

Seasonal Variation of Maternal Serum Vitamin D in Newfoundland and Labrador

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Abstract

Background: Research has suggested that vitamin D insufficiency and deficiency is common at northern latitudes, and that vitamin D insufficiency and deficiency may be common during pregnancy. We measured the serum 25-hydroxyvitamin D (25-[OH]D) status of pregnant women across the province of Newfoundland and Labrador in both summer and winter to investigate seasonal differences, age associations, and differences in geospatial distribution across the province.

Methods: We uniformly and randomly sampled blood from pregnant women in each of 79 census consolidated subdivisions across Newfoundland and Labrador from January to March 2007 and from July to September 2007.

Results: We obtained 304 samples from the end of winter (March) and 289 samples from the end of summer (September). Mean serum 25-(OH)D concentration was 52.1 nmol/L in winter and 68.6 nmol/L in summer ($P < 0.001$); 89% were vitamin D insufficient in the winter and 64% in the summer ($P < 0.001$); 6.6% were vitamin D deficient in winter and 1.7% in summer ($P = 0.003$), and younger women tended to be more vitamin D insufficient in the winter than older women. The geospatial distribution of vitamin D insufficiency tends to follow a north-south distribution in the winter.

Conclusions: A significant proportion of pregnant women in Newfoundland and Labrador are vitamin D insufficient. Vitamin D insufficiency may have important adverse health consequences for both the mother and the fetus. Further study is necessary to address health outcomes and effects of vitamin D supplementation and lifestyle changes in this population.

Résumé

Contexte : La recherche a laissé entendre que l'insuffisance et la carence en vitamine D sont courantes aux latitudes boréales, et qu'elles pourraient être courantes pendant la grossesse. Nous avons mesuré, en été et en hiver, le taux sérique de 25-hydroxyvitamine D (25-[OH]D) de femmes enceintes vivant dans la province de Terre-Neuve-et-Labrador afin d'explorer les différences saisonnières, les associations en fonction de l'âge et

les différences en fonction de la distribution géospatiale partout dans la province.

Méthodes : De janvier à mars 2007 et de juillet à septembre 2007, nous avons prélevé, de façon uniforme et aléatoire, du sang chez des femmes enceintes dans chacune des 79 subdivisions de recensement unifiées de Terre-Neuve-et-Labrador.

Résultats : Nous avons obtenu 304 prélèvements de sang à la fin de l'hiver (mars) et 289, à la fin de l'été (septembre). La concentration sérique moyenne de 25-(OH)D était de 52,1 nmol/l en hiver et de 68,6 nmol/l en été ($P < 0,001$); 89 % des participantes présentaient une insuffisance en vitamine D en hiver et 64 %, en été ($P < 0,001$); 6,6 % des participantes présentaient une carence en vitamine D en hiver et 1,7 %, en été ($P = 0,003$). De plus, les jeunes femmes étaient plus susceptibles de présenter une insuffisance en vitamine D en hiver que les femmes plus âgées. La distribution géospatiale de l'insuffisance en vitamine D tend à suivre une distribution nord-sud en hiver.

Conclusion : Dans la province de Terre-Neuve-et-Labrador, une proportion significative de femmes enceintes présente une insuffisance en vitamine D. Celle-ci peut entraîner d'importantes conséquences indésirables pour la santé tant de la mère que du fœtus. D'autres études s'avèrent nécessaires pour traiter des issues de santé et des effets de la supplémentation en vitamine D et de l'apport de modifications au mode de vie au sein de cette population.

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INTRODUCTION

Vitamin D enhances the intestinal absorption of calcium and phosphorus.¹ Deficiency of vitamin D results in muscle weakness, osteopenia and osteoporosis, osteomalacia with associated bone pain, and bone deformities.¹ Aside from disorders of bone metabolism, vitamin D has also been implicated in cancer pathogenesis,² immune dysregulation,³ and disturbances in glucose homeostasis⁴ potentially leading to diabetes.⁵

The main source of vitamin D in humans is cutaneous conversion of precursors from incident ultraviolet light. During exposure to sunlight, UVB radiation is absorbed by 7-DHC, which is present in the plasma membranes of both epidermal keratinocytes and dermal fibroblasts.⁶ This absorption

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results in the rearrangement of 7-DHC to form previtamin D₃, which is entrapped into the lipid bilayer of the plasma membrane.⁷ This precursor rearranges to the more thermodynamically stable vitamin D₃, which is ejected from the lipid bilayer into the extracellular space as it becomes more hydrophilic.⁸ The vitamin D binding protein in the dermal capillary bed has an affinity for vitamin D₃ and draws it into the vascular circulation from the extravascular space, from which it exerts its systemic effects.

