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Original Article

Phenotypes of sleep-disordered breathing symptoms to two years of age based on age of onset and duration of symptoms

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ABSTRACT

Objective: Childhood sleep-disordered breathing (SDB) symptoms may comprise multiple phenotypes depending on craniofacial anatomy, tonsil and adenoid growth, body habitus, and rhinitis symptoms. The primary objective of this study is to identify and characterize the different SDB phenotypes to two years of age.

Methods: Data from 770 infants in the Edmonton sub-cohort of the Canadian Healthy Infant Longitudinal Study (CHILD) were analyzed to identify SDB phenotypes based on age of onset and duration of symptoms. Parents completed the 22-item sleep-related breathing disorder (SRBD) scale. Children with a SRBD ratio greater than 0.33 were considered positive for SDB at each quarterly assessment between three months and two years. The STATA Proc trajectory extension identified SDB phenotypes based on their age of onset and duration of symptoms and attributed the percentage chance of a participant being assigned to each phenotype. Multivariate linear regression identified factors associated with increased risk of being assigned to each SDB phenotype.

Results: Trajectory analysis identified four phenotypes: no SDB (65.7%), early-onset SDB (15.7%) with peak symptoms at nine months, late-onset SDB (14.2%) with peak symptoms at 18 months, and persistent SDB (5.3%) with symptoms from 3 to 24 months. Rhinitis was associated with all three SDB symptom trajectories ($p < 0.05$). Children with gastroesophageal reflux disease presented with early ($p = 0.03$) and late SDB ($p < 0.001$). Maternal obstructive sleep apnea syndrome (OSAS) was associated with persistent ($p = 0.01$) and late SDB ($p < 0.001$). Atopy (positive skin prick test at one year) was associated with persistent SDB ($p = 0.04$). Infants born prior to 36.5 weeks gestational age were more likely to present with late SDB ($p = 0.03$).

Conclusion: Childhood SDB symptoms, rather than being a homogenous disorder, may comprise multiple overlapping phenotypes each with unique risk factors.

1. Introduction

Sleep disordered breathing (SDB), which may range from habitual snoring to obstructive sleep apnea, affects up to 10% of children, with a peak prevalence between two and eight years of

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age [1–3]. An increased risk of snoring has been observed among first-born children [4] and children of mothers who smoked during pregnancy [5], while children who were breastfed for more than two months were less likely to develop SDB [6]. Several studies have shown that SDB is more common among atopic children [7,8] although one study has reported that inner-city snoring children referred for a laboratory sleep study (polysomnography; PSG) were less likely to have asthma [9]. Self-reported proximity to road traffic was associated with self-reported habitual snoring in preschool children although the strength of the association was reduced when controlling for single-parent families and socioeconomic deprivation [8].

We present findings from the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort study where we sought to determine patterns of SDB symptoms (SDB phenotypes) based on age of onset and duration of symptoms. Childhood SDB may comprise multiple overlapping phenotypes depending on a child's craniofacial anatomy, tonsil and adenoid growth, body habitus, and presence of rhinitis symptoms [10]. We hypothesized that the different symptom phenotypes may be distinguished by age of onset and duration of symptoms.

Each phenotype may be associated with different genetics (eg, parental history of SDB) and environmental exposures. Increased lymph-adenoid tissue can be triggered by respiratory syncytial virus [11], environmental tobacco smoke [12,13], and environmental pollutants [14]. We have identified individual factors (eg, atopy, body mass index [BMI], gestational age [GA]) and environmental exposures (eg, breast-feeding, socioeconomic status (SES), daycare attendance) associated with the development of each SDB symptom.

2. Methods

2.1. Study participants

CHILD is a longitudinal birth cohort study designed to assess the influence of gene–environment interactions on the development of allergy and asthma. CHILD Edmonton families ($N = 822$) participated in an add-on study examining the longitudinal relationship between sleep and neurodevelopment. The sleep-related breathing disorder (SRBD) scale, the Brief Infant Sleep questionnaire (BISQ), parental history of obstructive sleep apnea syndrome (OSAS) based on the global sleep assessment questionnaire (GSAQ), and home PSG were collected specifically for the ancillary study. Mothers aged 18 years and over were recruited during the second or third trimester of pregnancy, and seen at delivery, when their children were 3–4 months of age, and then annually. Parents completed questionnaires regarding their children's sleep and SDB symptoms every three months. Family and child characteristics (ie, SES, ethnicity), maternal and infant nutrition, and maternal stress were assessed longitudinally throughout the study. Informed consent was obtained from all mothers and from consenting fathers. Approval for this research study was obtained from the Research Ethics Board (REB) at the University of Alberta (Pro00002099).

