Assessment of Vitamin D, exercise, and lipid profile associated with Excessive Daytime Sleepiness in School Children

Myongsoon Sung, Seonkyeong Rhie, Ju Hee Kim, Seung Won Lee, Eun Kyo Ha, Hye Mi Jee, Eun-Gyong Yoo, Kyu Young Chae, Man Yong Han

PII: S1389-9457(20)30509-8

DOI: https://doi.org/10.1016/j.sleep.2020.11.017

Reference: SLEEP 4644

To appear in: *Sleep Medicine*

Received Date: 6 August 2020

Revised Date: 16 November 2020

Accepted Date: 18 November 2020

Please cite this article as: Sung M, Rhie S, Kim JH, Lee SW, Ha EK, Jee HM, Yoo E-G, Chae KY, Han MY, Assessment of Vitamin D, exercise, and lipid profile associated with Excessive Daytime Sleepiness in School Children, *Sleep Medicine*, https://doi.org/10.1016/j.sleep.2020.11.017.

Assessment of Vitamin D, exercise, and lipid profile associated with Excessive Daytime Sleepiness in School Children

Running head: risk factors of EDS in children

Myongsoon Sung[1†], Seonkyeong Rhie[2†], Ju Hee Kim[2], Seung Won Lee[3], Eun Kyo Ha[4], Hye Mi Jee[2], Eun-Gyong Yoo[2], Kyu Young Chae[2*], Man Yong Han[2*]

[1]Department of Pediatrics, Soon Chun Hyang University Gumi Hospital, Soon Chun Hyang University College of Medicine, Gumi, Korea

[2]Departments of Pediatrics, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Korea

[3]Department of Data Science, Sejong University College of Software Convergence, Seoul, Korea

[4]Department of Pediatrics, Kangnam Sacred Heart Hospital, Hallym University Medical Center, Seoul, Korea

[†]These authors contributed equally to this work.

[*]Corresponding author

Professor Man Yong Han, MD

Department of Pediatrics, CHA University School of Medicine

59, Yatap-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, 13496, Republic of Korea

Phone: +82-31-780-6262; Fax: +82-31-780-5239

Email: drmesh@gmail.com

Professor Kyu Young Chae, MD, PhD

Department of Pediatrics, CHA University School of Medicine

59, Yatap-ro, Bundang-gu, Seongnam-si, Gyeonggi-do, 13496, Republic of Korea

Phone: +82-31-780-5230; Fax: +82-31-780-5239

Email: barnabas@cha.ac.kr

*These authors contributed equally to this work.

Abstract

Previous research reported associations of excessive daytime sleepiness (EDS) with a low vitamin D level, obesity, and sexual maturity. The aim of this study was to identify the association and rank the importance of these with EDS. This study examined 618children who were 10 to 12 year-old. The pediatric daytime sleepiness scale (PDSS) was used to evaluate EDS and sleep patterns. EDS was defined as a total PDSS score above 17. We ranked the importance of the relationship of these factors with EDS using random forest analysis. EDS (*n* = 111, 18%) was positively associated with more advanced pubertal stage in girls, chronic cough, urticaria, and allergic rhinitis. Multivariable analysis with adjustment for confounding indicated that children with low level of 25-hydroxyvitaminD_3 (25(OH)D_3 (<20ng/mL) and high-density lipoprotein-cholesterol (HDL-C) (<40mg/dL) levels had an increased risk of EDS (25(OH)D_3:adjusted odds ratio [aOR] = 1.73; 95% confidence interval [CI]: 1.06 to 2.81; *P* = 0.028; HDL-C: aOR = 2.84; 95% CI: 1.05 to 7.68; *P* = 0.039). Random forest analysis indicated that 25(OH)D_3 level, exercise, and body mass index (BMI) were over three. This study indicated high levels of 25-(OH)D_3 and HDL-C and performing regular exercise decreased the risk of EDS.

Keywords: Excessive daytime sleepiness; Children; Serum 25-Hydroxyvitamin D_3; body mass index; regular exercise

1. Introduction

Excessive daytime sleepiness (EDS) is defined as being unable to maintain wakefulness and alertness during the major waking episodes of the day, and sleep occurs almost daily unintentionally or at inappropriate times for at least three months [1, 2]. It is important for clinicians to recognize EDS, because it may indicate an undiagnosed sleep disorder or other conditions and it can also impair development and daily function [2, 3]. Moreover, EDS in school children makes it difficult for them to adjust to school life and concentrate on their work [2-4]. Some clinicians now consider EDS a major health problem that affects from 25% to 40% of children and adolescents [4].

Previous research established that EDS in children is significantly associated with obesity, lack of physical exercise, the mid-puberty stage, and allergic diseases, such as asthma and allergic rhinitis (AR) [5-10]. Some other studies demonstrated that a low vitamin D level may be associated with EDS, and that exposure to sunshine and or dietary vitamin D supplements may reduce EDS [11, 12]. A low vitamin D level in school children may also contribute to the progression to dyslipidemia [13], so children with EDS may also have abnormal lipid profiles. Thus, it is necessary to examine the factors associated with EDS in school children, including serum vitamin D level, lipid profile, obesity, pubertal stage, allergic status, and other environmental and life style factors so that appropriate interventions can be implemented.

However, the detailed relationships of EDS with these different factors and their relative importance remain unclear. Previous studies of pediatric populations were limited by the validity and variety of questionnaires used for assessment and or by the absence or

incomplete analysis of blood samples. Therefore, the aims of the present study were to identify factors associated with EDS and to rank the importance of these different factors, including demographic, environmental, and life style characteristics; vitamin D level; hematological results; and lipid profile. We also investigated the association of EDS in school children with the severity of AR, pubertal stage, and results from acoustic rhinometry and physical examinations.