Humans receive a minor amount of vitamin D from food, and oily fish such as salmon, mackerel, and sardines are the main food sources of vitamin D₃, with minimal contributions from egg yolks. Currently fortified foods include milk, orange juice, and some breads and cereals.¹ However, more than 90% of the vitamin D requirements for most people comes from casual exposure to sunlight.^{1,9}

The cutaneous production of vitamin D is mitigated by several factors. The melanin of the skin is a natural sunscreen because it efficiently absorbs UVB photons; people with increased melanin pigmentation require longer exposure to sunlight to produce the same amount of vitamin D.¹⁰ Commercial sunscreens also absorb UVB photons before they enter the skin.¹¹ Environmental factors such as time of day, season, and latitude dramatically influence the cutaneous production of vitamin D.¹² As the zenith angle of the sun increases in the higher latitudes in winter, the ozone layer absorbs more UVB photons because of the increased distance the photons must travel through the ozone. Because of this absorption, beyond 37° latitude (north and south) there are marked decreases (from 80% to 100%, depending on latitude) in the number of UVB photons reaching the earth's surface during the winter months.^{9,12} In far northern (and far southern) countries, very little vitamin D₃ is peripherally converted in the skin during the winter because of the angle of solar declination. Similarly, the zenith angle of the sun in the early morning or late afternoon is such that vitamin D₃ production in the skin is reduced even in midsummer. Therefore, the times of maximal peripheral conversion of 7-DHC to vitamin D₃ occur in midday from mid-spring

to mid-autumn, because the sun's zenith angle permits enough UVB photons to reach the earth's surface. However, these are the times of the day that sunscreen protection is recommended. Sunscreen with an SPF of 15 may reduce the peripheral conversion of vitamin D by up to 26 times.¹³

The correlation of vitamin D deficiency to other disease processes both in utero and in early childhood is likely important to the developing fetus for several reasons. Although historically poorly studied,¹⁴ vitamin D deficiency in pregnancy has recently been shown to be an independent risk factor for decreased birth weight¹⁵ (and further study results on supplementation with vitamin D during pregnancy are forthcoming¹⁶). Future bone mineral accrual (as late as nine years from birth) may also be related to maternal vitamin D status.¹⁷ There are vitamin D receptors in the brain, and vitamin D deficiency in the mother has been shown to reduce the amount of brain growth factors in rat fetuses.¹⁸

Vitamin D insufficiency or deficiency in pregnancy or during the neonatal period may have important negative health consequences. A recent study of northern US black and white pregnant women and neonates revealed high levels of vitamin D deficiency and insufficiency, despite a consistent intake of prenatal vitamin supplements containing vitamin D.¹⁹ These authors found maternal vitamin D deficiency to be an independent risk factor for preeclampsia.²⁰ Maternal vitamin D status may also have a significant effect on newborn BMC and developing fetal bone.²¹

Therefore, studying the vitamin D status of pregnant women is important for understanding both the epidemiology of hypovitaminosis D and the potential risk for various diseases (such as type 1 diabetes⁵), especially since successful supplementation is possible.

Several studies have shown demonstrated Vitamin D deficiency in residents of North America, including children,^{22,23} adolescents,²⁴ and African Americans.²⁵ However, little is known of the vitamin D status of pregnant women in northern latitudes. In Newfoundland and Labrador, Canada's easternmost province, a previous pilot study of the vitamin D status of local children, newborns, and pregnant women demonstrated a clinically significant deficiency of vitamin D in the populations under study. In this current province-wide study, the serum 25(OH)vitamin D levels of pregnant women in both late winter and late summer were measured and compared to determine the absolute and temporally relative status of vitamin D in this Newfoundland and Labrador population.²⁶