2.2. Study variables

2.2.1. SDB symptom trajectories (primary outcome variable)

The 22-item item SRBD scale, based on the pediatric sleep questionnaire (PSQ), was completed quarterly by parents from three months to two years of age. The SBRD scale uses the 22-item yes/no SBRD [15] questionnaire which includes items on snoring, excessive daytime sleepiness, and attention deficit hyperactivity disorder (ADHD) symptoms. The SRBD ratio is obtained by dividing the sum of all 'yes' responses by the total number of non-missing items (yes or no). Infants with an SRBD ratio greater than 0.33 were considered to have SDB at that quarterly assessment [15].

The STATA Proc Traj [16,17] extension uses a finite mixture model to simultaneously estimate multiple longitudinal trajectories using maximum likelihood. We used STATA Traj (05/2017) [18,19] (logistic) to identify and assign phenotypes to each child based on a positive or negative SRBD at each time point between three months and two years of age. Participants had to have at least one SRBD ratio to be included in the trajectory analysis. Linear, quadratic, and cubic trajectory models were considered for model development [20]. The optimal number of trajectories was selected based on the lowest Bayesian Information Criteria (BIC). The STATA Traj plug-in provides the probability of an individual being included in each of the SDB trajectories (0–100%). Participants are also assigned to a trajectory based upon the group trajectory for which they have the highest probability of membership.

2.2.2. Atopy (primary exposure variable)

Atopy was assessed at one year of age using skin-prick testing (SPT) with highly standardized ALK allergens. Atopy was defined as having at least one positive SPT (wheal $\geq$2 mm greater than negative control) to any of the tested allergens at age one year.

2.2.3. Assessment of potential confounding variables previously associated with SDB

Details of all the confounding variables are available in the Supplementary Material.

2.2.4. Daycare/Dayhome

Parents were asked whether their child regularly went to a location away from home (eg, daycare, babysitter, activities with mom) for at least 1 h per day on average, or at least 7 h total in a week at 3, 6, 12, 18, and 24 months.

2.2.5. Rhinitis symptoms

Infants were classified as having rhinitis at 3, 6, 9, and 12 months of age if parents reported yes to at least one of the following questions: (1) dry mouth during the day, (2) dry mouth on waking up in the morning, (3) child has a stuffy nose that is congested at night, or (4) mouth breathes most of the time.

2.2.6. Rhinitis treatment

Infants were classified as having rhinitis treatment at 3, 6, 12, 18, and 24 months of age if they were treated with any of the following nasal steroid or sprays: fluticasone propionate, fluticasone furoate, mometasone furoate, budesonide, beclomethasone, ciclesonide, flunisolide or polyethylene glycol/propylene glycol.

2.2.7. Gastroesophageal reflux disease

Infants were classified as having gastroesophageal reflux disease (GERD) if they were treated with any of the following medications: ranitidine, omeprazole, lansoprazole, or pantoprazole at 3, 6, 12, 18, and 24 months of age.

2.2.8. Treatment with inhaled corticosteroids

Infants were classified as being treated with inhaled corticosteroids if they were treated with any of the following medications: fluticasone propionate, beclomethasone, fluticasone propionate, and salmeterol, at 3, 6, 12, 18, and 24 months of age.

Apnea Hypopnea Index: A single-night home PSG study (NOX-T3) was completed at 12 months of age [21]. Scoring was completed by Sleep Strategies using a modified AASM pediatric scoring rubric [22] based on the channels available (Supplementary Material: Appendix 1).

2.2.9. Maternal diet during pregnancy

A food frequency questionnaire (FFQ) developed by the Fred Hutchinson Cancer Research Center was modified to reflect Canadian multi-ethnic food choices and was completed at enrollment, and asked pregnant mothers to report the frequency and portion size of food since becoming pregnant [23].

