of the study; management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Patient and Public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

REFERENCES

- 1.Momen NC, Plana-Ripoll O, Agerbo E, Benros ME, Børghlum AD, Christensen MK, et al. Association between Mental Disorders and Subsequent Medical Conditions. *N Engl J Med.* 2020;382(18):1721-31.
- 2.DE Hert M, Correll CU, Bobes J, Cetkovich-Bakmas M, Cohen D, Asai I, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. *World Psychiatry.* 2011;10(1):52-77.
- 3.Dayan CM, Panicker V. Hypothyroidism and depression. *Eur Thyroid J.* 2013;2(3):168-79.
- 4.Chen MH, Wei HT, Bai YM, Huang KL, Ko NY, Su TP et al. Sexually transmitted infection among adolescents and young adults with bipolar disorder: a nationwide longitudinal study. *J Clin Psychiatry* 2019; 80(2):18m12199.
- 5.Druss BG, Walker ER. Mental disorders and medical comorbidity. *Synth Proj Res Synth Rep.* F2011;(21):1-26.
- 6.Brainstorm consortium. Analysis of shared heritability in common disorders of the brain. *Science.* 2018;360(6395):eaap8757.
- 7.Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. *International Journal of Epidemiology.* 2014;43(2):434-42.
- 8.Thomas R, Sanders S, Doust J, Beller E, Glasziou P. Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Pediatrics.* 2015;135(4):e994-1001.

9. Doshi JA, Hodgkins P, Kahle J, Sikirica V, Cangelosi MJ, Setyawan J, et al. Economic impact of childhood and adult attention-deficit/hyperactivity disorder in the United States. *J Am Acad Child Adolesc Psychiatry*. 2012;51(10):990-1002.e2.
10. Holden SE, Jenkins-Jones S, Poole CD, Morgan CL, Coghill D, Currie CJ. The prevalence and incidence, resource use and financial costs of treating people with attention deficit/hyperactivity disorder (ADHD) in the United Kingdom (1998 to 2010). *Child Adolesc Psychiatry Ment Health*. 2013;7(1):34.
11. Schatz DB, Rostain AL. ADHD with comorbid anxiety: a review of the current literature. *J Atten Disord*. 2006;10(2):141-9.
12. Cortese S, Faraone SV, Konofal E, Lecendreux M. Sleep in children with attention-deficit/hyperactivity disorder: meta-analysis of subjective and objective studies. *J Am Acad Child Adolesc Psychiatry*. 2009;48(9):894-908.
13. Cortese S, Moreira-Maia CR, St. Fleur D, Morcillo-Peñalver C, Rohde LA, Faraone SV. Association Between ADHD and Obesity: A Systematic Review and Meta-Analysis. *American Journal of Psychiatry*. 2016;173(1):34-43.
14. Nigg JT, Johnstone JM, Musser ED, Long HG, Willoughby MT, Shannon J. Attention-deficit/hyperactivity disorder (ADHD) and being overweight/obesity: New data and meta-analysis. *Clin Psychol Rev*. 2016;43:67-79.
15. Chen Q, Hartman CA, Haavik J, Harro J, Klungsøyr K, Hegvik TA, et al. Common psychiatric and metabolic comorbidity of adult attention-deficit/hyperactivity disorder: A population-based cross-sectional study. *Plos One*. 2018;13(9):e0204516.
16. Cortese S, Sun S, Zhang J, Sharma E, Chang Z, Kuja-Halkola R, et al. Association between attention deficit hyperactivity disorder and asthma: a systematic review and meta-analysis and a Swedish population-based study. *Lancet Psychiatry*. 2018;5(9):717-26.
17. Schans J van der, Çiçek R, de Vries TW, Hak E, Hoekstra PJ. Association of atopic diseases and attention-deficit/hyperactivity disorder: A systematic review and meta-analyses. *Neurosci Biobehav Rev*. 2017;74(Pt A):139-48.

