25-Hydroxyvitamin D supplementation and health-service utilization for upper respiratory tract infection in young children

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25-hydroxyvitamin D, supplementation and health service utilization for URTI in young children

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Short Title
Vitamin D and HSU for URTI in childhood

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**TARGet Kids! Collaboration**


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**Potential conflicts of interest and financial disclosure**

The authors have no conflicts of interest or financial relationships relevant to this article to disclose.
Author Contributions
J.O. and J.M. designed the research study. T.T., D.O., P.P and C.B. helped to refine the study design. J.O., J.M. and K.T. analysed the data. All authors contributed to the interpretation of results. J.O. and J.M. drafted the manuscript. All authors read and approved the final manuscript. J.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.

Ethical Standards Disclosure
This study was approved by the Hospital for Sick Children Research Ethics Board and Institute for Clinical Evaluative Sciences (ICES). All TARGet Kids! participating parents provided consent for their child’s data to be linked with health administrative data.

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Objective: Upper respiratory tract infections (URTI) are the most common and costly condition of childhood. Low vitamin D levels have been hypothesized as a risk factor for URTI. The primary objective was to determine if vitamin D serum levels were associated with health service use for URTI including: hospital admission, emergency department visits or outpatient sick visits. The secondary objectives were to determine whether oral vitamin D supplementation in pregnancy or childhood was associated with health services use for URTI.

Design: Cohort study. Health service use was determined by linking each child's provincial health insurance number to health administrative databases. Multivariable quasi Poisson regression was used to evaluate the association between 25-hydroxyvitamin D, vitamin D supplementation and health service use for URTI.

Setting: Toronto, Canada.


Results: 4962 healthy children age 0-5 years were included. 52% were male and mean 25-hydroxyvitamin D was 84 nmol/L (range 11-355). There were 105 (2%), 721 (15%) and 3218 (65%) children with at least 1 hospital admission, ED visit or outpatient sick visit respectively for URTI. There were no statistically significant associations between 25-hydroxyvitamin D or vitamin D supplementation and health service use for URTI.

Conclusions: A clinically meaningful association between vitamin D (continuously and dichotomized at <50 and <75 nmol/L) and health service use for URTI was not identified. While vitamin D may have other benefits for health, reducing health service use for URTI does not appear to be one of them.
Keywords

Vitamin D
25-hydroxyvitamin D
Health service utilization
Upper respiratory infections
Early childhood

Abbreviations
HSU: Health service utilization
URTI: Upper respiratory tract infections
ICES: Institute for Clinical Evaluative Sciences
CIHI: Canadian Institute for Health Information
DAD: Discharge Abstract Database
NACRS: National Ambulatory Care Reporting System
OHIP: Ontario Health Insurance Program
Total HSU: any health service utilization (HA + ED + SV)
HA: Hospital admissions
ED: Emergency department visits
SV: Outpatient sick visits
PHIPA: Personal Health Information Protection Act
OR: odds ratio
RR: relative risk
aRR: adjusted relative risk
CI: confidence intervals
INTRODUCTION

Upper respiratory tract infections (URTI) are the most common infectious disease for children in North America and account for a large portion of health service utilization (HSU).\(^1\) Preschool children experience 6 to 8 URTI per year,\(^2\) with approximately 50% seeking medical attention in the outpatient or emergency department setting, and roughly 1% requiring hospitalization.\(^3-6\) A number of studies have suggested that low vitamin D levels may play a role in susceptibility to URTI in children. Suggested mechanisms have included: improved immune and inflammatory response, through T-helper cell regulation, immunoglobulin production and stimulation of the antimicrobial peptide cathelicidin.\(^7-9\) Two meta-analyses, including RCTs with both children and adults, found that vitamin D had a protective effect against respiratory tract infections (OR 0.64, 95% CI: 0.49 – 0.84)\(^10\) and (OR 0.582, 95% CI: 0.417 – 0.812)\(^11\). However, a meta analysis of RCTs, involving only children, found no association between vitamin D and risk of acute respiratory infections (RR) 0.79, 95% CI: 0.55 – 1.13).\(^12\)

