Title: Parent-reported symptoms of sleep disordered breathing is associated with increased behavioral problems at 2 years of age: The Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort study.

Tamana, Sukhpreet K, PhD[1]; Smithson, Lisa, PhD[1]; Lau, Amanda, MSc[1]; Mariasine, Jennifer, MA[2]; Young, Rochelle MScN[3]; Chikuma, Joyce, MSc[1], Lefebvre, Diana L, PhD[4]; Subbarao, Padmaja, MD[5,6]; Becker, Allan B, MD[7]; Turvey, Stuart E, MD PhD[8]; Sears, Malcolm R, MB[4]; CHILD Study Investigators[9]; Pei, Jacqueline, PhD[2]; Mandhane, Piush J, MD PhD[1].

[1]Departments of Pediatrics, University of Alberta;
[2]Educational Psychology, University of Alberta;
[3]Sleep Medicine, Alberta Health Services
[4]Division of Respirology, Department of Medicine, McMaster University;
[5]Department of Pediatrics, University of Toronto;
[6]Respiratory Medicine, Hospital for Sick Children;
[7]Department of Pediatrics and Child Health, University of Manitoba;
[8]Department of Pediatrics, University of British Columbia,
[9]Canadian Healthy Infant Longitudinal Development Study. A complete list of active investigators in the CHILD study is provided in the Supplementary Appendix.

Address where work was conducted
University of Alberta, Pediatrics
4-590, 11405-87 Avenue
Edmonton, AB, CAN T6G 1C9
780-407-2753

Corresponding Author
Dr. Piush Mandhane mandhane@ualberta.ca

Co-authors email address:
Dr. Sukhpreet K. Tamana, tamana@ualberta.ca
Dr. Lisa Smithson, smithson@ualberta.ca
Ms. Amanda Lau, al30@ualberta.ca
Ms. Jennifer Mariasine, jennifer.mariasine@ualberta.ca
Ms. Rochelle Young, Rochelle.young@albertahealthservices.ca
Ms. Joyce Chikuma, chikuma@ualberta.ca
Dr. Diana L Lefebvre, lefeb@mcmaster.ca
Dr. Padmaja Subbarao, padmaja.subbarao@sickkids.ca
Dr. Allan B. Becker, becker@umanitoba.ca
Dr. Stuart E. Turvey, sturvey@cfri.ca
Dr. Malcolm R. Sears, searsm@mcmaster.ca
Dr. Jacqueline Pei, jpei@ualberta.ca

Abstract

Objectives: To examine the association between the age of onset and duration of parent-reported symptoms of sleep disordered breathing (SDB) and behavioral problems at age two years.

Methods: Parent-reported SDB symptoms were assessed quarterly between three months and two years among 583 Canadian Healthy Infant Longitudinal Development (CHILD) Edmonton-site participants. Parent-reported SDB symptoms were clustered into phenotypes using group-based trajectory analysis based on age of onset and duration of symptoms. Home-based polysomnography (PSG) was completed at one year. The Child Behavior Checklist (CBCL) preschool-version (Mean T-score 50, standard deviation 10 points) assessed total, externalizing (attention), and internalizing (anxiety, depression) behaviors at two years.

Results: Four phenotypes were identified: no SDB (64.7%), early-onset SDB (15.7%, peak symptoms at 9 months), late-onset (14.2%, peak symptoms at 18 months), and persistent SDB symptoms (5.3%, peak symptoms from 3 through 24 months). Persistent SDB (9.5 points, 95%CI 1.7, 17.2; p=0.02) predicted the greatest magnitude of effect of total behavior problems, compared to children without SDB. Children with early-onset SDB (3.5 points, 95%CI 1.6, 5.4; $p \leq 0.001$) and late-onset SDB (6.1 points 95%CI 4.0, 8.3; $p \leq 0.001$) had increased total behavioral problems than children without SDB to two years. Additional analyses showed that the SDB phenotypes trajectories were important for internalizing but not for externalizing behavior problems. There were no significant associations between home-PSG and parent-reported behavior problems.

Conclusions: Findings suggest that the age of onset and duration of parent-reported SDB symptoms prior to age two years has adverse consequences for overall behavior problems.

Keywords: Sleep Disordered Breathing, Sleep Apnea, Behavior, Infants, Epidemiology, Population-based birth cohort

Statement of Significance.

Sleep disordered breathing (SDB) has adverse effects on behavior among school-aged children. It is unknown whether the age of onset and duration of SDB symptoms impact behavior in young children. Previous studies have generally assessed SDB symptoms annually using parent-

reported measurements. We examined associations between SDB phenotypes assessed as a trajectory of symptoms from 3 to 24 months using parent-reported 22-item sleep-related breathing disorder (SRBD) scale. Home polysomnography (PSG) was also completed at 12-months. We found that age of onset and duration of parent-reported SDB symptoms adversely effects behavioral development by two years of age. Our study supports early screening and intervention among young children with SDB to treat current behavioral problems and prevent behavioral morbidity in later childhood.

Introduction

Sleep disordered breathing (SDB), from habitual snoring to obstructive sleep apnea, affects up to 10% of children with a peak prevalence between two and eight years of age[1-3]. Neurobehavioral sequelae associated with SDB in school-aged children include poor learning, adverse executive functioning, and externalizing behavior problems such as attention deficit/hyperactivity disorder (ADHD) symptoms[4,5]. Less is known about the development of internalizing behavior problems such as anxiety and depression among children with SDB. The negative consequences of SDB may be irreversible; tonsil and adenoidectomy (T&A) for SDB in school-aged children produced no significant change on executive function[6,7] and only temporarily improved behavior[8,9]. T&A in preschool children has had more success, although results are mixed[10-18]. Determining the relationship between preschool SDB and subsequent neurobehavioral function has important implications for screening children and triaging limited pediatric surgical resources.