18. Kase BE, Rommelse N, Chen Q, Li L, Andersson A, Du Rietz E, Vos M, Cortese S, Larsson H, Hartman CA. Longitudinal Associations Between Symptoms of ADHD and BMI From Late Childhood to Early Adulthood. *Pediatrics*. 2021;147(6):e2020036657.
19. Cortese S, Adamo N, Del Giovane C, Mohr-Jensen C, Hayes AJ, Carucci S, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2018;5(9):727-38.
20. Cortese S, Castellanos FX. The relationship between ADHD and obesity: implications for therapy. *Expert Rev Neurother*. 2014; 14(5):473-479.
21. Cortese S. The Association between ADHD and Obesity: Intriguing, Progressively More Investigated, but Still Puzzling. *Brain Sci*. 2019;9(10):256.
22. Orri M, Boivin M, Chen C, Aunon-Munoz S, Geoffroy M-C, Ouellet-Morin I, et al. Cohort Profile: Quebec Longitudinal Study of Child Development (QLSCD). *Soc Psychiatry Psychiatr Epidemiol*. 2021;56(5):883-894.
23. Statistics Canada. Longitudinal Survey of Children and Youth (NLSCY). 14 mai 2009; Disponible sur: <http://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&SDDS=4450>
24. Achenbach T. DC: 0-3R La classification diagnostique - édition révisée. *Médecine et Hygiène*; 2009. 120 p.
25. Offord DR, Boyle MH, Racine Y. Ontario Child Health Study: correlates of disorder. *J Am Acad Child Adolesc Psychiatry*. 1989;28(6):856-60.
26. Tremblay RE, Desmarais-Gervais L, Gagnon C, Charlebois P. The Preschool Behaviour Questionnaire: Stability of its Factor Structure Between Cultures, Sexes, Ages and Socioeconomic Classes. *International Journal of Behavioral Development*. 1987;10(4):467-84.
27. Côté SM, Orri M, Brendgen M, Vitaro F, Boivin M, Japel C, et al. Psychometric properties of the Mental Health and Social Inadaptation Assessment for Adolescents (MIA) in a

- population-based sample. *International Journal of Methods in Psychiatric Research*. 2017;26(4):e1566.
28. Goodman R. The Strengths and Difficulties Questionnaire: a research note. *J Child Psychol Psychiatry*. 1997;38(5):581-6.
29. Faraone SV, Asherson P, Banaschewski T, Biederman J, Buitelaar JK, Ramos-Quiroga JA, et al. Attention-deficit/hyperactivity disorder. *Nat Rev Dis Primers*. 2015;1:15020.
30. Galéra C, Côté SM, Bouvard MP, Pingault JB, Melchior M, Michel G, et al. Early Risk Factors for Hyperactivity-Impulsivity and Inattention Trajectories From Age 17 Months to 8 Years. *Arch Gen Psychiatry*. 2011;68(12):1267-75.
31. Romano E, Tremblay RE, Farhat A, Côté S. Development and Prediction of Hyperactive Symptoms From 2 to 7 Years in a Population-Based Sample. *Pediatrics*. 2006;117(6):2101-10.
32. Vergunst F, Tremblay RE, Galera C, Nagin D, Vitaro F, Boivin M, et al. Multi-rater developmental trajectories of hyperactivity-impulsivity and inattention symptoms from 1.5 to 17 years: a population-based birth cohort study. *Eur Child Adolesc Psychiatry*. 2019;28(7):973-83.
33. Leblanc N, Boivin M, Dionne G, Brendgen M, Vitaro F, Tremblay RE, et al. The development of hyperactive-impulsive behaviors during the preschool years: the predictive validity of parental assessments. *J Abnorm Child Psychol*. 2008;36(7):977-87.
34. Statistics Canada. Overview of Survey Instruments for 1994-1995 Data Collection, Cycle 1. Ottawa, ON: Statistics Canada; 1995.
35. Radloff LS. The CESD-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1:385-401.
36. Haslbeck JMB, Waldorp LJ. How well do network models predict observations? On the importance of predictability in network models. *Behav Res Methods*. 2018;50(2):853-61.