Given the existing literature, supporting a relationship between vitamin D and URTI risk, we hypothesized that children’s 25-hydroxyvitamin D serum concentration and vitamin D supplement use would be negatively associated with HSU for URTI. To our knowledge, no study has yet evaluated vitamin D status and health service utilization for URTI in a prospective cohort of healthy young children. The primary objective of this study was to determine whether serum 25-hydroxyvitamin concentration in early childhood is associated with HSU for URTI including: a) any hospital admission (HA),
emergency department visit (ED) and outpatient sick visits (SV) (Total HSU), b) HA, c) ED and d) SV. Secondary objectives were to determine whether oral vitamin D supplementation in pregnancy or childhood is associated with Total HSU, HA, ED or SV for URTI.

METHODS

A cohort of healthy urban children, 0 to 5 years of age, who participated in the TARGet Kids! (The Applied Research Group for Kids) practice based research network, between December 2008 and March 2013, were included in this study. Subjects were recruited from 7 large paediatric or family medicine group practices in Toronto, Canada (latitude 43.4°N). Children were excluded if they had conditions affecting growth, chronic condition(s) except for asthma or severe developmental delay. A detailed questionnaire, adapted from the Canadian Community Health Survey, was completed by the parent or guardian of each child at the time of enrolment to collect data on subject characteristics and demographics. Measurements

Exposure definitions. The primary exposure was serum 25-hydroxyvitamin D as a continuous variable in nmol/L. Total 25-hydroxyvitamin D was measured from blood serum collected during a well-child visit (between December 2008 and March 2013) using a competitive two-step chemiluminescence assay (LIAISON 25 OH Vitamin D TOTAL Assay; DiaSorin) at the Mount Sinai Services Laboratory. Intra-assay
imprecision of the assay was 7.2% at a concentration of 213 nmol/L, and an inter-assay
imprecision of 4.9% at 32 nmol/L, 8.9% at 77 nmol/L and 17.4% at 213 nmol/L. These
values are well within acceptable limits for biochemical measurements.\textsuperscript{16,17,25-}
hydroxyvitamin D concentration was measured continuously as well as dichotomized at
<50 and <75 nmol/L, respectively, based on AAP/IOM and CPS reference cut-points.\textsuperscript{18-20}
The secondary exposures were measured at the same visit or the first TARGet Kids!
visit if laboratory data was unavailable:
1) Single nutrient oral vitamin D prenatal supplementation measured by parental report
using the question: 1) “Did your child’s biological mother take any vitamins or
supplements during her pregnancy?” This captured supplementation during the entire
pregnancy and was not broken down by trimester. We only included single nutrient
vitamin D supplements in order to differentiate from those women taking a prenatal
multivitamin (approximately 90% of women were taking a prenatal multivitamin).
2) Oral vitamin D supplementation in childhood measured by parental report using the
following questions: 1) “does your child take a vitamin D containing supplement
regularly?” and 2) “in a typical day, how much does your child take?”- We combined the
dose of vitamin D in international units (IUs) from multivitamins and single nutrient
vitamin D supplements to estimate current total daily intake of supplemental vitamin D.

\textit{Outcome definitions.} All residents of Ontario are insured through the Ontario Health
Insurance Plan (OHIP), universal single-payer health-care system, and are provided a
unique health insurance number (OHIP number). For this study, prospectively collected
data from the TARGet Kids! practice based research network, were linked to 3 health administrative databases at the individual level using encrypted OHIP number, with 98% success. This type of linkage allowed for protection of the participants identities while examining their HSU across different databases. Linkage occurred 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 health administrative databases used were:

1) The Canadian Institute for Health Information (CIHI) discharge abstract database (DAD) to obtain data on HA.

2) CIHI National Ambulatory Care Reporting System (NACRS) to obtain data on ED.

3) OHIP physician claims database to obtain information on fee-for-service physician billings for SV.