2. Materials and Methods

2.1 Participants

This study enrolled children from the general pediatric population who were 10 to 12 year-old and attended 11 elementary schools in Korea from March to August of 2017. The parents were asked to respond to the questionnaires prior to the physical examination, acoustic rhinometry, and blood sampling. The parents of 618 children returned completed questionnaires, agreed to participate in this study. Also, they agreed to acoustic rhinometry and blood sampling tests. Pediatricians and well-trained pediatric technicians performed the physical examinations, including a sexual maturity rating (SMR) [14], acoustic rhinometry, and blood sampling. This study was approved by the Institutional Review Board of the CHA Bundang Medical Center (IRB No. 2017-04-049). Besides, all processes were performed in accordance with the related regulations and guidelines.

2.2 Definition of daytime sleepiness

Sleepiness was estimated using the Korean version of Pediatric Daytime Sleepiness Scale (PDSS), in which a higher score means more daytime sleepiness [15, 16]. The PDSS has 8

questions, each with a score of 0 to 3 (range: 0 to 24), and assesses sleepiness during class, homework, daytime, and morning. It also assesses the difficulty of remaining awake and mood stability. EDS was defined by a PDSS total score above 17, which is more than 1standard deviation above the median in a previous study of Korean students of the same age [15]. Daytime sleepiness and average sleep onset and wake time for last 7 days was determined by direct query of students. Sleep duration was computed from sleep onset and wake time. Data indicating sleep duration over 12 h or less than 3 h per day were excluded, because these answers may indicate a misunderstanding of the questions.

2.3 Possible causes of daytime sleepiness

Among the questionnaire items that assessed individual life style and environmental exposures, specific items that had significant associations with EDS in previous studies (e.g., weight, age, gender, BMI, Tanner stage [SMR], allergic disease, chronic coughing) [2-12] based on a *P* value below 0.05 were also considered. The environmental and individual life style factors examined were: exposure to secondary tobacco smoke (0 to 20 cigarettes per day), type of ventilation (window *vs.* central-mixed), frequency of exercise, total chemical burden (TCB), and household mold odors (no *vs.* yes). The frequency of exercise was determined by the answer to the question: “How many days per week does your child exercise, besides physical education in school, and experience sweating or shortness of breath for more than 30 minutes”; the possible answers were: none, 1 to 2, 3 to 6, and 7 days per week. TCB was calculated from the total time of exposure to 12 different cleaning products [17]. This questionnaire also collected data on certain general characteristics of each child (sex, birth date, prenatal and postnatal history, height, weight, parental history of allergic

diseases, and age at menarche). However, the questionnaire items didn't include sleep disordered breathing, such as apneas or hypopneas or insufficient ventilation during sleep.

2.4 Diagnosis of allergic diseases and definition of chronic cough

The diagnosis of allergic diseases (asthma, AR, and atopic dermatitis [AD]) was based on the Korean International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, according to the 12-month history of each child, as previously described [18]. Allergic conjunctivitis was defined by an affirmative answer to a question that asked about the presence of nose problems accompanied by itchy and watery eyes during the past 12 months. Urticaria was defined by an affirmative answer to a question that asked about the presence of burning, itching, or a rash resembling a mosquito bite or swelling on the skin during the past 12 months. Based on previous studies [19], a "chronic cough" was defined by an affirmative answer to the yes-or-no question: "In the past 12 months, has your child had a problem with a cough whose duration was more than 4 weeks?" The period of the chronic cough was also recorded (1 month ago *vs*. more than 1 month ago).

2.5 Sexual maturity

The sexual maturity of children was measured using the SMR scale [14]. Parents were given a sequence of pictures showing different stages of sexual maturity, and they indicated the presence of pubic hair and breasts in their female children and the presence of pubic hair, penis, and testes, in their male children. For scoring of males, a visible sign of testicular enlargement with development of pubic hair was assigned SMR 2; penile growth as SMR 3; and increased testes volume as SMR 4. For scoring of females, breast buds or development of

pubic hair was assigned SMR 2; and the score increased from SMR 3 to 5 as pubic hair increased and breast development progressed.

2.6 Rhinitis severity, symptom score, and acoustic rhinometry

Rhinitis severity and symptoms were assessed using the Total Five Symptom Score (T5SS). Nasal symptoms were scored as the sum of the scores of four nasal symptoms (watery rhinorrhea, sneezing, nasal obstruction, and nasal pruritus) on a scale of 0 to 3 (0, none; 1, mild; 2, moderate; and 3, severe) during the last 12-months, as previously described [20]. The severity of nasal symptoms was assessed using a visual analogue scale (VAS, scale bar range: 0 to 10) which asked about the severity of symptoms during the past month. Nasal patency was measured using acoustic rhinometry, based on standardized international recommendations. A well-trained pediatric technician applied the probe to each student's nostrils, and then asked the participant to hold his or her breath for approximately 5 seconds. The nasal volume from 0 to 5 cm inside the nasal cavity was defined as baseline nasal airway patency. Decongested nasal airway patency was defined by measuring the volume 15 min after administration of a topical alpha agonist to each nostril. This examination was repeated at least 3 times until the standard deviation of the values was less than 15%.

2.7 Vitamin D and anemia levels and lipid profile

Serum levels of 25-hydroxyvitaminD_3 ($25(OH)D_3$) were determined using an ELISA kit (Immunodiagnostic Systems, COBAS 6000 Roche, Manheim Germany) after extraction with acetonitrile. For analysis, children were classified as deficient (<20 ng/mL), insufficient (20 to 29.9 ng/mL), or sufficient (≥30 ng/mL) [21]. To evaluate anemia, hemoglobin, serum

ferritin, and iron levels were measured. Hemoglobin was measured using an automatic electronic cell calculator, serum ferritin was analyzed using an electrochemiluminescence immunoassay (Aterica Waterloo, ON, USA), and serum iron was measured using a modular analyzer (Cobas 8000, Roche Diagnostics GmbH, Mannheim, Germany). Non-fasting venous blood samples were collected, centrifuged, and analyzed within 2 h of collection using a Cobas 8000 c702 Chemistry Autoanalyzer (Roche, Basel, Switzerland) for determination of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG).