ABBREVIATIONS

7-DHC	7-dehydroxycholesterol
BMC	bone mineral content
CCS	census consolidated subdivision
SPF	sun protection factor
T1DM	type 1 diabetes mellitus
UVB	ultraviolet B
UVR	ultraviolet radiation

METHODS

Blood samples are routinely taken from pregnant women to screen for various conditions. Provincially, these samples are sent to the Newfoundland and Labrador Public Health Laboratory, Health and Community Services, in St. John's. An anonymous list of all antenatal samples received at the Newfoundland and Labrador Public Health Laboratory from January to March 2007, and July to September 2007 was analyzed. Newfoundland has 79 census consolidated subdivisions used in the national census. In order to measure serum samples uniformly from across the province, up to five samples for both late winter and late summer from each of the 79 CCSs were requested using a random number generator. If a requested sample had insufficient volume to perform the required analysis, a replacement sample was requested randomly from the remaining samples from that CCS. If a CCS had no available samples, the average serum 25-(OH)D of the surrounding CCSs was assigned to that "null" CCS.

Current address was acquired for each sample via blinded request through the Newfoundland and Labrador Centre for Health Information using a unique provincial hospital identifier. New unique identifiers for each sample were generated to maintain patient anonymity, and the samples were delivered to the Health Sciences Centre laboratory with only the new unique identifier, age, and geographical location of habitation as identifying information.

Serum 25-(OH)D was measured randomly throughout the pregnancy, although most women have testing done early in the second trimester. 25-(OH)D analysis was performed at the Health Sciences Centre laboratory, the tertiary care hospital servicing the Province of Newfoundland and Labrador, under the supervision of the Division Chief of Clinical Biochemistry. Measurement of 25-(OH)D in serum was performed using a standard radioimmunoassay protocol (Diasorin, Stillwater MN).

The selection of vitamin D ranges has been controversial.²⁷⁻²⁹ Some committees have suggested a cut-off concentration for 25-(OH)D deficiency of < 27.5 nmol/L,³⁰ while others have suggested < 25 nmol/L.³¹ Various organizations have published guidelines on the prevention of rickets based on specified concentrations (< 27.5 nmol/L for the American Academy of Pediatrics³² and < 25 nmol/L for the Canadian Paediatric Society³³). The population sample for our study included adolescents and young adults. Studies in adolescents found that parathyroid hormone concentrations increased when 25-(OH)D concentrations decreased below 25 nmol/L.^{34,35} We chose a 25-(OH)D concentration of 25 nmol/L for vitamin D deficiency in this study.

Vitamin D insufficiency is also a variably defined serum concentration. Optimal concentrations of 25-(OH)D greater than 75 nmol/L are found to be consistent with improved bone health³⁶ and other health outcomes,³⁷ and expert opinion suggests an optimal 25-(OH)D concentration of 70 to 80 nmol/L.³⁸ Consequently, a cut-off 25-(OH)D of 75 nmol/L for vitamin D insufficiency was selected for this study.

The power of the study was determined by means and variances originating from our pilot study on vitamin D in Newfoundland and Labrador.²⁶ An expected mean 25-(OH)D of 50 nmol/L and a standard deviation of 20 nmol/L were selected with an alpha of 0.05 and a power of 0.80 to observe a difference of 5 nmol/L between the January to March and July to September time periods. This would require at least 252 samples from each time period. Five samples from each of the 79 census consolidated subdivisions would yield approximately 400 samples each, and with a conservative estimate of 20% subdivisions with no births due to low population density over a three-month period (estimated from known provincial statistics), five samples from each CCS, giving approximately 320 samples, would be sufficient to achieve 252 samples from each time period.