2.2.10. Respiratory tract infection

Parents reported whether their child had respiratory tract infection (RTI) at 3, 6, and 12 months of age and were asked the total number of RTI since the last assessment.

2.2.11. Parental history of OSAS

Paternal OSAS symptoms were assessed by the GSAQ at enrollment. Mothers completed the GSAQ when their children were one year of age.

2.2.12. Marital status

Mothers reported their marital status at enrollment as either (1) married or common law, (2) divorced or separated, (3) single (never been married), (4) widowed during pregnancy. Marital status was categorized as married/common law or divorced/single/widowed.

2.3. Statistical analysis

We used generalized estimating equations (GEE) to examine differences between trajectories for time-varying covariates including rhinitis symptoms (stuffy nose, mouth breathing), RTI, and wheeze symptoms. To identify predictors of each trajectory group, we chose to analyze the probability of inclusion in each trajectory to account for the imprecision of group trajectory assignment. Univariate regression analysis (linear regression) was used to identify predictors associated with an increased or decreased absolute percent probability of being included in each of the phenotypes. For multivariate analyses, missing values on all variables other than primary outcome variable (SRBD trajectories) were replaced with the mean or reference (for continuous and categorical variables, respectively) and a dummy variable was included in the analysis in order to account for the replacement. Significant ($p < 0.10$) or clinically important predictors in univariate analyses were included in multivariate analyses to identify unique predictors of each phenotype. Significant interactions ($p < 0.1$) that changed the main effect by more than 10% were included in the analysis. Data were analyzed using STATA 14 (STATA corp.).

3. Results

Of those with SDB data, three children had severe developmental delay and were excluded from the subsequent trajectory analysis. Over 93% (770/822) of CHILD Edmonton participants had a response to the SRBD for at least one quarterly questionnaire. Among children with SDB data, 68.5% (510/745) of children were Caucasian compared with 55.9% (19/34) of children without data ($p > 0.05$; Table 1). Mothers of children with SDB data had a mean age of 31.3 years [95% confidence interval (CI): 31.0, 31.6] compared to a mean age of 30.7 years for children without SDB data (95% CI: 29.2, 32.2, $p > 0.05$). Only 6.2% of children with SDB data were from families with marital divorce or separation (45/730) compared to 21.1% (8/38) of children without data ($p \leq 0.001$). No other significant differences among those with and without SDB data were reported (Table 1).

Children with SDB data had a 12.6-h mean parent-reported total sleep duration at age two years [standard deviation (SD) 1.2; $N = 594$]. Over 11% (69/608) of children with SDB data had wheeze symptoms by 12 months of age and 29% (178/607) of children attended a location away from home (eg, daycare) for at least 7 h a week at 12 months of age. The average number of colds between six and 12 months of age for participants with SDB data was 1.6 (95% CI: 1.4, 1.7).

3.1. Parent-reported SDB trajectories

Parent-reported SDB symptoms, any SRBD positive at any time point, were reported in 28.1% ($N = 216/770$) of children between three months and two years of age. Only 12.9% (73/566) had SDB symptoms at two years of age. Trajectory analysis identified four phenotypes: children with no SDB symptoms (64,7%; Fig. 1), early-onset SDB symptoms (15.7%), late-onset SDB symptoms (14.2%), and persistent SDB symptoms (5.3%).

Children with no SDB symptoms had a mean SRBD ratio of 0.1 (SD = 0; Supplementary Table S1) at 12 months and 0.14 (SD 0.11) at 24 months. Children with early-onset SDB had a peak of SDB symptoms starting at nine months (mean SRBD = 0.29, SD 0.12), while children with late-onset SDB had a peak of SDB symptoms at 18 months (mean SRBD = 0.34, SD 0.09). Children with persistent SDB symptoms had significant SDB 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). The prevalence of 'always snoring' was as high as 26% among children with persistent SDB (Supplementary Table S2). While 20% of children with early-onset SDB were snoring for more than half the time at three months of

Table 1
Demographic characteristics for children with and without data regarding sleep-disordered breathing at two years of age ($N = 822$).[a]