2.8 Ethics statement

The study protocol was approved by the Institutional Review Board of the CHA Bundang Medical Center (IRB No. 2017-04-049). Written informed consent was obtained from the parents or guardians of all participants following a detailed explanation of the study.

2.9 Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA) and the R system for statistical computing version 2.8.134 (Vienna, Austria). Frequencies and continuous variables were compared using the χ^2 test and Student's *t*-test, respectively. Multivariable regression models were used to estimate adjusted odds ratios (aORs) and 95% confidence intervals (CIs), with adjustment for age, sex, BMI z-score, vitamin D deficiency, location of residence, presence of allergic diseases, and physician-diagnosed asthma, AR, and AD in parents. Pearson and Spearman correlation methods were used for analysis of associations between various factors and daytime sleepiness.

For analysis of the association of different variables with daytime sleepiness after multivariable regression, the random forest method was used to quantify the predictive performance of each factor. Random forest analyses were performed using the R system, and a variable importance ranking of each random forest was created. Mean decreases accuracies and Gini were calculated to model accuracy from permuting the value in each feature and measuring the importance of each variable in estimating the target variable. To ease interpretation of the graphical displays, a suitable ordering of the components was identified using seriation [22]. Random forest to regression has the benefit to analyzing the data with a non-linear trend or extrapolation without importance. Moreover, this analysis easily and intuitively demonstrates the quantitative priorities of each risk factor [23]. Statistical significance was defined as a P value below 0.05.

3. Results

3.1 Demographic data, clinical characteristics, and laboratory results

We examined 618 children, 111 (18.0%) who had excessive daytime sleepiness (EDS) and 507 (82.0%) who were healthy controls (Table 1). The two groups had no significant differences in age, sex, BMI z-score, weight status, birth weight, and presence of allergic diseases (asthma, AR, AD; $P > 0.05$ for all comparisons).

Blood sampling was conducted in all participating children, but only 485 children (393 from the control group and 92 from the EDS group) had usable results, because of a rejection by the child or an error of the sampling. The control and EDS groups had no significant differences in lipid profile (total cholesterol, TG, LDL-C, and HDL-C), hematological

parameters (hemoglobin, serum iron and ferritin levels, and total eosinophil count), and vitamin D status ($P > 0.05$ for all comparisons).

3.2 Sleep patterns and sleepiness

Analysis of mean PDSS scores (Table 2) indicated a higher score in the EDS group than the control group (19.11±2.08 *vs.* 9.86±3.87). In addition, children with EDS slept more ($P = 0.006$), woke up later ($P < 0.001$), and went to bed later ($P < 0.001$). Further analysis (Table 3) indicated that children who were older (–0.29, 95% CI: –0.04 to –0.016, $P < 0.001$) and had higher BMI (–0.015 95% CI: –0.026 to –0.003, $P < 0.015$) had shorter sleep durations, but age and BMI had no impact on PDSS score ($P > 0.05$ for both). Boys had longer sleep durations than girls, but gender had no impact on PDSS score ($P = 0.534$).

3.3 Association of hematologic parameters, lipid profile, and 25(OH)D_3 level with EDS

Analysis of the blood samples (Table 4) indicated the control and EDS groups had significant differences in the levels of HDL-C ($P = 0.045$). Multivariable analysis with adjustment for confounding factors indicated that children with low HDL-C levels (<40 mg/dL) had an increased risk of EDS (aOR = 2.84; 95% CI: 1.05 to 7.68; $P = 0.039$). The multivariable analysis also indicted that children with low 25(OH)D_3 levels (<20 ng/mL) had an increased risk of EDS (aOR = 1.73; 95% CI: 1.06 to 2.81; $P = 0.028$), although this difference was not significant when there was no adjustment for confounding ($P = 0.064$). The two groups had no differences in the levels of hemoglobin, serum ferritin and iron; total eosinophil count; or total cholesterol, LDL-C, and TGs ($P > 0.05$ for all comparisons).

3.4 Associations of EDS with environmental or life style factors in EDS group

Our analysis indicated that EDS was associated with multiple environmental and life style factors (Fig.1). In particular, EDS was positively associated with more advanced pubertal stage in girls, urticaria, chronic cough, allergic conjunctivitis, total eosinophil count, nasal congestion index, presence and severity (T5SS) of AR, total chemical burden (intensity), mold exposure, and exposure to second-hand smoke. However, EDS was negatively associated with the amount of exercise, 25(OH)D_3 level, baseline nasal patency, and mixed-mode ventilation.

3.5 Importance of different variables on causing EDS

We considered all variables simultaneously and used the random forest method to identify the most significant factors (Fig.2). Figure 2 showed the mean decrease accuracy of each risk factors such as 25(OH)D_3 level (mean decrease accuracy= 3.80), amount of exercise (3.77), and BMI (3.50). These are the most significant factors to EDS, and otherwise sexual development in boys (3.0), baseline nasal volume (2.8), TGs (2.3), and chronic cough (2.0) also powerful factors for causing EDS.

4. Discussion

In the present study, we identified factors related with EDS in school children by use of a questionnaire, blood sampling, and acoustic rhinometry, and we then ranked the importance of these different factors. The major results were that low 25(OH)D_3 level, lack of exercise, and high BMI were the most important factors contributing to EDS, of which low 25(OH)D_3 level was the strongest factor.

