a rate of 2,464 prescriptions per 100,000 PYs in June 2011. The warning resulted in an immediate drop in the prescription rate of 513.4 (95% CI: −1,020.9, −5.9) prescriptions per 100,000 PYs, representing a 21% decrease in the prescription rate (R^2 = 0.82). In the postwarning period, there was a change in direction in the trend, with the prescription rate decreasing by 42.4 prescriptions per month per 100,000 PYs (95% CI: −92.9, 8.1) during this period. There were no important differences in patient characteristics before or after the warning (data not shown).

Our bupropion analysis revealed no difference in the observed and predicted prescription rate (R^2 = 0.94; data not shown), with no immediate decrease or postwarning rate change. Similarly, no difference was present for nicotine replacement therapies (data not shown). Our analysis excluding data before September 2007 revealed a similar but attenuated pattern for varenicline (prewarning rate: 14.4 [95% CI: 7.2, 21.6] prescriptions per month per 100,000 PYs; immediate change: −279.4 (95% CI: −469.8, −89.0) prescriptions per 100,000 PYs; postwarning rate: −30.8 (95% CI: −46.9, −14.6) prescriptions per month per 100,000 PYs; R^2 = 0.77).

Safety concerns regarding the cardiovascular effects of varenicline were associated with a decrease in its prescription in the United Kingdom. Although the labeling change was specific to cardiovascular patients, this decrease was independent of patient characteristics. The decreased rate was not accompanied by an increase in the prescription of other cessation drugs. Although evidence suggests that the benefits of varenicline outweigh any increased cardiovascular risk,[3] this warning was sufficient to alter clinical practice.

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Goat's Milk, Plant-based Milk, Cow's Milk, and Serum 25-hydroxyvitamin D Levels in Early Childhood

To the Editor:

Commercial availability and parental interest in alternative milk beverages for children have been increasing. We previously identified a relationship between higher consumption of alternative milk beverages and lower vitamin D levels in early childhood.[1] Based on existing research, it is unclear whether this is true for both animal-based (goat's milk) and plant-based (soy, almond, rice, etc.) milk beverages. Vitamin D fortification of alternative milk beverages is voluntary in both the United States and Canada.[2–4] Our objective was to determine whether the relationship between alternative milk beverage consumption and children's 25-hydroxyvitamin D is different for goat's milk, plant-based milk beverages, and cow's milk.

In this cross-sectional study, children 1–6 years old seen for routine primary healthcare were recruited between 2008 and 2013 in Toronto, Canada (latitude 43.4°N).[5] A parent-completed questionnaire based on the Canadian Community Health Survey, anthropometric and laboratory measurements were collected by trained research assistants and phlebotomists using standardized methods during the primary healthcare visit.[1,5,6]

We measured serum 25-hydroxyvitamin D concentration using the DiaSorin LIAISION 25-hydroxyvitmain D TOTAL chemiluminescence assay, with an interassay imprecision of 4.9 nmol/L using DEQAS (www.mountsinaiservices.com). Consumption of cow's milk, goat's milk, and plant-based milk beverages were measured as cups per day.[1]

We used multiple linear regression to test the association between each milk type consumed (goat, plant, and cow) and children's 25-hydroxyvitamin D level, adjusted for clinically relevant covariates identified a priori (age, sex, body mass index *z* score, vitamin D supplementation, margarine consumption [vitamin D fortified in Canada], skin pigmentation, outdoor play time,

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and seasonality). 25-hydroxyvitamin D was positively skewed and was log-transformed. Residual analysis indicated a good fit. We conducted multiple imputation for missing data (no variable had >12% missing data). The R Project was used for statistical analyses. This study was approved by the Hospital for Sick Children and St. Michael's Hospital Research Ethics Boards. Parents of children consented to study participation.