The spectrum of SDB during childhood may encompass overlapping phenotypes associated with a child's facial morphology, tonsil and adenoid growth, body habitus, and rhinitis symptoms [19]. The different SDB phenotypes, distinguished by age of onset and duration of symptoms, may be associated with different neurobehavioral consequences. The UK Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort showed that SDB prior to age two years predicts ADHD symptoms at seven years even after the resolution of SDB symptoms[20]. However, the ALSPAC cohort cannot determine preschool SDB phenotypes as they assessed SDB annually, did not use validated SDB questionnaires, and did not use objective measures of sleep or SDB.

We present findings from a sub-cohort within the Canadian Healthy Infant Longitudinal Development (CHILD) study[21] in which we explored whether the age of onset and duration of parent-reported SDB (SDB phenotypes) were associated with behavioral problems at age two years. We also examined whether current parent-reported symptoms of SDB at age two years were associated with increased behavioral problems. We hypothesized that children with earlier onset SDB would show increased behavioral problems compared to children without SDB.

Methods

Study Population

CHILD is a multi-center population-based longitudinal birth cohort study initially designed to examine gene-environment influences on the development of atopy and asthma. CHILD families in Edmonton participated in a sub-study examining the longitudinal relationship between sleep and neurodevelopment[21,22]. Pregnant mothers aged 18 and over were recruited in the second or third trimester, and children were seen at delivery, 3 months of age, and then annually. Parents completed questionnaires about family and child characteristics (i.e. socioeconomic status (SES), ethnicity, child gender), maternal and infant nutrition, and maternal stress at recruitment and then regularly throughout the larger CHILD study. In addition, CHILD Edmonton families also completed questionnaires about their child's sleep, and participated in a home-polysomnography (PSG) sleep study. CHILD Edmonton families also completed neurodevelopmental assessments and parent-reported behavioral questionnaire during 12 month and 24 month clinic visits. Informed consent was obtained from all mothers, and consenting fathers. CHILD study ethics approval was obtained from the University of Alberta Health Ethics Research Office (Pro00002099).

Study Variables

SDB (primary exposure variable): SDB was assessed quarterly from three months by parent-report using the 22-item sleep-related breathing disorder (SRBD) scale[23], based on the pediatric sleep questionnaire (PSQ). The SRBD scale[23] uses 22 yes/no items, which includes snoring, excessive daytime sleepiness, and ADHD symptoms.[24] The SRBD ratio was determined by dividing the sum of all 'yes' responses by the total number of non-missing items (yes or no). At each quarter, children were classified as having SDB if they had a SRBD ratio ≥ 0.33. SDB

was objectively assessed for one night at the one year study visit (mean age of 13.2 months (95%CI: 9.5, 22.2) using portable level three home polysomnography (PSG) (NOX-T3 portable sleep monitor). Home PSG was not undertaken at any other time point. The NOX-T3 PSG recorded pulse oximetry, real-time audio, and chest/abdominal respiratory inductance plethsymography[25]. NOX-T3 scoring was completed by Sleep Strategies using a scoring rubric based on the American Academy of Sleep Medicine (AASM) paediatric scoring guidelines[26] modified to reflect the channels available. Measures of apneas, hypopneas, apnea-hypopnea index (AHI), sleep duration, and total time in bed were obtained from the PSG.

Behavior Problems: Parents completed the Child Behavior Checklist (CBCL) 1½-5 preschool version[27] at two years. The CBCL is a standardized measure of childhood mental health and has good internal reliability and validity in a number of population settings[28,29]. The CBCL yields a T-score (adjusted for age) for total problems, internalizing problems, and externalizing problems composite scales[27,29]. The total behavior problems T-score (primary outcome) is the sum of the internalizing and externalizing composite scales, the sleep issues scale, perceived stress scale, and other problems not classified under the prior groups. The externalizing behavior problems T-score (secondary outcome) is the sum of the inattention and aggressiveness subscales. The internalizing behaviors problems T-score incorporates the withdrawal, somatic, and anxious/depressed subscales. The CBCL normative mean is 50 and higher scores indicate increased behavior problems. T-scores greater than 65 suggest clinical behavioral problems. As recommended by the CBCL manual, 10 points (1 standard deviation) change in a T-score greater than the normative mean of 50 is indicative of problematic behaviors in comparison to a non-clinical sample[27].

Covariates

Covariates associated with SDB or childhood behavior were assessed longitudinally (see online supplemental methods section for a more complete treatment of the covariates assessed).

Sleep times and duration: Sleep duration and sleep times were determined using the parent-reported Brief Infant Sleep Questionnaire[30] (BISQ) administered quarterly from 3 months of age. Total sleep time was the sum of daytime and nighttime sleep (hours and minutes). Trajectory patterns of sleep duration throughout the first two years of life are described in the

online supplement (see Figure S2-S3). Sleep duration was objectively assessed at 12 months of age by PSG.

Social-emotional development and language: Social-emotional (caregiver questionnaire) and language development (objectively evaluated by trained research assistants) were assessed using the Bayley Scale of Infant Development Third Edition (BSID-III)[31] at age 12 months and 24 months. The BSID-III composite score (*Mean* 100, *SD*=15) for the social-emotional development scale and the language scale were included as potential confounders.

Statistical Analysis

We used STATA Traj[32,33] (December 2016 Version), to identify and assign SDB phenotypes to each child based on age of onset and duration of parent-reported SDB symptoms between three and 24 months, consistent with prior research[34-37]. We describe the SDB trajectories in detail separately[38]. A similar analysis was completed to determine sleep duration trajectories based on the BISQ[39]. Analyses of the behavior data were conducted using the CBCL total behavior problem, externalizing behavior problems, and internalizing behavior problem composite scales. The CBCL total behavior problem T-score was re-scored to exclude the sleep problem questions to avoid misinterpretation of the study findings. Univariate regression analysis was used to independently examine the association between SDB, sleep duration, environmental, and child and family characteristics associated with total behavior problems (primary outcome), externalizing behavior (secondary outcome), and internalizing behavior (secondary outcome) T-scores (continuous) at two years of age.