Vitamin D deficiency may contribute to symptoms of sleepiess by upregulating known sleep-regulating substances, such as TNFα [24] and NFκB [25], which function as master switches for inflammation and trigger the cellular inflammatory cascade. Previous research proposed that this mechanism explains the relationship of low level of vitamin D with increased risk of EDS [11, 12], in agreement with the present study. Additionally, vitamin D deficiency have a strong relationship with shorter sleep duration and less sleep efficiency after adjusting for BMI and age, but no relationship with sleep stages, periodic limb movements, and arousal index from polysomnography in recent study [26]. Vitamin D supplementation can reduce the symptoms of EDS in patients with low levels of vitamin D [27]. Therefore, vitamin D level appears to play a crucial role in predicting the severity of EDS, and vitamin D supplements could be used to treat school children with this condition. However, we have no data from polysomnography in present study and didn't analysis this relationship, so future studies are required to evaluate this relationship.

We found that total cholesterol and TGs had no relationship with EDS, although a low HDL-C level was associated with EDS. A previous study demonstrated that the rate of hypertriglyceridemia and low LDL-C was significantly more common in adults with EDS and severe obstructive sleep apnea syndrome, than in a non-EDS group [28]. To our best knowledge, the present study is the first to report an association between EDS and lipid profile in school children. Further studies are needed to verify the negative effects low HDL-C level on EDS in this population.

Exercise has a strong inverse association with obesity [29,30], and previous research indicated that individuals who regularly performed physical exercise had a lower prevalence of EDS, possibly because regular exercise has anti-inflammatory effects, in that it alters

cytokine responses may thereby prevent EDS [31-33]. Additionally, some previous studies have demonstrated that EDS was associated with central obesity [34, 35]. Inflammatory responses are associated with obesity and obstructive sleep apnea syndrome, and these conditions are related to poor sleep quality or insufficient sleep, the main manifestation of EDS [31-35]. The reason for the close relationships of EDS, physical exercise, and BMI may be that the physical exercise leads to physiological adaptations that increase slow-wave sleep time and decrease fluid accumulation, the systemic inflammatory response, and body weight gain.

Previous research reported that EDS was more common among females who are adolescents and adults, but there was no gender difference among children [36, 37] in agreement with the present study. Children in mid-puberty have increased levels of gonadal hormones, and this could disrupt sleep patterns and the circadian clock, and then lead to EDS [37]. Thus, our results indicated that girls with a higher Tanner stage (after adjustment for confounding factors) was associated with EDS in agreement with previous studies which reported a female- preponderance of EDS at mid-puberty [36]. However, we found that a higher Tanner stage in boys was also associated with EDS, even though the boys in this study (10 to 12 year-old), were some pre-pubertal boys. We would like to explain that our results are not the only proof of the statistical significance of association between EDS and puberty. Thus, further research is warranted to examine the relationship between EDS and puberty and the underlying mechanisms.

We found that the presence of an allergic disease such as asthma or AR or urticaria, is associated with EDS, in agreement with previous studies [6, 10]. The nocturnal symptoms of asthma or AR can interrupt sleep, lead to fragmented nighttime sleep, and may therefore

cause EDS. Additionally, chronic cough maybe associated with asthma and AR in school children, because almost 70% of children with chronic cough use asthma medications [37]. In agreement, we found that chronic cough was positively associated with EDS. Itching from urticaria could lead to fragmented nighttime sleep, and this could also explain our finding of a positive relationship of urticaria with EDS. However, unfortunately, no previous studies have examined the association between EDS and urticaria.

Also, we found that EDS had associations with several environmental factors (TCB, mold exposure, secondary smoking, and ventilation type), and the overall prevalence of EDS in the present study was 18.0%. Some previous studies reported an association of smoking and EDS in adults [39] but our identification of these other effect factors is a novel finding. Notably, the prevalence of EDS in the present study is similar that from a questionnaire-based study (17% to 21% of school-aged children and adolescents) [40], but lower than another previous study (25% to 40% of children and adolescents) [4].

There are several limitations to the present study. First, the sample size of the control group was much larger than that of the EDS group. Second, we could not directly measure daytime sleepiness and daytime napping. Unfortunately we did not assess sleepiness defined by the PDSS, but inferred it presence indirectly based on differences in weekday and weekend sleep durations. Third, this study was a cross-sectional analysis that used questionnaires, so there is a possibility of recall bias by the parents regarding sleep time of their children. Additionally, this investigation was conducting during a 2 month period (June to July 2017) and we only examined school children who lived in a single province in Korea. Therefore, our findings may not be applicable to other seasons and geographic regions. We need further studies in other areas of Korea to verify the findings presented here.

Nevertheless, the strengths of the present study are that we analyzed data from blood sampling and acoustic rhinometry. Also, the questionnaire comprehensively examined, the impact of various and environmental factors on EDS, such as TCB, mold exposure, secondary smoking, and ventilation type. Thus, unlike previous studies of this topic, we were able to rank the relative importance of different factors on EDS in school children.

Our study indicated that school children with high vitamin D levels and those who performed more exercise were less likely to have EDS, but those who were obese, had allergies, and had a more advanced Tanner stage were more likely to have EDS. Certain environmental factors also affected the probability of EDS in school children. Strategies to prevent EDS in school children should focus on the modifiable factors identified here.

Acknowledgements

This study was supported by the Seongnam Atopy Project (SAP2017). Grant funding was provided by the Metropolis of Seongnam and the Soonchunhyang University Research Fund.

Contributions

Dr. Sung and Han had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Dr. Chae and Han

Acquisition, analysis, and interpretation of data: All authors.

Drafting the manuscript: Dr. Sung and Rhie

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Dr. Han and Rhie

Obtained funding: Dr. Jee

Study supervision: Dr. Chae and Han

Ethics declarations

Competing interests

The authors have indicated they have no potential conflicts of interest to disclose.

Funding: This study was supported by the Seongnam Atopy Project (SAP2017). Grant funding was provided by the Metropolis of Seongnam and the Soonchunhyang University Research Fund.