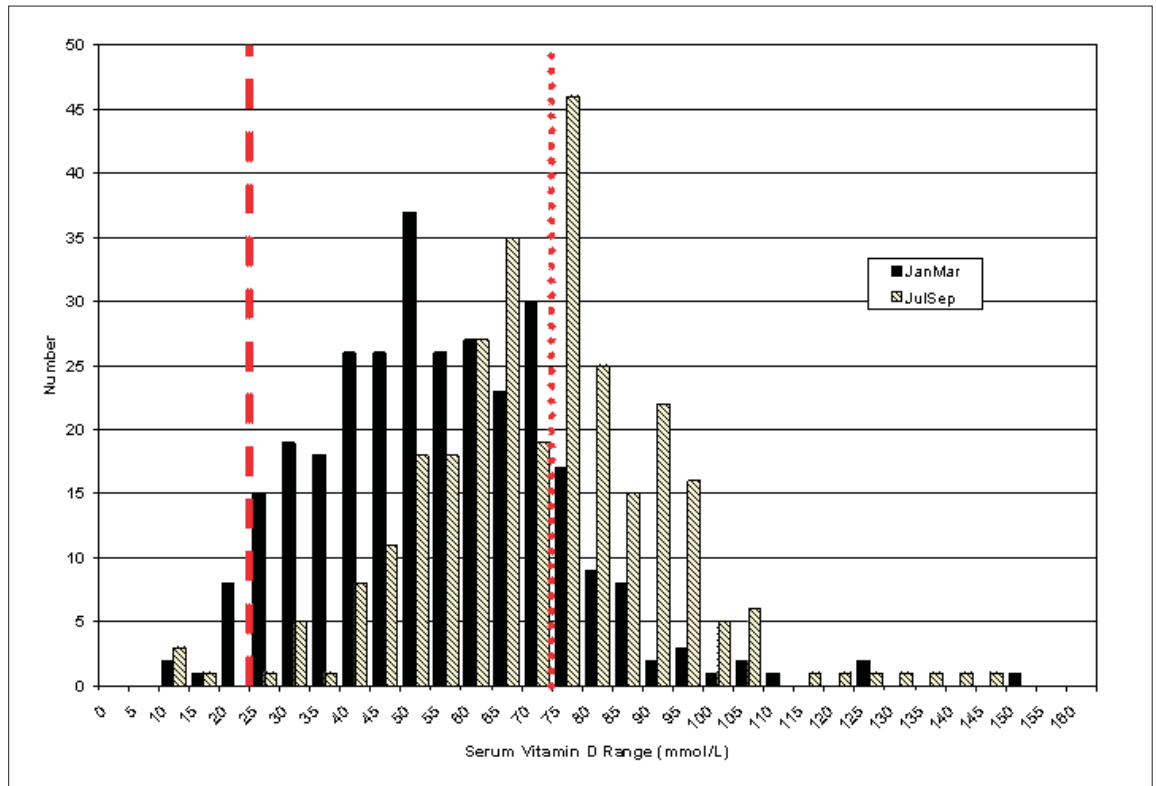
Matlab version 7.0.1 (The MathWorks Inc., Natick MA) was used for all statistical analysis and WinBUGS³⁹ was used to create the geospatial maps. Student *t* tests were used to compare the average serum vitamin D values, and chi-square tests were used to compute the difference between the proportion of patients who were vitamin D insufficient and vitamin D deficient. All statistical tests were two-sided, and a 5% level of significance was used throughout.

The Memorial University Faculty of Medicine and Eastern Health Human Investigations Committee and the ethics committees of each hospital board approved this study.

RESULTS

In 2004, the total number of live births in Newfoundland and Labrador was 4511.⁴⁰ The Newfoundland and Labrador Public Health Laboratory provided a possible 1110 samples for July-September 2007 and 1206 for January-March 2007, suggesting excellent coverage for the total number of live births. No information was available for the number of potential samples in the other six months of the year. In total, 304 samples from January to March 2007 and 289 samples from July to September 2007 were selected, as indicated by our outlined selection algorithm, for final analysis. There was no statistically significant difference between the ages of the women for both of the time periods ($P = 0.54$; 95% CI -0.64, 1.21) (Table).

Figure 1. A histogram of the serum 25-(OH)D from all samples of two time periods (January to March 2007 and July to September 2007)



The dashed line is at 25 nmol/L, the study cut-off for vitamin D deficiency, and the dotted line is at 75 nmol/L, the study cut-off for vitamin D insufficiency (see text).

