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25-hydroxyvitamin D and health service utilization for asthma in early childhood

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ABSTRACT

Background: Asthma is the most common chronic illness of childhood and a common reason for hospital admission. Studies suggest that low vitamin D levels may be associated with health service utilization (HSU) for childhood asthma. The primary objective was to determine if vitamin D serum levels in early childhood were associated with HSU for asthma including: a) hospital admissions, b) emergency department visits, and c) outpatient sick visits. Secondary objectives were to determine whether vitamin D supplementation in pregnancy or childhood were associated with HSU for asthma.

Methods: Prospective cohort study of children participating in the TARGet Kids! practice based research network between 2008 and 2013 in Toronto, Canada. HSU was determined by linking each child's provincial health insurance number to health administrative databases. Multivariable quasi Poisson and logistic regression were used to evaluate the association between 25-hydroxyvitamin D, vitamin D supplementation in pregnancy and childhood and HSU for asthma.

Results: 2926 healthy children ages 0-6 years had 25-hydroxyvitamin D data available and were included in the primary analysis. Mean (IQR) 25-hydroxyvitamin D level was 84 nmol/L (65-98 nmol/L), 218 and 1267 children had 25-hydroxyvitamin D levels <50 nmol/L and <75 nmol/L, respectively. In the adjusted models, there were no associations between 25-hydroxyvitamin D (continuously or dichotomized at 50 and 75 nmol/L), vitamin D supplementation in pregnancy or childhood and HSU for asthma.

Conclusions: Higher vitamin D blood values do not appear to be associated with HSU for asthma in this population of healthy urban children.
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Potential conflicts of interest and financial disclosure

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BACKGROUND

Asthma is the most common chronic illness of childhood. According to data from the Centre for Disease Control (CDC), the prevalence of asthma, in children ages 0-17 years, in the United States, was 10% for the period of 2008 to 2010. There were approximately 479,300 hospital admissions, 2.1 million emergency department visits, and 10.6 million physician visits for asthma, respectively, in the United States in 2009. Two, 11% and 67% of children with asthma required hospital admissions, emergency department visits and physician visits for asthma, respectively, resulting in a large health service burden.

It has been hypothesized that vitamin D has both in-utero and postnatal effects that may be associated with asthma incidence or severity including a role in: 1) lung growth and maturation through optimal smooth muscle proliferation and decreased inflammation, 2) immune function and tolerance to allergens, and 3) up-regulation of antimicrobial peptides leading to resistance to respiratory infections which are a common cause of asthma exacerbations. A systematic review and meta analysis in 2016 of randomized controlled trials (RCTs), in adults and children (4 studies included in the pooled results), found that vitamin D supplementation reduced the risk of at least one asthma exacerbation requiring acute care (either hospital admission or emergency department visit) (OR 0.39, 95% CI 0.19 – 0.78). However, only 2 of the RCTs were conducted in children (n=22 and n=89) and neither found statistically significant results, so the pooled results were primarily driven by the 2 RCTs in adults (n=250 and n=408).
We hypothesized that children’s 25-hydroxyvitamin D serum concentration and vitamin D supplement use would be negatively associated with HSU for asthma in healthy urban preschool children. The primary objective of this study was to determine whether serum 25-hydroxyvitamin concentration in early childhood is associated with increased health service utilization (HSU) for asthma including: a) hospital admissions (HA), b) emergency department visits (ED) and c) outpatient sick visits (SV). Secondary objectives were to determine whether oral vitamin D supplementation in pregnancy or childhood is associated with decreased HA, ED or SV for asthma.
METHODS

A prospective cohort study evaluating the association between 25-hydroxyvitamin D, vitamin D supplementation and HSU for asthma in healthy urban children was conducted. Exposures were measured prior to HSU in order to investigate a temporal relationship and limit the risk of reverse causality.