ORCIDs

Myongsoon Sung: https://orcid.org/0000-0002-6329-286X

Man Yong Han: https://orcid.org/0000-0002-9077-5779

Seonkyeong Rhie: https://orcid.org/0000-0003-3371-8310

Kyu Young Chae: https://orcid.org/0000-0003-4343-5853

References

[1] Banks S, Dinges DF. Behavioral and physiological consequences of sleep restriction. J Clin Sleep Med. 2007;3(5):519-28.

[2] Kothare SV, Kaleyias J. The clinical and laboratory assessment of the sleepy child. Semin Pediatr Neurol. 2008;15(2):61-9.

[3] Fallone G, Owens JA, Deane J. Sleepiness in children and adolescents: clinical implications. Sleep Med Rev. 2002;6(4):287-306.

[4] Mindell JA, Meltzer LJ. Behavioural sleep disorders in children and adolescents. Ann Acad Med Singapore. 2008;37(8):722-8.

[5] Panossian LA, Veasey SC. Daytime sleepiness in obesity: mechanisms beyond obstructive sleep apnea--a review. Sleep. 2012;35(5):605-15.

[6] Stuck BA, Czajkowski J, Hagner AE, et al. Changes in daytime sleepiness, quality of life, and objective sleep patterns in seasonal allergic rhinitis: a controlled clinical trial. J Allergy Clin Immunol. 2004;113(4):663-8.

[7] Liu Y, Zhang J, Li SX, et al. Excessive daytime sleepiness among children and adolescents: prevalence, correlates, and pubertal effects. Sleep Med. 2019;53:1-8.

[8] Calhoun SL, Vgontzas AN, Fernandez-Mendoza J, et al. Prevalence and risk factors of excessive daytime sleepiness in a community sample of young children: the role of obesity, asthma, anxiety/depression, and sleep. Sleep. 2011;34(4):503-7.

[9] Colrain IM, Baker FC. Changes in sleep as a function of adolescent development. Neuropsychol Rev. 2011;21(1):5-21.

[10] Kallin SA, Lindberg E, Sommar JN, et al. Excessive daytime sleepiness in asthma: What are the risk factors? J Asthma. 2018;55(8):844-50.

[11] McCarty DE, Reddy A, Keigley Q, et al. Vitamin D, race, and excessive daytime sleepiness. J Clin Sleep Med. 2012;8(6):693-7.

[12] Lee HJ, Choi H, Yoon IY. Impacts of serum vitamin D levels on sleep and daytime sleepiness according to working conditions. J Clin Sleep Med. 2020;16(7):1045-54.

[13] Jiang X, Peng M, Chen S, et al. Vitamin D deficiency is associated with dyslipidemia: a cross-sectional study in 3788 subjects. Curr Med Res Opin. 2019;35(6):1059-63.

[14] Euling SY, Herman-Giddens ME, Lee PA, et al. Examination of US puberty-timing data from 1940 to 1994 for secular trends: panel findings. Pediatrics. 2008;121 Suppl 3:S172-91.

[15] Rhie S, Lee S, Chae KY. Sleep patterns and school performance of Korean adolescents

assessed using a Korean version of the pediatric daytime sleepiness scale. Korean J Pediatr. 2011;54(1):29-35.

[16] Drake C, Nickel C, Burduvali E, et al. The pediatric daytime sleepiness scale (PDSS): sleep habits and school outcomes in middle-school children. Sleep. 2003;26(4):455-8.

[17] Liu X, Lao XQ, Wong CC, et al. Frequent use of household cleaning products is associated with rhinitis in Chinese children. J Allergy Clin Immunol. 2016;138(3):754-60 e6.

[18] Sung M, Baek HS, Yon DK, et al. Serum Periostin Level Has Limited Usefulness as a Biomarker for Allergic Disease in 7-Year-Old Children. Int Arch Allergy Immunol. 2019;180(3):195-201.

[19] Song DJ, Song WJ, Kwon JW, et al. KAAACI Evidence-Based Clinical Practice Guidelines for Chronic Cough in Adults and Children in Korea. Allergy Asthma Immunol Res. 2018;10(6):591-613.

[20] Lee S, Koh HY, Yon DK, et al. Association of Sensitization to Different Aeroallergens With Airway Function and Nasal Patency in Urban Children. Allergy Asthma Immunol Res. 2019;11(4):572-82.

[21] Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357(3):266-81.

[22] Hahsler M, Hornik K, Buchta C. Getting things in order: an introduction to the R package seriation. Journal of Statistical Software. 2008;25(3):1-34.

[23] Ulrike Grömping. Variable Importance Assessment in Regression: Linear Regression versus

Random Forest. The American Statistician Volume 63, 2009 - Issue 4

[24] Peterson CA, Heffernan ME. Serum tumor necrosis factor-alpha concentrations are negatively correlated with serum 25(OH)D concentrations in healthy women. J Inflamm (Lond). 2008;5:10.

[25] Jablonski KL, Chonchol M, Pierce GL, et al. 25-Hydroxyvitamin D deficiency is associated with inflammation-linked vascular endothelial dysfunction in middle-aged and older adults. Hypertension. 2011;57(1):63-9.

[26] Baha AS , Zarmina E, David GI. Vitamin D and sleep in children. J Clin Sleep Med . 202;16:1119-23.

[27] McCarty DE. Resolution of hypersomnia following identification and treatment of vitamin d deficiency. J Clin Sleep Med. 2010;6(6):605-8.

[28] Huang JF, Chen LD, Lin QC, et al. The relationship between excessive daytime sleepiness and metabolic syndrome in severe obstructive sleep apnea syndrome. Clin Respir J. 2016;10(6):714-21.

[29] Yi DY, Kim SC, Lee JH, et al. Clinical practice guideline for the diagnosis and treatment of pediatric obesity: recommendations from the Committee on Pediatric Obesity of the Korean

Society of Pediatric Gastroenterology Hepatology and Nutrition. Korean J Pediatr. 2019;62(1):3-21.