Separate multivariate regression analyses were used to model the relationship between total behavioral problems and 1) current parent-reported SDB symptoms at age two years (SDB as a dichotomous predictor) and 2) SDB phenotypes based on parent-report up to two years using trajectory analysis while controlling for sleep duration and other factors previous associated with SDB or behavior. Multivariate analyses included an adjustment for reported versus actual sleep duration using the ratio of 12 months parent-reported nighttime sleep duration to nighttime sleep duration measured at 12 months of age by home PSG. Results for both models (current SDB and SDB phenotypes) are presented with a lower Bayesian information criteria (BIC) indicating better model fit. Data were analyzed using Stata 14 (STATA corp.).

Results

Of the 822 CHILD Edmonton participants originally consented, 712 (87%) were still enrolled at two years of age, of whom 583 (81%; Table 1) had CBCL data at 24 months. Those with CBCL data had higher family income, less divorce or separation, were more often Caucasian, and somewhat older mothers (see Table 1). There were no significant differences between participants with and without CBCL data in the proportion of children with parent-reported SDB at two years of age (6.8% vs. 7.4%; $p \geq 0.05$) or parent-reported sleep duration time at age two years (Mean 12.6 hours; 95%CI 12.2, 12.9 vs. 12.6 hours; 95%CI 12.5, 12.7, $p > 0.05$). Among our sample of children with behavior data only 1 participant was missing sleep data.

Severe behavioral problems (mean CBCL total behavior T-score above 65) were present in 44 of 583 children (7.5%) with 38 children (6.5%) having significant externalizing concerns (T-score above the clinical cutoff of 65) and 31 children (5.3%) having a CBCL internalizing T-score above the clinical cutoff of 65. Males exhibited significantly higher CBCL externalizing behavior T-scores (Mean = 46.9, *SD* = 9.54) than females (Mean = 44.96, *SD* = 9.04, $p \leq 0.01$). There was no difference by gender for internalizing problems.

SDB Trajectories: We describe the results for the development of the SDB trajectories groups in detail elsewhere[38]. Trajectory analysis yielded four independent phenotypes with participants assigned to only one group (Figure S1). Children with no SDB (64.7%) had a mean SRBD ratio of 0.10 (SD=0) at twelve months and 0.14 (SD 0.11) at 24 months. Children identified as developing SDB included three phenotypic groups: early-onset SDB symptom (15.7%), with a peak of SDB symptoms at nine months (Mean SRBD = 0.29, SD 0.12), late-onset SDB symptoms (14.2%) with a peak of SDB symptoms at 18 months (Mean SRBD = 0.34, SD 0.09), and persistent SDB (5.3%) with peak symptoms from three months of age (mean SRBD=0.32, SD 0.16) through to 24 months of age with a mean SRBD of 0.43 (SD 0.14). Children classed in the early-onset SDB group had a positive SRBD ratio at one time point from 3 months to 24 months.

Univariate results: Children with current parent-reported SDB symptoms and children in each of the three SDB phenotypes, derived from parent-report, showed increased behavioral morbidity compared to children with no SDB symptoms (refer to table S4). Home-PSG derived measures

of AHI, desaturation index, and sleep efficiency, assessed approximately one year of age, were not significantly associated with increased behavioral problems (refer to table S3).

Multivariate results: Based on our univariate results, we examined the influence of parent-reported symptoms of SDB on behavioral morbidity in adjusted multivariate analysis.

CBCL Primary Outcome Variable

Total Behavior Problems Composite T-Score: Two multivariate analyses were conducted using current SDB symptoms at age two years (Table 2; model 1) and SDB phenotypes identified using trajectory analysis (model 2) as predictors of total behavioral morbidity. The lower BIC for model 2 (BIC= 4153.2 vs. 4172.6) suggests that the duration and pattern of SDB phenotypes had a greater explanatory impact on total behavior problems at age two years than analyzing for current SDB symptoms alone.

Children with persistent SDB had a 9.5 points increase in CBCL total behavior T-score (95%CI 1.7, 17.2, $p<0.05$; table 2 model 2), compared to children without SDB symptoms. The influence of persistent SDB symptoms on total behavioral scores indicate a clinically significant change in behavior problems (clinical cut-point defined as a 10 point change (one standard deviation)[27]). While, children with late-onset SDB had a 6.1 points increase (95%CI 4.0, 8.3, $p\leq0.001$), and those with early-onset SDB had a 3.5 (95%CI 1.6, 5.4, $p\leq0.001$) points increase, compared to children without SDB. Each of the three SDB groups were still significantly associated ($p<0.05$) with increased total behavioral morbidity in a sensitivity analysis when both SDB phenotypes and current SDB at age two years were included in the same regression (see table S1 for details). The impact of SDB phenotypes remained significant even after adjusting for sleep duration trajectories, maternal stress at 24 months, social emotional difficulties at age 12 months, and language difficulties at age 24 months.

Short total sleep duration trajectories were significantly associated with increased total behavioral problems, with a 2.3 points increase in CBCL total behavior T-score (95%CI 0.4, 4.1, $p=0.02$) compared to intermediate sleepers (reference). Decline to short sleepers (0.2 points, 95%CI -1.6, 2.0, $p>0.05$) and long sleepers (-0.7 points, 95%CI -2.4, 0.9, $p>0.05$) showed no significant effect on their CBCL total behavior T-score compared to intermediate sleepers.

CBCL Secondary Outcome Variables

Externalizing Behavior Problems Composite Score T-Score: The lower BIC for the current SDB model suggests that having current symptoms at age two years had slightly greater explanatory capacity for externalizing behavior problems by age two years than the trajectory of SDB phenotypes based on age of onset and duration of SDB symptoms (BIC = 4199.6 vs 4204.3). Children with current SDB symptoms at two years had a 5.8 points increase in externalizing behavior T-score (95%CI 3.7, 8.0, $p \leq 0.001$; table 3; model 1) compared to children without current SDB symptoms at that age. The magnitude of effect of current SDB at two years on externalizing behavior was greater than all other significant factors in multivariate analysis. Only daytime sleep duration trajectories were significantly associated with increased externalizing behavior problems (table 3).

