

Association between vitamin D and respiratory outcomes in Canadian adolescents and adults

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doi: 10.3109/02770903.2015.1004339

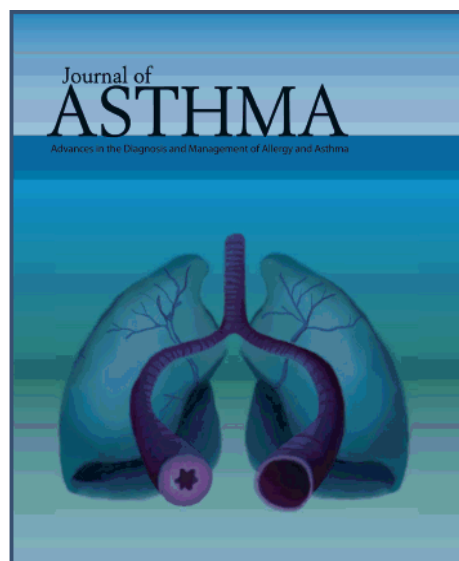
Abstract

Background: Asthma is one of the most prevalent chronic diseases worldwide, affecting more than 200 million people. Vitamin D deficiency has been reported among individuals with asthma and might play a role in asthma exacerbations. In this cross-sectional study, we investigated the association of serum 25-hydroxy vitamin D [25(OH)D] levels and current asthma, ever asthma, and lung function.

Methods: Data from 3,937 subjects aged 13-69 years who participated in the Canadian Health Measures Survey-Cycle 1 were considered in this study. Serum 25(OH)D levels were categorized into ≤ 49 nmol/L (low), 50-74 nmol/L (moderate) and ≥ 75 nmol/L (high).

Results: The proportion of subjects with current and ever asthma was greater in the lower 25(OH)D category than in moderate and high categories. After adjusting for potential confounders, subjects in the low 25(OH)D levels were more likely to have current asthma than those in the moderate levels (OR:1.54, 95% CI:1.01-2.36). Low 25(OH)D levels were also associated with ever asthma (OR:2.12, 95% CI:1.40-3.21) among those with a family history of asthma and this association was stronger in those with asthma onset before 20 years of age. High 25(OH)D levels were associated with lower mean value of FEV₁/FVC ratio. No significant association was observed between 25(OH)D levels and other lung function measurements.

Conclusion: In this study, 25(OH)D levels below 50 nmol/L were associated with an increased risk of current and ever asthma. Further exploration of this relationship is needed to determine the optimal level of vitamin D in the management of asthma in adolescents and adults.



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Running Head: Vitamin D and respiratory outcomes

Keywords: Asthma, Family history, Lung function, Serum 25-hydroxy vitamin D

Word count: Abstract (250) and Text (3,741)

ABSTRACT

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Results: The proportion of subjects with current and ever asthma was greater in the lower 25(OH)D category than in moderate and high categories. After adjusting for potential

confounders, subjects in the low 25(OH)D levels were more likely to have current asthma than those in the moderate levels (OR:1.54, 95% CI:1.01-2.36). Low 25(OH)D levels were also associated with ever asthma (OR:2.12, 95% CI:1.40-3.21) among those with a family history of asthma and this association was stronger in those with asthma onset before 20 years of age. High 25(OH)D levels were associated with lower mean value of FEV₁/FVC ratio. No significant association was observed between 25(OH)D levels and other lung function measurements.

Conclusion: In this study, 25(OH)D levels below 50 nmol/L were associated with an increased risk of current and ever asthma. Further exploration of this relationship is needed to determine the optimal level of vitamin D in the management of asthma in adolescents and adults.

INTRODUCTION

The World Health Organization reported that 235 million people worldwide currently suffer from asthma [1]. The developed and developing countries experience a substantial burden due to asthma morbidity [2]. The prevalence of asthma has been stable from 2008 to 2012 and was 8.1% in 2012 [3]. The burden of disease costs associated with asthma has been increasing [4] and the urgent care cost of uncontrolled asthma in Canada was 162 million US dollars in 2004 [5].

The link between vitamin D and asthma has been the subject of considerable scientific debate in recent years [6]. It is suggested that vitamin D plays a central role as an environmental and epigenetic contributor to the pathogenesis of asthma and its exacerbation, allergy and respiratory infection [7]. Vitamin D deficiency is reported to be prevalent among asthmatics, and results in poor control of symptoms, and steroid insensitivity [8]. In a recent large cross-sectional study of adults aged 21 to 50 years from Israel, vitamin D deficiency ($25(\text{OH})\text{D} \leq 25 \text{ nmol/L}$) was associated with asthma exacerbations but not with ever asthma [9]. In a randomized controlled trial conducted in US medical centers, adding oral vitamin D_3 to inhaled corticosteroids as part of the treatment of adult patients with symptomatic asthma and serum $25(\text{OH})\text{D}$ level less than 30 ng/mL (75 nmol/L) did not significantly alter the rate of first treatment failure during the 28-week follow-up [10]. Positive and negative results have been reported in the studies examining the relationship between vitamin D and asthma [11] and there is still a debate on the optimal range of vitamin D for patients with asthma [12,13].