37. Efron B. Bayesian inference and the parametric bootstrap. *Ann Appl Stat.* 2012;6(4):1971-97.
38. VanderWeele, T.J. Principles of confounder selection. *Eur J Epidemiol.* 2019;34:211-219.
39. Angriman M, Cortese S, Bruni O. Somatic and neuropsychiatric comorbidities in pediatric restless legs syndrome: A systematic review of the literature. *Sleep Med Rev.* 2017;34:34-45.
40. Auvin S, Wirrell E, Donald KA, Berl M, Hartmann H, Valente KD, et al. Systematic review of the screening, diagnosis, and management of ADHD in children with epilepsy. Consensus paper of the Task Force on Comorbidities of the ILAE Pediatric Commission. *Epilepsia.* 2018;59(10):1867-80.
41. Ruiz-Goikoetxea M, Cortese S, Aznarez-Sanado M, Magallón S, Alvarez Zallo N, Luis EO, et al. Risk of unintentional injuries in children and adolescents with ADHD and the impact of ADHD medications: A systematic review and meta-analysis. *Neurosci Biobehav Rev.* 2018;84:63-71.
42. Muskens JB, Velders FP, Staal WG. Medical comorbidities in children and adolescents with autism spectrum disorders and attention deficit hyperactivity disorders: a systematic review. *Eur Child Adolesc Psychiatry.* 2017;26(9):1093-103.
43. Buske-Kirschbaum A, Trikojat K, Tesch F, Schmitt J, Roessner V, Luksch H, et al. Altered hypothalamus-pituitary-adrenal axis function: A relevant factor in the comorbidity of atopic eczema and attention deficit/hyperactivity disorder? *Psychoneuroendocrinology.* 2019;105:178-86.
44. Trikojat K, Buske-Kirschbaum A, Schmitt J, Plessow F. Altered performance in attention tasks in patients with seasonal allergic rhinitis: seasonal dependency and association with disease characteristics. *Psychol Med.* 2015;45(6):1289-99.
45. Swanson JM, Volkow ND. Lessons From the 1918 Flu Pandemic: A Novel Etiologic Subtype of ADHD? *Journal of the American Academy of Child & Adolescent Psychiatry.* 2021;60(1):1-2.

46. Brikell I, Ghirardi L, D'Onofrio BM, Dunn DW, Almqvist C, Dalsgaard S, et al. Familial Liability to Epilepsy and Attention-Deficit/Hyperactivity Disorder: A Nationwide Cohort Study. *Biol Psychiatry*. 2018;83(2):173-80.
47. Chau YCY, Peng S-M, McGrath CPJ, Yiu CKY. Oral Health of Children With Attention Deficit Hyperactivity Disorder: Systematic Review and Meta-Analysis. *J Atten Disord*. 2017;1087054717743331.
48. Kerr DCR, Lunkenheimer ES, Olson SL. Assessment of child problem behaviors by multiple informants: a longitudinal study from preschool to school entry. *J Child Psychol Psychiatry*. 2007;48(10):967-75.
49. Green JG, DeYoung G, Wogan ME, Wolf EJ, Lane KL, Adler LA. Evidence for the reliability and preliminary validity of the Adult ADHD Self-Report Scale v1.1 (ASRS v1.1) Screener in an adolescent community sample. *Int J Methods Psychiatr Res*. 2019;28(1):e1751.
50. Salbach-Andrae H, Klinkowski N, Lenz K, Lehmkuhl U. Agreement between youth-reported and parent-reported psychopathology in a referred sample. *Eur Child Adolesc Psychiatry*. 2009;18(3):136-43.
51. Cortese S, Holtmann M, Banaschewski T, Buitelaar J, Coghill D, Danckaerts M, et al. Practitioner review: current best practice in the management of adverse events during treatment with ADHD medications in children and adolescents. *J Child Psychol Psychiatry*. 2013;54(3):227-46.