Population and Inclusion Criteria

Healthy children 0 to 6 years of age were recruited from well-child physician visits through the TARGet Kids! (The Applied Research Group for Kids) practice based research network between December 2008 and March 2013. Detailed information on the TARGet Kids! (www.targetkids.ca) cohort methodology has been previously described. Recruitment, survey data and blood sampling for TARGet Kids! occurred at 7 primary care practices (5 paediatric and 2 family medicine group practices) in Toronto, Canada (latitude 43°N). Trained research assistants embedded within the practices obtained data from families at well-child physician visits. Baseline was defined as the first TARGet Kids! visit. Children were excluded if they had conditions affecting growth, chronic condition(s) except for asthma, severe developmental delay or if they were born before 32 weeks gestation.
**Measurements**

Parents or guardians completed a detailed questionnaire at the time of enrolment (which will be referred to as 'baseline') on subject characteristics and demographics, adapted from the Canadian Community Health Survey.9

**Primary exposure (serum 25-hydroxyvitamin D levels):**

Baseline serum 25-hydroxyvitamin D was measured as a continuous variable in nmol/L (and dichotomized at <50 and <75 nmol/L) and was collected by trained phlebotomists during the well-child physician visit. Non-fasting serum samples were stored on ice and sent daily to the Mount Sinai Services Laboratory in Toronto, Canada (www.mountsinaservices.ca). A competitive two-step chemiluminescence assay (LIAISON 25 OH Vitamin D TOTAL Assay; DiaSorin)10 was used to measure total 25-hydroxyvitamin D. The Vitamin D External Quality Assessment Scheme (DEQAS), an internationally recognized method of assessing analytic reliability, was used for regular calibration of the assay.11 The assay was extensively tested and validated, with values falling within acceptable limits for biochemical measurements;10,12 intra-assay imprecision was 7.2% at a concentration of 213 nmol/L; and inter-assay imprecision of 4.9% at 32 nmol/L, 8.9% at 77 nmol/L and 17.4% at 213 nmol/L. 25-hydroxyvitamin D concentration was measured at one time point for each subject and varies with season (higher levels during the summer months and lower levels during the winter months). The sine curve method described by Zhang et al. was used to account for the seasonal variability in 25-hydroxyvitamin D.13 The sine curve method models the seasonal variability in 25-hydroxyvitamin D as a sine function of the blood collection date using
three parameters: angular frequency, amplitude and phase. Sine and cosine values were constructed from the Julian dates of the sample collection. These were then put into a regression model with 25-hydroxyvitamin D as the exposure and sine and cosine values as covariates. The resulting sine and cosine parameter estimates were used to adjust the 25-hydroxyvitamin D levels of the study population.

(seasonally_adjusted_vitaminD=vitaminD + 0.66047*sine + 2.85687*cosine)

See supplementary Table A and Figure A for data on the seasonal distribution of 25-hydroxyvitamin D concentrations.

Secondary exposures (parent-reported vitamin D supplement use):

Prenatal supplementation was measured at baseline by parental-report using the question: “Did your child’s biological mother take any vitamins or supplements during her pregnancy?” Single nutrient oral vitamin D supplementation for adults, which typically contain 1000 IU/day, was used as a binary (yes/no) exposure variable in order to differentiate from women taking prenatal multivitamins, which typically contain a lower dose of 400 IU/day of vitamin D. Data on vitamin D dosing or frequency in pregnancy was not available.

Vitamin D supplementation during childhood was measured at baseline as a continuous variable (IU/day) using the questions “does your child take any vitamins or supplements regularly?” and “in a typical day, how much does your child take?” The frequency and dose of vitamin D from multivitamins (usually 400 IU) and single nutrient vitamin D supplements for children (specific dose in IU was specified by parent/guardian) were
combined to measure total daily vitamin D intake from supplements as a continuous variable (IU/day).

Outcome definitions
Baseline TARGet Kids! data was linked at the individual level to 3 health administrative databases using each child’s encrypted Ontario Health Insurance Plan (OHIP) number. All residents of Ontario are provided a unique OHIP number through the universal single-payer health-care system, which covers all physician and hospital services. Linkage occurred, with 98% success, at the Institute for Clinical Evaluative Sciences (ICES) in Ontario, Canada, which is a prescribed registry under the Ontario’s *Personal Health Information Protection Act* (PHIPA) and permits the collection of health service data without patient consent.

The databases used for this study included: 1) The Canadian Institute for Health Information (CIHI) discharge abstract database, which records the primary diagnosis and secondary diagnoses for all patients discharged from acute care hospitals (HA); 2) The CIHI National Ambulatory Care Reporting System (NACRS), which collects data on all emergency department visits (ED); and 3) OHIP physician claims database which collects data on fee-for-service outpatient physician billings (SV).