The observation window for the outcomes included HSU visits that occurred 365 days before and after the exposure measurements (1 year before and after the date that 25-hydroxyvitamin D was measured for the primary analysis and 1 year before and after the date that vitamin D supplement data was captured for the secondary analyses).

International Classification of Disease 10th revision (ICD-10) defines URTI as a disorder characterized by an infectious process involving the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, or trachea). The ICD-10 diagnostic codes were used to identify HSU for URTI in the DAD (HA) and NACRS (ED) databases. The most
responsible diagnosis was used and has been shown to have the highest predictive accuracy. OHIP fee-for-service physician diagnostic codes were used to define a URTI for SV. See appendix A for included URTI diagnostic codes. In order to calculate Total HSU, HA + ED + SV were combined.

HSU before 28 days of life was excluded to avoid complications from birth. Health service episodes less than 2 weeks apart were considered a single event to avoid counting multiple visits for the same URTI. Priority was given to hospital admissions, then emergency department visits and then outpatient sick visits.

Other variables. Covariates that might influence the relationship between 25-hydroxyvitamin D and HSU were identified a priori through a literature review and measured at the time of laboratory analysis or first TARGGet Kids! visit (if laboratory data were unavailable). These included age, sex, number of children in the household, and daycare/preschool attendance, and zBMI. Weight was measured using a precision digital scale and height was measured using a length board for children under 2 years and a stadiometer (SECA) for children over 2 years. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. BMI z scores were calculated using World Health Organization growth standards.
Statistical analysis

The total number of HA, ED and SV for URTI were described as counts. For the primary analysis, multivariable quasi Poisson regression was used to account for over dispersion of the data. The association between 25-hydroxyvitamin D and a) Total HSU, b) HA, c) ED and d) SV for URTI were tested. An offset was used to account for variation in the window of observation. The models were adjusted by the covariates specified above regardless of statistical significance to avoid bias that can result from standard variable selection techniques. Sensitivity analyses were performed repeating the primary analysis but including only children with 25-hydroxyvitamin D levels below <50 and <75 nmol/L based on AAP/IOM and CPS reference cut-points respectively to evaluate consistency of findings.

We assessed for multicolinearity for all covariates using the variance inflation factor (VIF). All VIF were <5 so we concluded that multicolinearity was unlikely to be a problem in this analysis.

Circulating 25-hydroxyvitamin D concentration varied from season to season, with higher levels during the summer and lower levels during the winter. To account for variability in the date of blood sampling, we adjusted the exposure (25-hydroxyvitamin D) for seasonal variability using the sine curve method described by Zhang et al. This allowed us to adjust for seasonal variation in vitamin D. Considering HSU was measured in all seasons over a 2 year period and 25-hydroxyvitamin D was seasonally adjusted, season is unlikely to be a potential confounder and was not included as a
Non-linearity was explored through graphical presentation of the data and spline analysis using 3 knots. A likelihood ratio test was conducted between the linear and non-linear models (nested models) to compare the goodness of fit. A p-value of 0.96 meant we did not reject the linear model.

Multiple imputations were performed, using transcan in the R package Hmisc, on covariates (number of children in the household, daycare/preschool attendance and zBMI) in order to overcome bias that can result from missing data. No variables had more than 5% missing data. We did not impute missing data for the exposures or the outcomes.

For the secondary analyses, the above multivariable quasi Poisson regression models were repeated but with vitamin D supplementation in pregnancy and childhood as the exposure variables with the same covariates and HSU outcomes.