Of the 4,523 recruited children, 2,711 children had laboratory testing and were included in the study. The mean age was 2.9 years (SD 1.5) and 53% were male. Vitamin D supplementation was reported in 53% of children, and median 25-hydroxyvitamin D level was 80 nmol/L (interquartile range 66–99). Each cup of plant-based milk was associated with a 3.2 nmol/L (95% CI, 0.7, 5.6) lower median 25-hydroxyvitamin D level and each cup of cow's milk was associated with a 3.0 nmol/L (95% CI, 2.1, 3.9) higher median 25-hydroxyvitamin D level. Goat's milk consumption was not associated with children's serum 25-hydroxyvitamin D level although the trend was similar to cow's milk.

Comparing the relationship between volume of each milk type consumed and 25-hydroxyvitamin D level revealed similar associations for goat's milk and cow's milk whereas plant-based milk beverage consumption was associated with lower 25-hydroxyvitamin D than both cow's milk and goat's milk (Figure).

In summary, we identified a dose-dependent association between plant-based milk beverage consumption and lower 25-hydroxyvitamin D level in early childhood. This association was in the opposite direction to the relationship between consumption of animal-based milks and 25-hydroxyvitamin D. One explanation for the lower 25-hydroxyvitamin D levels among children who consume plant-based milk beverages may be a difference in the biological potency of vitamin D_2, found in plant-based milk, relative to vitamin D_3, found in animal-based milk. There has been considerable debate about whether vitamin D_2 is as effective as vitamin D_3 in raising serum 25-hydroxyvitamin D concentration.[7,8] Another explanation may be differences in regulatory requirements for vitamin D fortification of animal- and plant-based milk.

Future investigations are needed to elucidate the differences between the effects of plant-based milk beverage consumption and animal-based milk consumption on children's 25-hydroxyvitamin D levels.

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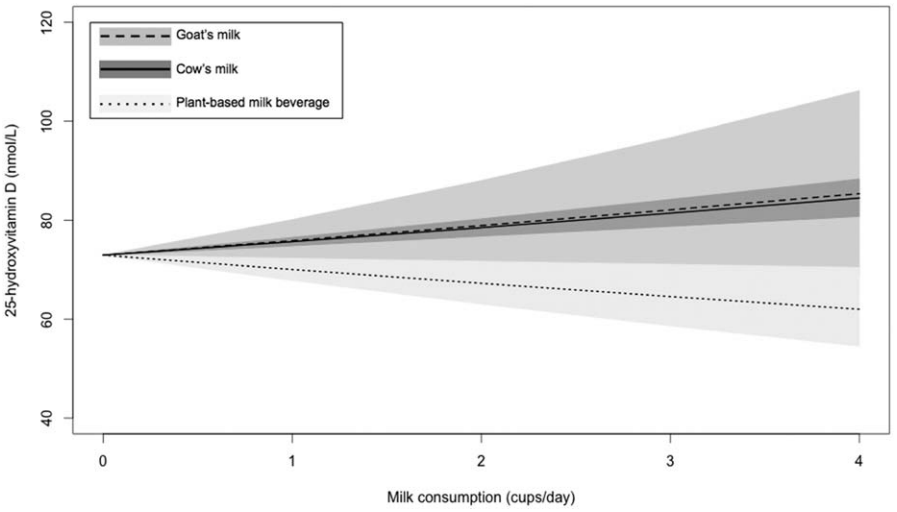

FIGURE. Adjusted association between milk consumption and children's serum 25-hydroxyvitamin D levels, by milk type.

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ERRATUM

Staged-informed Consent in the Cohort Multiple Randomized Controlled Trial Design: Erratum

In the article that appeared on page 389 of the May 2016 issue, an author's name was misspelled. The correction is as follows:

Helena M. Verkooijen

Reference

Young-Afat DA, Verkooijen HA, van Gils CH, van der Velden JM, Burbach JP, Elias SG, van Delden JJ, Relton C, van Vulpen M, van der Graaf R. Staged-informed Consent in the Cohort Multiple Randomized Controlled Trial Design. *Epidemiology* 2016;27:389–392.