Subjective sleep-related breathing disorders and executive function in children with intermittent or mild persistent asthma

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Authorship statement

DG, SS and KE designed and performed the study, collected and analyzed the data and wrote the initial draft. DC, DU VK and DZ contributed to the analysis of the data and revised the initial draft of the manuscript. All authors approved the final version of the manuscript.

Abstract

Objective: The impact on executive function performance of sleep-related disorders in asthmatic children has been scarcely studied in community settings. The aims of the present study were to assess the prevalence of sleep-related breathing disorders (SRBD) in children with intermittent or mild persistent asthma in primary care settings, and to examine possible correlations with measures of executive function.

Methods: We performed a case–control study including 76 children with asthma (intermittent or mild persistent), and 85 healthy controls. The parents of both patients and controls completed the Pediatric Seep Questionnaire (PSQ), and the Behavior Rating Inventory of Executive Function (BRIEF) questionnaire.

Results: We did not find any statistically significant differences regarding the scales of PSQ. Additionally, there were no statistical differences between asthmatic children and controls regarding the scales of the BRIEF questionnaire. In both asthmatic children and controls the score of the scale of obstructive sleep related breathing disorder was significantly correlated with the T scores of the two composite scales (BRI and MI) and the Global Executive Composite (GEC).
Conclusion: In children with intermittent or mild persistent asthma under the care of private general paediatricians there were no statistically significant differences regarding subjective SBD compared to healthy controls. Also there were no statistical differences between asthmatic children and controls regarding behavioral correlates of executive function during everyday life.

Keywords: children; asthma; sleep-related breathing disorder; executive function.

1. Introduction

Bronchial asthma is the most common chronic disorder in children. Sleep disordered breathing (SDB) is increasingly common in children and can result in disruption of sleep and health problems requiring intervention. SDB and asthma are both characterized by airways and systemic inflammation[1]; they share common risk factors (obesity, rhinitis and gastrooesophageal reflux) and their relationship appears to be bidirectional[2,3]. Asthmatic children are more likely to be habitual snorers or have SDB[2]. A history of poorly controlled asthma has been shown to be associated with more severe obstructive sleep apnoea (OSA)[4]. On the other hand, children with SDB are more likely to develop wheeze or asthma[2]. There are no data on the influence of asthma prophylactic treatment on SDB. Contrary, there is limited evidence supporting that surgical treatment of SDB (adenotonsillectomy) is associated with asthma improvement[2]. Bhattacharjee et al -using data from a large private insurance database – showed that in asthmatic children without co morbidities

adenotonsillectomy was associated with a significant reduction in asthma attacks as well as significant reduction in asthma medication refills[5].

The aims of the present study were to assess the prevalence of sleep-related disorders in children with intermittent or mild persistent asthma, and to investigate possible correlations of sleep-related disorders scales' scores with measures of different domains of executive function. Given the limited published data, our research hypothesis was that sleep-related disorders are more common in children with intermittent or mild persistent asthma compared to controls.

2. Methods

2.1 Study setting and population

Between November 2015 and July 2017 asthmatic patients were recruited from private primary care paediatric practices from Central Macedonia (Greece). A diagnosis of asthma was made by experienced general paediatricians on clinical grounds according to international guidelines (recurrent or chronic symptoms of wheezing, cough and/or dyspnoea that responded to antiasthmatic medication). Confirmation of wheezing by the paediatrician at any point was a prerequisite for making the diagnosis of asthma. All asthmatic children had intermittent or mild persistent asthma that required step 1 or step 2 personalized management[6]. The control group consisted of healthy children - with no history of wheezing - visiting the same primary care paediatric practices for well-child visits, who volunteered to participate in the study. Exclusion criteria included diabetes mellitus, chronic kidney disease, autistic spectrum disorders, attention deficit hyperactivity disorder, any neurocognitive delay, epilepsy, cerebral palsy and treatment with sedative or hypnotic medications. We also excluded children aged less than 5 years (where several other wheezing phenotypes exist), since day time napping is normal for this age group and cannot be used as an indicator of daytime sleepiness. Informed consent to participate in the study was obtained from the children's parents and in the adolescent age range from both the parents and the adolescents. Since we hypothesized that parental ability to pay out of pocket healthcare expenses reflects middle upper financial status, no data were collected on the socioeconomic status of study participants. All individuals fulfilling the inclusion and exclusion criteria that were approached consented to participate in the study. The study was performed in accordance with the declaration of Helsinki and the institutional review board approved the human research protocol

(Hippokrateion Hospital Scientific Council – 3 Sept 2015 Decision protocol number ΕΣ 627).