All of the P values were 2-tailed and p<0.05 was considered statistically significant. All statistical analyses were conducted with SAS 9.3 and R version 3.3.
RESULTS

Of the 4962 children who met the inclusion criteria and provided consent to participate, 2926 had 25-hydroxyvitamin D measured and were included in the primary analysis (see figure 1). 4672 and 4132 children were included in the secondary analyses, which evaluated maternal vitamin D supplementation and child vitamin D supplementation, respectively. Baseline characteristics of children with and without laboratory testing are outlined in Table 1. Children with laboratory testing were slightly older and were more likely to take a vitamin D containing supplement, otherwise there was no clinically meaningful difference between the two groups. Fifty two percent of the participants were male and mean 25-hydroxyvitamin D was 84 nmol/L (range 11-355 nmol/L, SD 29.7). 218 and 1267 children had 25-hydroxyvitamin D levels below 50 nmol/L and 75 nmol/L, respectively. Ten percent of mother’s took a single nutrient vitamin D supplement during pregnancy. Forty seven percent of children were regularly consuming a vitamin D containing supplement (average dose was 196 IU/day SD 276).

During the observation period, 4896 (97%) children had at least 1 HSU of which 19% were for URTI, 431 (9%) children had at least 1 HA of which 21% were for URTI, 2191 (44%) children had at least 1 ED visit of which 23% were for URTI and 4883 (about 98%) children had at least 1 SV of which 19% were for URTI.

For the primary analysis, we evaluated whether serum 25-hydroxyvitamin D concentration was associated with HSU for URTI. No statistically significant association
was found in the unadjusted or adjusted models between 25-hydroxyvitamin D (in 10 nmol/L increments) and Total HSU (aRR: 1.01 and 95% CI: 0.99–1.02) (see Figure 2), HA (aRR: 1.01 and 95% CI: 0.92–1.10), ED (aRR: 0.99 and 95% CI: 0.96–1.02), or SV (aRR: 1.01 and 95% CI: 1.00–1.02) (see Table 2 and 3).

In the sensitivity analysis, no statistically significant association was found in the unadjusted or adjusted models between 25-hydroxyvitamin D (in 10 nmol/L increments) and Total HSU (aRR: 0.94 and 95% CI: 0.81–1.09) (aRR: 0.98 and 95% CI: 0.93–1.03) among children with 25-hydroxyvitamin D levels <50 and <75 nmol/L, respectively.

Further, no statistically significant associations were identified between prenatal vitamin D supplementation and Total HSU, HA, ED or SV (see table 2). Similarly, no statistically significant associations were found between child vitamin D supplementation (in 100 IU/day increments) and Total HSU, HA, ED or SV (see table 2).

**DISCUSSION**

We conducted a cohort study to evaluate the relationship between children’s 25-hydroxyvitamin D concentration, prenatal and child vitamin D supplement use and HSU for URTI. Given that URTIs in young children are the most common reasons for seeking healthcare, understanding this relationship, could result in important preventive benefits. In this study, the reasons for HA, ED visits and SV were similar to other North
American studies, but we did not find clinically meaningful associations between children’s vitamin D serum level, prenatal or child vitamin D supplementation and HSU for URTI. To our knowledge no study has yet evaluated vitamin D status and HSU for URTI in a cohort of healthy young children.

Other studies, which have evaluated the association between vitamin D status and URTI, have produced mixed results. Two meta-analyses of RCTs, including both adults and children, found that vitamin D had a protective effect against respiratory tract infections. Another meta-analysis, which focused on RCTs in children, found no association between 25-hydroxyvitamin D and risk of acute respiratory infections.