International Classification of Disease 10th revision (ICD-10) diagnostic codes J45 “asthma” and J46 “acute severe asthma” were used to identify HSU for asthma in the DAD and NACRS databases for HA and ED visits, respectively. The most responsible
diagnosis was used in both DAD and NACRS as it has been shown to have the highest predictive accuracy. OHIP fee-for-service physician diagnostic code 493 “asthma or allergic bronchitis” was used to define HSU for asthma for SV as has been previously done. We excluded all well-child physician visits (code 916) to limit the inclusion of routine appointments for health maintenance.

Although vitamin D has seasonal variation, serum levels are believed to be relatively stable within an individual over time, and so we included HSU visits for asthma that occurred in the 2 years following the baseline exposure measurements (25-hydroxyvitamin D and vitamin D supplementation) as the observation window. Measuring HSU for asthma over a 2-year period also allowed us to account for seasonal changes in HSU for asthma. In order to avoid including potential complications from birth, we excluded HSU before 28 days of life. To avoid double counting HSU for the same asthma episode, we excluded multiple visits within the same 2 week period giving priority to hospital admissions, then emergency department visits and then outpatient sick visits.

Other variables

We identified potential confounders of the relationship between 25-hydroxyvitmain D, vitamin D supplements and HSU as well as predictors of HSU a priori through a literature review and were included as covariates in this analysis. All variables were measured at baseline and all models were fully adjusted for all variables. Covariates included child factors such as age, sex, body mass index (zBMI), daycare/preschool
attendance\textsuperscript{20-22}, child’s birth weight\textsuperscript{23} and gestational age.\textsuperscript{23} Parental and household factors included median neighbourhood income\textsuperscript{24}, number of children in the household\textsuperscript{22,}
and parental smoking.\textsuperscript{25} Age was grouped into 3 categories: 1) less than 2 years, 2) 2-4 years and 3) 4-6 years. Trained research staff collected physical measurements; weight was measured using a precision digital scale and standing height using a stadiometer (or a length board for children under 2 years). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.\textsuperscript{26} BMI $z$ scores were calculated using World Health Organization growth standards.\textsuperscript{27} Child’s birth weight and gestational age data came from the CIHI DAD database. Median after tax neighbourhood household income was calculated based on each subject’s postal code using the Statistics Canada Postal Code Conversion File and data from the 2006 Canadian Census.\textsuperscript{28} Parental smoking was defined as smoking by any member of the household.

\textit{Statistical analysis}

We compared children with and without measured 25-hydroxyvitamin D data in order to determine whether there were any meaningful clinical differences. The total number of ED and SV were described as counts, but HA was described as either yes or no due to the low outcome frequency. For the primary analysis, the association between 25-hydroxyvitamin D and HSU for asthma a) HA, b) ED and c) SV were tested.

Multivariable quasi Poisson regression was used for the outcomes ED and SV to account for over dispersion of the data and multivariable logistic regression was used for the HA outcome. The logarithm of observation time was used as an offset to account for variation
in the window of observation. We tested for multicollinearity using the generalized variance inflation factor test (VIF) to ensure the models produced stable effects.\textsuperscript{29} The models were adjusted by the covariates specified above regardless of statistical significance to avoid bias that can result from standard variable selection techniques.\textsuperscript{30,31}

To assess consistency of the findings among children with insufficient 25-hydroxyvitamin D levels (cut-offs based on the AAP/IOM and CPS guidelines), we conducted a sensitivity analysis by repeating the primary analysis (outcomes HA, ED and SV) including only children with 25-hydroxyvitamin D levels <50 and <75 nmol/L.\textsuperscript{32-34}

For the secondary analysis, the same multivariable quasi Poisson regression and multivariable logistic regression models were used as the primary analysis but with vitamin D supplementation in pregnancy and childhood as the exposure variables respectively.

We explored non-linearity through graphical presentation of the data and restricted cubic spline analysis using 3 knots. To compare the goodness of fit of the linear and non-linear models we used a likelihood ratio test. All covariates had <15% missing data. To avoid bias that can be introduced from missing data multiple imputations were conducted using transcan in the R package Hmisc.\textsuperscript{31} We only imputed data for the covariates.

Statistical analyses were conducted using SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC, USA) and R version 3.3 (http://www.R-project.org).\textsuperscript{35} 2-tailed $P$
values <0.05 were considered statistically significant.