Study patient characteristics and results for two time periods in 2007

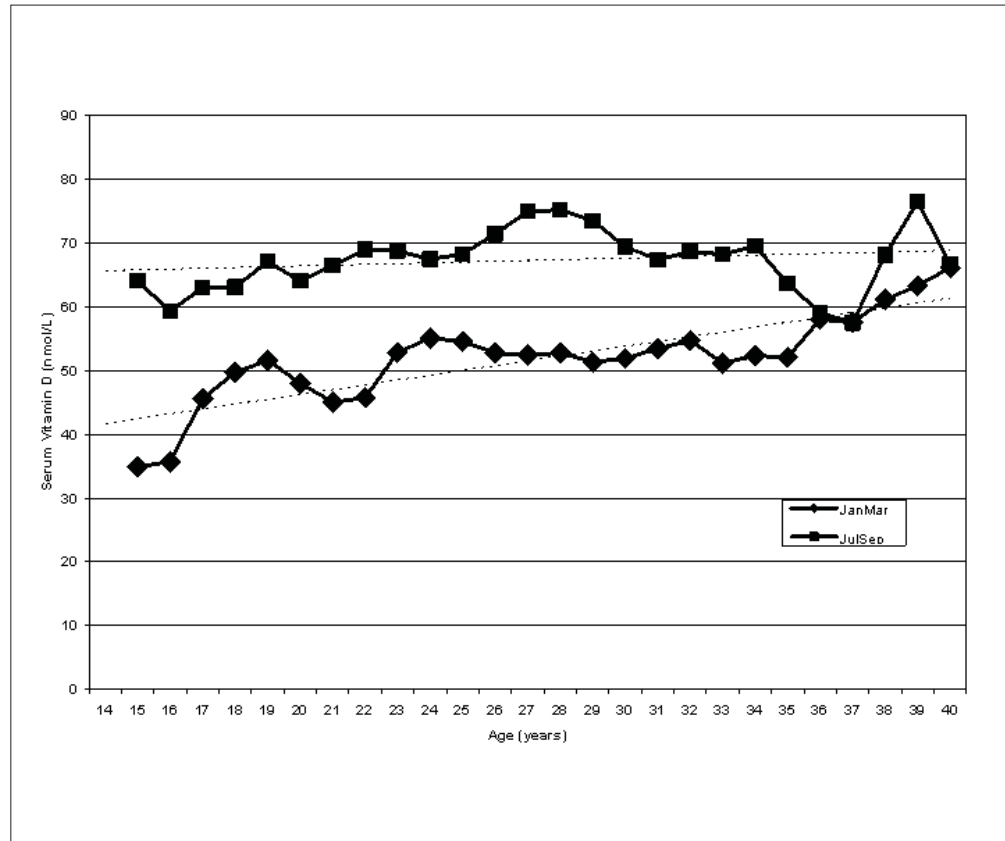
	January to March	July to September
Number of samples	304	289
Average age	27.0 years	26.7 years
Mean serum 25-(OH)D	52.1 nmol/L	68.6 nmol/L
Vitamin D insufficient (25-(OH) < 75nmol/L)	272	184
Vitamin D deficient (25-(OH)D < 25 nmol/L)	20	5

The average serum 25-(OH)D for January to March 2007 was 52.1 nmol/L and the average serum 25-(OH)D for July to September 2007 was 68.8 nmol/L. The difference in serum 25-(OH)D (an average 16.7 nmol/L) between the two time periods was statistically significant ($P < 0.001$; 95% CI -13.4, -20.0). The distribution of serum 25-(OH)D for both time periods (Figure 1) demonstrates a difference in means between the two time periods.

Twenty patients (6.6%) had vitamin D deficiency (< 25 nmol/L, Table) from January to March, and five patients (1.7%) had vitamin D deficiency from July to September 2007. The difference in the number of vitamin D deficient patients was statistically significant ($P = 0.0033$). A vitamin D deficiency cut-off of 27.5 nmol/L (instead of 25 nmol/L) would have increased this difference (32 vs. 7 patients). Two hundred seventy-two patients (89%) had vitamin D insufficiency (< 75 nmol/L) from January to March, and 184 patients (64%) had vitamin D insufficiency from July to September 2007. The difference in the number of vitamin D insufficient patients was statistically significant ($P < 0.001$).

The average serum 25-(OH)D versus age is plotted in Figure 2. Linear regression lines are added to these graphs and suggest that younger pregnant women are more at risk for vitamin D insufficiency in the January to March months than older pregnant women ($R^2 = 0.68$; $P < 0.001$). This disparity appears to correct itself in the July to September months ($R^2 = 0.03$; $P = 0.34$), possibly suggesting that the younger women may make up for their relative deficiency in the summer months through exposure to more sunlight.

Figure 2. The serum 25-(OH)D plotted for a given age for January to March and July to September 2007



Trend lines are added to denote the greater difference in serum 25-(OH)D between younger and older women for the January to March time period than in the July to September period.

However, the number of samples for younger (< 18 years) and older (> 35 years) women is less than 10 for each age division in these age ranges, whereas the number of samples for women between 18 and 35 is more than 10 for all ages in both time periods. This middle age range also has a difference in slope but less than with the extremes of age included.

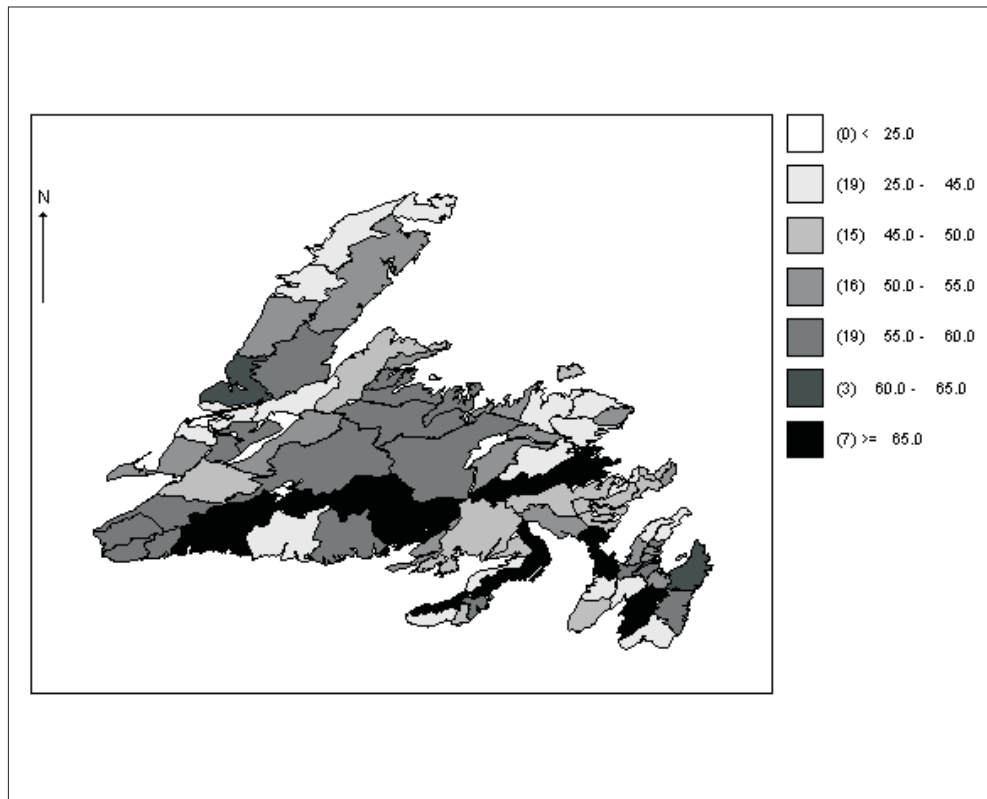
In the January to March time period five CCSs had no available samples (6.3%), and in the July to September time period eight CCSs had no available samples (10.1%) ($P = 0.38$). The geospatial distribution of serum 25-(OH)D is shown in Figure 3 for January to March and in Figure 4 for July to September. The range scale is different for each map because the average 25-(OH)D differs by approximately 16 nmol/L. As shown in Figure 3, most of the regions with higher average serum 25-(OH)D appear to be in the more southern portions of the province. In Figure 4, regions with higher average serum 25-(OH)D appear to be more randomly spread throughout the province.

DISCUSSION

This study has shown that a significant proportion of pregnant women in Newfoundland and Labrador are vitamin D insufficient. This proportion is greater in the winter. In addition, in this study significantly more women were vitamin D deficient or vitamin D insufficient in the winter than in the summer. Younger women tended to have lower serum 25-(OH)D concentrations in the winter than did older women. It is unknown whether differences in vitamin D supplementation in the winter months or in sunlight exposure during the summer months contribute to these observations. Information on the age distribution of serum 25-(OH)D may help guide public policy on potential supplementation. The geospatial distribution of serum 25-(OH)D suggested that lower serum 25-(OH)D concentrations were present in the more northerly portions of the province.

Vitamin D deficiency is a current concern in North America, and several studies help to define the scope of the problem, although it is difficult to compare studies that have used different cut-off values for insufficiency and deficiency.

Figure 3. The geospatial distribution of serum 25-(OH)D for 304 randomly selected pregnant women in Newfoundland between January and March 2007



Scale values are in nmol/L. The number in brackets is the number of census consolidated subdivisions within that given range.

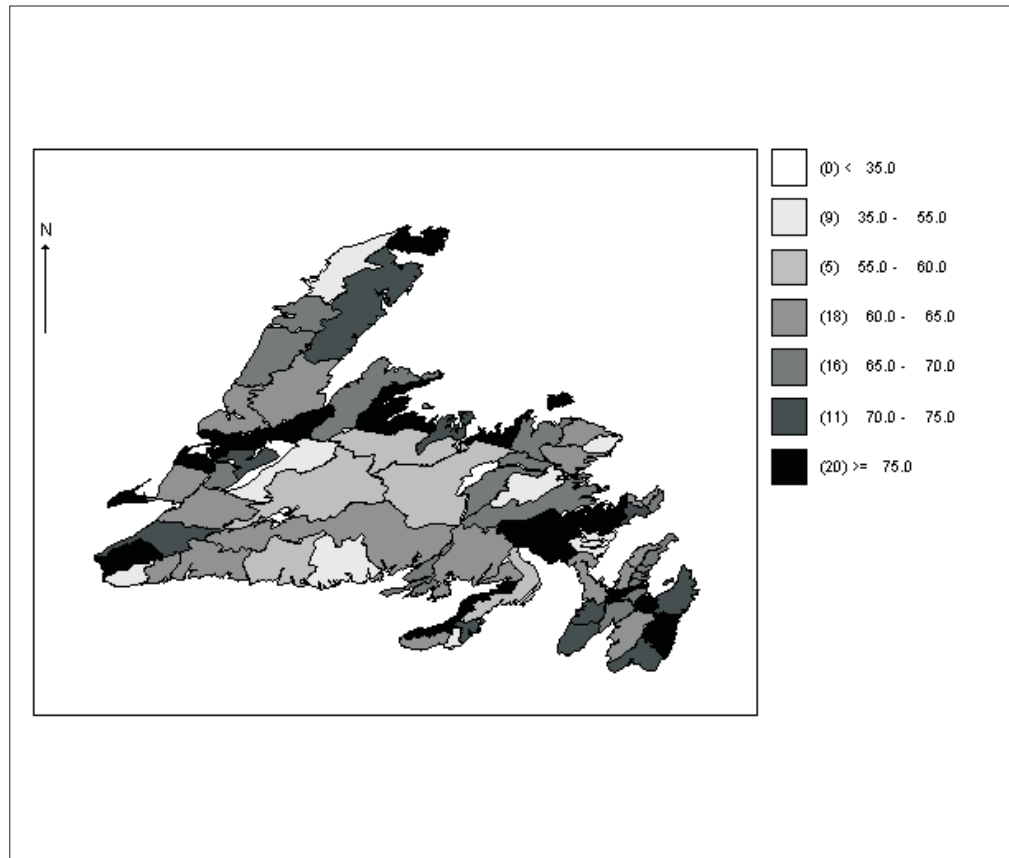
More than 90% of 150 children and adults who presented to a Minnesota hospital with non-specific musculoskeletal pain were found to be vitamin D deficient (< 50 nmol/L).²³ More than 50% of African American teenagers in Boston were found to be vitamin D deficient (< 37.5 nmol/L).²⁴ Approximately one half (48%) of white girls age 9–13 years were found to be vitamin D deficient at the end of winter and 17% were still vitamin D deficient at the end of summer; this was partly attributed to the recommended use of sunscreen and complete sun protection. At Boston Medical Centre, 32% of students and doctors (aged 18–29) were vitamin D deficient (< 50 nmol/L) at the end of winter. More than 50% of African Americans in the US (at much lower latitudes than NL) may be vitamin D deficient (< 50 nmol/L).²⁵ One Canadian study demonstrated significant vitamin D deficiency (< 40 nmol/L) in a cohort of 188 Calgarians.⁴¹