Internalizing Behavior Problems Composite T-Score: In contrast to externalizing behavior, SDB phenotypes had greater explanatory capacity for internalizing behavioral problems than current SDB symptoms alone (BIC= 4192.9 Vs 4206.4) (table 4). Children with early-onset SDB had a 3.8 (95%CI 1.9, 5.8, $p \leq 0.001$) points increase, while those with late-onset SDB symptoms had a 3.5 (95%CI 1.3, 5.7, $p \leq 0.001$) points increase, compared to children with no SDB symptoms. In a sensitivity analysis, only the early SDB trajectory group remained a significant predictor of internalizing morbidity at age two years ($p < 0.001$) after controlling for current SDB symptoms) (see table S2 for details).

Short sleep duration trajectories were significantly associated with worse internalizing behavioral problems (2.9 points 95%CI 1.0, 4.8 $p \leq 0.001$). Maternal depression, parenting dysfunction, social emotional difficulties, and language difficulties at age 24 months had significant but minimal effects on increased internalizing behavior problems at two years of age in adjusted analysis (table 4).

Discussion

This analysis of data from a population-based birth cohort study showed that parent-reported SDB symptoms during the first two years of life are associated with overall increased behavior problems at two years of age. Specifically, we identified that children with current SDB symptoms exhibited greater externalizing behavior problems such as inattention by age two years. In contrast, using a trajectory analysis to identify SDB phenotypes, we showed differing impacts of early-onset, late-onset, and persistent SDB symptoms on increased internalizing

behavior problems such as anxiety and depression by two years of age. The effects of parent-reported SDB on behavior exceeded those of any other potential covariate controlled for in our study including sleep duration, maternal stress, maternal nutrition during pregnancy, and family socioeconomic status. Similar to previous reports in younger children[40], we found that adverse behavioral outcomes related more to parent-reported SDB symptoms than PSG derived parameters.

The finding that the onset and duration of parent-reported SDB symptoms, during an early critical period in development, impacts early childhood total behavioral problems helps clarify the findings of previous studies. Our data suggest that children with persistent SDB to age two years are at risk for developing clinically relevant behavior problems (10 points increase or one standard deviation change in score). Prior reports of SDB effects on early childhood behavior have generally been from cross-sectional studies or referred clinical samples with limited control for potential confounders[40-42]. In their population-based cross-sectional survey of a birth cohort, Gottlieb et al[43] found increased behavior problems among preschool children with SDB compared to children without SDB even after adjusting for social factors. In contrast, a separate cross-sectional study[44] did not show increased behavior problems among preschoolers aged 3 to 4 years with current symptoms of snoring. However, ours is the first study to examine associations between both current SDB and trajectories of SDB symptoms determined using a gold standard parent measure, an objective assessment of SDB using PSG, and behavior problems in young children.

Our study further identified differences in the effects of SDB upon externalizing (e.g. ADHD symptoms) and internalizing behavior problems (e.g. anxiety/depression). Consistent with prior work, we found that current SDB symptoms at age two years are associated with increased externalizing behavior problems. The ALSPAC study[20] found that children with either 'early' SDB (SDB symptoms prior 18 months that then abated) or children with persistent SDB (symptoms that peak at 30 months and persist) both predicted ADHD symptoms at age 4 to 7 years. In this cohort, our data suggests that children with SDB symptoms that peak at age two years may be at risk for externalizing behavioral morbidity beginning in early childhood.

Increased internalizing behavior problems have been reported from clinical pediatric SDB cases[40,45,46]. We found that the SDB phenotypes (early- and late–onset) were significantly associated with increased internalizing behavior problems in adjusted analysis. Our findings

suggest that the age of onset and duration of SDB symptoms are important determinants of internalizing behaviors. The ALSPAC study[20] only found that children with 'later' SDB symptoms (symptoms that peak at 57 months) had the strongest effect on increased emotional difficulties at age 4 to 7 years. In contrast to ALSPAC, we identified a third group of children with SDB (i.e. persistent SDB symptoms), and showed differential effects on behavior for all three SDB groups.

This is the first population-based study to examine associations between SDB and behavior in the first two years of life. There are several strengths associated with this present study including large sample size and repeated longitudinal data. Prior studies have lacked objective measures of sleep using PSG, sufficient frequency of data to examine associations between SDB phenotypes and behavior[47-49], and measures of sleep duration. We examined the influence of SDB symptoms on behavior while controlling for several potential family and child, maternal, and environmental covariates previously shown to be associated with sleep or behavior. This included controlling for social emotional difficulties identified at age 12 months and language difficulties at 24 months assessed using a standardized tool. Finally, behavioral problems identified in our unselected population-based sample are unlikely to reflect a referral bias and thereby strengthens the evidence from studies reporting on SDB adverse effects on behavior.

We are unable to determine whether sleep problems precede internalizing behavior problems[50,51]. While we objectively assessed sleep duration using home-PSG, we acknowledge assessing sleep time via a single night of PSG may not be representative of the child's actual sleep duration. Although we included a ratio of parent-reported to PSG assessed sleep duration in the analysis, the majority of sleep assessments were measured using a validated parent-report which may under-estimate sleep duration and over-report sleep problems in young children[52]. The child's environment and behavior was assessed by parent-report, which may be biased for social-desirability. Our study is unlikely to be sufficiently powered to investigate the effect of persistent SDB symptoms on behavior. Also, we only found small statistical differences between the effects of current SDB symptoms and age and duration of SDB symptoms hence stressing the importance of current SDB symptoms on behavioral morbidity. However, early-onset SDB and late-onset SDB groups were still significantly associated with increased behavioral morbidity in a sensitivity analysis when both SDB phenotypes and current SDB were included in the same

regression. Our results may not be generalizable to the entire pediatric population as most of our sample had higher income, higher education, and Caucasian background. As a result, our findings need to be replicated in other populations.