**Ethics approval**

Parents provided informed consent for primary data collection in TARGet Kids! and for this data to be linked with health administrative data. This study was approved by the Hospital for Sick Children and Institute of Clinical Evaluative Sciences (ICES) Research Ethics Boards and a data sharing agreement was in place.

**ROLE OF THE FUNDING SOURCE**

The funding source had no involvement in the study design, collection, analysis, and interpretation of the data or writing of the report. The corresponding author confirms that she had full access to all of the data and all authors are responsible for the final report.
RESULTS

A total of 5049 children ages 0-6 years were recruited into the TARGGet Kids! cohort between December 2008 and March 2013 (figure 1). Baseline 25-hydroxyvitamin D data were available on 2926 children and maternal and child vitamin D supplement data were available for 4530 and 4006 children, respectively. At baseline, children with and without measured 25-hydroxyvitamin D data appeared similar (Table 1). The only clinically meaningful difference was that children with measured 25-hydroxyvitamin D data were slightly older. Of the 2926 children included in the primary analysis, 1036 (35%) were <2 years, 887 (30%) were 2-4 years and 1003 (34%) were 4-6 years old at baseline. One thousand five hundred and fifty nine (53%) were male and mean zBMI was 0.14 (interquartile range (IQR): -0.55 – 0.8). Mean 25-hydroxyvitamin D was 84 nmol/L (IQR 65-98 nmol/L); 218 (7%) and 1267 (43%) children had 25-hydroxyvitamin D levels below 50 nmol/L and 75 nmol/L, respectively. Four hundred and sixty three (10%) mothers took a single nutrient prenatal vitamin D supplement and 1883 (47%) of the children took a single nutrient vitamin D supplement or multivitamin at baseline (average dose adjusted for adherence was 196 IU/day). There were 7 (0.2%), 46 (1.6%), and 388 (13%) children with at least 1 HA, ED and SV for asthma in the cohort, respectively, and 7 HA, 54 ED and 849 SV individual visits for asthma in the observation window.

In the primary analysis, no statistically significant relationships were observed between 25-hydroxyvitamin D and all HSU outcomes [HA aOR 0.76, 95% CI: 0.54 – 1.08; ED aOR 0.92, 95% CI: 0.81 – 1.04; and SV aOR 1.03, 95% CI: 0.99 – 1.08] (Table 2). In the
sensitivity analysis no statistically significant relationships were observed among children with 25-hydroxyvitamin D <50 and <75 nmol/L and all HSU outcomes (Table 3).

For the secondary analysis, no statistically significant relationships were observed between prenatal vitamin D supplementation (yes/no) or child vitamin D supplementation (in 100 IU increments) and HSU outcomes (Table 2).
DISCUSSION:

In this prospective cohort study of healthy urban children ages 0-6 years, no statistically significant associations were identified between children’s 25-hydroxyvitamin D levels, prenatal or child vitamin D supplementation and health service utilization for asthma. To our knowledge no other study has prospectively evaluated the relationship between 25-hydroxyvitamin D serum levels in early childhood and health service utilization for asthma.

Previous studies, which have examined the association between 25-hydroxyvitamin D and HSU for asthma in children, found mixed results. A small cross-sectional study (n=100), by Alyasin et al. in 2011 in Iran (latitude 30°N), evaluated the association between 25-hydroxyvitamin D and asthma in children ages 6-18 years and found lower 25-hydroxyvitamin D levels were associated with increased odds of asthma; however they found no association between 25-hydroxyvitamin D levels and number of hospitalizations or unscheduled visits in the previous year. The mean 25-hydroxyvitamin D level was 145 nmol/L. This study was limited by the low frequency of hospitalizations (n=8) and unscheduled visits (n=28). Two other studies looked at the association between 25-hydroxyvitamin D in children and parent-reported hospitalizations or ED visits specifically caused by an asthma exacerbation. The first study, a cross-sectional analysis of children ages 6-14 years (n=616) in Costa Rica (latitude 10°N), found that lower vitamin D levels were associated with increased odds of any hospitalization in the previous year (OR 0.05, 95% CI: 0.004 – 0.71) among children.
with asthma. The median 25-hydroxyvitamin D level was 89 nmol/L. This study was limited by retrospective collection of the outcome. The second study, which was a secondary analysis of RCT data (n=1024) in children ages 5-12 years in the United States, found that insufficient vitamin D (<75 nmol/L) was associated with a higher odds (OR 1.5, 95% CI: 1.1-1.9) of any prospective parent-reported hospitalization or emergency department visit amongst children with asthma (after adjusting for age, sex, body mass index, income, and treatment group). The median 25-hydroxyvitamin D level was 88 nmol/L. This study was limited by parent-reported health services use. None of these studies evaluated the association in younger children.