Variable	Data absent % (sleep/total)	Data present % (sleep/total)	p
Categorical			
Male	59.5% (25/42)	50.5% (390/773)	0.25
Child ethnicity: Caucasian	55.9% (19/34)	68.5% (510/745)	0.13
Birth order: second born	54.8% (23/42)	56.4% (434/770)	0.84
Preterm: Born between 34 and 37 weeks	4.8% (2/42)	5.2% (40/770)	0.90
Higher income ≥$60,000	83.3% (25/30)	85.1% (619/727)	0.79
Marital divorce or separation	21.1% (8/38)	6.2% (45/730)	<0.001
Attend daycare at 12 months of age	0% (0/2)	29.3% (178/607)	0.50 (Fisher's exact)
Any wheeze at 12 months of age: yes	0% (0/5)	11.4% (69/608)	0.55 (Fisher's exact)
Continuous	Data absent Mean (95% CI)	Data present Mean (95% CI)	
Maternal age at time of child's birth	30.7 (29.2, 32.2)	31.3 (31.0, 31.6)	0.41
Number of colds between six and 12 months	1.8 (−0.6, 4.2) $N = 5$	1.6 (1.4, 1.7) $N = 609$	0.69

[a] Maximum sample size was 815 (gender) due to missing data.

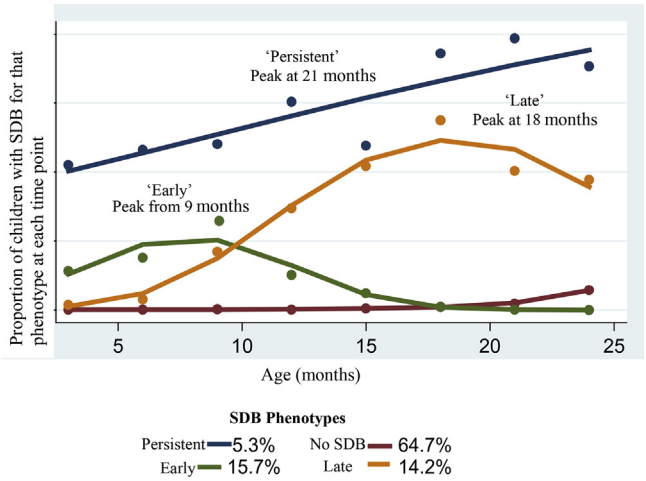

Fig. 1. Sleep-disordered breathing (SDB) trajectories between three months and two years.

age, only 2% reported snoring for more than half the time at 24 months of age. Only 1% of children with late-onset SDB were reported as snoring for more than half the time at six months but 16% of children with late-onset SDB were snoring at 24 months.

3.2. Univariate analyses

Measures of sleep quality and SDB, assessed by home PSG at one year, including apnea index, apnea-hypopnea index (AHI; continuous or using a cut-off of 1.5 or five events per hour), lowest saturation, desaturation index, sleep duration, and total time in bed were not significantly associated with the development of any of the three SDB symptom phenotypes (Supplementary Table S3). Socioeconomic factors, such as maternal education and family income, were not associated with developing SDB symptoms (Supplementary Table S4). Treatment with inhaled steroids was associated with both late and persistent SDB while nasal steroids were associated with persistent SDB. Neither treatment with nasal steroids/spray or inhaled corticosteroids was significantly associated with early SDB.

Fig. 2 provides an overview of the unique and common factors associated with the development of each of the SDB trajectories. Rhinitis ($p < 0.05$; Supplementary Table e5) and wheeze symptoms ($p < 0.05$) were associated with all SDB trajectories in GEE analysis. Compared to children with no SDB, children with persistent SDB were 6.9-times more likely to have rhinitis symptoms [standard error (SE) 1.8; $p < 0.001$], children with late SDB were 3.5-times more likely (SE 0.6; $p < 0.001$), and children with early SDB were 2.3-times more likely (SE 0.4; $p < 0.001$). Children with persistent SDB had 0.6 more episodes of RTI per reporting cycle compared to children without SDB ($p < 0.05$). There was no significant difference in RTI frequency between those children with early or late SDB and no SDB.