**Table 1. Comparisons between three study samples and initial sample at recruitment on key variables^a
(QLSCD, Canada)**

Characteristics [no (%) or mean (SD)]	Initial sample (n=2,120)	Early childhood sample (n=2,057)	p ^b	Middle childhood sample (n=1,631)	p ^b	Adolescent sample (n=1,548)	p ^b
Sex of child (male)	1080 (50.9)	1043 (50.7)	0.88	791 (48.5)	0.14	741 (47.9)	0.07
Low birth weight (<2500g)	71 (3.4)	69 (3.4)	0.99	56 (3.4)	0.89	48 (3.1)	0.68
Family socioeconomic status	-0.02 (0.97)	-0.02 (0.97)	1	0.01 (0.96)	0.32	0.04 (0.94)	0.09
Maternal age (y) at childbirth	29.30 (5.23)	29.34 (5.22)	0.82	29.27 (5.23)	0.88	29.35 (5.15)	0.79
Paternal age (y) at childbirth	32.26 (5.64)	32.22 (5.60)	0.84	32.24 (5.52)	0.91	32.25 (5.46)	0.97
Family dysfunction score	1.71 (1.46)	1.70 (1.45)	0.82	1.70 (1.44)	0.98	1.69 (1.44)	0.90
No intact family (single or blended)	406 (19.2)	388 (18.9)	0.81	301 (18.5)	0.58	284 (18.4)	0.53
Immigrant mother	253 (11.9)	221 (10.8)	0.23	138 (8.5)	<0.001	141 (9.1)	<0.01
Maternal depression	1.40 (1.34)	1.40 (1.34)	0.88	1.39 (1.33)	0.75	1.37 (1.31)	0.50
Maternal adolescent anti-sociality	0.21 (0.49)	0.21 (0.49)	0.98	0.21 (0.48)	0.94	0.21 (0.48)	0.99
Paternal depression	1.00 (0.96)	1.00 (0.96)	0.95	1.00 (0.94)	0.92	1.00 (0.95)	0.79
Paternal adolescent anti-sociality	0.56 (0.80)	0.56 (0.80)	0.92	0.57 (0.81)	0.60	0.58 (0.82)	0.40

^a All variables measured when child was 5 months of age. Data compiled from final master file of Québec Longitudinal Study of Child Development (1998-2015), Québec Government, Québec Statistics Institute.

^b p values based on unpaired t test or Mann-Whitney test for continuous variables and χ^2 test for categorical variables.

Table 2. Unadjusted associations between medical conditions and ADHD symptoms by age period (QLSCD, Descriptive statistics)

	Early childhood 5 months to 5 years (n=2,057)			Middle childhood 6 to 12 years (n=1,631)			Adolescence 13 to 17 years (n=1,548)		
	% (N)	ADHD scores Mean (SD)	SMD ^c	% (N)	ADHD scores Mean (SD)	SMD ^c	% (N)	ADHD scores Mean (SD)	SMD ^c
Atopic problems^a									
Asthma	14.9 (293/1961)	Yes: 4.12 (1.68) No: 3.77 (1.57)	0.22***	23.8 (383/1608)	Yes: 3.22 (2.39) No: 2.81 (2.19)	0.18**	26.8 (404/1509)	Yes: 3.23 (1.79) No: 2.99 (1.70)	0.14*
Food or digestive allergies	3.1 (54/1759)	Yes: 3.95 (1.82) No: 3.85 (1.57)	0.06	7.7 (122/1587)	Yes: 3.36 (2.37) No: 2.87 (2.23)	0.22*	9.7 (147/1509)	Yes: 3.04 (1.66) No: 3.06 (1.73)	-0.01
Eczema	7.6 (149/2054)	Yes: 3.76 (1.62) No: 3.86 (1.57)	-0.06	15.5 (246/1583)	Yes: 3.00 (2.38) No: 2.89 (2.22)	0.05	19.7 (297/1509)	Yes: 3.11 (1.71) No: 3.04 (1.73)	0.04
BMI^b	14.5 (298/2054)	Yes: 4.03 (1.66) No: 3.77 (1.60)	0.16**	12.1 (197/1622)	Yes: 3.27 (2.09) No: 2.85 (2.25)	0.19**	13.1 (201/1537)	Yes: 3.10 (1.80) No: 3.06 (1.70)	0.03
Epilepsy^a	0.2 (5/2057)	Yes: 6.15 (1.75) No: 3.80 (1.61)	1.46**	0.7 (11/1587)	Yes: 3.76 (3.34) No: 2.90 (2.23)	0.38	0.8 (12/1509)	Yes: 3.94 (1.16) No: 3.05 (1.73)	0.51*
Other chronic problems									
Diabetes ^a	/	/	/	0.4 (7/1587)	Yes: 2.71 (2.35) No: 2.91 (2.24)	-0.09	0.7 (10/1509)	Yes: 2.01 (1.94) No: 3.06 (1.72)	-0.61*
Hypertension ^b	/	/	/	0.1 (1/1438)	Yes: 5.42 (NA) No: 2.90 (2.23)	/	0.5 (8/1509)	Yes: 3.00 (1.75) No: 3.06 (1.73)	-0.03

Migraine ^b	/	/	/	1.9 (25/1351)	Yes: 3.39 (2.31) No: 2.87 (2.23)	0.23	5.3 (80/1509)	Yes: 3.27 (1.61) No: 3.04 (1.73)	0.13
Cholesterol ^b	/	/	/	1.2 (17/1438)	Yes: 2.78 (2.73) No: 2.90 (2.22)	-0.06	1.7 (26/1509)	Yes: 3.32 (1.58) No: 3.05 (1.73)	0.15
Infections									
Dental caries ^a	14.0 (271/1933)	Yes: 3.99 (1.56) No: 3.79 (1.59)	0.13	72.5 (1111/1532)	Yes: 3.01 (2.27) No: 2.62 (2.11)	0.17**	76.1 (971/1276)	Yes: 3.06 (1.68) No: 2.82 (1.71)	0.14*
Acute infections ^b	18.9 (381/2014)	Yes: 4.07 (1.69) No: 3.76 (1.57)	0.20***	17.4 (279/1608)	Yes: 2.97 (2.36) No: 2.90 (2.22)	0.03	10.4 (157/1509)	Yes: 3.31 (1.59) No: 3.02 (1.74)	0.17*
Injuries^b									
Injuries ^b	24.2 (497/2057)	Yes: 4.17 (1.56) No: 3.68 (1.61)	0.31***	19.2 (304/1587)	Yes: 3.11 (2.25) No: 2.86 (2.24)	0.11	31.6 (477/1509)	Yes: 3.22 (1.71) No: 2.98 (1.73)	0.14*
Burn ^b	1.3 (26/2057)	Yes: 3.74 (1.77) No: 3.80 (1.61)	-0.04	0.7 (11/1559)	Yes: 3.88 (2.97) No: 2.89 (2.22)	0.44	1.1 (17/1509)	Yes: 3.31 (1.51) No: 3.05 (1.73)	0.15
Poisoning ^b	0.6 (12/2057)	Yes: 4.16 (2.40) No: 3.80 (1.61)	0.22	0.3 (4/1559)	Yes: 3.68 (2.65) No: 2.89 (2.23)	0.35	0.4 (6/1509)	Yes: 4.68 (0.81) No: 3.05 (1.72)	0.94**
Sleep problems^b									
Night terrors	3.2 (66/2042)	Yes: 4.64 (1.78) No: 3.78 (1.59)	0.54***	1.1 (17/1544)	Yes: 3.99 (2.34) No: 2.87 (2.22)	0.50*	0.4 (6/1375)	Yes: 4.17 (1.38) No: 3.02 (1.69)	0.68
Bruxism	10.3 (210/2042)	Yes: 4.36 (1.66) No: 3.74 (1.58)	0.39***	16.3 (252/1542)	Yes: 3.10 (2.30) No: 2.85 (2.21)	0.12	8.0 (110/1370)	Yes: 3.21 (1.76) No: 3.01 (1.69)	0.12
Sleepwalking	10.0 (199/1997)	Yes: 4.35 (1.57) No: 3.76 (1.59)	0.37***	22.7 (350/1544)	Yes: 3.20 (2.28) No: 2.79 (2.20)	0.19**	13.2 (182/1374)	Yes: 3.22 (1.7) No: 2.99 (1.68)	0.13
Snoring	18.0 (370/2054)	Yes: 4.20 (1.57)	0.30***	13.6 (201/1480)	Yes: 2.81 (2.19)	-0.03	/	/	/