Two RCTs have assessed health services use following vitamin D supplementation in pregnancy. Griffiths et al. found no evidence that prenatal vitamin D supplementation (placebo, 800 IU/day or single bolus of 200,000 IU) from 27 weeks to delivery, in London England, influenced overall HSU in children in the first 3 years. They also found no association between 25-hydroxyvitamin D concentrations in the children at age 3 years of age (n=65) and HSU. However, this study was limited by a small sample size and only a small number of subjects had adequate (>50 nmol/L) vitamin D status at delivery. Grant et al. in Auckland New Zealand, found an association between vitamin D supplementation, during the last trimester of pregnancy and the first 6 months of infancy (placebo/placebo, 1000 IU/400 IU or 2000 IU/800 IU per day), among 260 mother-child dyads, and reduced primary care visits for acute respiratory infections from 6 to 18 months (p=0.048) for higher-dose vitamin D versus placebo. However, they
only had HSU data up to 18 months and combined data from different sources to
determine the outcome including: parent report up to 6 months of age, hospitalization
data up to 12 months and primary care visit data up to 18 months of age.\textsuperscript{38} In
collection, the current study had HSU outcome data over a 2 year period from 3
databases including information on HA, ED and SV (1 year before and 1 year after the
exposures were measured). Also, the mean 25-hydroxyvitamin D concentration at 18
months in the Grant et al. paper was 63 nmol/L, 61 nmol/L and 59 nmol/L in the
placebo, low and high dose arms respectively (n=221)\textsuperscript{38}, and this was lower than the
mean 25-hydroxyvitamin D level in the current study (84 nmol/L, n=2926).\textsuperscript{22}
Strengths of the current study included: a relatively large sample size of healthy young
children, with nearly 3000 serum 25-hydroxyvitamin D measurements, and HSU data on
all participants with sufficient power to detect a small association, as well as detailed
questionnaire data on vitamin D supplementation, as well as data on numerous potential
confounders.\textsuperscript{40,41} Further, this study was able to link clinical data from a large cohort
study and health administrative data from a publically funded health care system.
Limitations of this study include the observational nature thus causality cannot be
inferred. Secondly, health administrative data were not collected for the purposes of
doing research and thus the accuracy of physician billings may have led to
misclassification of the outcome. However, the use of the most responsible diagnosis has
been shown to have the highest predictive accuracy and lowest likelihood of
misclassification.\textsuperscript{22} Third, we were unable to measure the dose or adherence of vitamin
D taken during pregnancy and thus we were unable to determine whether a dose
relationship exists between prenatal supplementation and HSU. Forth, OHIP fee-for-service physician billing data for outpatient sick visits is limited to 1 diagnosis per encounter, and this may have resulted in missed outcomes. Finally, the mean 25-hydroxyvitamin D concentration in this population was 84 nmol/L (range 11 – 355 nmol/L), which is similar to other national studies but may not have been sufficiently low to demonstrate an association. However, in a sensitivity analysis, we did not identify an association with HSU in the population of children (n=218) with 25-hydroxyvitamin D concentration below 50 nmol/L.

The results from this study do not support the hypothesis that children’s 25-hydroxyvitamin D serum concentration or vitamin D supplement use (both during pregnancy and childhood) are negatively associated with HSU for URTI with parameter estimates near null and relatively tight confidence limits. Studies in children with higher risk of low 25-hydroxyvitamin D concentrations or combined mother/infant supplementation may be necessary to demonstrate an impact on HSU for URTI.

CONCLUSION

While vitamin D may be a potential preventive intervention for URTI, in this study we found no evidence to support an association between vitamin D status (continuously and dichotomized at <50 and <75 nmol/L), vitamin D supplementation in pregnancy or
childhood and health services utilization for URTI in children. However, most of the participants in the study had adequate vitamin D status.
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17. Singh RJ, Taylor RL, Reddy GS, Grebe SK. C-3 epimers can account for a significant proportion of total circulating 25-hydroxyvitamin D in infants, complicating accurate measurement and interpretation of vitamin D status. *J Clin Endocrinol Metab.* 2006;91(8):3055-3061.


<table>
<thead>
<tr>
<th>TABLE 1 – Socio-demographic characteristics of TARGet Kids! Cohort, Toronto Canada, 2008-13</th>
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<td>Age</td>
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<td>Prenatal supplementation multivitamin, yes</td>
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<td>Prenatal supplementation, single nutrient vitamin D, yes</td>
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<td>Child vitamin D supplements (combined dose from multivitamins and single nutrient vitamin D), IU</td>
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<td>Number of hospital admissions per child during observation window for URTI*</td>
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<tr>
<td>1+</td>
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<tr>
<td>Number of emergency department visits per child during observation window for URTI**</td>
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<tr>
<td>Number of outpatient sick visits per child during observation window for URTI***</td>
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<td>5</td>
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*110/517 (21%) of all hospital admissions were related to URTI (429 with unique ids)
**929/3954 (23%) of all emergency department visits were related to URTI (2189 with unique ids)
***7577/39429 (19%) of all outpatient sick visits were related to URTI (4940 with unique ids)
**TABLE 2** – Multivariate relative risk of HSU for URTIs in relation to 25-hydroxyvitamin D and vitamin D supplementation, Toronto, Canada, 2008-13