3.3. Multivariate analysis

Tables 2–4 provide the multiple variable analyses for early, late and persistent SDB symptom trajectories, respectively. For each SDB trajectory, each of the variables listed in the table were mutually adjusted for the other variables in the table. Prior daycare attendance was associated with the subsequent development of parent-reported SDB symptoms for each group in multivariate analysis. Daycare attendance at six months of age was associated with early SDB (Table 2) while daycare attendance at three months of age was associated with late SDB (Table 3) and persistent SDB (Table 4). Shorter sleep duration was associated with increased absolute percentage risk of reporting all three SDB phenotypes.

3.3.1. Early-onset parent-reported SDB symptoms

There was a notable interaction ($p = 0.07$) between children with GERD and sleep duration on the development of early SDB. Treatment for GERD symptoms at six months of age had a significant association with early-onset SDB (45% increased risk, SE 20.6, $p = 0.03$) when controlling for sleep duration and the GERD by sleep duration interaction. Among those with GERD, each increased hour of sleep was associated with a 3.4% reduced risk of reporting early SDB (SE 1.5; $p = 0.02$). Sleep duration was not associated with early SDB among children who did not report GERD treatment.

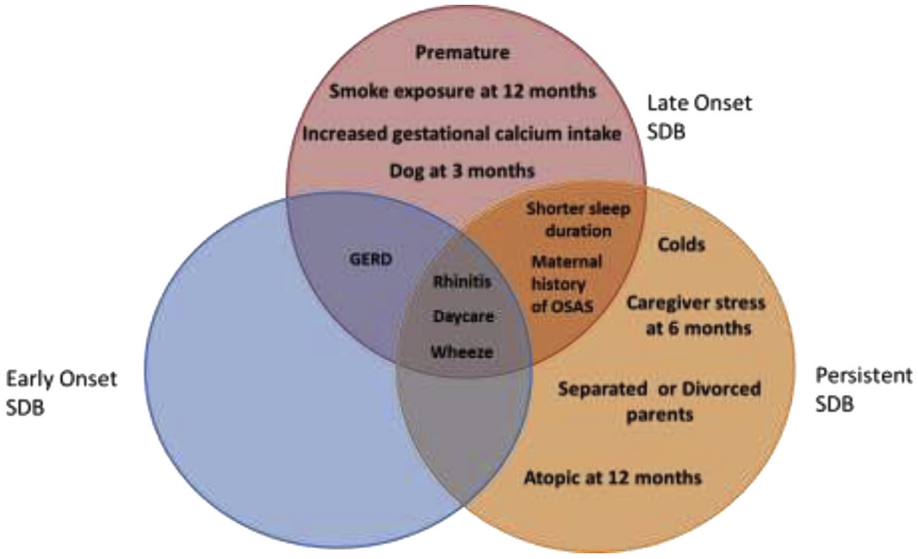

Fig. 2. Unique and common factors associated with the development of each of the sleep-disordered breathing (SDB) trajectories. GERD, gastroesophageal reflux disease; OSAS, obstructive sleep apnea syndrome.

Table 2
Factors associated with developing late-onset sleep-disordered breathing in multivariate analysis.

Variable	Absolute percentage change in risk (SE)	*p*
Sleep duration at 24 months (h)	−1.6 (0.8)	0.037
Risk for those participants missing sleep duration data	0.9 (2.2)	0.685
Maternal history of obstructive sleep apnea syndrome (reference: no maternal sleep apnea)	8.5 (1.9)	<0.001
Missing maternal obstructive sleep apnea syndrome data	−1.4 (3.9)	0.727
Maternal gestational calcium intake (per gram)	0.4 (0.1)	0.005
Risk for those participants missing calcium data	−2.4 (2.9)	0.392
Infant on gastroesophageal reflux medication at three months of age (reference: not on medication)	20.8 (5.8)	<0.001
Missing gastroesophageal reflux medication data	1.9 (8.9)	0.834
Born at 36.5 weeks gestational age or earlier (reference: born after 36.5 weeks gestational age)	9.9 (4.6)	0.033
Risk for those participants missing gestational age data	−0.4 (9.6)	0.965
At a daycare at three months of age (reference: not at daycare at three months of age)	11.4 (2.7)	<0.001
Risk for those participants missing daycare data	−2.4 (10)	0.813
No dog ownership at three months of age (reference)		
Own one dog at three months of age	4.6 (2.1)	0.031
Own two or more dogs at three months of age	−3.2 (3.3)	0.334
Risk for those participants missing dog data	3.6 (4.9)	0.458
Smoke exposure at 12 months of age (reference: no smoke exposure at 12 months)	6.5 (2.6)	0.014
Risk for those participants missing smoke exposure data at 12 months	5.1 (3.8)	0.174
Constant	22 (10.7)	