2.2 Sleep-related disorders, executive function measures and other measurements

Our group's research methods on sleep and executive function have been previously published[7]. Briefly, parents completed two validated pediatric questionnaires, the Pediatric Seep Questionnaire (PSQ), and the Behavior Rating Inventory of Executive Function (BRIEF) questionnaire, which were translated and validated in the Greek language following previous published methodology by the investigators after permission. For the BRIEF and PSQ questionnaires, translation and validation into the Greek language have been previously described[7,8]. The final Greek version of PSQ has been deposited with the copyright owners (Regent of the University of Michigan) (http://inventions.umich.edu/technologies/3766_pediatric-sleep questionnaire-designed-as-research-screen-for-symptoms-of-obstructive-sleep-apnea-and-other-sleep-disorders-in-children).

The PSQ was designed to assess symptoms of sleep disorders in children and it includes multiple scales to evaluate for different sleep disorders, including obstructive sleep- related breathing disorder (SRBD), snoring, daytime sleepiness, insomnia, and restless legs syndrome (RLS)[9]. The scales of obstructive SRBD, snoring, and daytime sleepiness have been validated against laboratory polysomnography and may be used as a valid and reliable alternative when polysomnography is not feasible [10]. This tool has been widely utilized and has shown adequate psychometric properties [11]. Scores greater than 0.33 are considered suggestive of a sleep-related disorder diagnosis. PSQ has recently been validated in asthmatic children [12].

The BRIEF questionnaire is an 86-item parent-report designed to evaluate behavioral correlates of executive function in 5- to 18-year-old children during everyday life. It includes eight subscales of executive function performance (Inhibit, Shift, and Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor), two composite scales (Behavioral Regulation Index (BRI) and Metacognition Index (MI)) and an overall summary score referred as Global Executive Composite (GEC). Raw scores are converted to T-scores according to previously published normative values. Higher scores indicate greater degrees of dysfunction[13]. This inventory is reported to have high internal consistency, good convergent validity, and good test–retest reliability[8,13].

Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, with the subjects in light clothing without shoes. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). Overweight and obesity was defined according to the revised International Obesity Task Force (IOTF) criteria[14]. BMI lambda-mu-sigma coefficients corresponding to the international IOTF cut-offs were used to calculate BMI z scores. Past medical history, current medications and disease severity were recorded by the treating physician.

2.3 Statistical analysis

The IBM SPSS 24.0 (SPSS Inc, Chicago, IL, USA) statistical package was used to analyze the data. Standard descriptive statistics, *t*-test or non-parametric methods (Mann-Whitney test, χ^2 test) were used as appropriate for the comparison between the groups. Bivariate correlation tests were used to assess relationships among PSQ and BRIEF scales. A *p*-value <0.05 was considered statistically significant.

3. Results

3.1. Demographic and anthropometric data

The study population included 76 children with intermittent or mild persistent asthma and 85 controls. All children were Caucasian and were under the care of general paediatricians in private community clinics. Demographic and anthropometric data are summarized in Table 1. Mothers answered the questionnaires in most of the cases (80%). Half of asthmatics (n=36, 50.7%) were on prophylaxis with inhaled corticosteroids (ICS) and about one third (n=25, 35.3%) on montelukast.

3.2 PSQ Data

There were no statistically significant differences between asthmatic children and controls regarding the scores of PSQ scales concerning SRBD, snoring, restless leg syndrome, insomnia, daytime sleepiness, parasomnias and behavior. Asthmatic children appeared to sleep for a statistically significant longer time according to parental reports (9.61±0.77 hours/day vs. 9.11±0.77 hours/day, p <0.001). Data regarding PSQ scales in asthmatic children and controls are summarized in table 2. The prevalence of high SRBD score (≥0.33) was 14.5% in asthmatics

compared to 7.1% in controls, but this difference was not statistically significant.

3.3. Data on executive function

There were no statistical differences between asthmatic children and controls regarding the eight subscales of executive function performance (Inhibit, Shift and Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor), two composite scales (Behavioral Regulation Index, BRI and Metacognition Index, MI) and an overall summary score referred as Global Executive Composite (GEC) of the BRIEF questionnaire (table 3). In asthmatic children and controls the score of the SRBD scale was correlated with the T scores of the two composite scales (BRI and MI) and the Global Executive Composite (GEC) (table 4).

4. Discussion

Children with intermittent or mild persistent asthma under the care of private general paediatricians had no statistically significant differences regarding subjective SDB compared to healthy controls. Also there were no statistical differences between asthmatic children and controls regarding behavioral correlates of executive function during everyday life.