		No: 3.72 (1.61)			No: 2.87 (2.20)				
Restless legs syndrome	22.4 (438/1952)	Yes: 4.26 (1.64) No: 3.71 (1.55)	0.35***	21.6 (331/1534)	Yes: 3.34 (2.39) No: 2.77 (2.16)	0.26***	12.2 (167/1368)	Yes: 3.44 (1.74) No: 2.97 (1.67)	0.28***
Short sleep duration	24.7 (492/1992)	Yes: 3.94 (1.61) No: 3.78 (1.58)	0.11*	21.4 (330/1541)	Yes: 2.89 (2.08) No: 2.89 (2.27)	0.00	15.8 (218/1378)	Yes: 3.25 (1.68) No: 2.98 (1.69)	0.16*

^a Cumulative frequency across periods

^b Frequency for index period

^c SMD: standardized mean difference, based on Cohen's d statistic (very small when <0.20; small: 0.20-0.50; medium: 0.50-0.80; large: 0.80-1.20; very large: 1.20-2.0; huge: > 2.0)

* p<0.05 ; ** p<0.01 ; *** p<0.001

ADHD: Attention-Deficit/Hyperactivity Disorder; BMI: Body Mass Index

Table 3. Associations of medical conditions with ADHD symptoms by age period (QLSCD, Multivariate statistics)

	Early Childhood 5 months to 5 years (n=2,057)			Middle childhood 6 to 12 years (n=1,631)			Adolescence 13 to 17 years (n=1,548)		
	β (95%CI)	β adjusted ^d (95%CI)	SMD adjusted	β (95%CI)	β adjusted ^d (95%CI)	SMD adjusted	β (95%CI)	β adjusted ^d (95%CI)	SMD adjusted
Atopic problems^a									
Asthma	0.35• (0.15, 0.56)	0.26• (0.06, 0.46)	0.17•	0.40• (0.15, 0.66)	0.21 (-0.02, 0.45)	0.11	0.23 (0.04, 0.43)	0.24 (0.04, 0.43)	0.14
Food or digestive allergies	0.07 (-0.37, 0.51)	0.12 (-0.31, 0.55)	0.07	0.49 (0.08, 0.90)	0.54• (0.17, 0.92)	0.27•	-0.01 (-0.31, 0.28)	-0.01 (-0.30, 0.28)	-0.01
Eczema	-0.10 (-0.39, 0.19)	-0.05 (-0.34, 0.23)	-0.03	0.11 (-0.19, 0.42)	0.20 (-0.07, 0.48)	0.10	0.07 (-0.15, 0.29)	0.08 (-0.14, 0.30)	0.05
BMI^b	0.26• (0.06, 0.46)	0.16 (-0.03, 0.36)	0.10	0.42 (0.09, 0.75)	0.27 (-0.03, 0.57)	0.13	0.04 (-0.22, 0.30)	0.00 (-0.26, 0.26)	0.00
Epilepsy^a	2.35• (0.94, 3.77)	2.05• (0.67, 3.43)	1.31•	0.88 (-0.45, 2.20)	0.83 (-0.38, 2.04)	0.41	0.86 (-0.12, 1.85)	0.89 (-0.09, 1.87)	0.52
Other chronic problems									
Diabetes ^a	/	/	/	-0.19 (-1.85, 1.47)	-0.17 (-1.68, 1.34)	-0.08	-0.99 (-2.06, 0.07)	-1.05 (-2.12, 0.01)	-0.61
Hypertension ^b	/	/	/	/	/	/	-0.03 (-1.22, 1.15)	-0.01 (-1.20, 1.18)	0.00
Migraine ^b	/	/	/	0.47 (-0.51, 1.46)	0.26 (-0.64, 1.16)	0.13	0.24 (-0.15, 0.63)	0.23 (-0.15, 0.62)	0.14
Cholesterol ^b	/	/	/	-0.06 (-1.12, 1.01)	0.05 (-0.93, 1.02)	0.02	0.27 (-0.40, 0.93)	0.27 (-0.39, 0.94)	0.16
Infections									
Dental caries ^a	0.21 (0.01, 0.42)	0.07 (-0.14, 0.28)	0.04	0.39• (0.14, 0.64)	0.13 (-0.10, 0.37)	0.06	0.24 (0.02, 0.46)	0.20 (-0.02, 0.42)	0.12
Acute infections ^b	0.32• (0.14, 0.50)	0.30• (0.12, 0.48)	0.19•	0.07 (-0.22, 0.36)	-0.02 (-0.29, 0.24)	-0.01	0.29 (0.01, 0.57)	0.29 (0.01, 0.58)	0.17
Injuries^b	0.49• (0.33, 0.65)	0.44• (0.28, 0.60)	0.28•	0.25 (-0.03, 0.53)	0.17 (-0.09, 0.42)	0.08	0.24 (0.06, 0.43)	0.29• (0.10, 0.48)	0.17•
Burn^b	-0.07 (-0.69, 0.56)	-0.16 (-0.77, 0.45)	-0.10	1.00 (-0.34, 2.33)	1.15 (-0.06, 2.36)	0.57	0.26 (-0.56, 1.08)	0.27 (-0.55, 1.09)	0.16