SE, standard error.

Table 3
Factors associated with developing early-onset sleep-disordered breathing in multivariate analysis.

Variable	Absolute Percentage change in risk (SE)	*p*
Infant GERD medication at six months of age (reference: not on medication)	45 (20.6)	0.029
Missing GERD medication data	27.8 (24.7)	0.26
Total sleep at six months		
GERD − Total sleep duration at six months of age (h)	−0.5 (0.5)	0.283
GERD + Total sleep duration at six months of age (h)	−3.4 (1.5)	0.022
Missing sleep duration data at six months of age	5.3 (7.7)	0.493
Missing GERD* total sleep duration at six months	−1.6 (1.7)	0.356
Missing sleep duration at six months *missing GERD at six months interaction	−3 (8.3)	0.715
Infant in daycare at three months of age (reference: not at daycare at six months of age)	−4.8 (2.2)	0.027
Missing daycare data	−1.4 (1.9)	0.471
Constant	17.9 (10.2)	0.08

GERD, gastroesophageal reflux disease; SE, standard error.

Table 4
Factors associated with developing persistent sleep-disordered breathing in multivariate analysis.

Variable		Absolute percentage change in risk (SE)	*p*
Atopy (positive skin prick test)	**Rhinitis treatment at 12 months**		
Negative	Negative	**Reference**	
Positive	Negative	3.6 (1.7)	0.037
Negative	Positive	35.6 (9.5)	<0.001
Positive	Positive	−3.6 (16.4)	0.826
Missing skin prick testing data at 12 months of age		−1.7 (2.4)	0.481
Missing rhinitis treatment at 12 months of age		3.1 (4.5)	0.483
Missing rhinitis treatment* missing atopy interaction		−2.6 (4.4)	0.548
Infant in daycare at three months of age (reference: not at daycare at 6 months of age)		3.9 (1.9)	0.041
Missing daycare data		−0.6 (1.7)	0.735
Total sleep duration at six months of age (h)		−0.8 (0.4)	0.031
Missing sleep duration data at six months of age		10.1 (5.7)	0.077
Parent(s) are single, separated or divorced at enrollment (reference: parents are married or common-law at time of enrollment)		7 (2.3)	0.003
Missing parental marital status data at time of enrollment		0.5 (2.4)	0.84
Positive Perceived Stress Index − short form at six months (PSI-SF >13)		3.4 (1.5)	0.024
Risk for those participants missing stress data		−1.1 (2.4)	0.649
Maternal history of obstructive sleep apnea syndrome (reference: no maternal sleep apnea)		3.4 (1.3)	0.011
Missing maternal obstructive sleep apnea syndrome data		2.3 (2.4)	0.346
Constant		3.4 (3.8)	0.364

SE, standard error.

3.3.2. Late-onset parent-reported SDB symptoms

Children with a maternal history of OSAS had an 8.5% absolute increased risk of developing SDB (SE 1.9, $p < 0.001$; Table 2). Late premature children (born between 34 and 36.5 weeks GA) had a 9.9% increased risk (SE 4.6; $p = 0.03$). Families with one dog in the house at three months of age had a 4.6% increased risk of developing late SDB (SE 2.1; $p = 0.03$) compared to families with no dogs in the home. Families with two or more dogs did not have a significantly different risk of developing late SDB. Children had a 1.6% reduced risk SE 0.8; $p = 0.04$) in presenting with late SDB for each hour that the children slept over 24 h at two years of age. Children with smoke exposure in their home at 12 months of age had a 6.5% (SE 2.6; $p = 0.02$) increased risk of parent-reported late-SDB symptoms. Finally, increased maternal calcium intake during pregnancy was significantly associated with an increased risk of developing late-onset SDB (0.4% absolute increased risk per 1 g consumption, SE 0.1; $p = 0.005$).