There have been recent studies on the serum vitamin D concentration in pregnant women. One study of 307 pregnant women in an obstetrical clinic showed that maternal 25-(OH)D concentrations may be inversely related to fasting blood glucose.⁴² Another study showed that despite theoretically adequate exposure to sunshine in rural India,

74% of pregnant women had vitamin D deficiency (< 50 nmol/L).⁴³ Other studies have shown correlations between vitamin D deficiency and insulin resistance,⁴⁴ and between pre-pregnancy obesity and poor vitamin D status.⁴⁵ Another study demonstrated that although 90% of 400 pregnant women in the northern United States reported using prenatal vitamin supplements, approximately 50% of white women and 80% of black women had 25-(OH)D concentrations less than 80 nmol/L.⁴⁶ Yet another study assessed vitamin D status in 596 women and followed the health and performance of their child at birth, at nine months, and at nine years.¹⁷ This study showed that reduced bone mineral accrual in children is associated with maternal vitamin D status during pregnancy. The same study suggested that a child's intelligence, psychological health, and cardiovascular health do not appear to be affected by the maternal vitamin D status during pregnancy.⁴⁷ Strong correlations between maternal and umbilical cord blood vitamin D concentrations have been shown.⁴⁸

As previously noted, serum vitamin D levels are related to UVR. In a previous study, we found a significant negative correlation between UVR and T1DM risk.⁴⁹ We also found

Figure 4. The geospatial distribution of serum 25-(OH)D for 289 randomly selected pregnant women in Newfoundland between July and September 2007



Scale values are in nmol/L. The number in brackets is the number of census consolidated subdivisions within that given range.

an association between season at the time of birth and the incidence of T1DM, with a peak incidence in babies born in the winter months of December to February. An analysis relating UVB radiation to monthly T1DM incidence suggests that the Newfoundland incidence of T1DM correlates with UVR not only in space but in time.⁴⁹ Therefore, links to the incidence of T1DM through serum 25-(OH)D concentrations may be important in Newfoundland and Labrador. A negative correlation between annual ambient UVR and T1DM prevalence has previously been reported in Australia.⁵⁰ Another recent investigation of climatic temperature and latitude appeared to explain 40% of the variation in T1DM incidence across 15 countries.⁵¹

Related to nutrition, a Newfoundland and Labrador survey found that 92% of 1927 randomly selected Newfoundland and Labrador residents between the ages of 19 and 74 years were not consuming adequate amounts of calcium in their diet.⁵² Inadequate dietary intake of calcium suggests that Newfoundland and Labrador residents may not be consuming enough vitamin D-fortified milk.

It has been hypothesized that vitamin D deficiency in pregnancy could lead to the future development of autoimmune diseases such as T1DM and multiple sclerosis,⁵³ and some studies suggest a link between vitamin D deficiency in pregnant women and postnatal and future disease in the child. A strong relationship between in vitro 25-(OH)D concentrations in the mother and the fetus has been demonstrated,^{54,55} and some studies have shown a high prevalence of vitamin D deficiency in pregnant women.⁵⁶ The results of this study are most likely understated since older, conservative definitions of vitamin D deficiency were used.⁵⁷ There may also be a link between vitamin D deficiency and the risk of breast cancer.⁵⁸ One case-control study showed that supplementing the diets of pregnant women with cod liver oil (a vitamin D containing supplement) was able to decrease the future risk of T1DM in the child.⁵⁹

CONCLUSIONS

This study has shown that a significant proportion of pregnant women in Newfoundland and Labrador are vitamin D insufficient, more so in the winter than in the summer. This

is an important public health issue, especially since umbilical cord blood vitamin D status correlates with maternal vitamin D status, and growing evidence shows that low maternal serum vitamin D is associated with adverse health outcomes in newborns and developing children. This is a factor that is modifiable with proper supplementation programs and health status monitoring. Further study is necessary to address health outcomes and effects of vitamin D supplementation and lifestyle changes in this population.

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