<table>
<thead>
<tr>
<th></th>
<th>Any health service utilization (Total HSU)**</th>
<th>Hospital admissions (HA)***</th>
<th>Emergency Department visits (ED)***</th>
<th>Outpatient sick visits (SV)***</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>aRR (95% CI)</td>
<td>RR (95% CI)</td>
<td>aRR (95% CI)</td>
</tr>
<tr>
<td>Serum 25-hydroxyvitamin D n=2962****</td>
<td>1.01 (0.99 – 1.02)</td>
<td>1.01 (0.99 – 1.02)</td>
<td>1.01 (0.93 – 1.10)</td>
<td>1.01 (0.92 – 1.10)</td>
</tr>
<tr>
<td>Prenatal vitamin D supplementation n=4672</td>
<td>1.01 (0.90 – 1.12)</td>
<td>0.95 (0.86 – 1.06)</td>
<td>0.89 (0.44 – 1.78)</td>
<td>0.89 (0.44 – 1.82)</td>
</tr>
<tr>
<td>Child vitamin D supplementation n=4132</td>
<td>1.00 (0.99 – 1.01)</td>
<td>1.01 (1.00 – 1.02)</td>
<td>1.03 (0.98 – 1.08)</td>
<td>1.03 (0.98 – 1.08)</td>
</tr>
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</table>

CI = confidence interval
RR = relative risk
aRR = adjusted relative risk
*Adjusted for age, sex, zBMI, number of children in the household and daycare/preschool attendance
** Any health service utilization for URTIs (HA + ED + SV)
***Health service utilization, risk of 1 hospital admission, 1 emergency department visit or 1 outpatient sick visits
****Serum 25-hydroxyvitamin D in 10 nmol/L increments
TABLE 3 – Quasi Poisson regression model for adjusted association between 25-hydroxyvitamin D and HSU for URTI, Toronto, Canada, 2008-13

<table>
<thead>
<tr>
<th></th>
<th>Any health service utilization for URTI Total HSU</th>
<th>Hospital admissions for URTI</th>
<th>Emergency Department visits for URTI</th>
<th>Outpatient sick visits for URTI</th>
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<tr>
<td></td>
<td>aRR</td>
<td>95% CI</td>
<td>aRR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Serum 25-hydroxyvitamin D (10 nmol/L change)</td>
<td>1.01</td>
<td>(0.99 – 1.02)</td>
<td>1.01</td>
<td>(0.92 – 1.10)</td>
</tr>
<tr>
<td>zBMI (0.5 unit change)</td>
<td>1.04↑</td>
<td>(1.02 – 1.06)</td>
<td>1.09</td>
<td>(0.97 – 1.23)</td>
</tr>
<tr>
<td>Age &lt;4 Reference = &lt;2 years</td>
<td>0.62↑</td>
<td>(0.55 – 0.69)</td>
<td>0.64</td>
<td>(0.31 – 1.29)</td>
</tr>
<tr>
<td>Age 2-4 Reference = &lt;2 years</td>
<td>0.80↑</td>
<td>(0.72 – 0.88)</td>
<td>0.95</td>
<td>(0.29 – 1.85)</td>
</tr>
<tr>
<td>Siblings 0 Reference = 1 sibling</td>
<td>1.03</td>
<td>(0.94 – 1.12)</td>
<td>0.72</td>
<td>(0.41 – 1.30)</td>
</tr>
<tr>
<td>Siblings 2 Reference = 1 sibling</td>
<td>0.98</td>
<td>(0.86 – 1.11)</td>
<td>0.44</td>
<td>(0.15 – 1.28)</td>
</tr>
<tr>
<td>Siblings 3+ Reference = 1 sibling</td>
<td>1.19</td>
<td>(0.96 – 1.48)</td>
<td>1.50</td>
<td>(0.43 – 5.18)</td>
</tr>
<tr>
<td>Gender Reference = male</td>
<td>0.93</td>
<td>(0.86 – 1.01)</td>
<td>0.87</td>
<td>(0.52 – 1.45)</td>
</tr>
<tr>
<td>Daycare Reference = no</td>
<td>1.20↑</td>
<td>(1.10 – 1.30)</td>
<td>2.04</td>
<td>(1.17 – 3.56)</td>
</tr>
</tbody>
</table>