Two systematic reviews of RCTs have been conducted assessing the association between vitamin D supplements in childhood and asthma health services use. The first by Martineau et al. in 2016, included 4 RCTs in the pooled results, and found that vitamin D reduced the risk of at least one asthma exacerbation requiring acute care (either hospital admission or emergency department visit) (OR 0.39, 95% CI 0.19 – 0.78). However, only 2 of these RCTs were in children, both having small sample sizes (n=22 and n=89, respectively) and neither found statistically significant results. The mean 25-hydroxyvitamin D levels were 65 nmol/L and 71 nmol/L at baseline, respectively. Thus the pooled results were primarily driven by the 2 RCTs in adults (n=250 and n=408 respectively). The other systematic review of RCTs by Riverin et al. in 2015, included children ages 3-18 years. Their primary outcome was hospital admissions or emergency department visits, but only one RCT by Yadav et al. in 2014 reported ED visits and thus pooled results were not possible. In this RCT (n=100 children ages 3-14 years) monthly
doses of vitamin D (60,000 IU) significantly reduced ED visits $p=0.015$; however, the
frequency of the outcome was low and 25-hydroxyvitamin D levels were not measured.\textsuperscript{41}

Strengths of this study included a relatively large sample size with almost 3000 serum 25-
hydroxyvitamin D measurements and HSU data on all participants. The study was a
prospective cohort study and thus we were able to assess whether a temporal relationship
existed between vitamin D status, prenatal and child vitamin D supplements and future
health service utilization for asthma removing the risk of reverse causality. HSU outcome
data was collected through a publically funded health care system and was not subject to
bias from parental-recall or healthcare accessibility issues. Detailed questionnaire data
were available for vitamin D supplement use during pregnancy and childhood as well as
multiple potential confounders, which allowed us to adjust the models for established risk
factors of HSU for asthma.

Limitations of this study included using observational data and thus we are not able to
infer causality. However, we were able to look at HSU prospectively over a 2-year period
following exposures. Furthermore, HSU outcome data was not collected for research
purposes thus misclassification of the outcomes may have occurred. However, we used
the most responsible diagnosis for HA and ED visits, which has been shown to have the
highest predictive accuracy.\textsuperscript{14} Although only 1 physician diagnosis was recorded per SV,
which may have led to missed outcomes, we suggest that an asthma exacerbation would
have most often been recorded by the physician as the primary reason for the SV.
We excluded all well-child physician visits (code 916) in an attempt to limit the inclusion of routine appointments for health maintenance; however, we do understand that some maintenance visits for asthma may have been included in our analysis. Additionally, the mean 25-hydroxyvitamin D concentration in this population was 84 nmol/L, which was above the IOM/AAP and CPS sufficiency cut-points (50 and 75 nmol/L) and may not have been sufficiently low to show an effect; however, the relationship does not appear to be different among children with lower levels of 25-hydroxyvitamin D according to the non-linear plot (figure 2) and we did not identify an association in the sensitivity analyses using these cut-points [50 nmol/L (n=218) and <75 nmol/L (n=1267)]. Finally, we did not measure dose or frequency of intake of single nutrient vitamin D during pregnancy and thus could not assess whether a dose response relationship exists. Furthermore, supplement data from questionnaires may be subject to recall bias.

Despite the high prevalence of HSU for asthma among young children, we did not find an association between 25-hydroxyvitamin D levels, vitamin D supplementation in pregnancy or childhood and any of the HSU outcomes. Based on these results, higher vitamin D levels may not decrease the burden of HSU for asthma in early childhood.
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Author contributions

J.A.O. conducted the literature search. J.A.O. and J.L.M. designed the research study. T.T., D.L.O., P.C.P. and C.S.B. helped to refine the study design. J.A.O., J.L.M. and K.E.T. analyzed the data. All authors contributed to the interpretation of results. J.A.O. and J.L.M. drafted the manuscript. All authors read and approved the final manuscript. J.A.O. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
REFERENCES:


