

The Relationship Between Cow's Milk and Stores of Vitamin D and Iron in Early Childhood



WHAT'S KNOWN ON THIS SUBJECT: Cow's milk consumption has opposite effects on vitamin D and iron levels in children; however, the amount of cow's milk intake required for sufficient stores of vitamin D and iron is poorly understood, and existing guidelines on consumption are unclear.



WHAT THIS STUDY ADDS: Two cups of cow's milk per day is sufficient to maintain healthy vitamin D and iron stores for most children. Wintertime vitamin D supplementation appears particularly important among children with darker skin pigmentation.

abstract

OBJECTIVE: To examine the association between cow's milk intake on both vitamin D and iron stores in healthy urban preschoolers.

METHODS: Healthy children 2 to 5 years of age were recruited from December 2008 through December 2010 through the TARGET Kids! practice-based research network. Cow's milk intake was measured by parental report. Vitamin D and iron stores were measured by using serum 25-hydroxyvitamin D and ferritin. Bivariate multivariable linear regression was used to examine the effect of cow's milk intake simultaneously on 25-hydroxyvitamin D and serum ferritin. Analyses were stratified by important clinical variables including skin pigmentation, bottle feeding, vitamin D supplementation, and season.

RESULTS: Among 1311 children, increasing cow's milk consumption was associated with decreasing serum ferritin ($P < .0001$) and increasing 25-hydroxyvitamin D ($P \leq .0001$). Two cups (500 mL) of cow's milk per day maintained 25-hydroxyvitamin D >75 nmol/L with minimal negative effect on serum ferritin for most children. Children with darker skin pigmentation not receiving vitamin D supplementation during the winter required 3 to 4 cups of cow's milk per day to maintain 25-hydroxyvitamin D >75 nmol/L. Cow's milk intake among children using a bottle did not increase 25-hydroxyvitamin D and resulted in more dramatic decreases in serum ferritin.

CONCLUSIONS: There is a trade-off between increasing 25-hydroxyvitamin D and decreasing serum ferritin with increasing milk intake. Two cups of cow's milk per day appears sufficient to maintain healthy vitamin D and iron stores for most children. Wintertime vitamin D supplementation was particularly important among children with darker skin pigmentation. *Pediatrics* 2013;131:e144–e151

AUTHORS: Jonathon L. Maguire, MD, MSc, FRCPC,^{a,b,c} Gerald Lebovic, PhD,^a Sharmilaa Kandasamy, BSc,^b Marina Khovratovich, MD,^c Muhammad Mamdani, PharmD, MA, MPH,^{a,d} Catherine S. Birken, MSc, MD, FRCPC,^c and Patricia C. Parkin, MD, FRCPC,^c on behalf of the TARGET Kids! Collaboration

^aThe Applied Health Research Centre of the Li Ka Shing Knowledge Institute of St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; ^bDepartment of Pediatrics, St. Michael's Hospital, Toronto, Ontario, Canada; ^cPediatric Outcomes Research Team (PORT), Division of Pediatric Medicine, Department of Pediatrics, University of Toronto, The Hospital for Sick Children, Toronto, Ontario, Canada; and ^dLeslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

KEY WORDS

vitamin D, child, preschool, parathyroid hormone, cross-sectional studies

ABBREVIATIONS

AAP—American Academy of Pediatrics

CI—confidence interval

CRP—C-reactive protein

Dr Maguire conceptualized and designed the study, designed the data collection instruments, analyzed data, drafted the manuscript, critically revised and reviewed the manuscript for important intellectual content, and approved the final manuscript as submitted; Dr Lebovic analyzed and interpreted the data, performed statistical analysis, and approved the final manuscript as submitted; Ms Kandasamy and Dr Mamdani drafted the manuscript, critically revised and reviewed the manuscript for important intellectual content, and approved the final manuscript as submitted; Dr Khovratovich designed the data collection instruments, coordinated and supervised data collection, approved the final manuscript as submitted; Dr Birken critically revised and reviewed the manuscript for important intellectual content, and approved the final manuscript as submitted; and Dr Parkin conceptualized and designed the study, analyzed data, critically revised and reviewed the manuscript for important intellectual content, and approved the final manuscript as submitted.

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Address correspondence to Jonathon Maguire, MD, MSc, FRCPC, Department of Pediatrics, St. Michael's Hospital, 30 Bond St, 15-014 Cardinal Carter, Toronto, Ontario M5B 1W8 Canada. E-mail: jonathon.maguire@utoronto.ca

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Consumption of milk and milk products is recommended by numerous international organizations, given its positive effects on bone health.^{1–3} In the United States and Canada, >70% of children consume cow's milk daily.^{4,5} Although vitamin D–fortified milk contributes to important body stores of vitamin D needed for maintaining bone health, cow's milk contains very little iron and consumption >500 mL per day has been associated with reduced iron stores in young children.^{6–9}

Vitamin D and iron are both essential micronutrients and adequate levels of each are critical for health and development in children.^{7,8} Vitamin D promotes calcium absorption, which is needed for preventing rickets and optimizing bone mass in children.^{6,7,10,11} Vitamin D may also be important for the prevention of a number of chronic conditions, including autoimmune,^{12–16} respiratory,^{17–21} and cardiovascular disease.^{6,7,10,11,22–26} Dietary iron is important for child health and development, as it plays a crucial role in early brain development.^{27–29} Iron deficiency with or without anemia has been associated with permanently impaired psychomotor development.^{27–36}

It is well established that 25-hydroxyvitamin D above 50 nmol/L is sufficient to prevent rickets.³⁷ Therefore, the Institute of Medicine and the American Academy of Pediatrics (AAP) have recommended that 25-hydroxyvitamin D levels in children be >50 nmol/L to avoid deficiency.^{6,7} Data from adults suggest that serum parathyroid hormone, a hormone that increases calcium resorption from bone, tends to be minimized once 25-hydroxyvitamin D is >75 nmol/L; therefore, the Canadian Pediatric Society has suggested that “optimal” 25-hydroxyvitamin D is >75 nmol/L.^{38,39} To our knowledge, there are no consensus recommendations regarding optimal iron stores for children. The optimal amount of cow's milk consumption to promote healthy vitamin D

and iron stores is poorly understood, particularly among young children; moreover, current guidelines as they relate to cow's milk consumption are unclear. The AAP Committee on Nutrition recommends that children who are ingesting <1000 mL per day of vitamin D–fortified milk receive supplemental vitamin D.⁷ Conversely, the AAPs Bright Futures Guidelines for Health Supervision suggest that cow's milk intake be limited to 2 cups (500 mL) per day for children 2 to 6 years of age to avoid iron deficiency.⁴⁰ It is unclear what clinicians are to tell parents when asked, “How much cow's milk should my child be drinking?”

The primary objective of this study was to examine the association between milk intake and both vitamin D and iron stores in healthy preschoolers. Our secondary objective was to examine how clinically relevant biological, environmental, and behavioral factors might change the effect of cow's milk intake on vitamin D and iron stores.

METHODS

Subjects and Design

We conducted a cross-sectional observational study of healthy children 2 to 5 years of age through the TARGet Kids! primary care practice-based research network in Toronto, Canada (latitude 43.4°N) between December 2008 and December 2010. TARGet Kids! is a collaboration between child health outcomes researchers in the Faculty of Medicine at the University of Toronto and 7 large primary care group practices from the Department of Pediatrics and the Department of Family and Community Medicine at the University of Toronto. The overall objective of TARGet Kids! is to advance the scientific base for recommendations regarding disease prevention (screening and surveillance for early detection of disease), anticipatory guidance, and interventions for common nutritional and developmental

disorders delivered by primary health care providers in office practice settings. Children were excluded from this TARGet Kids! study if they had any chronic illnesses (other than asthma) or acute inflammation (C-reactive protein [CRP] >10 mg/L), were on medications known to alter vitamin D or iron metabolism (ie, antiseizure medications), or had a gestational age <32 weeks. Children <2 years of age were excluded to minimize the effect of breastfeeding and iron-fortified formula use on cow's milk intake estimates.

Variables

Data were collected during a routine health maintenance physician visit by trained research assistants embedded in each practice. Clinically relevant biological, environmental, and behavioral variables were obtained from consenting parents by a standardized parent-completed data-collection form based on the Canadian Community Health Survey.⁴¹ The following survey data were collected: age, gender, date of visit, daily cow's milk consumption, vitamin D and iron supplementation, outdoor free play (minutes per day), and bottle use. Cow's milk consumption was measured from parental report based on response to the following question: “How many 250-mL cups of cow's milk does your child drink in a typical day?” Bottle use was measured based on response to the following question: “Does your child currently use a bottle?”

Weight was measured by using a precision digital scale ($\pm 0.025\%$; SECA, Hamburg, Germany) and standing height was measured by using a stadiometer (SECA). BMI was calculated as the weight in kilograms divided by the height in meters squared.^{42,43} BMI z-scores were calculated by using World Health Organization growth standards.⁴⁴ Skin pigmentation was measured by using research assistant–assigned

Fitzpatrick score, which is a 6-category skin pigmentation classification system that is widely used in dermatological research.⁴⁵

Venous blood was drawn by trained pediatric phlebotomists and sent daily to the Clinical Biochemistry Laboratory at Mount Sinai Hospital in Toronto, Ontario. Total 25-hydroxyvitamin D was measured from serum samples by using a competitive 2-step chemiluminescence assay with a Diasorin LIAISON 25-hydroxyvitamin D TOTAL (Diasorin S.P.A., Vercelli, Italy).⁴⁶ Extensive testing and validation of this machine has demonstrated an interassay imprecision of 4.9% at 32 nmol/L, 8.9% at 77 nmol/L, and 17.4% at 213 nmol/L.^{47,48} Serum ferritin was measured by using an electrochemiluminescence immunoassay on the Roche Modular E170 analyzer (Roche Diagnostics, Indianapolis, IN), which had an interassay imprecision of 7.5% at 6 $\mu\text{g/L}$, 4.2% at 30 $\mu\text{g/L}$, and 4.7% at 390 $\mu\text{g/L}$. To avoid falsely elevated serum ferritin owing to inflammation, children with CRP >10 nmol/L were excluded from the analysis.^{8,9}

Medidata RAVE (Medidata Solutions Inc. <http://www.mdsol.com/>) was used as the secure electronic data capture system and data repository for all TARGeT Kids! data.

Statistical Analysis

Our primary analysis aimed to examine the association between cow's milk intake and 25-hydroxyvitamin D and serum ferritin simultaneously. To accomplish this, a bivariate multivariable linear regression model was developed.⁴⁹ Serum ferritin and 25-hydroxyvitamin D (continuous variables) were modeled as simultaneous outcome variables with daily volume of milk consumption (continuous variable) as the main predictor variable. We then used this model to adjust for variables known or suspected to affect vitamin D or iron stores. These included gender, season (October

through April versus June through September), Fitzgerald skin pigmentation scale (light I–III versus dark IV–VI), current bottle use, minutes of outdoor free time per day, BMI (zBMI), and vitamin D and iron supplementation. These covariates were a priori specified and all were included in the final model. To accommodate skewed distributions of 25-hydroxyvitamin D and serum ferritin, both variables were log transformed. Marginal estimates were tested by using a Wald statistic, whereas the bivariate estimates were examined by using the Pillai test statistic.⁵⁰ Model checking was performed on the marginal models by using residual analysis. Bootstrap validation of the linear regression model (100 times) was used to obtain 95% confidence intervals (CIs).⁵¹ Our secondary analysis aimed to examine the association between cow's milk intake and serum ferritin and 25-hydroxyvitamin D across various clinical scenarios of gender, skin pigmentation, season, bottle use, and vitamin D supplementation. To accomplish this, biologically plausible interactions between cow's milk consumption and each of the covariates were added to the bivariate model developed for the primary analysis. This model was then used to examine how these interactions might modify the effect of cow's milk intake on median serum ferritin and 25-hydroxyvitamin D, and estimate the volume of cow's milk required to maintain 25-hydroxyvitamin D >75 nmol/L.

As this was an observational study, a moderate amount of missing data was expected. Although the data appeared missing completely at random, multiple imputation was implemented to determine the effect of missing data. Because of the inherent structure of the model, the imputation was implemented by using marginal models, and 5 datasets were used for each model.⁵² The resulting estimates were consistent, with the marginal model estimates

using complete case analysis, so reported results are from the complete case bivariate analysis.

Data were analyzed by using the R project for statistical computing.⁵³ This TARGeT Kids! study was approved by the research ethics board at The Hospital for Sick Children, and all parents of participating children consented to participation in the study.

RESULTS

Of the 3396 children who consented to participate, venous blood sampling was obtained in 1366 children; 1311 (96%) had CRP ≤ 10 and were included in the analysis (see Fig 1). Seventy-six percent of children had complete survey, anthropometric, and laboratory data. Mean daily cow's milk intake was 460 mL. Mean 25-hydroxyvitamin D was 88 nmol/L (95% CI: 87–89 nmol/L); 35% (95% CI: 33%–38%) had 25-hydroxyvitamin D <75 nmol/L and 6% (95% CI: 5%–7%) had 25-hydroxyvitamin D <50 nmol/L. Mean ferritin was 31 $\mu\text{g/L}$; 4% (95% CI: 3%–5%) had ferritin <12 $\mu\text{g/L}$. Subject characteristics are presented in Table 1. Imputation for missing values did not change descriptive characteristics.

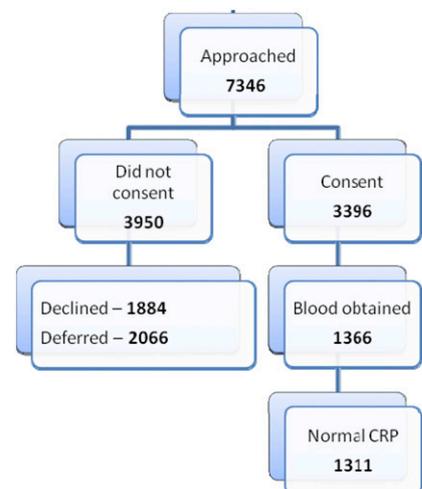


FIGURE 1 Participant flow and recruitment.

TABLE 1 Population Characteristics

Subjects	<i>n</i> = 1311
Age, mo, mean (SD)	48 (18)
Male gender, <i>n</i> (%)	661 (51)
Maternal education, <i>n</i> (%):	
Primary school	13(1)
High school	114 (9)
College or university	1105 (90)
BMI z-score, mean (SD)	0.27 (1.0)
Overweight, <i>n</i> (%)	288 (22)
Obese, <i>n</i> (%)	79(6)
Ever breast fed, <i>n</i> (%)	1219 (93)
Current breast feeding, <i>n</i> (%)	44(4)
Current bottle use, <i>n</i> (%)	151(11)
Daily milk intake, mL, mean (SD)	460 (310)
Daily vitamin D supplementation, <i>n</i> (%)	743 (61)
Daily iron supplementation, <i>n</i> (%)	163 (14)
Minutes of outdoor play time/d, mean (SD)	62 (56)
Season (October–April), <i>n</i> (%)	679 (50)
Skin pigmentation (Fitzpatrick), <i>n</i> (%):	
I (lightest)	131 (10)
II	537 (41)
III	458 (35)
IV	130 (10)
V	26(2)
VI (darkest)	25(2)

For the primary analysis, the adjusted bivariate model identified that increased cow's milk consumption was associated with increased 25-hydroxyvitamin D ($P < .0001$) and decreased serum ferritin ($P = .0001$). Each cup (250 mL) of cow's milk increased 25-hydroxyvitamin D on average by 6.5% (for example, a 5.5-nmol/L increase was associated with an increase in cow's milk consumption from 2 to 3 cups, 95% CI: 3.9–7.1) and decreased serum ferritin on average by 3.6% (for example, a 1- $\mu\text{g/L}$ decrease was associated with an increase in cow's milk consumption from 2 to 3 cups, 95% CI: 0.3–1.7). Children with serum ferritin $<12 \mu\text{g/L}$ drank 130 mL more cow's milk than children with serum ferritin $\geq 12 \mu\text{g/L}$ (95% CI: 50–210 mL). Vitamin D supplementation ($P < .001$), current bottle use ($P = .005$), light skin pigmentation ($P < .001$), summer season ($P < .001$), and lower zBMI ($P = .005$) all increased 25-hydroxyvitamin D and

winter season increased serum ferritin ($P = .01$) (see Fig 2 and Table 2).

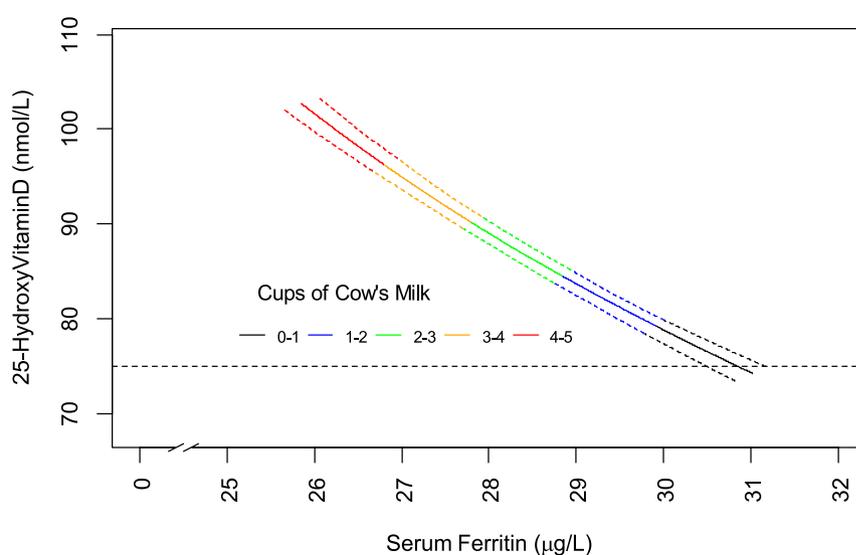
Our secondary analysis was to examine the association between cow's milk intake and serum ferritin and 25-hydroxyvitamin D across various clinical scenarios of gender, skin pigmentation, season, bottle use, and vitamin D supplementation.

For our secondary analysis, we examined the association between cow's milk intake and serum ferritin and 25-hydroxyvitamin D across various common clinical scenarios (see Fig 3). Among children not using a bottle, cow's milk consumption increased median 25-hydroxyvitamin D and decreased median serum ferritin as expected (see Fig 3 A and B). Up to 2 cups of cow's milk per day resulted in median 25-hydroxyvitamin D $>75 \text{ nmol/L}$, except for children with dark skin pigmentation (Fitzpatrick IV–VI) not receiving vitamin D supplementation during the winter who required 3 to 4 cups of cow's milk per day to maintain 25-hydroxyvitamin D $>75 \text{ nmol/L}$ (Fig 3A).

Among children using a bottle, cow's milk consumption did not increase median 25-hydroxyvitamin D and resulted in more dramatic decreases in median serum ferritin across all clinical scenarios (see Fig 3 C and D). Essentially no milk was needed to maintain median 25-hydroxyvitamin D $>75 \text{ nmol/L}$ among children using a bottle.

DISCUSSION

Our findings suggest that there is a trade-off between increasing 25-hydroxyvitamin D and decreasing serum ferritin with increasing milk intake; moreover, bottle use, gender, season, vitamin D supplementation, skin pigmentation, and BMI were significant modifiers of this trade-off. On average ~ 2 cups (500 mL) of cow's milk per day was sufficient to maintain median 25-hydroxyvitamin D $>75 \text{ nmol/L}$ with minimal impact on median serum ferritin; however, children with darker skin pigmentation who did not receive vitamin D supplementation during the winter required 3 to 4 cups of cow's milk per day to maintain 25-hydroxyvitamin

**FIGURE 2**

The adjusted effect of cow's milk intake on serum ferritin and 25-hydroxyvitamin D. Median serum ferritin ($\mu\text{g/L}$) is presented on the x-axis and median 25-hydroxyvitamin D (nmol/L) is presented on the y-axis. Colors represent cow's milk intake: black 0 to 1 cup, blue 1 to 2 cups, green 2 to 3 cups, orange 3 to 4 cups, and red 4 to 5 cups. Dashed colored lines represent 95% CIs. Dashed black line represents median 25-hydroxyvitamin D of 75 nmol/L. Data are presented for the average child.

TABLE 2 Effect of Clinically Important Variables on 25-Hydroxyvitamin D and Serum Ferritin

Clinical Variable	Percent Change in Ferritin	Change in Median Ferritin $\mu\text{g/L}$ (95% CI) ^{a,b}	<i>P</i> Value	Percent Change in 25-Hydroxyvitamin D	Change in Median 25-hydroxyvitamin D nmol/L (95% CI) ^{a,b}	<i>P</i> Value ^a
Milk intake, per cup	-3.6%	-1.0 (-0.3 to -1.7)	<.0001 ^c	6.5%	5.5 (3.9 to 7.1)	<.0001 ^c
Male gender	2.7%	0.7 (-0.9 to 1.7)	.38	-2.0%	-1.7 (-5.0 to 1.8)	.34
Vitamin D supplementation, yes	-0.8%	-0.2 (-2.0 to 1.7)	.82	13.2%	11.7 (6.7 to 15.4)	<.0001 ^c
Iron supplementation, yes	-2.8%	-0.8 (-3.2 to 1.8)	.54	-1.7%	-1.4 (-6.4 to 4.0)	.60
Outdoor free play, 60 min/d	-2.9%	-0.8 (-1.7 to 0.1)	.06	1.4%	1.2 (-0.7 to 3.0)	.22
Bottle use, yes	-7.5%	-2.1 (-4.5 to 0.5)	.12	10.1%	8.5 (2.5 to 14.9)	.005 ^c
Dark skin, Fitzpatrick IV-VI	2.3%	0.7 (-1.6 to 3.1)	.58	-9.9%	-8.3 (-12.4 to 4.0)	.0003 ^c
Season, winter	8.0%	2.3 (0.43 to 4.2)	.01 ^c	-10.7%	-9.0 (-12.1 to 5.6)	<.0001 ^c
zBMI, unit	1.6%	0.5 (-0.5 to 1.3)	.28	-2.9%	-2.4 (-4.0 to -0.75)	.005 ^c

^a Effect sizes shown for children with a milk intake of 2 cups (500 mL).

^b Negative values indicate a decrease in serum level, positive values indicate an increase in serum level.

^c Statistically significant effects.

D >75 nmol/L with consequently a larger fall in serum ferritin. Among children using a bottle, cow's milk intake appeared not to increase 25-hydroxyvitamin D, yet had a more pronounced effect on reducing serum ferritin.

Vitamin D–fortified cow's milk has been identified as the major dietary source of vitamin D for young children.^{54–56} Gordon et al¹¹ found a 7-nmol/L increase in 25-hydroxyvitamin D per 250-mL cup of cow's milk in African American toddlers 12 to 24 months of age during the winter months, which is similar to our finding of 5-nmol/L increase per cup. A randomized controlled trial of vitamin D–fortified cow's milk in toddlers in New Zealand found a 10-nmol/L increase in 25-hydroxyvitamin D per 250 mL cup of vitamin D–fortified milk.⁵⁷ Studies using national surveys in the United States and Canada reported similar findings but could not quantify the effect per cup of cow's milk owing to data limitations.^{56,58}

Cow's milk is believed to have a dose-dependent negative effect on iron stores in young children^{9,59–63}; however, to our knowledge, this effect has not been rigorously evaluated. In addition, no other study has attempted to quantify the relative contribution of cow's milk consumption on both vitamin D and iron stores simultaneously. As the early years are critical for both vitamin D– and iron-related health out-

comes, understanding combined, rather than independent, relationships between these micronutrients has important practice and policy implications.

Our finding that cow's milk consumption among children using a bottle not only did not increase median 25-hydroxyvitamin D, but resulted in more dramatic decreases in median serum ferritin, support a number of studies that have identified that children using a bottle are at increased risk of iron deficiency.^{64–70} A possible explanation for our findings could be parental underreporting of milk intake among bottle users. Another is that fluids other than milk in the bottle, like juice, do not contribute to vitamin D stores and may contribute to decreases in serum ferritin. Alternatively, any fluid intake from the bottle may replace vitamin D– and iron-containing solid foods. Regardless, reported cow's milk consumption among children using a bottle appears to have little benefit on micronutrient stores, suggesting that bottles should not be filled with cow's milk or used at all in this age group.

Limitations of our study include the parent-reported nature of our exposure assessment (daily cow's milk consumption), which may be subject to recall measurement error. Our population of children was recruited during routine primary health care in the largest Canadian city but may not be

representative of nonurban children or those in other urban environments at other latitudes; however, the prevalence of low vitamin D and iron stores in our population is similar to that reported in other regions of Canada and the United States.^{56,70–72} Some may argue that the absolute effect of cow's milk intake on median serum ferritin and 25-hydroxyvitamin D is small; however, at a population level these effects will result in undetected iron and vitamin D deficiency in a sizable proportion of children. Finally, because of the cross-sectional nature of our study, we cannot determine causality in the relationship between volume of cow's milk consumption, vitamin D, and iron stores.

Our findings are consistent with both AAP recommendations of milk intake depending on the clinical scenario.^{7,40} For most children, 2 cups (500 mL) of cow's milk per day was sufficient to maintain healthy vitamin D stores with minimal impact on serum ferritin, which is consistent with AAP Bright Futures Guidelines.⁴⁰ Children with darker skin pigmentation not receiving vitamin D supplementation during the winter required up to 4 cups (1000 mL) of cow's milk to maintain healthy vitamin D stores, which is consistent with AAP guidelines on preventing vitamin D deficiency.⁷ However, 4 cups of cow's milk resulted in a larger decrease in

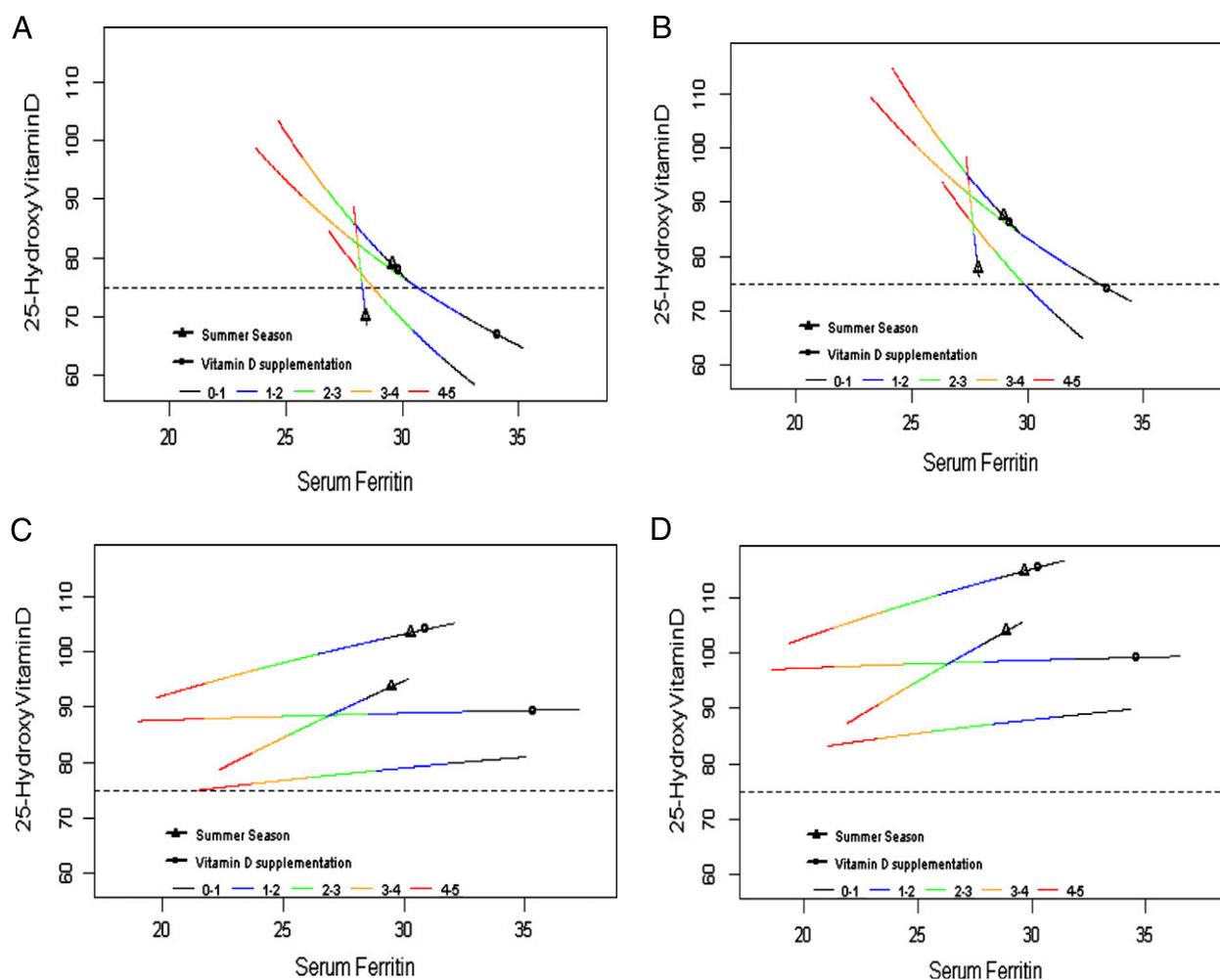


FIGURE 3

Effect of cow's milk intake on serum ferritin and 25-hydroxyvitamin D in multiple scenarios. Median serum ferritin ($\mu\text{g/L}$) is presented on the x-axis and median 25-hydroxyvitamin D (nmol/L) is presented on the y-axis. A and B display model results for children not currently using a bottle versus C and D for children using a bottle. A and C describe model results for children with dark skin pigmentation versus B and D for children with light skin pigmentation. Colors represent cow's milk intake: black 0 to 1 cup, blue 1 to 2 cups, green 2 to 3 cups, orange 3 to 4 cups, and red 4 to 5 cups. The dashed line represents median 25-hydroxyvitamin D of 75 nmol/L. Lines identified by the triangle represent summer season (May–September) and lines identified by the circle represent children receiving vitamin D supplementation. The dashed line represents median 25-hydroxyvitamin D of 75 nmol/L.

serum ferritin, highlighting the importance of vitamin D supplementation during the winter among children with darker skin pigmentation to maintain vitamin D stores. Cow's milk consumption among bottle users had no positive effect on either micronutrient, suggesting that bottle use is not helpful for micronutrient status in this age group.

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The Relationship Between Cow's Milk and Stores of Vitamin D and Iron in Early Childhood

Jonathon L. Maguire, Gerald Lebovic, Sharmilaa Kandasamy, Marina Khovratovich, Muhammad Mamdani, Catherine S. Birken, Patricia C. Parkin, on behalf of the TARGet Kids! and Collaboration

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