Contrary to our findings, the core of the literature points towards a link between asthma and SDB[2,3,15]. Brockmann et al in a systematic review published in 2014 reported a significant association between asthma and SDB in children; they concluded that children with asthma had a significantly higher risk for SDB (OR 1.9, 95% CI 1.7 - 2.2).When only studies that used polysomnography were included in this meta-analysis, the overall OR was 1.49(95%CI 1.04 - 2.13)[3].

We believe that our findings could be explained by the fact that the asthmatic children in our sample belong to the milder end of the spectrum of this heterogeneous disease. Goldstein et al reported a “dose-dependent” effect of asthma as children with more severe asthma in their study had increased odds ratio for snoring and a positive PSQ[16]. Also the majority of studies in

Brockmann et al's aforementioned systematic review come from hospital settings signifying asthma of increased severity compared to our study[3]. Additionally, the fact that families in the present study afforded private paediatric care may have introduced bias due to higher socioeconomic status[17]. An alternative explanation could be that of questioning the diagnosis of asthma in our asthmatic group ("diagnostic transfer", i.e. overdiagnosis of asthma). This cannot be ruled out since we have had no spirometric data; however, we believe it is unlikely given that confirmation of wheezing by the paediatrician was a prerequisite for making the diagnosis of asthma and that children in the control group had no history of wheezing[18].

There are only 3 papers in the literature with similar findings. Ramagopal et al reported that a parentally reported history of asthma decreased the likelihood of polysomnographically diagnosed OSA. The authors speculated that their findings could be attributed to referral bias (parents of asthmatic children being more vigilant to nocturnal symptoms)[19]. Urschitz et al reported that history of asthma was not a risk factor for habitual snoring)[20]. Finally, in a recent retrospective study from Italy, Zaffanello et al reported that children with wheeze/asthma and unaffected ones had a similar obstructive apnoea-hypopnoea index) and oxygen desaturation index. In the same study asthmatics had longer total sleep times (9.1 ± 1.1 hours in asthmatics versus 8.7± 0.9 in controls, p =0.02) similar to our findings[21]. We cannot provide a biologically plausible explanation for this finding.

In our study there were no statistical differences between asthmatic children and controls regarding the BRIEF scales of executive function performance. This is in contrast to the findings of the only study that has used this questionnaire to evaluate behavioral correlates of executive function in asthmatic children[22]. Fryt et al found more parentally reported difficulties in asthmatic children compared to controls regarding their emotional control, holding information in their working memory and initiating everyday activities[22]. All asthmatics in Fryt's study were on ICS compared to only half of the participants in our study; therefore this discrepancy could be attributed to different disease severity, i.e. milder asthma in our sample. BRIEF questionnaire has been used to investigate impact of SDB on executive function in children with chronic kidney disease[7] and type 1 diabetes mellitus[23]. The lower executive function performance in patients with these chronic conditions could be in part attributed to sleep-related disorders. Given that in the present study there were no statistically significant differences between asthmatic children and

controls regarding the scores of PSQ scales it is no surprise that there was no impact on executive function. In the same direction, SRBD score was correlated with the T scores of BRI, MI and GEC in both asthmatics and controls. Our findings are compatible with those of a large American study that showed that mild and moderate asthma symptoms were not related to neurocognitive functioning [24]. Along the same lines, Milton et al meta-analyzing studies of academic achievement found that children with asthma performed as well as their healthy peers[25].

5. Limitations and strengths

The results of the present study should be interpreted in the light of potential limitations and strengths. One limitation of the study is the relatively small population sample. Our asthmatic children were on the mild end of the asthma spectrum and there were no data regarding asthma control, medication adherence or pulmonary function. However, this mirrors the pragmatic situation of paediatric asthma follow up in the community by generalists. Ideally, polysomnographic data should have been used to evaluate sleep disorders, given that polysomnography is the gold standard for diagnosing obstructive sleep apnoea. Unfortunately, there is no organized paediatric sleep laboratory in our area; this is a common limitation of studies in this field[15]. However, in the present study we used the PSQ that includes scales validated against formal sleep studies. PSQ was administered once only possibly introducing a recall bias. The evaluation of both sleep-related disorders and executive functioning relied on parental report with its potential biases (mono-informant bias or common rater effect, using the same informant to determine both sleep and executive function problems may inflate correlations due to item overlap)[23]. In future studies it would be worth adding data on executive function from questionnaires filled in by teachers and study participants themselves[22]. Furthermore, inclusion of formal executive function tests would be appropriate in future studies. Despite these limitations, our findings may add data to under-investigated fields. Strengths of this study include its prospective nature, the inclusion of a control group and physician diagnosis of asthma (in contrast to self reporting of asthma symptoms). Inclusion and exclusion criteria were clear and the sleep questionnaire that we have used has been recently validated in asthmatic children[12]. This is only the second study using BRIEF to evaluate behavioral correlates of executive function in asthmatic children. The present study has considerable more participants than the first study[22] and is one of the very few studies on children with intermittent or mild persistent asthma receiving care away

from specialized hospital settings.

6. Conclusions

In children with intermittent or mild persistent asthma under the care of private general paediatricians there were no statistically significant differences regarding subjective SDB compared to healthy controls. Also there were no statistical differences between asthmatic children and controls regarding behavioral correlates of executive function during everyday life.

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8. Data availability statement:

The data that support the findings of this study are available upon request from the corresponding author, The data are not publicly available due to privacy restrictions

Tables

Table1. Demographic and anthropometric characteristics of children with bronchial asthma (BA) and controls

	BA N=76	Control group N=85	***P***
	(mean ± SD or %)	(mean ± SD or %)	
Age (years)	8.08±2.74	10.11±3.47	<0.001
Male sex	41 (53.9%)	37 (43.5%)	0.187
Height z score	0.8±1.29	1.08±1.06	0.166
BMI z score	0.76±0.98	0.57±1.05	0.293

Table 2. Differences in Pediatric Sleep Questionnaire scales

	BA	Controls	*p*
Sleep Scale	mean ± SD	mean ± SD	
SRBD	0.21 ±0.15	0.18±0.12	0.184
Snoring	0.09±0.19	0.06±0.16	0.278
Restless leg syndrome	0.17±0.2	0.13±0.18	0.273

Insomnia	0.07±0.12	0.10±0.16	0.317
Daytime sleepiness	0.11±0.18	0.06±0.13	0.157
Parasomnias	0.27±0.26	0.2±0.25	0.088
Behaviour	0.5±0.27	0.505±0.305	0.634

Table 3. Behavior Rating Inventory of Executive Function (BRIEF) scales scores in patients and controls

BRIEF scale	BA (mean±SD)	Controls (mean±SD)	*P*
Inhibit T score	49.32±7.70	50.03±9.06	0.614
Shift T score	49.5±9.81	49.51±9.37	0.991
Emotional control T score	50.88±10.24	51.30±10.91	0.814
BRI T score	49.9189.15	50.41±10.33	0.764
Initiate T score	51.73±8.96	51.26±10.47	0.777
Working memory T score	47.29±8.33	47.96±8.24	0.639
Plan/organize T score	46.85±10.02	49.33±9.53	0.145
Org. of material T score	49.67±9.49	48.13±9.07	0.324
Monitor T score	47.305±10.33	49.78±9.85	0.153

MI T score	48.37±9.43	48.88±8.88	0.754
GEC T score	48.44±8.15	49.35±9.17	0.572

BA, Bronchial asthma; BRI, Behavioral Regulation Index; GEC, Global Executive Composite; MI, Metacognition Index.

Table 4. Correlations between SRBD scale and Behavior Rating Inventory of Executive Function (BRIEF) scales

	Controls		BA	
	SRBD			
	R	p	R	P
BRI T score	0.505	<0.005	0.265	<0.05
MI T score	0.524	<0.005	0.642	<0.005
GEC T score	0.565	<0.005	0.542	<0.005

BRI: Behavioral Regulation Index

GEC: Global Executive Composite

MI: Metacognitive Index

SRBD: Scale of Obstructive Sleep Related Breathing Disorder of the Pediatric Sleep Questionnaire

1. Malakasioti G, Gourgoulianis K, Chrousos G, Kaditis A. Interactions of obstructive sleep-disordered breathing with recurrent wheezing or asthma and their effects on sleep quality. *Pediatric pulmonology.* Nov 2011;46(11):1047-1054.
2. Sanchez T, Castro-Rodriguez JA, Brockmann PE. Sleep-disordered breathing in children with asthma: a systematic review on the impact of treatment. *Journal of asthma and allergy.* 2016;9:83-91.
3. Brockmann PE, Bertrand P, Castro-Rodriguez JA. Influence of asthma on sleep disordered breathing in children: a systematic review. *Sleep medicine reviews.* Oct 2014;18(5):393-397.
4. Ramagopal M, Mehta A, Roberts DW, et al. Asthma as a Predictor of Obstructive Sleep Apnea in

Urban African-American Children. *Journal of Asthma.* 2009/11/05 2009;46(9):895-899.

5. Bhattacharjee R, Choi BH, Gozal D, Mokhlesi B. Association of adenotonsillectomy with asthma outcomes in children: a longitudinal database analysis. *PLoS medicine.* Nov 2014;11(11):e1001753.
6. Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention,2019.* 2019.
7. Stabouli S, Gidaris D, Printza N, et al. Sleep disorders and executive function in children and adolescents with chronic kidney disease. *Sleep medicine.* Mar 2019;55:33-39.
8. Stabouli S, Papadimitriou E, Gidaris D, et al. Reliability and validity of the Greek Version of BRIEF and BRIEF-SR. *European Journal of Paediatric Neurology.* 2017;21(Supplement 1):e210-e211.
9. Chervin RD, Weatherly RA, Ruzicka DL, et al. Subjective sleepiness and polysomnographic correlates in children scheduled for adenotonsillectomy vs other surgical care. *Sleep.* Apr 2006;29(4):495-503.
10. Chervin RD, Weatherly RA, Garetz SL, et al. Pediatric sleep questionnaire: prediction of sleep apnea and outcomes. *Archives of otolaryngology--head & neck surgery.* Mar 2007;133(3):216-222.
11. Spruyt K, Gozal D. Pediatric sleep questionnaires as diagnostic or epidemiological tools: a review of currently available instruments. *Sleep medicine reviews.* Feb 2011;15(1):19-32.
12. Ehsan Z, Kercsmar CM, Collins J, Simakajornboon N. Validation of the pediatric sleep questionnaire in children with asthma. *Pediatric pulmonology.* Mar 2017;52(3):382-389.
13. Gioia GA, Isquith PK, Retzlaff PD, Espy KA. Confirmatory factor analysis of the Behavior Rating Inventory of Executive Function (BRIEF) in a clinical sample. *Child neuropsychology : a journal on normal and abnormal development in childhood and adolescence.* Dec 2002;8(4):249-257.
14. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. *Pediatric obesity.* Aug 2012;7(4):284-294.
15. Castro-Rodriguez JA, Brockmann PE, Marcus CL. Relation between asthma and sleep disordered breathing in children: is the association causal? *Paediatr Respir Rev.* Mar 2017;22:72-75.
16. Goldstein NA, Aronin C, Kantrowitz B, et al. The prevalence of sleep-disordered breathing in children with asthma and its behavioral effects. *Pediatric pulmonology.* Dec 2 2014.
17. Chen E, Shalowitz MU, Story RE, et al. Parents' childhood socioeconomic circumstances are associated with their children's asthma outcomes. *The Journal of allergy and clinical immunology.* Sep 2017;140(3):828-835 e822.
18. Lowe L, Murray CS, Martin L, et al. Reported versus confirmed wheeze and lung function in early life. *Archives of disease in childhood.* June 1, 2004 2004;89(6):540-543.
19. Ramagopal M, Scharf S, Roberts D, Blaisdell C. Obstructive sleep apnea and history of asthma in snoring children. *Sleep Breath.* 2008/11/01 2008;12(4):381-392.

20. Urschitz MS, Guenther A, Eitner S, et al. Risk factors and natural history of habitual snoring. *Chest.* Sep 2004;126(3):790-800.
21. Zaffanello M, Gasperi E, Tenero L, et al. Sleep-Disordered Breathing in Children with Recurrent Wheeze/Asthma: A Single Centre Study. *Children.* Nov 14 2017;4(11).
22. Fryt J, Pilecka W, Smolen T. Does Asthma Disturb Executive Functions and Self-regulation in Children? *Polish Journal of Applied Psychology.* 2013;12(2):55-74.
23. Caruso NC, Radovanovic B, Kennedy JD, et al. Sleep, executive functioning and behaviour in children and adolescents with type 1 diabetes. *Sleep medicine.* Dec 2014;15(12):1490-1499.
24. Annett RD, Aylward EH, Lapidus J, Bender BG, DuHamel T. Neurocognitive functioning in children with mild and moderate asthma in the childhood asthma management program. The Childhood Asthma Management Program (CAMP) Research Group. *The Journal of allergy and clinical immunology.* Apr 2000;105(4):717-724.
25. Milton B, Whitehead M, Holland P, Hamilton V. The social and economic consequences of childhood asthma across the lifecourse: a systematic review. *Child: Care, Health and Development.* 2004;30(6):711-728.