Poisoning ^b	0.36 (-0.56, 1.27)	0.28 (-0.61, 1.18)	0.18	0.64 (-1.57, 2.85)	0.34 (-1.68, 2.36)	0.17	1.60 (0.24, 2.96)	1.57 (0.21, 2.93)	0.92
Sleep problems^b									
Night terrors	0.88● (0.48, 1.28)	0.84● (0.46, 1.23)	0.54●	1.12 (0.05, 2.20)	0.72 (-0.26, 1.70)	0.35	1.10 (-0.26, 2.46)	1.08 (-0.28, 2.43)	0.63
Bruxism	0.63● (0.40, 0.86)	0.59● (0.36, 0.81)	0.38●	0.26 (-0.05, 0.57)	0.22 (-0.06, 0.51)	0.11	0.20 (-0.14, 0.55)	0.21 (-0.14, 0.55)	0.12
Sleepwalking	0.61● (0.37, 0.85)	0.49● (0.25, 0.72)	0.31●	0.40● (0.13, 0.67)	0.34● (0.09, 0.59)	0.17●	0.24 (-0.04, 0.51)	0.23 (-0.04, 0.51)	0.14
Snoring	0.49● (0.30, 0.67)	0.42● (0.25, 0.60)	0.27●	-0.06 (-0.39, 0.27)	-0.13 (-0.43, 0.18)	-0.06	/	/	/
Restless legs syndrome	0.57● (0.40, 0.75)	0.51● (0.34, 0.68)	0.32●	0.57● (0.30, 0.84)	0.39● (0.14, 0.64)	0.19●	0.49● (0.21, 0.77)	0.48● (0.20, 0.76)	0.28●
Short sleep duration ^c	0.18 (0.01, 0.34)	0.15 (-0.01, 0.31)	0.10	0.00 (-0.27, 0.27)	-0.07 (-0.32, 0.18)	-0.03	0.27 (0.02, 0.52)	0.27 (0.02, 0.52)	0.16

^a Cumulative frequency across periods

^b Frequency for index period

^c Sleep duration per day in hours: pre-school < 10; childhood < 9h30; adolescence < 8

^d Adjusted on sex of child, family socioeconomic status

ADHD: Attention-Deficit/Hyperactivity Disorder; BMI: Body Mass Index

● Multiple testing corrected p-values significant after correction for multiple testing via the Benjamini-Hochberg procedure