3.3.3. Persistent parent-reported SDB symptoms

There was a significant interaction between children with a positive skin-prick test (atopic) at one year of age and treatment with nasal steroids or spray at 12 months of the development of persistent SDB symptoms (Table 4). Atopic children not treated with nasal steroids had a 3.6% absolute increased risk of having persistent SDB symptoms (SE 1.7, $p = 0.04$). Children treated with nasal steroids who were skin-prick test negative had a 35.6% absolute increased risk of having persistent SDB symptoms (SE 9.5, $p < 0.001$). Atopic children treated with nasal steroids did not report an increased risk of persistent SDB symptom (−3.6%, SE; $p = 0.83$). Children with a maternal history of OSAS had a 3.4% absolute increased risk of developing SDB (SE 1.3, $p = 0.01$; Table 4). Children of mothers who reported being divorced, separated or widowed at time of enrollment had a 7.0% (SE 2.3; $p = 0.003$) increased risk of reporting persistent SDB symptoms while children of caregivers who reported increased perceived stress at 6 months (perceived stress scale $\geq$13) had a 3.4% increased risk (SE 1.5; $p = 0.02$). Children had a 0.8% reduced absolute percent risk reduction (SE 0.4; $p = 0.03$) in presenting with late SDB for each hour that the children slept over 24 h at six months of age. There was no significant interaction between maternal marital status and daycare attendance on persistent SDB.

4. Discussion

We identified four different parent-reported SDB symptom trajectories using data from a population-based birth cohort study; no SDB, early SDB, late SDB, and persistent SDB. Rhinitis and prior daycare attendance were associated with all SDB trajectories. We identified several unique risk factors for each SDB trajectory. Children prescribed GERD medication were more likely to present with early or late SDB symptoms. Children with a maternal history of OSAS were more likely to present with late or persistent SDB symptoms. Atopic children were more likely to present with persistent SDB symptoms. Late premature infants were more likely to present with late SDB. These findings suggest that different risk factors are associated with different phenotypes as represented by the age of onset and duration of SDB symptoms.

Our findings help to clarify the results of prior studies that have examined risk factors for SDB without stratification by phenotype. We found that rhinitis and daycare attendance were associated with three of the SDB symptom phenotypes supporting the role of viral infections [11] on SDB symptoms. Atopy was only associated with one of the phenotypes helping clarify the prior conflicting literature [7–9]. Polotsky et al., reported that adults with a family history of OSAS are two-to four-times more likely to develop OSAS compared to those adults without a family history of OSAS [24]. We found that maternal history of OSAS was associated with late SDB; a hypothesized precursor of adult SDB. Consistent with this hypothesis, dog ownership in childhood was associated with adult SDB using data from the Dunedin birth cohort study [25]. Dog ownership in the newborn period [26] has been associated with OSAS in prior studies as well. Prior studies have shown that greater dog exposure has a greater protective effect against the development of atopic disease [27]. The increased risk of SDB from owning two or more dogs may be mitigated by a decreased risk of developing atopy-associated SDB. Smoke exposure at one year of age was associated with late SDB consistent with other studies [5].

BMI, SES, breastfeeding duration [6], or being first born [4] were not associated with any of the phenotypes despite their associations with SDB in prior studies. These risk factors may be associated with a phenotype that emerges after two years of age. Several prenatal nutrition variables have been associated with subsequent neurodevelopmental and health outcomes. We have previously shown that prenatal fruit consumption is associated with cognitive development [28]. Prenatal calcium intake has been associated with higher birth weight [29], lower blood pressure in infants [30], and a lower risk of atopic disease and wheeze symptoms [31]. Both low birth weight [5] and atopy have been associated with an increased risk of SDB. We hypothesize that increased prenatal calcium may protect against the development of early-onset symptoms associated with persistent SDB; these children may eventually present with SDB but at a later onset.