Due to the recent advances in understanding of the immunological functions of vitamin D, a panel from the Institute of Medicine (IOM) concluded that a serum level of 50 nmol/L is sufficient for the bone health of 97% of the population [14]. In the conclusion of their

manuscript the authors reported “serum concentrations of 25OHD above 30 ng/ml (75 nmol/liter) are not consistently associated with increased benefit, and risks have been identified for some outcomes at 25OHD levels above 50 ng/ml (125 nmol/liter).[14]” In a previous study of Canadian children aged 6 to 12 years, we reported a U-shaped relationship between 25(OH)D levels and current wheeze using the data from the first cycle of the Canadian Health Measures Survey (CHMS-Cycle 1) [15]. In addition, being in the low 25(OH)D category was significantly associated with ever asthma, and the rate of increase in forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) with age was greater in the moderate category than the low and high categories [15]. In the present study, we examined the hypothesis that the association between vitamin D and respiratory outcomes would be dependent on the vitamin D levels in Canadian adolescents and adults using the data from CHMS-Cycle 1.

METHODS

We used the data from the CHMS-Cycle 1, a cross-sectional survey, conducted between March 2007 and February 2009 in four provinces in Canada [16]. A multistage sampling design was used to collect data on self-reported and direct measures of health from a representative sample of Canadians aged 6 to 79 years living in private households. Information on respiratory symptoms and diseases, and personal and family characteristics was obtained from the household survey. Within 14 days of the household interview, participants were invited to visit a Mobile Examination Clinic (MEC) for measurement of a number of relevant characteristics. In total 5604 individuals randomly selected from 15 sites from British Columbia, Alberta, Ontario and Quebec participated in the survey. Asthma in children differs in many ways from asthma in adults, and even among adults childhood-onset asthma may differ considerably from late-onset asthma [17]. The role of vitamin D may also vary between children and adults. In a previous prospective study examining the age-specific effects of vitamin D in patients with asthma, an inverse association was observed between 25(OH)D levels and serum IgE levels in children but not in adults [18]. Further, in the CHMS-Cycle 1, asthma-related and lifestyle-related questions for children were slightly different from those questions for adolescents and adults [16]. Because of the age-specific differences in the characteristics of asthma, the association between vitamin D and asthma, and asthma-related and life-style related questions in CHMS-Cycle 1, independent analyses were conducted in children, and adolescents and adults to examine the association between vitamin D and respiratory outcomes using the data from CHMS-Cycle 1. The results from the study investigating the association between vitamin D and respiratory outcomes in children of ages 12 years and below have been reported elsewhere [15].

After excluding children of ages 12 years and below and adults of ages 70 years and above, 3,976 subjects of ages 13 to 69 years were considered. Of these subjects, 3,863 had 25(OH)D measurements and 3,735 (of 3,863) had valid lung function measurements. Ever asthma was determined from the household questionnaire from responses to the question “Now I’d like to ask about certain chronic health conditions which you may have. We are interested in “long-term conditions” which are expected to last or have already lasted 6 months or more and that have been diagnosed by a health professional: Do you have asthma? “. Age of asthma onset was obtained from the question “How old was the participant when this was first diagnosed?” Current asthma was obtained from the responses to the question “Have you had any asthma symptoms or asthma attacks in the past 12 months?” The family history of asthma was obtained from the response to the question “Has anyone in your immediate family ever had asthma?” The number of hours that the respondent spent on sedentary activities in a week was provided as a derived variable in the CHMS-Cycle 1 database. A series of three questions were included in the questionnaire to determine the time spent on three types of sedentary activities: “In a typical week in the past 3 months, how much time did you usually spend on (i) computer, computer games and Internet, (ii) video games, television or videos and (iii) reading”. For all activities, time spent at school or work was excluded.

Venous blood samples were collected using routine methods at the time participants attended the MEC, processed, and stored at -18C in a freezer. Serum levels of 25(OH)D were assessed by a chemiluminescence assay using the LIAISON 25-Hydroxyvitamin D total assay (Diasorin Ltd, Stillwater, MN).

Spirometry was performed at the MEC using the Respironics KoKo spirometer (PDS Instrumentation, Louisville, CO) according to American Thoracic Society guidelines by a health

measurement specialist. The FEV₁, FVC, FEV₁/FVC ratio, and forced expiratory flow between 25% and 75% of forced vital capacity (FEF_{25%-75}) were considered in these analyses. The reference values proposed by Hankinson et al. was used to obtain percent-predicted lung function values [19]. This study was approved by the Health Research Ethics Board of the University of Alberta.

STATISTICAL ANALYSIS

Serum 25(OH)D levels were categorized into ≤ 49 nmol/L (low), 50-74 nmol/L (moderate), and ≥ 75 nmol/L (high). The authors have used these categories previously in a study examining the association between serum 25(OH)D levels and respiratory outcomes in children [15]. The calendar months of data collection were grouped into four seasons with winter spanning over four months reflecting the long Canadian winter (spring: April and May; summer: June to August; fall: September to November; winter: December to March). Analysis of variance and chi-squared tests were used for bivariate analyses. Multiple logistic regression was used to identify factors associated with current and ever asthma. Multiple linear regression was used to identify factors associated with lung function parameters. Five-hundred bootstrap weights of probability weight provided by Statistics Canada were used to estimate the standard errors of the estimated parameters.

Restricted cubic spline terms of age were used in the multiple regression analysis of lung function outcomes to account for the non-linear association of age with lung function parameters [20]. For restricted cubic splines, the position of three knots at 18, 29 and 50 years was determined from the distribution of age in the association with FVC. Of those variables that were measured in the CHMS-Cycle 1, biologically relevant variables and potential confounders for the association between vitamin D and respiratory outcomes were considered in the univariate

analysis. Variables were included in the multiple regression models if there was evidence of association at $p\text{-value} < 0.2$ with dependent variable in the univariate analysis. The significance of the interaction effects between 25(OH)D levels and other variables in the final main effects model (age, sex, family history of asthma and weekly sedentary hours) were tested. A $p\text{-value}$ of less than 0.05 was considered significant.

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RESULTS

Overall prevalence of ever asthma and current asthma was 8.1%, and 4.7%, respectively. As seen in Table 1, there were no significant differences observed in mean height, weight and 25(OH)D levels between those with and without ever asthma or with and without current asthma. Those with current asthma, and ever asthma were significantly younger than those without. No significant differences were observed between mean 25(OH)D levels between the four seasons (data not shown).

The participants' characteristics, proportion with current asthma within each characteristic, and unadjusted odds ratios of the association between current asthma and each characteristic are shown in Table 2. A greater proportion of the subjects (39.3%) had moderate 25(OH)D levels (Table 2). The proportion of current asthma was lower in the subjects with moderate 25(OH)D levels (4.1%) in comparison to low (6.4%) and high (4.2%) 25(OH)D levels, but these differences were not statistically significant ($p=0.075$). In addition, current asthma was significantly associated with attending school and greater number of hours spent in sedentary activities (Table 2).

The proportion of subjects with ever asthma within each characteristic and the unadjusted odds ratios of the association between ever asthma and each characteristic are shown in Table 3. The results observed for ever asthma were similar to those observed for current asthma. The proportion of ever asthma was lower in the subjects with moderate 25(OH)D levels (7.5%) in comparison to low (9.5%) and high (7.7%) with differences being not statistically significant ($p=0.28$). Among subjects with ever asthma, 62.9% developed asthma before 20 years (early-onset) and 37.1% developed asthma after 20 years (late-onset).

As seen in Table 4, after controlling for age, sex, family history of asthma, and sedentary activities, subjects in the low 25(OH)D category had a 54% increased odds of current asthma in comparison to those in the moderate category (OR: 1.54, 95% CI: 1.01-2.36). In the multiple logistic regression analysis of ever asthma, the interaction between 25(OH)D categories and family history of asthma was significant. After allowing for the interaction and adjusting for age, race and sedentary activity, subjects in the low 25(OH)D category with a family history of asthma has a more than two fold increase in odds of ever asthma in comparison to the moderate category (OR: 2.11, 95% CI: 1.40-3.21).

The results from the stratified analysis by age of onset of asthma (≤ 20 years vs. >20 years) among subjects with asthma are shown in Table 5. Among subjects with early onset of asthma, those in the low 25(OH)D category with a family history of asthma had an almost 3-fold increase in the odds of ever asthma in comparison to those in the moderate category (OR: 2.84, 95% CI: 1.35-6.00). There was no significant association between 25(OH)D categories and ever asthma among subjects with late-onset of asthma.

As shown in Table 6, there were no significant differences in the mean values of actual and percent predicted FVC, FEV₁, and FEF_{25%-75%} between the three 25(OH)D categories. The mean FEV₁/FVC ratio was lowest in the high 25(OH)D category and highest in the low 25(OH)D category; however this pattern was not observed in the percent predicted FEV₁/FVC ratio. Table 7 shows the association of 25(OH)D categories with lung function parameters from the multiple linear regression analysis. After adjusting for age, gender, height, weight, smoking status, and race, subjects in the low 25(OH)D category had lower mean values of FVC, FEV₁, FEV₁/FVC ratio, and FEF_{25%-75%} compared to those in the moderate category, however these differences were not statistically significant. A significant interaction was observed between

linear and non-linear terms of age and 25(OH)D levels in the multiple regression analysis of $FEF_{25\%-75\%}$. With age, height and weight fixed at the mean values, subjects in the high 25(OH)D category had significantly lower mean values of FEV_1/FVC ($p=0.02$) in comparison to those in the moderate 25(OH)D category (Table 7).

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DISCUSSION

In this study, low 25(OH)D level was associated with a more than two-fold increased odds of ever asthma in those with family history of asthma, and an almost 50% increased risk of current asthma compared to the moderate 25(OH)D level. Importantly, the association of lower vitamin D level with ever asthma was only evident in those who developed asthma before 20 years of age and had a family history of asthma. The association of FEV₁/FVC with 25(OH)D level was dependent on age.

Several studies have assessed vitamin D status in Canada [21,22]. Using the 50 nmol/L value as the cutoff, the prevalence of vitamin D deficiency was 27.2% in our study similar to those reported in other studies. Vitamin D deficiency is mainly a consequence of dietary, lifestyle, and behavioral factors [6]. A study of the economic burden of vitamin D deficiency reported that the burden could be reduced by 7.3% in Canada if mean serum vitamin D levels were increased to 105 nmol/L [23].

In our previous study [15], children in the low 25(OH)D category were more likely to have a report of ever asthma in comparison to those in the moderate category, similar to the finding in the current study among adolescents and adults. In contrast to the finding in the current study, a family history of asthma did not modify the relationship between 25(OH)D levels and ever asthma in children. In that previous study we also reported that children in both low and high 25(OH)D categories were more likely to have a report of current wheeze [15], whereas in this study among adolescents and adults only being in the low 25(OH)D category was significantly associated with current asthma. The reasons for these differences are unknown but might be related to the asthma outcomes used in the two studies (current wheeze vs. asthma symptom or attack in the last 12 months). The results observed for the association between 25(OH)D levels and lung function in the current study among adolescents and adults were also

not wholly consistent with those observed for children in our previous study [15]. The increase in FEV₁ and FVC with age was greater in the moderate 25(OH)D category than low and high 25(OH)D categories in children[15] whereas a significant association was observed only between FEV₁/FVC ratio and 25(OH)D levels in adolescents and adults. The reasons for these inconsistent results in the two age groups are similarly unknown but might be related to ongoing lung growth in children and differences in lifestyle factors between the two groups.

In the cross-sectional study of adults aged 21 to 50 years from Israel, serum 25(OH)D levels were categorized into four categories (0-25, 25.1-50, 50.1-90, ≥ 90.1 nmol/L) and subjects in the first 25(OH)D category (0-25 nmol/L) were more likely to report asthma exacerbations in comparison to those in the reference category (50.1-90 nmol/L) (10). In this study, no significant association was observed between 25(OH)D levels and ever asthma and family history of asthma was not considered as a confounder or an effect modifier (10). In our study, serum 25(OH)D levels were categorized into three categories (≤ 49 , 50-74, ≥ 75 nmol/L) and subjects in the low 25(OH)D category (≤ 49 nmol/L) were more likely to have current report asthma in comparison to those in the moderate category (50-74 nmol/L) and association of lower low 25(OH)D category with ever asthma was observed in those who developed asthma before 20 years of age and had a family history of asthma.

Family history of asthma is recognized to be an important risk factor for asthma in children [24] and adults [25,26]. Our study found that low vitamin D levels synergistically increased the risk of ever asthma only among those with a family history of asthma. This is a novel finding and suggests that individuals with a family history of asthma might have a unique immune and/or genetic phenotype, in which vitamin D deficiency increases the likelihood of the development of asthma. Further, the interaction of vitamin D with family history asthma for ever

asthma was evident only in those who developed asthma at 20 years of age or younger (early-onset) but not in those who developed asthma after 20 years of age (late-onset). The latter observation raises the possibility that the immunological mechanism for the relationship between vitamin D and ever asthma in subjects with early-onset asthma may be different from that in subjects with late-onset asthma.

In our study, subjects who spent more than 35 hours per week on sedentary activities had an increased odds of current and ever asthma in comparison to those who spent 19 hour or less on sedentary activities. This finding has been reported in several studies and physical activity was a protective factor for the incidence of asthma in a systematic review and meta-analysis [27]. Increased reporting of non-sedentary activities was also protective of lower vitamin D status ($25(\text{OH})\text{D} < 25 \text{ nmol/L}$) in a cross-sectional study of Danish adults aged 30 to 60 years [28]. Although reporting non-sedentary activities was associated with asthma and low vitamin D status in these two studies, it was not an effect modifier of the relationship between vitamin D levels and current or ever asthma in our study.