Younger children with SDB may be at increased risk for long-term behavioral morbidity. Future research will examine trajectories of parent-reported SDB symptoms to determine their impact on long-term behavior. Future studies may also examine the role of genetics, physiological responses, cerebral insult, and craniofacial anatomy on the association between SDB phenotypes and associated neurobehavioral consequences. Surgery (T&A) may not reliably eliminate the associated behavior problems. The findings support the need for intervention studies to determine whether targeted early intervention of SDB among young children can help remediate early behavior problems.

Conclusion

SDB during the first two years of life is associated with detrimental effects on behavioral development in young children. Consistent with prior studies, current parent-reported SDB symptoms are strongly associated with increased externalizing behavior problems including ADHD like symptoms. Our findings extend these conclusions to younger children. Furthermore, we provide the first evidence to show that the age of onset or duration of parent-reported SDB symptoms may influence later internalizing behavioral deficits even after controlling for maternal and environmental factors. These findings highlight the need to screen young children with behavioral problems for potentially reversible sleep problems, such as SDB, to reduce later mental health problems.

Abbreviations list

SDB: Sleep disordered breathing

SRBD: Sleep related breathing disorder

CBCL: Child Behavior Checklist

ADHD: Attention deficit/hyperactivity disorder

PSG: Polysomnography

AHI: Apnea-hypopnea index

T&A: Tonsil and adenoidectomy

AASM: American Academy of Sleep Medicine

BIC: Bayesian information criteria

Acknowledgements

We are grateful to all the families who took part in this study, and the whole CHILD team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. The Canadian Institutes of Health Research (CIHR) and the Allergy, Genes and Environment (AllerGen) Network of Centres of Excellence provided core support for CHILD. This research was specifically funded by CIHR and the Women and Children's Health Research Institute (WCHRI) at the University of Alberta.

Author Contributions:

P.M. conceived the study, obtained funding for the study and helped with statistical analysis and manuscript development. S.T. drafted the first version of the manuscript, completed the statistical analysis, and drafted the final version of the manuscript. L.S. helped draft the manuscript and contributed to statistical analysis. A.L. helped with data collection and statistical analysis. J.M. helped with designing and executing the CHILD neurodevelopmental testing and data collection. J.P. and R.Y. helped with designing and executing the CHILD neurodevelopmental testing. J.C. and D.L. helped with data collection and drafting the manuscript. M.R.S., A.B.B., P.S. and, S.E.T. helped obtain funding, advised on the CHILD study design, and participated in data collection. All authors provided critical comments on the manuscript content and approved the final version of the manuscript.

Disclosure Statements

Funding sources:

- Canadian Institutes of Health Research (CIHR)
- The Allergy Genes and Environment Network of Centres of Excellence (AllerGen NCE)
- Women's and Children's Health Research Institute (WCHRI)

Financial statements

The authors declare no competing financial interests

Non-financial statements

The authors declare no competing non-financial interests

Conflict Statement

The authors have no conflict of interest to declare related to this manuscript.

References

1. Bonuck KA, Chervin RD, Cole TJ, et al. Prevalence and persistence of sleep disordered breathing symptoms in young children: a 6-year population-based cohort study. Sleep. 2011; 34 (7): 875-884.
2. Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. Proc Am Thorac Soc. 2008; 5 (2): 242-252.
3. DelRosso LM. Epidemiology and Diagnosis of Pediatric Obstructive Sleep Apnea. Curr Probl Pediatr Adolesc Health Care. 2016; 46 (1): 2-6.
4. Gregory AM, Caspi A, Moffitt TE, Poulton R. Sleep problems in childhood predict neuropsychological functioning in adolescence. Pediatrics. 2009; 123 (4): 1171-1176.
5. Beebe DW, Wells CT, Jeffries J, Chini B, Kalra M, Amin R. Neuropsychological effects of pediatric obstructive sleep apnea. J Int Neuropsychol Soc. 2004; 10 (7): 962-975.
6. Marcus CL, Moore RH, Rosen CL, et al. A randomized trial of adenotonsillectomy for childhood sleep apnea. N Engl J Med. 2013; 368 (25): 2366-2376.
7. Mitchell RB, Garetz S, Moore RH, et al. The use of clinical parameters to predict obstructive sleep apnea syndrome severity in children: the Childhood Adenotonsillectomy (CHAT) study randomized clinical trial. JAMA otolaryngology-- head & neck surgery. 2015; 141 (2): 130-136.
8. Giordani B, Hodges EK, Guire KE, et al. Changes in neuropsychological and behavioral functioning in children with and without obstructive sleep apnea following Tonsillectomy. J Int Neuropsychol Soc. 2012; 18 (2): 212-222.
9. Biggs SN, Vlahandonis A, Anderson V, et al. Long-term changes in neurocognition and behavior following treatment of sleep disordered breathing in school-aged children. Sleep. 2014; 37 (1): 77-84.
10. Montgomery-Downs HE, Crabtree VM, Gozal D. Cognition, sleep and respiration in at-risk children treated for obstructive sleep apnoea. Eur Respir J. 2005; 25 (2): 336-342.
11. Biggs SN, Walter LM, Jackman AR, et al. Long-Term Cognitive and Behavioral Outcomes following Resolution of Sleep Disordered Breathing in Preschool Children. PLoS One. 2015; 10 (9): e0139142.
12. Amiri S, AbdollahiFakhim S, Lotfi A, Bayazian G, Sohrabpour M, Hemmatjoo T. Effect of adenotonsillectomy on ADHD symptoms of children with adenotonsillar hypertrophy and sleep disordered breathing. Int J Pediatr Otorhinolaryngol. 2015; 79 (8): 1213-1217.
13. Passali D, Passali FM, Cambi J, Bellussi L. Role of adenotonsillectomy in OSAS children and behavioural disturbance. Otolaryngol Pol. 2013; 67 (4): 187-191.
14. Landau YE, Bar-Yishay O, Greenberg-Dotan S, Goldbart AD, Tarasiuk A, Tal A. Impaired behavioral and neurocognitive function in preschool children with obstructive sleep apnea. Pediatr Pulmonol. 2012; 47 (2): 180-188.
15. Tran KD, Nguyen CD, Weedon J, Goldstein NA. Child behavior and quality of life in pediatric obstructive sleep apnea. Arch Otolaryngol Head Neck Surg. 2005; 131 (1): 52-57.
16. Wei JL, Bond J, Mayo MS, Smith HJ, Reese M, Weatherly RA. Improved behavior and sleep after adenotonsillectomy in children with sleep-disordered breathing: long-term follow-up. Arch Otolaryngol Head Neck Surg. 2009; 135 (7): 642-646.
17. Wei JL, Mayo MS, Smith HJ, Reese M, Weatherly RA. Improved behavior and sleep after adenotonsillectomy in children with sleep-disordered breathing. Arch Otolaryngol Head Neck Surg. 2007; 133 (10): 974-979.

18. Constantin E, Kermack A, Nixon GM, Tidmarsh L, Ducharme FM, Brouillette RT. Adenotonsillectomy improves sleep, breathing, and quality of life but not behavior. J Pediatr. 2007; 150 (5): 540-546, 546 e541.
19. Kheirandish-Gozal L, Gozal D. Genotype-phenotype interactions in pediatric obstructive sleep apnea. Respiratory physiology & neurobiology. 2013; 189 (2): 338-343.
20. Bonuck K, Freeman K, Chervin RD, Xu L. Sleep-disordered breathing in a population-based cohort: behavioral outcomes at 4 and 7 years. Pediatrics. 2012; 129 (4): e857-865.
21. Subbarao P, Anand SS, Becker AB, et al. The Canadian Healthy Infant Longitudinal Development (CHILD) Study: examining developmental origins of allergy and asthma. Thorax. 2015; 70 (10): 998-1000.
22. Takaro TK, Scott JA, Allen RW, et al. The Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort study: assessment of environmental exposures. J Expo Sci Environ Epidemiol. 2015; 25 (6): 580-592.
23. Chervin RD, Hedger K, Dillon JE, Pituch KJ. Pediatric sleep questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. Sleep Med. 2000; 1 (1): 21-32.
24. Witmans M, Young R. Update on pediatric sleep-disordered breathing. Pediatr Clin North Am. 2011; 58 (3): 571-589.
25. Hoffman AG BD. Portable sleep apnea testing: An update. Canadian Journal of Respiratory Therapy. 2012; 48 (2): 7-14.
26. C. I. American Academy of Sleep Medicine. In: The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. 2007, Westchester: American Academy of Sleep Medicine.
27. Achenbach TM, Ruffle TM. The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies. Pediatr Rev. 2000; 21 (8): 265-271.
28. Achenbach TM. *Manual for the Child Behavior Checklist/4-18 and 1991 Profile.* . Burlington: University of Vermont, Department of Psychiatry 1991.
29. Achenbach TM, Edelbrock C, Howell CT. Empirically based assessment of the behavioral/emotional problems of 2- and 3- year-old children. J Abnorm Child Psychol. 1987; 15 (4): 629-650.
30. Sadeh A. A brief screening questionnaire for infant sleep problems: validation and findings for an Internet sample. Pediatrics. 2004; 113 (6): e570-577.
31. Bayley N. *Bayley Scales of Infant and Toddler Development, Third Ediiton.* . San Antonio, TX: Harcourt Assessment; 2006.
32. Nagin DS. Analyzing developmental trajectories: a semiparametric, group-based approach. . Psychological Methods. 1999; 4 (2): 139-157.
33. Nagin DS. *Group-Based Modeling of Development.* Cambridge, MA: Harvard University Press; 2005.
34. Touchette E, Dionne G, Forget-Dubois N, et al. Genetic and environmental influences on daytime and nighttime sleep duration in early childhood. Pediatrics. 2013; 131 (6): e1874-1880.
35. Touchette E, Mongrain V, Petit D, Tremblay RE, Montplaisir JY. Development of sleep-wake schedules during childhood and relationship with sleep duration. Arch Pediatr Adolesc Med. 2008; 162 (4): 343-349.
36. Touchette E, Cote SM, Petit D, et al. Short nighttime sleep-duration and hyperactivity trajectories in early childhood. Pediatrics. 2009; 124 (5): e985-993.

37. Touchette E, Petit D, Seguin JR, Boivin M, Tremblay RE, Montplaisir JY. Associations between sleep duration patterns and behavioral/cognitive functioning at school entry. Sleep. 2007; 30 (9): 1213-1219.
38. Ding FC, Kamal M, Tamana SK, et al. Atopy is Associated with Persistent Sleep Disordered Breathing to 2 Years of Age; A CHILD Birth Cohort Study Project. American Journal of Respiratory and Critical Care Medicine. 2017; (A7025): 195.
39. Smithson L, Tamana S, Lau A, et al. Sleep disruption and shorter sleep duration is associated with reduced cognitive and language development by aged 2 years. In preparation 2017.
40. Jackman AR, Biggs SN, Walter LM, et al. Sleep-disordered breathing in preschool children is associated with behavioral, but not cognitive, impairments. Sleep Med. 2012; 13 (6): 621-631.
41. Owens J, Opipari L, Nobile C, Spirito A. Sleep and daytime behavior in children with obstructive sleep apnea and behavioral sleep disorders. Pediatrics. 1998; 102 (5): 1178-1184.
42. Chervin RD, Archbold KH, Dillon JE, et al. Inattention, hyperactivity, and symptoms of sleep-disordered breathing. Pediatrics. 2002; 109 (3): 449-456.
43. Gottlieb DJ, Vezina RM, Chase C, et al. Symptoms of sleep-disordered breathing in 5-year-old children are associated with sleepiness and problem behaviors. Pediatrics. 2003; 112 (4): 870-877.
44. Hiscock H, Canterford L, Ukoumunne OC, Wake M. Adverse associations of sleep problems in Australian preschoolers: national population study. Pediatrics. 2007; 119 (1): 86-93.
45. Aronen ET, Liukkonen K, Simola P, et al. Mood is associated with snoring in preschool-aged children. J Dev Behav Pediatr. 2009; 30 (2): 107-114.
46. Yilmaz E, Sedky K, Bennett DS. The relationship between depressive symptoms and obstructive sleep apnea in pediatric populations: a meta-analysis. J Clin Sleep Med. 2013; 9 (11): 1213-1220.
47. Owens JA, Mehlenbeck R, Lee J, King MM. Effect of weight, sleep duration, and comorbid sleep disorders on behavioral outcomes in children with sleep-disordered breathing. Arch Pediatr Adolesc Med. 2008; 162 (4): 313-321.
48. Zhao Q, Sherrill DL, Goodwin JL, Quan SF. Association Between Sleep Disordered Breathing and Behavior in School-Aged Children: The Tucson Children's Assessment of Sleep Apnea Study. Open Epidemiol J. 2008; 1: 1-9.
49. Mulvaney SA, Goodwin JL, Morgan WJ, Rosen GR, Quan SF, Kaemingk KL. Behavior problems associated with sleep disordered breathing in school-aged children--the Tucson children's assessment of sleep apnea study. J Pediatr Psychol. 2006; 31 (3): 322-330.
50. Shanahan L, Copeland WE, Angold A, Bondy CL, Costello EJ. Sleep problems predict and are predicted by generalized anxiety/depression and oppositional defiant disorder. J Am Acad Child Adolesc Psychiatry. 2014; 53 (5): 550-558.
51. Sivertsen B, Harvey AG, Reichborn-Kjennerud T, Torgersen L, Ystrom E, Hysing M. Later emotional and behavioral problems associated with sleep problems in toddlers: a longitudinal study. JAMA Pediatr. 2015; 169 (6): 575-582.
52. Tikotzky L, Sadeh A. Sleep patterns and sleep disruptions in kindergarten children. J Clin Child Psychol. 2001; 30 (4): 581-591.

Tables

Table 1 – Demographic characteristics for children with and without CBCL data at age two years

Categorical	Data Absent % (behavior/total)	Data Present % (behavior/total)	p-value
Male	50.7% (117/231)	50.9% (297/583)	0.97
Child ethnicity: Caucasian	52.4% (121/231)	69.5% (405/583)	0.01
Birth order: Second born	54.1% (125/231)	56.4% (329/583)	0.64
Late preterm: born between 34-37 weeks	4.4% (10/228)	5.5% (32/583)	0.52
Higher income > $60, 000	54.0% (138/231)	86.3% (503/583)	<0.001
Marital divorce or separation	9.5% (22/231)	5.3% (31/583)	0.02
Attend daycare at age 2 years: yes*	57.1% (32/56)	50.9% (262/515)	0.37
Current SDB symptoms at age 2 years*	7.4% (4/54)	6.8% (35/512)	0.88
Continuous	Data Absent *Mean* (95%CI)	Data Present *Mean* (95%CI)	
Maternal age at time of child's birth	29.9 (29.3, 30.6)	31.8 (31.5, 32.1)	<0.001
Maternal depression at 1 year	8.9 (7.0, 10.8)	7.6 (7.0, 8.3)	0.14
BIDS-III Social-emotional development at age 1 year	10.7 (10.2, 11.1)	10.5 (10.3, 10.8)	0.65
BISQ Parent reported total sleep duration at age 2 years in hours	12.6 (12.2, 12.9)	12.6 (12.5, 12.7)	0.81

Caption: BIDS-III = Bayley Infant Development Scale – Third Edition; BISQ=Brief Infant Sleep Questionnaire; SDB = Sleep disordered breathing – parent reported symptoms.

Note: *Data on daycare attendance at age 2 years was missing for 175 at age 2 years, and current SDB symptoms, reported on the Pediatric Sleep Questionnaire at age 2 years, was missing for 177 participants.

Table 2 -Multivariate analysis examining associations between parent-reported symptoms of SDB and total behavior problems at age two years (n = 582).

		Model 1: Current SDB BIC: 4172.6		Model 2: SDB Phenotypes BIC: 4153.2	
	Factor	Coefficient 95%CI	p-value	Coefficient 95%CI	p-value
SDB symptoms	SDB Symptoms at age 2 years: Yes	6.2 (4.1, 8.2)	<0.001	-	-
	Late onset	-	-	6.1 (4.0, 8.3)	<0.001
	Early onset	-	-	3.5 (1.6, 5.4)	<0.001
	Persistent	-	-	9.5 (1.7, 17.2)	0.02
Total sleep duration	Short sleepers	2.0 (0.1, 3.9)	0.04	2.3 (0.4, 4.1)	0.02
	Decline to short sleep	0.1 (-1.7, 1.9)	0.92	0.2 (-1.6, 2.0)	0.80
	Long sleepers	-1.2 (-2.9, 0.5)	0.16	-0.7 (-2.4, 0.9)	0.40
	Gestational age at delivery	-0.5 (-1.0, 0.9 x10^{-2})	0.06	-0.5 (-0.9, 0.2 x10^{-1})	0.07
	Maternal nutritional status during pregnancy using the HEI-2010	-0.1 (-0.2, 0.4 x10^{-1})	<0.001	-0.1 (-0.2, -0.1)	<0.001
	Gestational age at time of food frequency questionnaire completion	0.1 (0.1 x10^{-1}, 0.2)	0.03	-	-
	Household smoke at 1 year: Yes	2.2 (0.2 4.3)	0.03	2.3 (0.3, 4.4)	0.02
	BSID-III social emotional development at age 1 year	-0.1 x10^{-1} (-0.1, 0.2)	<0.001	-0.1 (-0.1, -0.3x10^{-1})	<0.001
	Parenting stress at 2 years using the PSI-SF Scale	0.2 (0.1, 0.3)	<0.001	0.2 (0.1, 0.3)	<0.001
	BSID-III language at age 2 years	-0.1 (-0.2, -0.1)	<0.001	-0.1 (-0.2, -0.1)	<0.001
	Maternal Body Mass Index at 1 year	0.1 (0.1, 0.3 x10^{-1})	0.03	-	-
	Constant	73.6 (43.6, 103.5)	<0.001	84.0 (59.9, 108.2)	<0.001

Caption: BSID-III = Bayley Scale of Infant Development Third Edition, lower scaled score represents delayed development; HEI-2010 = Healthy Eating Index 2010, higher score represents better diet quality; PSI-SF=Parenting Stress Index-Self Report, higher score presents increased levels of parenting stress; SDB = Sleep Disordered Breathing.

Table 3 -Multivariate analysis examining associations between parent-reported symptoms of SDB and externalizing behavior problems at age two years (n = 582).

		Model 1: Current SDB BIC: 4199.6		Model 2: SDB Phenotypes BIC: 4204.3	
	Factor	Coefficient 95%CI	p-value	Coefficient 95%CI	p-value
SDB symptoms	SDB Symptoms at age 2 years: Yes	5.8 (3.7, 8.0)	<0.001	-	-
	Late onset	-	-	5.6 (3.3, 7.8)	<0.001
	Early onset	-	-	2.8 (0.8, 4.8)	0.01
	Persistent	-	-	5.8 (-2.4, 14.0)	0.16
Daytime sleep Duration	Intermediate sleepers	-2.1 (-3.9, -0.2)	0.03	-2.0 (-3.9, -0.1)	0.04
	Short sleepers	-1.3 (-3.0, 0.4)	0.13	-1.1 (-2.8, 0.6)	0.19
	Decrease to intermediate	-1.8 (-4.1, 0.5)	0.12	-1.7 (-4.0, 0.6)	0.15
	HEI-2010 during pregnancy	-0.1 ($-0.2, 0.0 \times 10^{-2}$)	0.03	-0.1 ($-0.2, -0.1 \times 10^{-1}$)	0.03
	Household smoke at 3 months: Yes	2.0 (0.1×10^{-2}, 4.0)	0.05	2.0×10^{-1} (0.3, 4.0)	0.05
	BSID-III language at age 2 years	-0.1 ($-0.2, 0.4 \times 10^{-1}$)	<0.001	-0.1 ($-0.2, 0.3 \times 10^{-1}$)	<0.001
	Maternal depression during pregnancy using the CES-D scale: Yes	0.2 (0.1, 0.3)	<0.001	0.2 ($0.1, 0.3 \times 10^{-1}$)	<0.001
	Parent-child interaction at 2 years using the P-CDI scale	0.6 (0.4, 0.8)	<0.001	0.6 (0.4, 0.8)	<0.001
	Constant	49.0 (36.1, 61.8)	<0.001	48.2 (36.8, 59.7)	<0.001

Caption: BSID-III = Bayley Scale of Infant Development Third Edition, lower scaled score represents delayed development; CES-D = Centre for Epidemiological Studies – Depression, higher scores represent increased maternal symptoms of depression; P-CDI = Parent-Child Dysfunction Index, higher scores reflect increased perceived difficulties; SDB = Sleep Disordered Breathing.

Table 4 -Multivariate analysis examining associations between parent-reported symptoms of SDB and internalizing behavior problems at age two years (n = 582).

		Model 1: Current SDB BIC: 4206.4		Model 2: SDB Phenotypes BIC: 4192.9	
	Factor	Coefficient 95%CI	p-value	Coefficient 95%CI	p-value
	SDB Symptoms at age 2 years: Yes	2.4 (0.2, 4.6)	0.03	-	-
SDB symptoms	Late onset	-	-	3.5 (1.3, 5.7)	<0.001
	Early onset	-	-	3.8 (1.9, 5.8)	<0.001
	Persistent	-	-	7.8 (-0.3, 15.8)	0.06
Total sleep duration	Short sleepers	2.9 (1.0, 4.9)	<0.001	2.9 (1.0, 4.8)	<0.001
	Decline to short sleepers	0.7 (-1.1, 2.6)	0.45	0.8 (-1.1, 2.6)	0.41
	Long sleepers	0.3 (-1.4, 2.0)	0.72	0.5 (-1.2, 2.2)	0.53
	T3 sleep efficiency at age 1 year	0.1 (-0.1×10^{-1}, 0.3)	0.07	0.1 (0.8×10^{-3}, 0.3)	0.05
	Maternal nutritional status during pregnancy using the HEI-2010	-0.1 (-0.2, 0.8×10^{-3})	0.05	-0.1 (-0.2, 0.3×10^{-2})	0.04
	Household smoke at 1 year: Yes	2.9 (0.8, 5.0)	0.01	2.8 (0.7, 4.8)	0.01
	BSID-III social emotional development at age 1 year	-0.1 (-0.1, 0.1×10^{-1})	0.05	-0.1 (-0.1, -0.2×10^{-1})	0.01
	BSID-III language at age 2 years	-0.1 (-0.2, -0.1)	<0.001	-0.1 (-0.2, -0.1)	<0.001
	Maternal depression at age 1 year using the CES-D scale	0.1 (0.3×10^{-1}, 0.3)	0.01	0.1 (0.3×10^{-1}, 0.2)	0.01
	Parent-child interaction at age 2 years using the P-CDI scale	0.7 (0.5, 0.8)	<0.001	0.6 (0.5, 0.8)	<0.001
	Constant	48.1 (29.5, 66.6)	<0.001	49.5 (32.0, 67.0)	<0.001

Caption: BSID-III = Bayley Scale of Infant Development Third Edition, lower scaled score represents delayed development; CES-D = Centre for Epidemiological Studies – Depression, higher scores represent increased maternal symptoms of depression; HEI-2010 = Healthy Eating Index 2010, higher score represents better diet quality; P-CDI = Parent-Child Dysfunction Index, higher scores reflect increased perceived difficulties; SDB = Sleep Disordered Breathing.