1: A 0.5 unit increase in zBMI was associated with a 4% increased incidence rate of any HSU (Total HSU) for URTI, 9% increased incidence rate of ED visits for URTI and 3% increased incidence rate of SV for URTI.
2: Children >4 years had a 38% lower risk of incidence rate of any HSU for URTI compared to children <2 years.
3: Children 2-4 years had a 20% lower risk of incidence rate of any HSU for URTI compared to children <2 years.
4: Attending daycare was associated with a 20% increased incidence rate of HSU for URTI compared to children who did not attend daycare.
Children included in the primary analysis n=2926

Children recruited between December 2008-March 2013 and linked with health administrative data. Included in the analysis n=5049

Excluded children because missing age n=61 and missing date n=32 (unable to calculate offset)

Excluded children from primary analysis because no blood sample n=2036

FIGURE 1: participant selection
FIGURE 2 - unadjusted relative risk of 25-hydroxyvitamin D (in 10 nmol/L increments) and total health service utilization for upper respiratory tract infections in a 2 year period.
APPENDIX A

Diagnostic codes for Upper Respiratory Tract infections (URTI)

2A) ICD-10 diagnostic codes for URTI

Hospital admissions based on data from The Discharge Abstract Database (DAD) and Emergency Department visits based on data from National Ambulatory Care Reporting System (NACRS) using ICD-10 diagnostic codes.

<table>
<thead>
<tr>
<th>URTI</th>
<th>ICD-10 Diagnostic code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute upper respiratory tract infections</td>
<td>J00-J06</td>
</tr>
<tr>
<td>Influenza</td>
<td>J09-J11</td>
</tr>
<tr>
<td>Bronchitis *</td>
<td>J20, J40-J42</td>
</tr>
<tr>
<td>Other diseases of upper respiratory tract</td>
<td>J31, J32, J36, J37</td>
</tr>
<tr>
<td>Otitis media</td>
<td>H65, H66, H67</td>
</tr>
<tr>
<td>Cough</td>
<td>R05</td>
</tr>
<tr>
<td>Pain in throat</td>
<td>R07.0</td>
</tr>
</tbody>
</table>

2B) Physician billing diagnostic codes for URTI

Outpatient visits based on data from OHIP database, which contains data on physician billings.

<table>
<thead>
<tr>
<th>URTI</th>
<th>Diagnostic code (physician billings)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcal sore throat (bacterial disease), scarlet fever</td>
<td>034</td>
</tr>
<tr>
<td>Otitis media</td>
<td>380, 381, 382</td>
</tr>
<tr>
<td>Common cold/nasopharyngitis-acute</td>
<td>460</td>
</tr>
<tr>
<td>Acute sinusitis and chronic sinusitis</td>
<td>461, 473</td>
</tr>
<tr>
<td>Acute tonsillitis</td>
<td>463</td>
</tr>
<tr>
<td>Croup/laryngitis-acute/tracheitis-acute</td>
<td>464</td>
</tr>
<tr>
<td>Acute bronchitis *</td>
<td>466</td>
</tr>
<tr>
<td>Influenza</td>
<td>487</td>
</tr>
</tbody>
</table>

*Bronchitis is included as a URTI as it is likely miscoded