The exact mechanism by which vitamin D modulates the risk of asthma is not completely understood. The active form of vitamin D is involved in the regulation of expression of the antimicrobial peptide cathelicidin in bronchial epithelial cells, which is important in the defense against respiratory infections. Through this mechanism vitamin D likely protects against asthma exacerbation [29]. Vitamin D likely also acts as a physiological regulator modifying inhibition and enhancement of processes potentiating Th_2 responses [30]. Furthermore, vitamin D receptors (VDR) have been localized in both respiratory epithelial cells and in bronchial smooth muscle. VDR bound with the active form of vitamin D controls the transcription of target genes involved in signaling pathways [31]. Furthermore, there have been reports of an association of some single

nucleotide polymorphisms of the VDR gene with asthma and atopy [32,33], which suggests a plausible explanation for our novel findings in this study.

In this study, lung function parameters did not significantly vary across vitamin D categories in multiple linear regression models after adjusting for potential confounders, except for the inverse association between high 25(OH)D category with FEV₁/FVC ratio in comparison to the moderate category. However, several prior studies have reported a significant association between vitamin D level and lung function measurements. [34,35]. A study using the CHMS-Cycle 1 data found, among male obese subjects aged 18 years and above, a significant association between log-transformed 25(OH)D level and residual FVC, and FEV₁/FVC obtained after removing the variations due to age, sex and ethnicity [36]. Our finding of a significant association between vitamin D and asthma, but not one between vitamin D and the lung function measurements does not altogether exclude an effect of vitamin D on lung function, since lung function changes in asthma are typically reversible, and may not be present at the time of measurement. According to the Global Initiative for Asthma (GINA) guidelines, mild persistent asthma is defined as FEV₁ or peak flow rate (PFR) $\geq$ 80% predicted with < 20%-30% variability and symptom frequency greater than one per week but less than one per day, recognizing the possibility of normal lung function in subjects with asthma [37]. In a study from Alberta, of the 500 adult patients with asthma who were referred by their physician to a university-based asthma clinic, 52% had percent-predicted FEV₁ > 80% [38].

In our study, ever asthma was determined from the self-report of health professional diagnosis of asthma by the participants, which has been used extensively in large population-based epidemiological studies. In a study examining the validity of self-report of asthma, mean lung function measurements (FEV₁, FEF_{25%-75}, FEV₁/FVC ratio) were the lowest in subjects with

physician-diagnosed asthma, followed by subjects reporting wheezing (without asthma), and the asymptomatic group, respectively [39]. However, some error or misclassification of asthma diagnosis by the health professional cannot be ruled out in our study. In an observational study of 90 adult subjects with a history of asthma diagnosis by the physicians in the community in Nova Scotia, only 59% met the Canadian Thoracic Society criteria for the diagnosis of asthma at the time of testing [40]. In this study, 100% had positive symptom history, 28.9% had variable air flow obstruction and 56.7% had confirmation of airway hyper-responsiveness by methacholine challenge test [40].

The present study has several strengths. First, the data for this study came from a nationally representative, large and population-based sample. Second, our outcome and covariates were derived from a standardized questionnaire and vitamin D levels were obtained from the blood samples. Since the study used the data collected from a representative sample of Canadian adolescents and adults, the results could be generalized to the Canadian population. There are several limitations in our study. The severity of asthma could not be determined from the CHMS-Cycle 1 and was not considered in our study. Information on use of medications related to asthma was not collected in CHMS-Cycle 1 and was not considered as a potential confounder for the association between vitamin D and respiratory outcomes. Low vitamin levels observed in our study might have been related to overall poor health [41], nutrition or lifestyle factors [42], or use of corticosteroids [43]. Except for some lifestyle factors, other factors were not considered in our study. In addition, information on the use of vitamin D supplement was not collected in CHMS-Cycle 1. Because the serum 25(OH)D level was measured only at one time point in this cross-sectional study, the temporal sequence of events

cannot be determined and a causal relationship between vitamin D and respiratory outcomes cannot be ascertained.

In conclusion, vitamin D may be playing an important role in the management of asthma. Further evidence is required from randomized controlled trials to determine the optimal levels of vitamin D in the management of asthma in adolescents and adults.

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ACKNOWLEDGEMENTS

The research and analysis are based on the data from Statistics Canada and opinions expressed herein do not represent the views of Statistics Canada

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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JUST ACCEPTED

Table 1. Distribution of characteristics for overall sample and by current and ever asthma*

Factor	Table 1. Anthropometric characteristics of the study population									
	Overall		Ever asthma				Current asthma			
			No		Yes		No		Yes	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Age (years)	39.91	(14.01)	40.05	(13.97)	36.98†	(14.55)	40.15	(13.84)	37.08‡	(15.72)
Height (cm)	168.82	(8.59)	168.83	(8.57)	168.66	(9.01)	168.93	(8.51)	167.66	(9.43)
Weight (kg)	76.32	(16.61)	76.27	(16.53)	77.28	(18.16)	76.34	(16.40)	76.03	(18.98)
25(OH)D (nmol/L)	66.75	(24.11)	66.91	(24.13)	63.44	(23.29)	66.94	(24.13)	64.60	(23.31)

*p-values are from ANOVA

[†]p <0.005

[‡]p <0.01

Table 2. Characteristics of the study sample, proportion of current asthma by factors and odds ratio for the relationship of factors with current asthma

Factor	Distribution in the sample (%)	Proportion of current asthma (%)	Unadjusted OR (95% CI)	p-value*
Vitamin D Level				0.075
Low (≤ 49 nmol/L)	27.2	6.4	1.6 (1.09, 2.36)	
Moderate (50-74 nmol/L)	39.3	4.1	1.00	
High (≥ 75 nmol/L)	33.6	4.2	1.03 (0.63, 1.70)	
Sex				0.21
Female	50.2	5.3	1.00	
Male	49.8	4.2	0.78 (0.51, 1.18)	
Body mass index				0.31
Normal or under weight	45.3	4.0	1.00	
Overweight	34.2	4.3	1.09 (0.56, 2.12)	
Obese	20.5	5.7	1.48 (0.89, 2.46)	
Family history of Asthma				<0.001
No	77.1	3.1	1.00	
Yes	22.9	10.7	3.8 (2.38, 6.06)	
Household income				0.22
Low	18.8	8.7	2.22 (0.81, 6.1)	
Middle	31.5	4.1	1.00	
High	49.7	3.5	0.85 (0.52, 1.4)	
Attending school				0.03
No	80.2	4.1	1.00	
Yes	19.8	7.2	1.84 (1.07, 3.16)	
Daily sun exposure				0.58
<1 hour	29.0	5.3	1.35 (0.74, 2.47)	
1-3 hour	38.7	4.0	1.00	
>3 hour	32.3	5.2	1.32 (0.67, 2.59)	
Use of electric heating system				0.67
No	65.6	4.4	1.00	
Yes	34.4	5.0	1.15 (0.57, 2.33)	
Use of gas furnace				0.64
No	47.5	4.8	1.00	
Yes	52.5	4.3	0.89 (0.51, 1.55)	
Weekly sedentary hours				0.02
≤ 19	45.7	3.7	1.00	

20-34	40.9	4.6	1.23 (0.52, 2.9)	
>35	3.4	8.6	2.43 (1.41, 4.21)	
Consumption of milk (daily)				0.35
Less than once	43.1	4.8	1.14 (0.72, 1.8)	
At-least once	48.2	4.2	1.00	
More than twice	8.7	7.5	1.86 (0.76, 4.58)	
Smoking status				0.54
Never	52.4	4.4	1.00	
Current	21.5	5.9	1.39 (0.76, 2.53)	
Former	26.1	4.5	1.02 (0.53, 1.97)	
Liver or kidney diseases				0.39
No	95.6	4.6	1.00	
Yes	4.4	6.8	1.51 (0.54, 4.25)	
Race				0.19
Caucasian	81.4	4.3	1.00	
Other	18.6	6.6	1.58 (0.77, 3.25)	
Smoking inside home				0.38
No	84.4	4.5	1.00	
Yes	15.6	6.1	1.39 (0.62, 3.13)	
Seasonality				0.64
Winter	30.3	5.4	1.00	
Spring	19.2	5.2	0.94 (0.37, 2.42)	
Summer	24.7	3.9	0.71 (0.27, 1.91)	
Fall	25.7	4.5	0.81 (0.23, 2.86)	
Use of sunscreen				0.19
Never	30.3	4.3	1.00	
Always/often	31.5	5.2	1.23 (0.75, 2)	
Sometimes/rarely	38.2	3.9	0.9 (0.38, 2.13)	
Region				0.29
Ontario	38.9	3.7	1.00	
Quebec, New Brunswick	30.5	5.0	1.39 (0.67, 2.87)	
British Columbia, Alberta	30.5	5.7	1.59 (0.88, 2.86)	

*p-values are from univariate logistic regression of current asthma.

Table 3. Proportion of ever asthma by factors and odds ratio for the relationship of factors with ever asthma*

Factor	Proportion of ever asthma (%)	Unadjusted OR (95% CI)	p-value†
Vitamin D categories			0.28
Low (≤ 49 nmol/L)	9.5	1.29 (0.93, 1.79)	
Moderate (50-74 nmol/L)	7.5	1.00	
High (≥ 75 nmol/L)	7.7	1.02 (0.7, 1.51)	
Sex			0.04
Female	9.5	1.00	
Male	6.7	0.68 (0.47, 0.99)	
Body mass index			0.25
Normal or under weight	7.6	1.00	
Overweight	6.6	0.85 (0.51, 1.44)	
Obese	9.4	1.25 (0.84, 1.85)	
Family history of asthma			<0.001
No	5.8	1.00	
Yes	16.2	3.15 (2.1, 4.72)	
Household income			0.004
Low	14.6	2.27 (1.24, 4.14)	
Middle	7.0	1.00	
High	6.2	0.87 (0.55, 1.38)	
Attending school			0.004
No	7.1	1.00	
Yes	12.2	1.82 (1.26, 2.65)	
Daily sun exposure			0.48
<1 hour	8.4	1.17 (0.75, 1.82)	
1-3 hour	7.3	1.00	
>3 hours	8.8	1.22 (0.82, 1.83)	
Use of electric heating system			0.37
No	7.4	1.00	
Yes	8.7	1.19 (0.78, 1.82)	
Use of gas furnace			0.63
No	8.2	1.00	
Yes	7.6	0.92 (0.64 1.33)	
Weekly sedentary hours			0.054
≤ 19	6.8	1.00	
20-34	8.1	1.2 (0.74, 1.94)	
>35	12.4	1.93 (1.22, 3.04)	

Consumption of milk (daily)			0.09
Less than once	8.1	1.1 (0.86, 1.41)	
At least once	7.4	1.00	
More than twice	11.7	1.64 (0.95, 2.84)	
Smoking status			0.19
Never	7.6	1.00	
Current	10.3	1.4 (0.95, 2.06)	
Former	7.4	0.97 (0.64, 1.47)	
Liver or kidney disease			0.49
No	8.0	1.00	
Yes	9.9	1.26 (0.57, 2.82)	
Race			0.50
Caucasian	7.8	1.00	
Other	9.3	1.2 (0.67, 2.14)	
Smoking inside home			0.48
No	7.9	1.00	
Yes	9.4	1.21 (0.66, 2.23)	
Seasonality			0.38
Winter	9.0	1.00	
Spring	9.1	0.96 (0.47, 1.98)	
Summer	6.7	0.70 (0.33, 1.47)	
Fall	7.7	0.81 (0.32, 2.01)	
Use of sunscreen			0.90
Never	7.6	1.00	
Always/often	8.2	1.09 (0.72, 1.65)	
Sometimes	7.9	1.04 (0.69, 1.57)	
Region			0.52
Ontario	7.2	1.00	
Quebec, New Brunswick	8.1	1.13 (0.63, 2.01)	
British Columbia, Alberta	9.3	1.32 (0.71, 2.46)	

* The distribution (%) of these factors in the sample is given in Table 2

†p-values from univariate logistic regression of ever asthma

Table 4. Results from the multiple logistic regression of current asthma and ever asthma

Factor	Current asthma		Ever asthma	
	Odds Ratio (95% CI)	p-value‡	Odds Ratio (95% CI)	p-value‡
Age (1 year)	0.99 (0.98, 1.00)	0.082	0.99 (0.98, 1.00)	0.034
Sex				
Female	1.00		1.00	
Male	0.81 (0.56, 1.18)	0.25	0.68 (0.47, 0.99)	0.044
Weekly sedentary hours				
≤ 19 hours	1.00		1.00	
20-34 hours	1.25 (0.54, 2.87)	0.57	1.27 (0.80, 2.03)	0.28
≥ 35 hours	2.27 (1.27, 4.08)	0.01	1.85 (1.21, 2.82)	0.008
Vitamin D levels*				
≤ 49 nmol/L	1.54 (1.01, 2.36)	0.047	0.85 (0.54, 1.35)	0.45
50-74 nmol/L	1.00		1.00	
≥ 75 nmol/L	1.03 (0.60, 1.75)	0.90	1.20 (0.68, 2.12)	0.50
Family history of asthma†				
No	1.00		1.00	
Yes	3.63 (2.17, 6.07)	<0.001	2.49 (1.35, 4.60)	0.008
Vitamin D levels (with family history of asthma)				
≤ 49 nmol/L	-		2.11 (1.44, 3.21)	0.002
50-74 nmol/L	-		1.00	
≥ 75 nmol/L	-		0.80 (0.41, 1.55)	0.47

* Odds ratios of vitamin D levels for ever asthma corresponds to absence of family history of asthma.

† Odds ratios of family history of asthma for ever asthma corresponds to the vitamin reference category,(50-74 nmol/L).

‡ p-values are from multiple logistic regression

Table 5. Relationship between ever asthma and vitamin D categories for early and late onset of asthma.

Factor	Age of onset $\leq$ 20 years		Age of onset $>$ 20 years	
	Odds Ratio (95% CI)	p-value‡	Odds Ratio (95% CI)	p-value‡
Age (years)	0.96 (0.94, 0.97)	<0.001	1.03 (1.02, 1.05)	0.001
Sex				
Female	1.00		1.00	
Male	0.71 (0.44, 1.13)	0.13	0.7 (0.36, 1.37)	0.26
Vitamin D levels*				
$\leq$ 49 nmol/L	2.85 (1.35, 6.00)	0.01	1.04 (0.47, 2.28)	0.90
50-74 nmol/L	1.00		1.00	
$\geq$ 75 nmol/L	0.78 (0.42, 1.44)	0.40	0.72 (0.32, 1.65)	0.40
Family history of asthma†				
No	1.00		1.00	
Yes	3.20 (1.49, 6.86)	0.006	2.11 (0.83, 5.37)	0.10
Vitamin D levels (with family history of asthma)				
$\leq$ 49 nmol/L	2.85 (1.35, 6.00)	0.01	-	
50-74 nmol/L	1.00		-	
$\geq$ 75 nmol/L	0.78 (0.42, 1.44)	0.40	-	

* Odds ratios of vitamin D levels in the age of onset $\leq$ 20 years category corresponds to absence of family history of asthma

† Odds ratios of family history in the age of onset $\leq$ 20 years category corresponds to vitamin D level at 50-74 nmol/L

‡ p-values are from multiple logistic regression

Table 6. Distribution of lung function for overall sample and by vitamin D categories

Factor	Overall	Vitamin D categories			p-value*
		Low Mean (SD)	Moderate Mean (SD)	High Mean (SD)	
Percent predicted FVC (%)	99.26 (11.27)	98.22 (11.74)	99.65 (11.02)	99.87 (10.93)	0.45
Percent predicted FEV ₁ (%)	95.94 (12.19)	95.32 (12.22)	96.18 (12.03)	96.25 (12.16)	0.72
Percent predicted FEV ₁ /FVC (%)	96.54 (7.64)	97.01 (7.12)	96.37 (7.72)	96.20 (8.0)	0.28
FVC (L)	4.21 (0.95)	4.17 (0.97)	4.25 (0.97)	4.23 (0.92)	0.74
FEV ₁ (L)	3.30 (0.77)	3.28 (0.78)	3.32 (0.78)	3.28 (0.74)	0.77
FEV ₁ /FVC (%)	78.33 (6.89)	78.95 (6.55)	78.21 (6.9)	77.73 (7.12)	0.01
FEF _{25%-75%} (L/s)	3.05 (1.05)	3.07 (1.06)	3.08 (1.03)	3.00 (1.04)	0.36

* p-values are from analysis of variance for comparison between vitamin D categories

Table 7. Results from the multiple linear regression analysis of lung function outcomes

Factor	FVC (ml)	FEV ₁ (ml)	FEV ₁ /FVC (%)	FEF _{25%-75%} (ml)
	β (SE)†	β (SE)†	β (SE)†	β (SE)†
Vitamin D (ref - moderate)				
≤ 49 nmol/L	-86.06 (52.45)	-60.94 (37.59)	-0.3 (0.57)	-71.75 (72.6)
≥ 75 nmol/L	6.59 (30.51)	12.41 (18.37)	-0.95 (0.35)‡	20.81 (38.17)
Age*				
Linear	22.23 (3.29)¶	7.08 (3.02)‡	-0.12 (0.03)§	-5.02 (4.64)
Non-linear	-51.57 (3.61)¶	-37.82 (3.22)¶	-0.13 (0.05)‡	-38.48 (4.97)¶
Sex				
Male (ref - female)	574.32 (34.25)¶	459.82 (29.64)¶	0.08 (0.41)	427.24 (79.2)¶
Height*	63.2 (1.37)¶	42.15 (1.01)¶	-0.14 (0.02)¶	21.32 (3.08)¶
Weight*	-2.39 (1.01)‡	-0.26 (0.69)	0.03 (0.01)§	4.88 (1.42)§
Smoking status (ref - Never)				
Current	-	-154.45 (37.2)§	-4.25 (0.41)¶	-426.26 (49.04)¶
Former	-	-40.56 (29.68)	-1.1 (0.38)‡	-140.69 (61.32)‡
Race				
Others (ref - Caucasian)	-385.25 (64.09)¶	-219.31 (49.47)¶	1.99 (0.48)§	-
Vitamin D and age interaction				
≤ 49 nmol/L and linear	-	-	-0.11 (0.07)	-
≥ 75 nmol/L and linear	-	-	-0.23 (0.05)¶	-
≤ 49 nmol/L and non-linear	-	-	0.15 (0.1)	-
≥ 75 nmol/L and non-linear	-	-	0.3 (0.06)¶	-
Intercept	4187.41 (29.78)¶	3284.94 (16)¶	79.45 (0.44)¶	3110.6 (61.28)¶

* Variables were centralized

†β (SE) - Regression coefficient (Standard error)

‡p-value ≤ 0.05

§p-value ≤ 0.01

¶p-value ≤ 0.001

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