[30] Ronald J, Headid III, Park SY. The impacts of exercise on pediatric obesity. Clin Exp Pediatr . 2020 Aug 4. doi: 10.3345/cep.2020.00997. Online ahead of print.

[31] Kwon AM, Shin C. Structural equation modelling for the effect of physical exercise on excessive daytime sleepiness. Public Health. 2016;141:95-9.

[32] Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol (1985). 2005;98(4):1154-62.

[33] Alves Eda S, Ackel-D'Elia C, Luz GP, et al. Does physical exercise reduce excessive daytime sleepiness by improving inflammatory profiles in obstructive sleep apnea patients? Sleep Breath. 2013;17(2):505-10.

[34] Gangwisch JE, Malaspina D, Boden-Albala B, et al. Inadequate sleep as a risk factor for obesity: analyses of the NHANES I. Sleep. 2005;28(10):1289-96.

[35] Cappuccio FP, Taggart FM, Kandala NB, et al. Meta-analysis of short sleep duration and obesity in children and adults. Sleep. 2008;31(5):619-26.

[36] John B. Sleep duration and daytime sleepiness in Indian adolescents: is there a gender difference? Indian J Pediatr. 2014;81(11):1243.

[37] Lindberg E, Janson C, Gislason T, et al. Sleep disturbances in a young adult population: can gender differences be explained by differences in psychological status? Sleep. 1997;20(6):381-7.

[38] Thomson F, Masters IB, Chang AB. Persistent cough in children and the overuse of medications. J Paediatr Child Health. 2002;38(6):578-81.

[39] Jaussent I, Morin CM, Ivers H, et al. Incidence, worsening and risk factors of daytime sleepiness in a population-based 5-year longitudinal study. Sci Rep. 2017;7(1):1372.

[40] Fricke-Oerkermann L, Pluck J, Schredl M, et al. Prevalence and course of sleep problems in childhood. Sleep. 2007;30(10):1371-7.

Table 1. Demographic and clinical characteristics of children in the control and EDS groups (n=618).*

	Healthy Controls (n=507)	Excessive daytime sleepiness (n=111)	*P*-value**
Demographics			
Age, years	10.96±0.89	11.07±0.76	0.219
Sex, male, n (%)	261 (51.5)	55 (49.5)	0.713
BMI *z* score	-0.04±1.03	-0.01±1.00	0.780
Weight status,* n (%)**			0.169
Obese	31 (6.1)	5 (4.5)	
Overweight	48 (9.5)	17 (15.3)	
Healthy	428 (84.4)	89 (80.2)	
Birth weight, kg	3.25±0.43	3.19±0.43	0.234
Allergic disease			
Asthma, n (%)	11 (2.2)	5 (4.6)	0.158
Allergic rhinitis, n (%)	277 (55.1)	69 (62.2)	0.173
Atopic dermatitis, n (%)	81 (16.3)	20 (18.2)	0.631
Laboratory findings, n (%)	393 (77.9)	92 (82.9)	
Lipid profile			
Total cholesterol, g/dL	168 [153 to 187]	167 [153 to 189]	0.889
Triglycerides, g/dL	104 [77 to 143]	111 [83 to 138]	0.415
LDL-C, g/dL	98 [81 to 112]	93 [84 to 115]	0.962
HDL-C, g/dL	57 [51 to 65]	58 [48 to 65]	0.482
Vitamin D status			0.167
>30 ng/mL, n (%)	32 (8.1)	7 (7.6)	
20 to 30 ng/mL, n (%)	198 (50.4)	37 (40.2)	
<20 ng/mL, n (%)	163 (41.5)	48 (52.2)	
Hematologic profile			
Hemoglobin, g/dL	13.7 (0.8)	13.5 (1.2)	0.060
Iron, µg/dL	102.5 (34.8)	102.8 (37.6)	0.942
Ferritin, ng/mL	52.6 (26.8)	54.8 (33.2)	0.498
Total eosinophil count (>4%), n (%)	105 (27.5)	32 (36.0)	0.113

Values are presented as number (%), mean ± standard deviation, or median [interquartile range]

BMI, body mass index; SD, standard deviation; IQR, Interquartile range; LDL-C, low-density lipoprotein

cholesterol; HDL-C, high-density lipoprotein cholesterol

[*] n refers to the number of completed questionnaires, appropriate responses to questions in the questionnaire, or appropriate blood sampling results

[**] *P* values are from a χ^2 test or Student's *t*- test

[***] Obesity was defined as a BMI z-score more than 1.64 and overweight as a BMI z-score of 1.04 to 1.6

Table 2. PDSS score and sleep patterns of children in the control and EDS groups.

	n*	Healthy Control	Excessive daytime sleepiness	*P* value
PDSS	618	9.86±3.87	19.11±2.08	
Bed time, o'clock (pm)	381	11:00±0:52	11:34±0:57	**<0.001**
Bed time, n (%)	618	507	111	**<0.001**
Before midnight		461 (90.9)	85 (76.6)	
After midnight		46 (9.1)	26 (23.4)	
Wake time, o'clock (am)	612	7:33±0:27	7:47±0:25	**<0.001**
Sleep duration, (hour)	377	8.58±0.88	8.25±0.98	**0.006**

Values are presented as number (%) or mean ± standard deviation

PDSS, pediatric daytime sleepiness score

* Number of completed questionnaires or appropriate responses to questions in the questionnaire

Numbers in bold indicate a significant difference (P < 0.05)

Table 3. Association of age, gender, and body mass index with sleep duration and PDSS score.

	Sleep duration		**PDSS score**	
	β (95% CI)	***P* value***	**β (SE)**	***P* value***
Age	−0.029 (−0.041 to −0.016)	**<0.001**	0.032 (−0.011 to 0.076)	0.147
BMI *z* score	−0.015 (−0.026 to −0.003)	**<0.015**	−0.016 (−0.053 to 0.022)	0.415
	Mean (95% CI)	***P* value****	**Mean (95% CI)**	***P* value****
Gender				
Boy	8.63 (8.52 to 8.75)	**0.010**	11.40 (10.84 to 11.95)	0.534
Girl	8.40 (8.25 to 8.54)		11.65 (11.06 to 12.25)	

BMI, body mass index; β, coefficient; SE, standard error; 95% CI, 95% confidence interval; PDSS, Pediatric Daytime Sleepiness Scale

* *P* values are from a generalized linear regression analysis with gamma function

** *P* values are from Student's t test

Numbers in bold indicate a significant difference ($P < 0.05$)

Table 4. Association of hematological parameters, lipid parameters, and 25(OH)D_3 level with excessive daytime sleepiness

		Total	Control	EDS	*P* value	aOR (95% CI)	*P* value*
Hemoglobin, n (%)	>12 g/dL	461	374 (81.1)	87 (18.9)	0.592	ref	
	≤12 g/dL	10	8 (80.0)	2 (20.0)		1.22 (0.25 to 5.96)	0.807
Serum-ferritin, n (%)	>25 ng/mL	427	345 (80.8)	82 (19.2)	0.970	ref	
	≤25 ng/mL	58	48 (82.8)	10 (17.2)		0.89 (0.42 to 1.88)	0.765
Serum-iron, n (%)	> 60 ug/mL	440	357 (81.1)	83 (18.9)	0.853	ref	
	≤60 ug/mL	45	36 (82.0)	9 (20.0)		1.11 (0.51 to 2.44)	0.789
Total eosinophil count, n (%)	<4%	334	277 (82.9)	57 (17.1)	0.113	ref	
	≥4%	137	105 (76.6)	32 (23.4)		1.40 (0.83 to 2.37)	0.213
25(OH)D_3, n (%)	≥20 ng/mL	211	163 (77.3)	48 (22.7)	0.064	ref	
	<20 ng/mL	274	230 (83.9)	44 (16.1)		**1.73 (1.06 to 2.81)**	**0.028**
Total cholesterol, n (%)	<170 mg/dL	253	204 (80.6)	49 (19.4)	0.924	ref	
	170-199 mg/dL	168	136 (81.0)	32 (19.0)		1.07 (0.64 to 1.78)	0.801
	≥200 mg/dL	64	53 (82.8)	11 (17.2)		0.92 (0.44 to 1.93)	0.824
HDL-C, n (%)	>45 mg/dL	422	348 (82.5)	74 (17.5)	**0.045**	ref	
	40-45 mg/dL	42	32 (76.2)	10 (23.8)		1.73 (0.78 to 3.85)	0.182
	<40 mg/dL	21	13 (61.9)	8 (38.1)		**2.84 (1.05 to 7.68)**	**0.039**
LDL-C, n (%)	<110 mg/dL	336	274 (81.5)	62 (18.5)	0.830	ref	
	110-130 mg/dL	104	84 (80.8)	20 (19.2)		1.11 (0.62 to 1.97)	0.731
	>130 mg/dL	45	35 (77.8)	10 (22.2)		1.15 (0.53 to 2.52)	0.722
Triglyceride, n (%)	<90 mg/dL	187	157 (84.0)	30 (16.0)	0.089	ref	

90-130 mg/dL	149	112 (75.2)	37 (24.8)	1.68 (0.95 to 2.96)	0.075
>130 mg/dL	149	124 (83.2)	25 (16.8)	1.07 (0.58 to 1.97)	0.834

aOR, adjusted odd ratios; CI, confidence interval; 25(OH)D_3, 25-hydroxyvitaminD_3; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol

*P values calculated by generalized linear regression analysis with logit function after adjustment for age, gender, BMI z score, secondary smoking, and exposure to mold odors

Numbers in bold indicate a significant difference ($P < 0.05$)

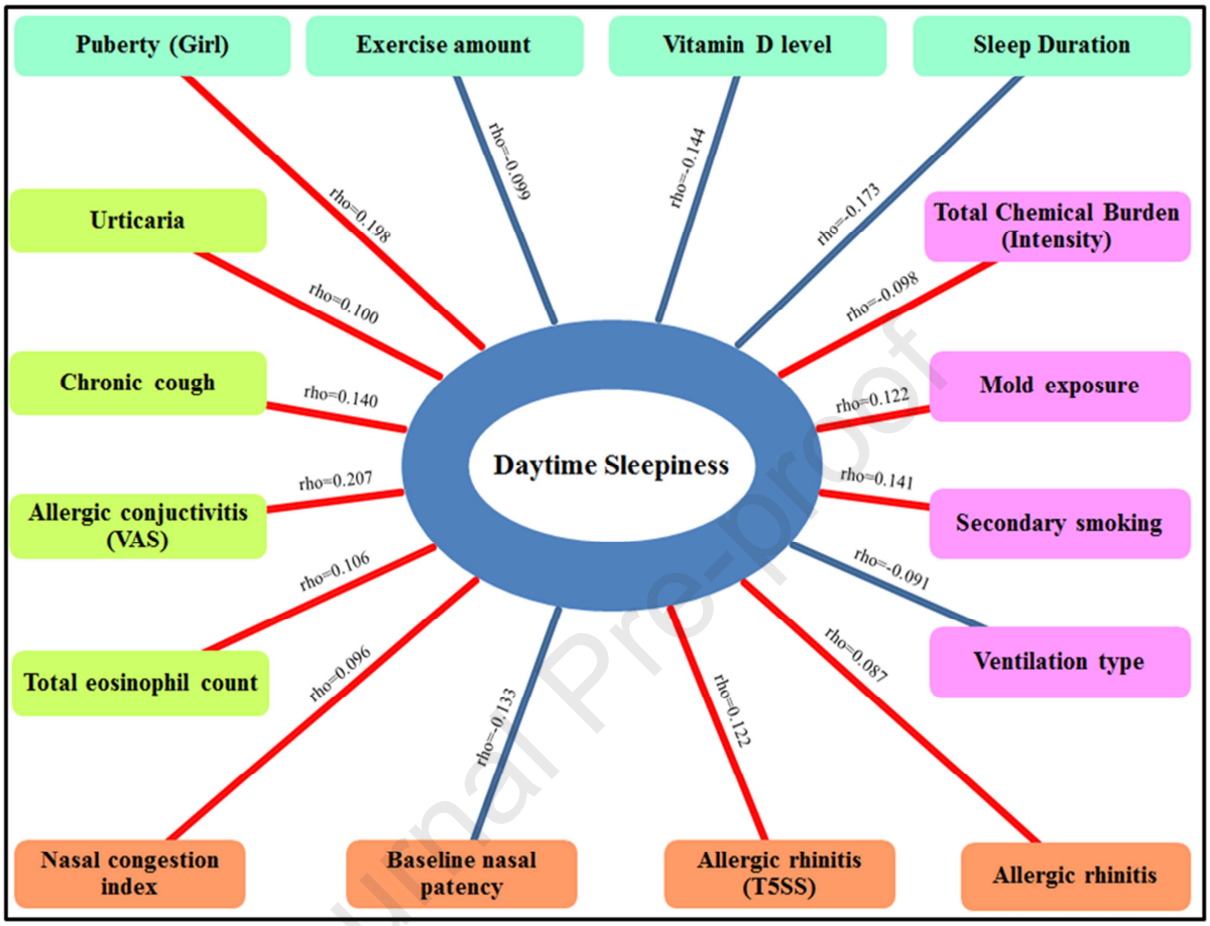

Figure 1. Factors significantly associated with PDSS score ($P < 0.05$).

Red line: positive correlation; blue line: negative correlation; top row: life style and diet; right column: environmental factors; bottom row: allergy-related factors; left column: other factors

Rho; correlation coefficient

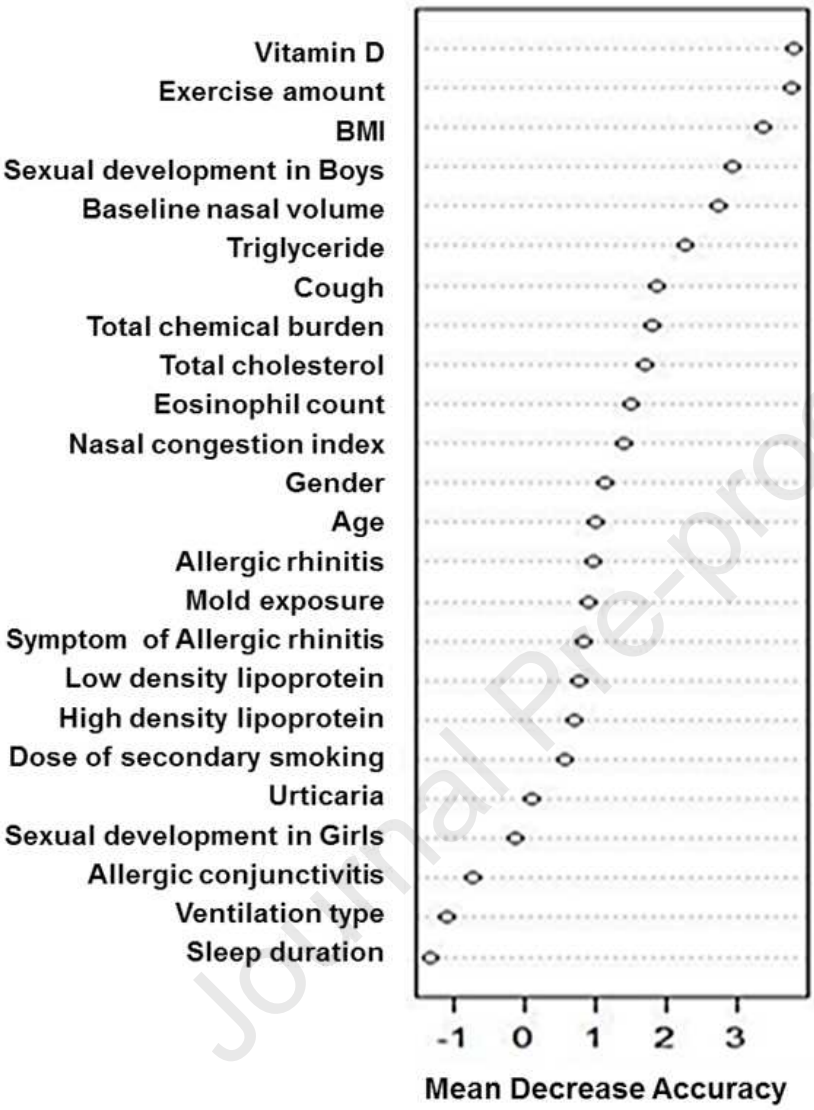

Figure 2. Random forest analysis of the importance of different variables on PDSS score in children.

High positive values indicate high importance, and small positive or negative values indicate low importance

Vitamin D, 25-hydroxyvitaminD_3; BMI, body mass index

- Study examined 618children who were 10 to 12 year-old and 111 children (18%) were excessive daytime sleepiness (EDS).
- Low 25-hydroxyvitaminD_3 (25(OH)D_3) level, lack of exercise, and high body mass index were the most important factors contributing to EDS.
- High levels of 25-(OH)D_3 and performing regular exercise decreased the risk of EDS.

Contributions

Dr. Rhie, Sung, and Han had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Dr. Chae and Han

Acquisition, analysis, and interpretation of data: All authors.

Drafting the manuscript: Dr. Sung and Rhie

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Dr. Han and Rhie

Obtained funding: Dr. Jee

Study supervision: Dr. Chae and Han