We completed a home PSG at one year of age as the SRBD has not been validated for children less than two years of age. There may be a number of potential explanations for why we did not find any associations between phenotypes and PSG measures of SDB at one year of age. PSG and the SRBD scale may each be assessing different aspects of sleep and sleep disruption. The majority of sleep assessments were assessed using parent report which may over-report sleep problems in young children [32]. Finally, home PSG in particular may have poor reliability as scoring the PSG for apneas and hypopneas can be challenging due to missing data. CHILD Edmonton examines the consequences of mild OSAS or SDB (the majority of children with sleep difficulties). This study is not sufficiently powered to examine the health outcomes of those 2–3% of children with moderate to severe OSAS. Consequently, AHI and desaturations may not be associated with the milder phenotypes. We propose to repeat the home PSG at eight years of age, through the peak prevalence of childhood SDB, among the CHILD Edmonton cohort to determine whether these phenotypes are associated with PSG measures of SDB severity at an older age with a more reliable measurement.

This is the first population-based study to identify different phenotypes and unique risk factors associated with each of the phenotypes in the first two years of life. There are several strengths associated with this present study, including large sample size and repeated longitudinal data. The CHILD Edmonton cohort has extensive markers of prenatal and postnatal environmental exposures including SES and longitudinal BMI assessments. We identified several unique predictors for each phenotype, such as elements of the maternal gestational diet while controlling for several potential family, child, environmental, and maternal covariates previously associated with SDB. Prior studies have lacked the frequency of data to identify phenotypes [33–35], PSG measures of sleep in preschool, and concurrent measures of sleep duration. Results from this study will need to be replicated in other cohort studies.

The current study has several limitations. The child's environment, largely assessed by parent report, may be biased for social desirability limiting our ability to identify differences in SDB

trajectories by SES. Our findings need to be replicated in other populations as less than few of our families had children in daycare prior to 12 months of age (a reflection of the Canadian maternity leave policy) and most of our sample had a higher income, higher education, and Caucasian background. Limited home PSG equipment precluded us from repeating the PSG study at two years of age or completing PSG on parents to confirm the diagnosis of OSAS. Associations between RTI, wheeze, GERD, and SDB are likely bidirectional. Treatment or intervention studies are required to determine the bidirectional contributions of GERD, wheeze, and SDB on each other. The CHILD study excluded children born prior to 34 weeks of age and thus we could not examine the impact of prematurity.

Identifying different parent-reported SDB phenotypes, each with unique and common risk factors, has several clinical implications. Clinicians may consider earlier treatment for GERD among non-atopic children with SDB symptoms. In contrast, atopic children with SDB symptoms (persistent SDB) may warrant treatment with nasal steroids and an earlier referral for consideration of tonsillectomy or adenoidectomy. Understanding the natural history of children with SDB symptoms may help prioritize limited PSG resources for those children whose SDB symptoms persist beyond 12 months of age. Finally, each of the SDB symptom phenotypes have been associated with different degrees of adverse neurobehavioral outcomes [36] emphasizing the importance of early identification and treatment.

Following the CHILD Edmonton cohort will allow us to determine whether a fourth SDB symptom phenotype, possibly associated with obesity, emerges through school-age and adolescence. Future research through the CHILD Edmonton cohort will also allow us to determine whether these phenotypes are associated with different behavioral, neurodevelopmental, or cardio-metabolic outcomes through pre-school, school-age, and adolescence.

5. Conclusion

Our results suggest that childhood SDB may not be a homogenous disorder. Rather, childhood parent-reported SDB may represent multiple overlapping phenotypes. We identified three parent-reported SDB symptom trajectories to two years using data from the CHILD Edmonton birth cohort. The SDB trajectories were associated with common and unique risk factors in multivariate analyses. Rhinitis was associated with all SDB trajectories while BMI through the first two years was not associated with any of the phenotypes. Children prescribed GERD medication were more likely to present with early and persistent SDB. Atopy was associated with persistent SDB symptoms while males present with early SDB. Late premature infants were more likely to present with late SDB. Future studies will examine whether each of the identified SDB symptom phenotypes are associated with different behavioral and cognitive outcomes.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.sleep.2018.04.008.

Conflicts of interest

The authors have no conflicts of interest to declare.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.04.008.

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