INTERRELATIONSHIPS BETWEEN VITAMIN D AND BODY MASS INDEX AND WAIST CIRCUMFERENCE IN CANADA

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Abstract

60 % of Canadians have suboptimal vitamin D (<75 nmol/L) and 25% are obese. Obesity has been reported to be a risk factor for low vitamin D, but there is uncertainty about the magnitude of the association. Linear regression was performed using data from the nationally representative cross-sectional Canadian Health Measures Survey (2007-2009). Height, weight, waist circumference (WC), and vitamin D levels were directly measured. There were 5298 participants aged 6 to 79 years. Using a conservative p value of 0.001, body mass index (BMI) category obese / obese I was positively associated and WC was inversely associated with vitamin D level in crude analysis. WC was inversely associated with vitamin D level in multivariate analysis. The pattern of relationship is not the same as other studies, yet this was a large study with direct measurements. There may be issues with linearity of relationships or subgroups disturbing the relationship.

Tables

Figures

Boxes

Table of Contents

1. Introduction

Vitamin D is known as the sunshine vitamin and can be obtained from sun induced skin synthesis, diet or supplements. Obesity is postulated to be a cause of low vitamin D, although the magnitude of the association is variable. This thesis reports an investigation of the relationship between vitamin D and obesity using direct measurements of height, weight, waist circumference and vitamin D, obtained in the nationally representative Canadian Health Measures Survey.

1.1 Suboptimal vitamin D

Suboptimal vitamin D is common. (1-3) The optimum level of vitamin D needed for health is controversial. (4) Levels above 20 nmol/L are well known to protect bone health. (5) Heaney reviewed evidence that increasing vitamin D to 80 nmol/L improves calcium absorption, prevents osteoporotic fractures and reduces falls. (6) Parathyroid hormone levels and calcium absorption stabilize at the level of 80 nmol/L. (7) One study showed that peak neuromuscular performance of lower extremity function is achieved above 100 nmol/L. (8) Vitamin D levels above 75 – 100 nmol/L are widely proposed to be optimal levels and prevent infections, autoimmune disorders, cancers, and reduce all cause mortality. (9-12)

Multiple studies have surveyed Canadians' vitamin D levels. (Table 1) (3, 13-27) Approximately 90% of Canadians have sufficient vitamin D to prevent rickets and osteomalacia. Although 10% of the population is at risk for rickets and osteomalacia, the actual prevalence is lower. (27A and B) Approximately 60% of Canadians have vitamin D below the proposed optimum level of 75 nmol/L. (3) Vitamin D is obtained from sun induced skin synthesis and diet including supplements, further details are in the next

section. Despite vitamin D fortification of milk (10 µg /L) and margarine (1.2 µg /10g), Canadians demonstrate suboptimal levels of vitamin D. The Canadian population is especially at risk for low vitamin D due to a colder climate requiring more clothing, and therefore less skin exposure to weaker sunshine than warmer areas. Winter sunshine is too weak to synthesize vitamin D north of 35 degrees latitude. (28) Increased immigration to Canada has increased the population risk of low vitamin D due to cultural practices that limit sun exposure, melanin pigment which acts as a natural sunscreen and possible inadequate dietary intake (ie: lactose intolerance being more common in some ethnic groups). (29)

At a population level, physical activity has been decreasing with increases in overweight and obesity. (30-32) Obesity and low physical activity are risk factors for low vitamin D that will be discussed further.

Table 1: Vitamin D Status of Canadians, by latitude

Setting Latitude	Author	Season	Population	n	Vitamin D Level 25 (OH)D (nmol/L)		
					Deficient*	Insufficient*	Sub-optimal*
Toronto 43 N	Vieth 2001 (26)	October 1995 – March 1997	Community volunteers Women	796		<40 nmol/L 15% white 26% not white	
Toronto 43 N	Liu 1997 (20)	September 1994 and March 1995	Long term care Age > 65 years	155 53% male	<25 nmol/L 9% fall 18% spring	< 40 nmol/L 38% fall 60% spring	
Toronto 43 N	Gozdzik 2008 (17)	Winter 2007	University Students Age 18 – 35 years	107		<50 nmol/L 75%	<75 nmol/L 93%
Toronto 43 N	Maguire 2011 (33)	November 2007 to May 2008	Healthy children age 24 to 30 months	91		< 50 nmol/L 32%	<75 nmol/L 82%
Sherbrooke 45 N	Gagnon 2010 (15)		white women age 18 – 41 years	153		<50 nmol/L 4%	
Quebec 45N – 48N	Barake 2010 (13)	January to March and June to September	Elderly free living	405		<37.5 nmol/L 5.7-12.6% men 1.9-8.7% female	
Quebec 45 N – 48 N	Mark 2010 (21)	January – May 1999	Quebec Ages 9, 13, 16	1753	<27.5 nmol/L 2% age 9 5 % age 13 11% age 16		<75 nmol/L 93%
Newfound-land Avalon Peninsula 46 N	Newhook 2009 (22)	Winter and summer separately	Infants Children Mothers	51 48 50			<75 nmol/L 92%infants 89%children 90%mothers
Newfound-land & Labrador 46 - 58 N	Sloka 2009 (25)	January to March 2007 and July to Sept 2007	Pregnant women	593	<25 nmol/L 7 % winter 2 % summer		<75 nmol/L 89% winter 64% summer
Calgary 51N	Stoian 2011 (34)	12 month period	Children 2 – 13 years 60% boys	1442	< 25 nmol/L 2%	25 – 75 nmol/L 37%	
Edmonton 53 N	Genuis 2009 (16)	June 2001 – March 2007	Community dwelling adults	1433	<25 nmol/L 3 %	<40 nmol/L 17%	

Table 1: Vitamin D Status of Canadians, by latitude, continued

Setting Latitude	Author	Season	Population	n	Vitamin D Level 25 (OH)D (nmol/L)		
					Deficient	Insufficient	Sub-optimal
Edmonton 53 N	Roth 2005 (23)	April 2003	Pediatric emergency Age 2 – 16 years	68		< 40 nmol/L 34%	
Manitoba 55 N	Lebrun 1993 (19)	June & July	Aboriginal Mothers Children	160	<25 nmol/L 76 % mothers 43% children		
Manitoba 55 N	Weiler 2007 (27)	June 2002 to March 2004	White women Aboriginal women	355		<37.5 nmol/L 19%white 31%aboriginal	<75 nmol/L 62% white 84% urban aboriginal 96% rural aboriginal
Nunavut 56 N – 72 N	El Hayek 2010 (14)	August to November 2007 and August to September 2008 Summer n = 282 and Follow up February - April for n=52	Nunavut Child Inuit Health Survey	282	<25 14 %	<37.5 nmol/L 37%	<75 nmol/L 79% summe 97% winter
Canadian Multicentre Osteoporosis Study**	Greene-Finestone 2010 (18)	March – September 2009	Community dwelling Age >35 years	1912 30% male	<27.5 2 %	<50 nmol/L 20%	<75 nmol/L 57% men 61% women
Canadian Health Measures Survey***	Langlois 2010 (3)	March 2007 – February 2009	Community dwelling	5 306 48% male	<27.5 nmol/L 5% male 3% female	<37.5 nmol/L 13% male 8 % female	<75 nmol/L 67 % male 62 % female

*The definitions of terms deficient, insufficient and suboptimal vitamin D are variable and are listed by study. Generally, deficient is less than 25 nmol/L, insufficient is less than 50 or 37.5 nmol/L and suboptimal is less than 75 nmol/L.

**The Canadian Multicentre Osteoporosis Study was conducted in 7 cities: Vancouver (49N), Calgary (51N), Saskatoon (52N), Toronto (45N), Kingston (44N), Quebec City (46N) and Halifax (44N).

***The Canadian Health Measures Survey reported by Langlois is the same data set used in the current study and uses 15 centres including Vancouver (49 N), Williams Lake (52 N), Edmonton (53 N), Red Deer (52 N), Kitchener Waterloo (43 N), Toronto (45 N), St. Catherine's, Northumberland County ON, Montreal Centreville (45 N), Longueil, Mauricie Sud, Quebec (48 N) and Moncton (46 N).

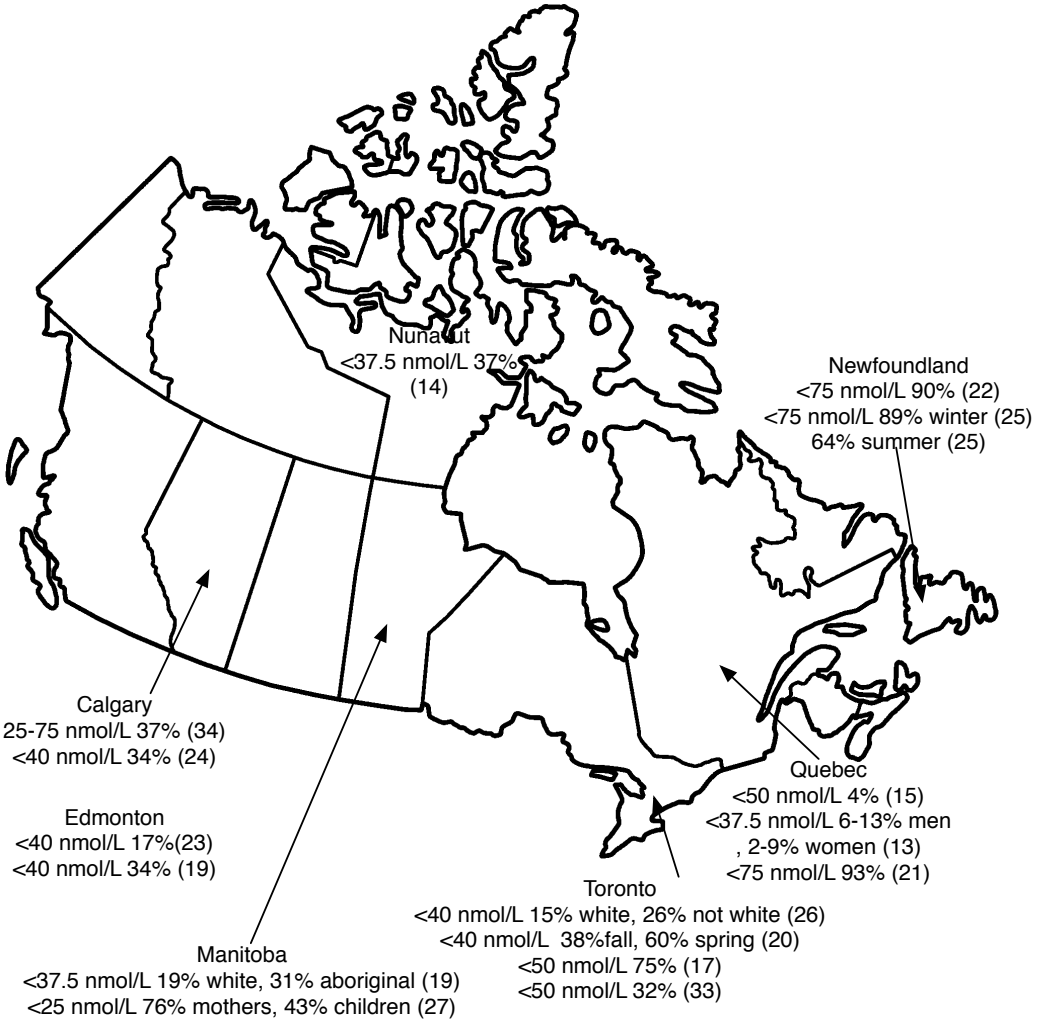


Figure One: Vitamin D status of Canadians by province/territory

CaMOS = Canadian Multicentre Osteoporosis Study (7 cities) and
CHMS = Canadian Health Measures Survey (15 sites)

Low vitamin D levels are present throughout Canada and in identifiable subgroups including aboriginals, elderly, and infants. (3, 13-23, 25, 26, 33, 34) Studies which grouped vitamin D samples by season were able to demonstrate seasonal effects with lower average levels of vitamin D measured in winter and early spring compared to summer. (14, 20, 25) No pattern of variation with latitude was seen in the Canadian data (43 N – 72 N) (see Table 1 and Figure 1).

Various methods are available for the measurement of vitamin D including liquid chromatography-tandem mass spectrometry, high performance liquid chromatography, radio immunoassays (IDS and DIASORIN) and chemiluminescent assays (IDS, Advantage, LIASON). (35) Methods are comparable across laboratories, using liquid chromatography-tandem mass spectrometry as a gold standard. (36) However, a limitation of immunoassays is that they are unable to distinguish between vitamin D3 and D2.

Methods used in Canadian studies of vitamin D are listed in Table 2 below. There is a wide variety in transparency of reporting methods and, when reported, in quality assessment methods. However, no overall pattern of association between vitamin D level and methods is apparent.

Table 2: Methods of assessment of Vitamin D in Canadian Studies

Author	Method of Assessment	Between Assay CV Interassay variability	Within Run CV Intra assay variability	Limit of Detection	Quality controls
Vieth 2001(26)	Diasorin radioimmunoassay (Stillwater, MN, USA)	< 16%	< 10%	Not stated.	Not specified.
Gozdzik 2008(17)	DIASORIN TOTAL competitive chemoluminescence immunoassay	7%	5%	10 nmol/L	Validated against DIASORIN radioimmunoassay
Maguire 2011 (33)	Abstract only, not stated	Not stated	Not stated	Not stated	Not stated
Gagnon 2010(15)	Abstract only, not stated	Not stated	Not stated	Not stated	Not stated
Barake 2010(13)	Diasorin radioimmunoassay	<8%	Not stated	Not stated	Not stated
Mark 2010(21)	RIA (Immunodiagnostics Ltd)	5.9 – 6.0%	Not stated	Not stated	DEQAS*
Newhook 2009(22)	Micromass Quattro Ultima PT mass spectrometer				
Sloka 2009(25)	Radioimmunoassay (Diasorin, Stillwater MN)	Not stated	Not stated	Not stated	Not stated
Stoian 2011(34)	Commercial immunoradiometric assay kits, Abstract only	Not stated	Not stated	Not stated	Not stated
Rucker 2002(24)	Commercial immunoradiometric assay kit (Diasorin Inc Stillwater MN)	11.7-12.5%	9.4 – 11.0%	Not stated	Not stated
Genuis 2009(16)	High pressure liquid chromatography, mass spectrometry	Not stated	Not stated	Not stated	Not stated
Roth 2005(23)	Diasorin/Incstar kit (Stillwater MN USA)	12% at 60 nmol/L	Not stated	Not stated	Not stated
Lebrun 1993(19)	Radio-immune competititve protein binding assay diagnostic test.	Not stated	Not stated	Not stated	Not stated
Weiler 2007(27)	RIA (Diasorin)	6 – 13%	Not stated	Not stated	Not stated

Table 2: Methods of assessment of Vitamin D in Canadian Studies, continued

Author	Method of Assessment	Between Assay CV Interassay variability	Within Run CV Intra assay variability	Limit of Detection	Quality controls
El Hayek 2010(14)	LIASON total Diasorin assay	4.5-6.2	5.3 - 11.1	Not stated	Participant in DEQAS*
Greene-Finestone 2010(18)	Liaison (Diasorin Incorporated) chemiluminescent assay	2.9 – 5.5 %	6.3 – 12.9%	10 nmol/L	Supplied by Diasorin and external quality controls used. Multiple repeat determinations. Negligible assay drift. Lab participates in DEQAS*
Langlois 2010(3)	LIASON 25 OHD TOTAL assay (Diasorin Ltd). Chemiluminescent assay.	3.2-8.5 %	6.9-12.7%	10 nmol/L & 350 nmol/L	External quality controls from Diasorin and Biorad. Participates in DEQAS.*

*DEQAS (Vitamin D external quality assessment scheme, UK)

1.2 Sources of vitamin D

Vitamin D is mainly obtained through sun induced skin synthesis. (37,38) When skin is exposed to ultraviolet B light at 290 to 315 nm, 7 dehydrocholesterol is cleaved to form previtamin D3. (39) Previtamin D3 undergoes thermal cleavage into vitamin D3, also called cholecalciferol. Vitamin D3 is converted in the liver by 25-hydoxylase into 25 hydroxyvitamin D (25OHD), also called calcidiol. Using 1 α-hydroxylase, the kidneys and other tissues convert 25OHD into 1,25 dihydroxyvitamin D ($1,25(OH)_2D$) also called calcitriol. $1,25(OH)_2D$ is the active form of the vitamin. Its half-life is 15 hours and it is tightly regulated by parathyroid hormone such that it remains at adequate levels despite low vitamin D stores. (40) 25OHD is the form of vitamin D used to measure vitamin D status. Its half-life is 15 days. It measures the sum of skin synthesis and ingestion from diet and/or supplements. "Vitamin D" is used to refer to "25OHD" in this manuscript.

Vitamin D response to sun exposure is affected by time of day, latitude, season, air pollution, cloud cover, the amount of exposed skin and time spent in sun. (41) At latitudes distant from the equator, winter sunlight is insufficient to allow skin synthesis of vitamin D. (28) In addition, melanin acts as a natural sunscreen for darkly pigmented persons. (42)

Sun tanning equipment predominantly emits UVA light, but 1-5% is emitted as UVB light. (43,44) In one study, indoor UV tanners had twice the vitamin D level as non-tanners. (45) However, increasing exposure time does not increase previtamin D3 beyond a plateau. (46,47)

Increased skin aging and skin cancers with indoor and outdoor tanning have been well described. (43, 47-52) Indoor UV tanning is an unsafe method to obtain adequate vitamin D; however, there are nearly 3000 tanning salons in Canada. (53) The Second National Sun Survey showed up to 21% of Albertans aged 16 to 24 years used indoor tanning equipment in 2006. (53,54)

A very moderate sun exposure is needed to obtain 1000 IU of vitamin D per day: 5-20 minutes of sun exposure to hands, face and arms every other day is sufficient for lighter skin persons. Darker skin persons require up to 5 to 10 times this exposure. (55,56)

Unfortunately, advising Canadians to increase their sun exposure in summer months is a confusing public health message and potentially could result in the undesirable effect of increasing risk of skin cancer. (57)

Vitamin D can also be obtained from diet including oily fish, cod liver oil, egg yolk, organ meats such as beef liver and shitake mushrooms. (58) The recommended daily intake from the Institute of Medicine is based on maintaining bone health and assumes virtually no sun induced skin synthesis. (5) Recommended daily allowances of 600 IU/d = 15 µg/d for ages 1 to 70 years and 800 IU/day = 20 µg/d for ages 71 and older would correspond to 97.5% of the population having vitamin D levels greater than 50 nmol/L. The upper limit is 4000 IU/day = 100 µg/d for ages 9 years and older, 3000 IU = 75 µg/d for those aged 4-8 years, 2500 IU = 63 µg/d for those aged 1-3 years, 1500 IU = 38 µg/d for those aged 7 to 12 months and 1000 IU = 25 µg/d for those aged 0 to 6 months. (5)

Vitamin D is also found in fortified foods such as cow's milk and margarine in Canada, cow's milk and cereals in the USA and in supplements. Population levels of vitamin D are not available pre-fortification, however, since fortification, the prevalence of rickets has decreased. (59) Rickets is a manifestation of low levels of vitamin D, which is discussed below.

Vitamin D3 is obtained from cutaneous synthesis. Vitamin D2 can be obtained from the ultraviolet irradiation of yeast producing ergocalciferol, used in some supplements. Vitamin D2 and D3 differ by their side chains. The side chain of D2 contains a double bond between carbons 22 and 23, and a methyl group on carbon 24. Vitamin D3 is thought to be more efficacious than vitamin D2 as a supplement to raise and maintain vitamin D levels. (60-62)

1.3 Biological effects of vitamin D

Vitamin D affects intestinal calcium and phosphorus absorption. When vitamin D is low, serum calcium is low which promotes the release of parathyroid hormone. Parathyroid hormone increases reabsorption of calcium and causes the release of calcium and phosphorus from bone. (37)

1.4 Effects of high vitamin D

Vitamin D toxicity presents with hypercalcemia, vomiting, thirst, polyuria, renal stones and renal calcification with possible kidney failure and death. (63) The Women's Health Initiative study found a small increase in kidney stones with 400 IU = 10 µg of vitamin D3 and 1000 mg of calcium administered daily. (64)

The serum level of vitamin D that is potentially toxic has not been agreed upon but is probably above 200 to 250 nmol/L. (65) Heaney states toxicity occurs above 500 nmol/L. (63, 66)

0.5% of Canadians in the CHMS had vitamin D levels above 220 nmol/L and none had vitamin D above 375 nmol/L. (3)

Vitamin D hypersensitivity is a concern for persons with lymphoma and with granulomatous diseases such as sarcoidosis and tuberculosis. Hypersensitivity occurs when extra renal tissues or cells such as monocytes convert 25OHD to $1,25(OH)_2D$ and results in hypercalcemia. (67)

1.5 Effects of low vitamin D

Low vitamin D causes insufficient mineralization of bone. In children this is manifest as rickets: craniotabes, enlarged epiphyses, rachitic rosary and floppy muscles. (68, 69) Radiologic examination reveals generalized demineralization, widening of the epiphyseal plates and fraying and cupping of the metaphyses of long bones, particularly the radius. (68) Low vitamin D in adults manifests as osteomalacia: generalized or localized bone pain, polyarthralgia and muscle weakness. (68) Radiologic examination reveals normal or coarse trabecular demineralization with a ground glass appearance with erased cortical margins, subperiosteal bone reabsorption and subchondral cysts. (68) The most characteristic sign of osteomalacia is pseudofractures. (68) Bone biopsy reveals increased osteoid surface and reduction of mineralization activity. (68)

1.6 Risk factors for low vitamin D

All Canadians are at risk for low vitamin D during winter due to low light levels north of 35 degrees latitude. (28) Many subgroups such as immigrant groups and aboriginal people can also be identified as being at increased risk for low vitamin D. (14, 19, 27, 29) These include those who avoid the sun, are darkly pigmented or have insufficient dietary sources. (70) Melanin acts as a natural sunscreen. The elderly and breast fed infants are also at increased risk. Breast fed infants receive 25 – 78 IU of Vitamin D per litre of human milk which is insufficient. (One International Unit of vitamin D is the biological equivalent of 0.025 µg of vitamin D (cholecalciferol)). Older persons may have inadequate intake, are more likely to stay indoors and, with thinner skin, do not synthesize vitamin D as readily as younger persons. Obese people are also known to be at higher risk than non-obese and this will be discussed. (15, 24, 71-80)

1.7 Body mass index and waist circumference

Body mass index (BMI) or Quetelet's Index was defined in 1842 as a person's weight in kilograms divided by his/her height in metres squared (kg/m^2). (81, 82) If the weight is measured in pounds and the height in inches, then BMI = weight in pounds / height in inches squared x 703. (83)

BMI does not distinguish between lean body mass and fat body mass. General obesity in adults is defined as BMI being 30 kg/m^2 or more. BMI has been shown to be 42% sensitive and 97% specific when compared to a gold standard diagnosis of obesity such as dual energy X-ray absorptiometry. (81) Prentice and Jebb reviewed several limitations of BMI in specific populations such as older persons and Asians. (84)

For adults, underweight is defined as BMI < 18.5 kg/m^2; healthy weight is defined as 18.5 <= BMI < 25.0, overweight is defined as 25.0 <= BMI < 30.0 and obese is defined as BMI >= 30.0 kg/m^2. (85, 86) In the CHMS, obesity in adults is defined as obese I 30.0-34.9 kg/m^2, obese II 35.0 – 39.9 kg/m^2 and obese III >= 40.0 kg/m^2.

For children, BMI is age and sex specific and uses growth curves for diagnosis. (87) Internationally, overweight and obesity are defined in children using the International Obesity Task Force criteria or the World Health Organization criteria. (88, 88A) In NHANES (USA) and the CHMS, underweight in children is defined as being less than the 5th percentile BMI for age and sex, overweight in children is defined as being at or above the 85th percentile BMI for age and sex and obesity is defined as being at or above the 95th percentile BMI for age and sex using the Centers for Disease Control growth charts from the year 2000. (89, 90)

A further complexity is that in many studies, BMI has been calculated from self-reported height and weight. This may have introduced systematic bias. (91, 92)

Central fat mass, central obesity or abdominal obesity can be measured by waist circumference. (93, 94) Distribution of adipose tissue predicts obesity-related health risks, including type 2 diabetes, atherogenic dyslipidemia, hypertension and cardiovascular disease. (95) Abdominal obesity in adults is defined as a waist circumference 102 cm or larger in men and 88 cm or larger in women. (96)

Abdominal obesity is a component of Metabolic Syndrome, also called syndrome X. Various definitions of Metabolic Syndrome have been proposed, however all include the criteria of abdominal obesity, hypertension, elevated fasting glucose and

lipid levels, and hyperinsulinemia. (97 – 100) Metabolic Syndrome presents increased risk for type II diabetes and cardiovascular disease. (97 - 101)

1.8 Vitamin D and obesity

Vitamin D has been found to be lower in obese children and adults but the magnitude of the association is highly variable. (Table 3) The majority of studies have used direct measurements of height and weight in combination with methods of body fat assessment such as bioelectrical impedance and dual energy X-ray absorptiometry. (71-79) Analysis of NHANES III revealed that low vitamin D is associated with obesity and other cardiac risk factors including hypertension and diabetes (102). In the Framingham data (42 N), low vitamin D was associated with high BMI. (80) The relationship between low vitamin D and high BMI has been shown in "healthy" Canadians in Calgary, 51 N, (24) and Sherbrooke, 45 N. (15) Obese subjects also require a higher amount of supplemental vitamin D intake than non-obese subjects to maintain adequate levels. (103)

An ethnic difference in vitamin D levels has been identified. Low vitamin D is more prevalent in obese blacks than obese whites. (104) This difference is not due to differences in vitamin D binding protein. (105) Differences in levels of melanin pigment and behavioral differences in vitamin D intake (both sun exposure and diet) are likely causes for the ethnic difference.

Table 3: Associations of BMI and waist circumference with vitamin D

Adiposity measure*	Regression coefficient	P value	Participants & Setting	Reference
BMI	0.036	0.001	323 girls, 15 years $\pm$ 0.5 Beijing (39 N)	Foo, 2009(106,107)
BMI	-0.07	0.001	10,229 adults Norway (62 N)	Jorde 2010(108)
BMI	-0.136	0.001	45 >65 years Netherlands (52 N)	Snijder 2005(109)
BMI	-0.151	0.017	248 obese adults No supplements Switzerland (47N)	Ernst 2009(110)
BMI	-0.18	0.005	250 overweight and obese adults New Zealand (36 S)	McGill 2008(111)
BMI	-0.4	<0.0001	302 healthy adults Washington DC USA (38 N)	Parikh 2004(112)
BMI	-0.42	0.001	738 cancer patients Illinois, USA (41 N)	Vashi 2011(113)
BMI	-0.93	0.032	102 children Aged 9 to 13 Madrid, Spain (40 N)	Rodriguez-Rodriguez 2010(71)
BMI	-1.12	0.002	292 women aged 50-79 Women's Health Initiative	Chacko 2011(114)
BMI	-1.4	0.006	307 adolescents Boston, USA (42 N)	Gordon 2004(115)
BMI	-2.81	<0.0001	3890 adults Framingham USA (42 N)	Cheng 2010(80)

Table 3 : Associations of BMI and waist circumference with vitamin D, continued

Adiposity measure*	Regression coefficient	P value	Participants & Setting	Reference
Waist Circumference	-0.153	0.010	357 children 4 – 11 years Belgium IDEFICS (50 N)	Sioen 2011(116)
Waist Circumference	-0.137	0.002	453, >65 years Netherlands (52 N)	Snijder 2005(109)
Waist circumference	-0.14	0.03	250 overweight and obese adults New Zealand (36 S)	McGill 2008(111)
Waist Circumference	-3.11	<0.0001	3890 adults Framingham USA (42 N)	Cheng 2010(80)
Waist Circumference	-3.57	0.0001	292 women Aged 50-79 Women's Health Initiative	Chacko 2011(114)

*BMI and waist circumference were directly measured in all studies.

The reasons why obesity may be associated with low vitamin D have not been established. Studies have investigated five possible mechanisms that might account for such an association:

A. Vitamin D may affect metabolic processes causing obesity; (111, 117)

B. Vitamin D may be sequestered in fat as a result of obesity; (118)

C. Decreased outdoor exercise may lead directly to decreased sun induced vitamin D and at the same time, to obesity; (107, 119-121)

D. There may be behavioral differences between obese and non-obese persons including decreased sun exposure, decreased milk intake, or decreased use of supplements; (110, 122, 123)

E. Elevated $1,25(OH)_2D$ in obesity may act to decrease liver production of 25(OH)D. (124)

(See Figure 2)

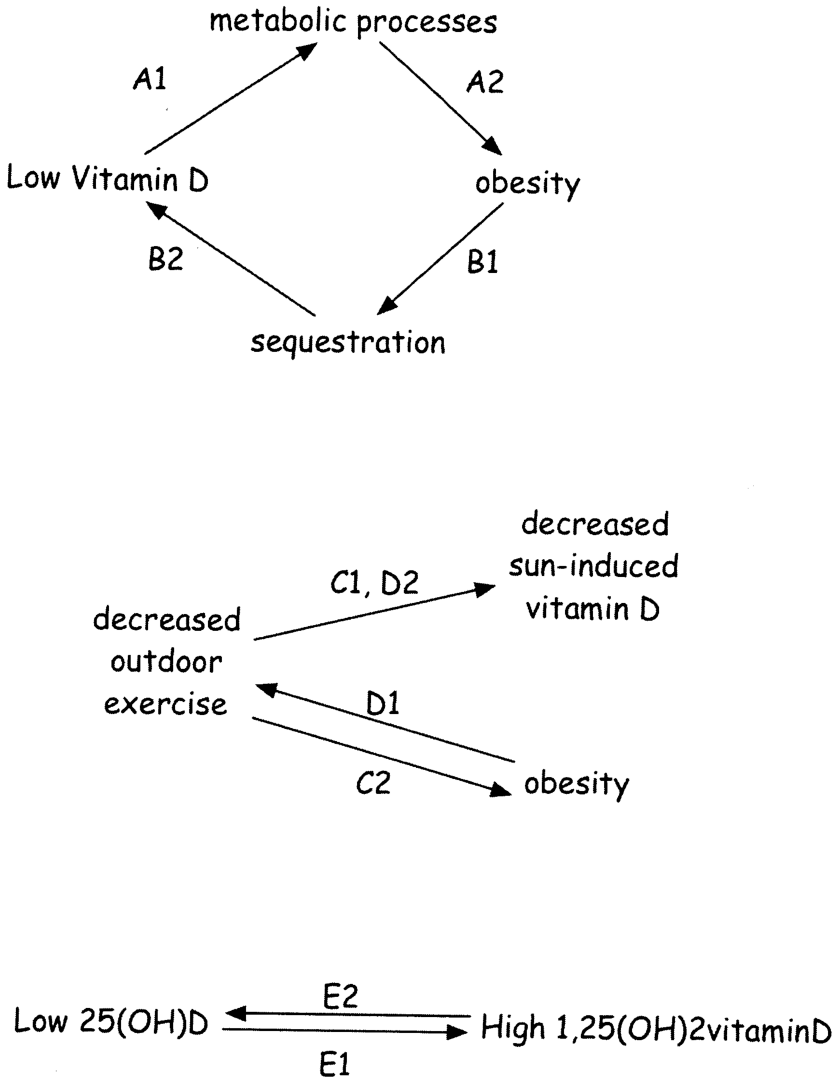


Figure 2: Possible mechanisms of low serum vitamin D3 in obesity.

Low vitamin D may decrease metabolic processes (A1) and lead directly to obesity (A2). Or, obesity may lead to sequestration (B1) and decreased bioavailability of vitamin D (B2). Decreased outdoor exercise may lead to decreased sun induced vitamin D (C1) and obesity (C2). Or, obese persons may be less likely to exercise outdoors (D1) and thus have decreased vitamin D (D2). Low 25(OH)D in obesity may lead to high 1,25(OH)2 vitamin D (E1) which impairs hepatic synthesis of 25 (OH)D (E2).

In particular, not only is the magnitude of association uncertain, but also it is not known if low vitamin D is a cause or a result of obesity.

A Effect of vitamin D on metabolic processes causing obesity: *In vitro* evidence suggests that vitamin D can affect lipolysis and lipogenesis by affecting calcium influxes. Women with a rare vitamin D genotype (homozygous rs3782905) have a mean waist circumference 4.4 cm larger than women without the variant. rs3782905 is within the Vitamin D receptor gene. (125) However, the limited evidence available from longitudinal studies and RCTs does not show strong support for a causative effect of vitamin D on body weight. (129)

A 2.5 year prospective study of 479 children showed that low vitamin D (< 50 nmol/L) was associated with an increase in BMI of 0.1 kg/m^2/year, (p=0.05) and an increase in waist circumference of 0.8 cm/year, p = 0.03 . (126) A 14 year longitudinal study of 2656 adults was interpreted as showing that change in BMI was a significant predictor of serum vitamin D status; however; the standard deviations of the change in vitamin D levels between the BMI groups were large and overlapping. (108) A 5 year study of 1356 adults found no association between 5 year change in adiposity and vitamin D. (127) However, an 11 year Norwegian prospective study of 2460 adults showed baseline vitamin D less than 50 nmol/L was associated with 1.6 times increased odds for incident obesity. (128)

Chung et al evaluated randomized controlled clinical trials of vitamin D supplementation in adults and changes in body weight or BMI. Three RCTs were identified and all found no difference in weight change with or without vitamin D supplementation. (129) The doses were 300 IU daily, 20 000 or 40 000 IU weekly or 120

000 IU every 2 weeks and follow up was 3 years, 1 year, and 6 weeks, respectively. Two trials were identified in which vitamin D and calcium were given. One trial of 36,000 postmenopausal women found a statistically significant but very small reduction in average body weight: 0.13 kg (95% confidence interval -0.21, -0.05) in the supplemented group. The second much smaller trial of 63 women on a weight loss diet for 15 weeks did not find a significant difference between those receiving supplements and controls. (129)

Soares et al reviewed 15 RCTs on calcium and 7 RCTs on vitamin D and concluded that the evidence that calcium and vitamin D accelerated weight or fat loss in obese people was inconsistent. (130)

B Sequestration in body fat: Evidence for theory B is more convincing. After receiving whole body ultraviolet radiation, the change in blood concentration of vitamin D was 57% less in 19 obese persons than in 19 controls, despite the greater exposed surface area of the obese. (131) Content of the vitamin D precursor in skin was found to be the same and *in vitro* conversion following UV irradiation was found to be the same in 4 samples. This suggests that obese persons have decreased bioavailability of vitamin D, possibly due to deposition in fat stores.

C and D Sun exposure and physical activity: The relationship between obesity, sun exposure and vitamin D status is complex. Obesity associated with low vitamin D status was not due to decreased intake of vitamin D (72) via inadequate diet or sun avoidance. (132) However, vitamin D status in obese persons has been found to vary by season, suggesting a role for sun exposure. (110,122) A study of 381 elderly adults showed sunscreen use, hours spent outside per week and percent of skin exposed did not differ

across categories of percent body fat. (123)

Exercise may act as a confounding factor due to time spent in outdoor sunshine and/or its effects on BMI. Exercise may be an independent predictor of vitamin D status. (Figure 2)

In the Framingham Third Generation Study, the association of lower vitamin D concentrations with greater BMI was not explained by differences in physical activity or vitamin D intake. (80) Yet, BMI greater than or equal to 30 kg/m^2 and physical inactivity were associated with low vitamin D in healthy Americans aged 55 to 74. (133) Dong found the associations between low serum vitamin D and high adiposity and between high serum vitamin D and physical activity in American adolescents. (119) Vitamin D was positively associated with recreational activity in 1343 postmenopausal women in the Women's Health Initiative. (134) In a separate study, weight lifting was associated with higher vitamin D levels in young men; however, no investigation of dietary input, supplement use or sun exposure was done (135). Physical exercise was found to be associated with higher vitamin D level in diverse populations. (107, 120, 121) Low vitamin D status was associated with poor physical fitness in Qatari girls. (136) In 2317 men, cross-sectional analysis showed that vitamin D was positively associated with maximal treadmill exercise. (137) Maimoun and Sultan reviewed the effect of physical activity on vitamin D and calcium in athletes and sedentary controls after short- and long-term exercises. (138) The effects on vitamin D were influenced by characteristics of exercise (type, duration and intensity) and of athlete (training status, age and sex). Higher vitamin D was reported in weight lifters, male triathletes, track and field athletes, decathletes, and post menopausal endurance trained women but not in male cyclists,

triathletes or swimmers. (Triathletes are in both groups).

Brock cites 11 studies in which exercise affected vitamin D status, only 2 of which (Brock 2007 and Scragg 2008) measured physical activity and sun exposure. (133) As expected, outdoor exercise was associated with higher vitamin D levels than indoor exercise. Scragg reviewed evidence that leisure time physical activity increased levels of vitamin D, after adjustment for sun exposure and time of year. (121) The prevalence of low vitamin D in elderly Hispanic Americans who reported outdoor exercise was half of those who did not. (139) Vitamin D levels increased with increasing frequency and intensity of outdoor and indoor physical activity in an analysis of the NHANES III data. (121) The increase in vitamin D was higher in those with outdoor activities and higher in Whites compared to Mexican Americans and non-Hispanic Blacks.

E Hepatic inhibition: Early studies showed elevated $1,25(OH)_2D$ in obesity and suggestions were made that $1,25(OH)_2D$ may inhibit hepatic production of 25OHD, thus one would expect high $1,25(OH)_2D$ in obese persons with low 25OHD. By contrast, later studies have shown low $1,25(OH)_2D$ in obese persons with low 25OHD. (124, 140)

Five possible mechanisms for a relationship between obesity and vitamin D have been put forth, but the evidence is inconsistent. This adds to the uncertainty about the nature of the relationship between vitamin D and obesity.

1.9 Vitamin D and leanness

The published literature concerning vitamin D and leanness is sparse. The Tromso study of 10 229 individuals found that low BMI was associated with low vitamin D in cross-sectional analysis. (108)

Athletes are at risk for low vitamin D status due to decreased sun exposure (if training indoors, sun avoidant, darkly pigmented or living in northern latitudes) and insufficient dietary intake. Elite gymnasts and Canadian soccer athletes were found to have a low serum vitamin D level. (141, 142) Low BMI and low vitamin D was found in adolescent runners and thought to be due to nutritional deficiency. (143) Bone mineral density was not considered. Larson-Meyer reviewed the vitamin D status of 7 groups of athletes and demonstrated inadequate intake of vitamin D. (144)

A condition termed the "female athlete triad" is defined as malnutrition, osteoporosis and amenorrhea. (145) Low vitamin D in the female athlete triad is thought to be due to disordered eating and inadequate intake. (145) Low vitamin D and low estrogen both contribute to inadequate bone mass, which is associated with increased risk of stress fractures.

Athletes with low vitamin D are at risk for sub-optimal performance, inflammation and increased infections. (144, 146-148) Montero et al reviewed evidence that exercise affects innate and adaptive immunity directly. Further, intense exercise coupled with malnutrition may alter cell-mediated immunity. (149) Vitamin D is necessary for proper functioning of the immune system, particularly innate immunity. (150)

The relationship between vitamin D and obesity/leanness remains unclear and there is a need for further research. There is variation in the magnitude of association between BMI and waist circumference and vitamin D. Although multiple mechanisms between low vitamin D and obesity have been postulated, there is uncertainty in the evidence about these mechanisms. There is a sparsity of data about leanness and

vitamin D.

2. Objective

In view of the uncertainties in the relationship between obesity and vitamin D, there is a need for further investigation using objective measurements of height, weight, waist circumference, and vitamin D. Therefore, the objective of this work was to investigate the relationship between BMI and waist circumference and vitamin D status in Canadians.

3. Hypothesis

The hypotheses are two-fold. Vitamin D will be lower in underweight and overweight/obese individuals and higher in healthy weight individuals. BMI and waist circumference will show an inverse association with vitamin D.

4. Methods

4.1 Study participants

The Canadian Health Measures Survey (CHMS) was designed to obtain data on the health of the nation. (151-153) The first such survey (cycle one) was conducted between March 2007 and February 2009. It combined a household questionnaire with direct physical measurements including blood and urine tests. Canadians aged 6 to 79 years were targeted. The survey targeted 96% of Canadians in this age range. First Nations living on reserve, full time military, residents of institutions and Canadians in certain remote regions were not represented. (154)

CHMS is a complex survey. (155) Area frame clusters from the Labor Force Survey were used to define 257 potential collection sites. Each collection site was

defined to include 10, 000 persons and a maximum travel distance between dwelling and Mobile Examination Centre of 100 km in rural areas or 50 km in urban areas, while not crossing metropolitan census areas. Due to complex logistics and the costs of operating the Mobile Examination Centre, only 15 sites were chosen: Vancouver, Williams Lake, Edmonton, Red Deer, Kitchener-Waterloo, Toronto (3), St. Catherine's, Northumberland County ON, Montreal Centre-ville, Longueuil, Mauricie Sud, Quebec City, and Moncton. (156, 157) Sites were selected proportional to the population. Dwellings were then sampled using the 2006 census as a frame and stratifying by age group: 6-11, 12-19, 20-39, 40-59, and 60-79. Two people were selected in some households with children aged 6 to 11 due to the need to accompany children to the Mobile Examination Centre. (154)

4.2 Ethics

This study was a secondary analysis of existing data sources and did not require ethics approval. The CHMS underwent extensive ethics consultations including review by the Health Canada Research Ethics Board and Office of the Privacy Commissioner. (158) Participation was voluntary and respondents could opt out of any part of the survey. Respondents aged 14 or older provided informed written consent. Those under age 14 provided written assent along with the written consent of a parent or guardian.

4.3 Measurements

Height, weight and waist circumference were all directly measured at the Mobile Examination Centre based on the 3rd edition of the *Canadian Physical*

Activity, Fitness and Lifestyle Approach by Certified Exercise Physiologists or Certified Personal Trainers with a degree in kinesiology. (31, 32, 159) Height was measured on all respondents who were able to stand using a fixed stadiometer with a vertical backboard and a moveable headboard (ProScale M150 digital stadiometer, Acurate Technology Inc, Fletcher, USA). (31, 32, 154) The participant's weight was measured on a Mettler Toledo © digital scale (Mettler Toledo Canada, Mississauga Canada). (31, 32, 154) BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference in centimetres was measured on all participants using a Gulick measuring tape (Fitness Mart, Gay Mills USA). The World Health Organization protocol was followed: midpoint between last floating rib and top of the iliac crest in mid-axillary line. (160) Pregnant women, those with colostomies, and people using wheel chairs did not undergo waist circumference measurement. (154)

Blood specimens were collected by trained phlebotomists at the Mobile Examination Centre for those able to attend or in the respondent's home for those unable to attend the Centre. (156) Respondents with morning appointments underwent overnight fasting. Those with afternoon and evening appointments underwent a two hour fast.

Complete blood counts using a HMX Hematology Analyzer (Beckman Coulter Inc., Miami, Florida) were performed at the Mobile Examination Centre. Whole blood was then centrifuged and stored at minus 20 C in the Centre. Specimens for vitamin D testing were sent once a week on dry ice by overnight delivery using a courier

company certified to handle dangerous goods to Health Canada, Ottawa. Shipments were timed to arrive only on weekdays and temperatures were monitored. (154) Vitamin D levels were measured by a chemiluminescence assay using the LIAISON 25-hydroxyvitamin D TOTAL assay (Diasorin, Ltd.). The lower and upper detection limits are 10 nmol/L and 375 nmol/L, respectively. (3) In house testing estimated the assay coefficient of variation within runs as 3.2% to 8.5% and between runs as 6.9% to 12.7%. (3) Ten percent of samples were run in duplicate for quality control purposes. The Health Canada laboratory participates in the proficiency vitamin D testing through DEQAS (Vitamin D external quality assurance scheme). (3)

4.4 Statistical methods

Linear regression modeling was used to examine the relationship between the primary outcome, serum vitamin D, and a) measured BMI and b) waist circumference. Measured BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5 – 24.9 kg/m^2), overweight (25.0 – 29.9 kg/m^2), obese I (30.0-34.9 kg/m^2), obese II (35.0-39.9kg/m2) or obese III (>=40.0 kg/m^2) in adults. (64,65) In children, BMI was defined as < 5% underweight, 5.00 % to 84.99% as normal weight, 85.00 % to < 95% as overweight and >= 95.00% as obese using the Centers for Disease Control growth curves from the year 2000. (89) The CDC growth curves allow comparison with NHANES data and with a national reference. Use of the WHO or International Task Force on Obesity growth curves would affect the prevalence of obesity. WHO growth curves are based on optimal growth conditions and may not reflect the Canadian population. The International Task Force on Obesity growth curves have a low sensitivity for school age children. (89A)

The CHMS has 15 primary sampling units (PSUs) initially. For the purposes of variance estimation, the Atlantic region PSU was collapsed into the Quebec region PSUs thus there are 11 degrees of freedom at that level. (161)

The relationship between serum vitamin D level and obesity measures was investigated in univariate linear regression. Bootstrap weights provided with the data were used to account for the complex sampling design in point and variance estimation. (154) Although the primary analysis was BMI and waist circumference, other covariates of interest were chosen *a priori* based on their well-defined role in vitamin D metabolism (such as age, sex, sun exposure, season, sunscreen use, milk intake, fish intake, pregnancy and ethnicity) or previously published relationship (such as smoking and socioeconomic variables (education and income)). Medication use was asked as three separate questions in the CHMS leading to four categories: self reported any prescription drug use, self reported any over the counter drug use, self reported any vitamin or herbal supplement, and self reported any (legal) drug use in the preceding month. (Appendix Two) The full list of covariates include measured BMI, waist circumference, as well as age, sex, self reported any prescription drug use, self reported any over the counter drug use, self reported any vitamin or herbal supplement, self reported any (legal) drug use in the preceding month, education (less or equal to/greater than high school graduation, N/A for children), household income (less or equal to/greater than 20 000/year), frequency of milk intake per year, frequency of fish intake per year, pregnancy, season of blood draw, smoking category (never, former and current), always or often sunscreen use,

sunshine exposure (equal to/less than or greater than 1 hour per day in the summer between 11 am and 4pm), and ethnicity (white or not white).

Sensitivity analysis with elimination of vitamin D values greater than 150 nmol/L was conducted to determine if some of the data was exerting leverage. Bubble plots were drawn with the full data set and in the limited to <150 nmol/L data set.

Tests for interaction and collinearity were undertaken. All variables associated with vitamin D were examined by using multiple linear regression models. Predictors that were significant at $p<0.05$ were kept in the models.

Because of physiologic differences between adults and children and males and females, data were analyzed together and separately for adults and children, by BMI categories, by sex and by use of any vitamin or herbal product. Tests of interaction were conducted for subgroup analysis. (162-164)

SAS (Statistical Analysis Systems) software, version 9.3, was used. (165-169, Appendix One) SAS PROC SURVEY REG considers bootstrap weights. To take account of the multiplicity of analysis, a conservative alpha level of <0.001 was defined as the threshold of statistical significance.

5. Results

5.1 Participation in the CHMS and description of sample

In total, 5604 persons reported to the Mobile Examination Centre giving an overall response rate of 51.7% (151). (Figure 3) This figure is not simply the result of multiplying the individual response rates due to the inclusion of up to 2 members per household. The vitamin D level was measured for 5, 298 participants. Respondents who refused to have their blood drawn, did not have enough blood drawn or had medical reasons for not having their blood drawn (for example, chemotherapy) were excluded (n=298). (3) There were 8 participants with levels less than detectable who were excluded.

Figure 3: Participation in the Canadian Health Measures Survey

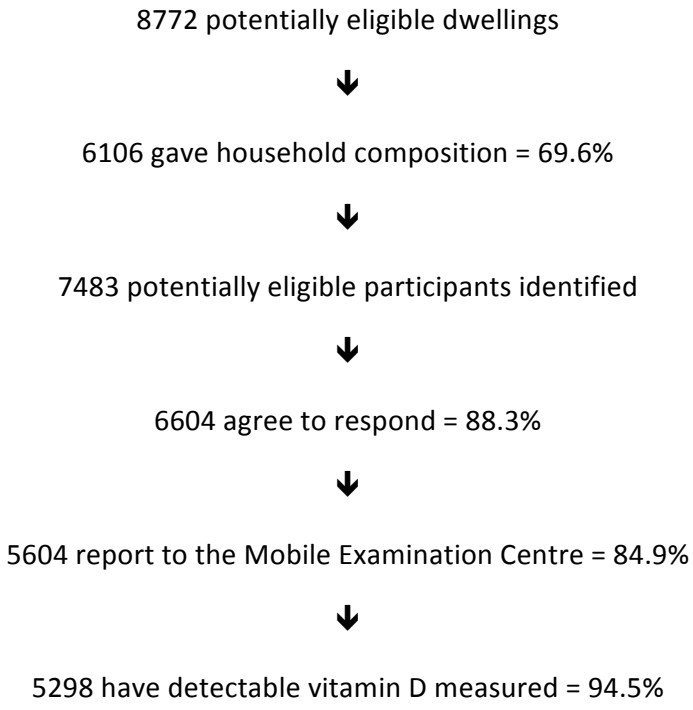


Table 4 presents the medians and standard errors for vitamin D level by BMI category in adults. The standard errors are overlapping for underweight, normal weight and overweight. The obese categories show lower vitamin D than normal weight.

Table 4: Vitamin D status of Canadians in the Canadian Health Measures Survey by BMI for adults

Underweight BMI < 18.5 kg/m^2	Normal weight BMI 18.5 – 24.9 kg/m^2	Overweight BMI 25.0-29.9 kg/m^2	Obese I BMI 30.0–34.9 kg/m^2	Obese II BMI 35.0 – 39.9 kg/m^2	Obese III BMI >=40.0 kg/m^2
Median nmol/L (Standard Error) n	Median nmol/L (Standard Error) n	Median nmol/L (Standard Error) n	Median nmol/L (Standard Error) n	Median nmol/L (Standard Error) n	Median nmol/L (Standard Error) n
60.70 (10.90) 48	66.65 (1.64) 1342	66.79 (1.35) 1337	61.33 (2.56) 557	57.62 (2.45) 210	52.11 (5.96) 124

Table 5 presents the medians and standard errors for vitamin D level by BMI category in children. Standard errors are overlapping between underweight and normal weight groups. Overweight and obese groups have lower vitamin D than the normal weight group.

Table 5: Vitamin D status of Canadians in the Canadian Health Measures Survey by BMI for children

Underweight BMI < 5.0%	Normal weight BMI 5.0-84.9%	Overweight BMI 85.0-94.9%	Obese BMI >= 95.0%
Median nmol/L (Standard error) n	Median nmol/L (Standard error) n	Median nmol/L (Standard error) n	Median nmol/L (Standard error) n
69.21 (4.62) 56	72.74 (1.80) 1184	66.39 (1.98) 225	58.85 (3.70) 183

Table 6 presents characteristics of the sample. Approximately half were male. Half had used prescription drugs in the month preceding the sample, two thirds had used over the counter medication and a third had used vitamins, herbals or supplements. Roughly ten percent did not use any medication in the month preceding the sample. Approximately two thirds never use sunscreen and roughly one quarter were exposed to less than one hour of summer sunshine daily. By self report, 86% were white.

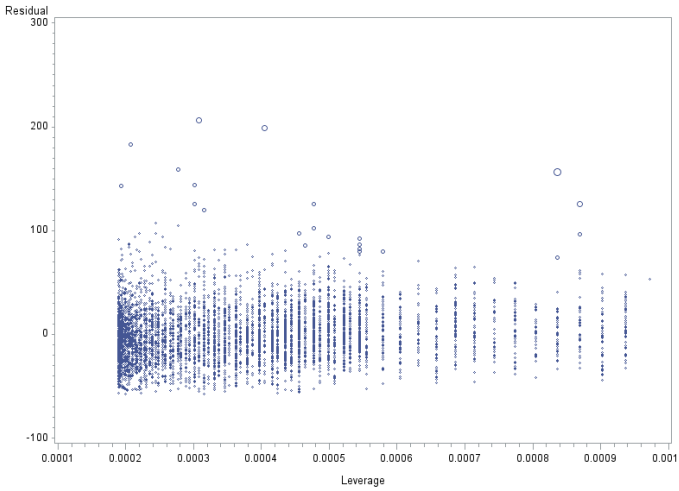
Table 6: Characteristics of 5298 persons in whom vitamin D was measured

	n (measured)	Percentage
Sex		
Male	5298	48%
Drug use		
Any prescription drug	5298	48%
Any over the counter drug	5298	71%
Any vitamin or herbal drug	5296	34%
Any (legal) drug	5298	88%
Income		
< 20 000 CAN / year	5049	8%
Smoking		
Ex smoker	4380	25%
Current smoker		17%
Never smoker		56%
Summer sunshine exposure		
< 1 hour	5292	27%
Sunscreen use		
Never	4415	61%
Ethnicity		
White	5146	86%

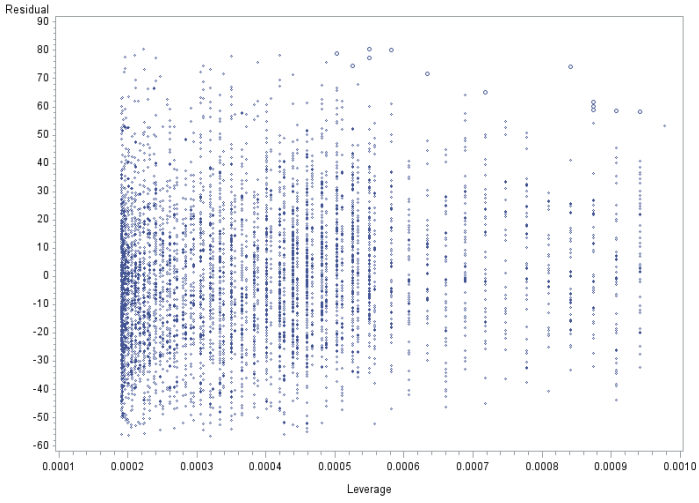
In the total of 5298 people in which vitamin D was detectable, the median level of vitamin D was 66.94 nmol/L (IQR 83.96 – 50.82). The distribution of vitamin D in the study population has been previously described. (3) Briefly, 4.1% of the participants had concentrations below 27.5 nmol/L and fewer than 0.5% had a concentration over 220 nmol/L.

Plots of residuals of continuous variables (age, milk, fish, waist circumference) against vitamin D showed a large, dense cloud of data. No heteroscedasticity was seen. A bubble plot showed significant leverage which was removed when analysis was limited to the 5258 participants with vitamin D less than 150 nmol/L (40 fewer persons). (Figure 4)

Figure 4: Bubble plots demonstrating leverage in full data set (A) eliminated by the removal of persons with vitamin D > 150 nmol/L in the limited data set (B)



A



B

5.2 Crude associations between vitamin D and various factors

In the complete data set, (n=5298), crude analysis showed statistically significant relationships ($p < 0.001$) between vitamin D and obese BMI and waist circumference, frequency of milk intake, sunshine exposure, sunscreen use, any prescription or any legal drug use in the preceding month, income, and ethnicity. (Table 7) Regression coefficients for obese / obese I BMI showed a positive relationship with vitamin D whereas the regression coefficient for waist circumference showed an inverse relationship with vitamin D. Sunshine exposure, sunscreen use and any prescription use, any legal drug use and household income showed inverse relationships with vitamin D. Nonwhite ethnicities had a lower vitamin D than white ethnicities. Frequency of milk intake showed a positive relationship with vitamin D.

Sensitivity analysis (removing the 40 persons with vitamin D levels > 150 nmol/L) showed similar relationships to the full data set, except waist circumference and income became non-significant.

Table 7: Crude associations between various factors and vitamin D levels in all participants and those with vitamin D < 150 nmol/L

	Full Data			Vitamin D < 150 nmol/L	
	n=5298			n = 5258	
	Coefficient (standard error)	P value* (n)	r^2 (%)	Coefficient (standard error)	P value * (n)
BMI category Ref = normal					
Underweight	-1.21 (3.09)	0.70 (5266)	0.02	-1.75 (2.90)	0.56 (5226)
Overweight	-0.85 (1.05)	0.43		-1.18 (0.99)	0.26
Obese/ObeseI**	6.48 (0.80)	**<0.0001**		5.46 (0.73)	**<0.0001**
ObeseII	9.20 (2.27)	0.002		8.16 (2.36)	0.005
ObeseIII	12.84 (3.85)	0.007		11.82 (3.81)	0.01
Waist circumference Cm	-0.25 (0.04)	**0.0001** (5258)	1.66	-0.22 (0.039)	0.0002 (5218)
Milk Times/year	0.012 (0.0013)	**<0.0001** (5298)	0.95	0.011 (0.0011)	**<0.0001** (5258)
Fish Times/year	0.60 (0.34)	0.11 (5298)	0.005	0.57 (0.31)	0.10 (5258)
Sunshine Ref = <1 hr / day	-6.29 (1.00)	**<0.0001** (5292)	0.26	-6.21 (0.75)	**<0.0001** (5252)
Sunscreen Ref = never	-5.38 (1.18)	**0.0008** (4415)	0.47	-4.96 (0.84)	**0.0001** (4379)
Season Ref = winter	-5.17 (3.41)	0.16 (5298)	0.91	-4.56 (2.98)	0.15 (5258)
Any prescription Ref=no	-6.49 (1.21)	**0.0002** (5298)	0.014	-5.8061 (1.02)	**0.0001** (5258)
Any over the counter Ref = no	-4.94 (1.21)	0.002 (5298)	0.22	-4.5282 (1.15)	0.002 (5258)
Any vitamin Ref = no	-4.97 (1.36)	0.004 (5296)	0.015	-4.20 (1.19)	0.005 (5258)
Any drug Ref = no	-7.15 (1.22)	**0.0001** (5298)	0.18	-6.64 (1.03)	**<0.0001** (5258)
Age Years	0.028 (0.044)	0.54 (5298)	2.01	0.05668 (0.042)	0.20 (5258)
Sex Ref = male	-3.92 (1.09)	0.004 (5298)	0.15	-4.09 (0.99)	0.002 (5258)

Table 7: Crude associations between various factors and vitamin D levels in all participants and those with vitamin D < 150 nmol/L, continued.

	Full Data			Vitamin D < 150 nmol/L	
	n=5298			n = 5258	
	Coefficient (standard error)	P value* (n)	r^2 (%)	Coefficient (standard error)	P value * (n)
Education Ref = highschool graduation	-3.38 (2.04)	0.12 (5163)	0.02	-2.35 (1.96)	0.25 (5123)
Household Income Ref < 20 000	-8.22 (1.88)	**0.001** (5049)	0.0062	-7.18 (1.95)	0.004 (5010)
Pregnant Ref = no	7.38 (4.19)	0.11 (5290)	0.95	6.38 (4.27)	0.16 (5250)
Ethnicity Ref = not white	-21.73 (1.89)	**<0.0001** (5146)	0.02	-20.65 (1.74)	**<0.0001** (5106)
Smoking category Ref = never Ex smoker Current	 -3.82 (1.70) 2.72 (2.14)	 0.04 (4380) 0.23	 0.16	 -4.30 (1.60) 3.55 (1.31)	 0.02 (4348) 0.02

*bolded p values are statistically significant at p<0.001

** For children and adolescents, BMI is categorized into underweight, normal weight, overweight and obese. For adults, BMI is categorized into underweight, normal weight, overweight, obese I, obese II and obese III.

When the data were limited to those with < 150 nmol/L of vitamin D and stratified by age, a statistically significant relationship between vitamin D and obese / obese I was seen in adults >=18 years only. (Table 8) No relationship was seen with waist circumference. In adolescents (12-18 years) and adults, frequency of milk intake was positively associated with vitamin D. Nonwhite ethnicity had lower vitamin D than white ethnicity. Sunshine, any prescription drug use, any legal drug use, and sex were also significantly inversely associated with vitamin D in adults.

Table 8: Crude associations between various factors and vitamin D levels in participants with vitamin D < 150 nmol/L, stratified by age

	Children		Adolescents		Adults	
	=<12 years		12-18 years		>=18 years	
	n = 1023		n = 613		n= 3622	
	Coefficient (standard error)	p value* (n)	Coefficient (standard error)	p value * (n)	Coefficient (standard error)	p value* (n)
BMI category Ref = normal						
Underweight	-8.96 (3.06)	0.01 (1023)	11.90 (5.69)	0.06 (613)	-2.66 (4.89)	0.60 (3590)
Overweight	4.58 (1.46)	0.01	2.82 (2.33)	0.25	-2.26 (1.10)	0.06
Obese/Obese I**	10.00 (3.48)	0.01	8.93 (3.44)	0.02	4.67 (0.81)	**0.0001**
Obese II					7.59 (2.43)	0.01
Obese III					11.25 (3.76)	0.01
Waist circumference cm	-0.43 (0.12)	0.005 (1023)	-0.24 (0.10)	0.04 (611)	-0.21 (0.05)	0.0012 (3584)
Milk Times/year	0.01 (0.0028)	0.004 (1023)	0.015 (0.0020)	**<0.0001** (613)	0.01 (0.0014)	**<0.0001**
Fish Times/year	1.24 (0.57)	0.05 (1023)	0.29 (0.85)	0.74 (613)	0.62 (0.34)	0.09 (3622)
Sunshine Ref = <1 hr / day	-9.35 (3.80)	0.03 (1022)	-6.59 (3.80)	0.11 (612)	-5.62 (0.78)	**<0.0001** (3618)
Sunscreen Ref = never	-3.92 (2.06)	0.08 (974)	-4.92 (2.82)	0.11 (559)	-4.34 (1.15)	0.003 (2846)
Season Ref = winter	-4.55 (5.87)	0.45 (1023)	-10.41 (4.87)	0.06 (613)	-3.96 (2.70)	0.17 (3622)
Any prescription Ref=no	-0.66 (2.71)	0.81 (1022)	-7.00 (3.33)	0.06 (613)	-7.34 (1.08)	**<0.0001** (3622)
Any over the counter Ref = no	-5.61 (1.56)	0.004 (1022)	-3.55 (2.68)	0.21 (613)	-5.03 (1.36)	0.003 (3622)
Any vitamin Ref = no	-1.19 (2.20)	0.60 (1021)	2.54 (3.61)	0.50 (613)	-5.16 (1.30)	0.002 (3622)
Any drug Ref = no	-4.12 (2.07)	0.07 (1023)	-2.77 (4.20)	0.52 (613)	-9.20 (0.97)	**<0.0001** (3622)
Age Years	-1.67 (0.56)	0.01 (1023)	-0.41 (0.85)	0.63 (613)	0.18 (0.056)	0.01 (3622)
Sex Ref = male	1.59 (1.93)	0.43 (1023)	1.26 (2.85)	0.67 (613)	-5.13 (1.09)	**0.0007** (3622)

Table 8: Crude associations between various factors and vitamin D levels in participants with vitamin D < 150 nmol/L, stratified by age, continued

	Children		Adolescents		Adults	
	=<12 years		12-18 years		>=18 years	
	n = 1023		n = 613		n= 3622	
	Coefficient (standard error)	p value* (n)	Coefficient (standard error)	p value * (n)	Coefficient (standard error)	p value* (n)
Education Ref = highschool graduation	0.18 (3.96)	0.96 (1000)	-5.48 (6.29)	0.40 (596)	-2.08 (2.03)	0.33 (3527)
Household Income Ref < 20 000	-10.62 (4.04)	0.02 (997)	-3.98 (8.24)	0.64 (543)	-6.94 (2.04)	0.006 (3470)
Ethnicity Ref = not white	-16.79 (6.18)	0.02 (984)	-21.86 (2.57)	**<0.0001** (590)	-21.11 (1.85)	**<0.0001** (3532)
Smoking category Ref = never Ex smoker Current			 -7.28 (13.92) 1.36 (7.58)	 0.61 (612) 0.86	 -4.57 (1.62) 3.56 (1.36)	 0.02 (3613) 0.02

*bolded p values are statistically significant at p<0.001.

** For children and adolescents, BMI is categorized into underweight, normal weight, overweight and obese. For adults, BMI is categorized into underweight, normal weight, overweight, obese I, obese II and obese III.

Crude analysis in females only, stratified by age, showed BMI and waist circumference were not statistically significantly associated with vitamin D ($p<0.001$). (Table 9) Nonwhite ethnicity had lower vitamin D than white ethnicity in adolescents and adults. Frequency of milk intake was positively associated while sunshine and any prescription drug use were inversely associated with vitamin D in adult females. Ex-smoker status showed an inverse relationship with vitamin D in adult females.

Table 9: Crude associations between various factors and vitamin D levels in females with vitamin D < 150 nmol/L, stratified by age

	<=12 years		12-18 years		>=18 years	
	n=502		n=290		n = 1925	
	Coefficient (standard error)	p value* (n)	Coefficient (standard error)	p value* (n)	Coefficient (standard error)	p value* (n)
BMI category Ref = normal Underweight Overweight Obese/ObeseI*** ObeseII ObeseIII	 -8.88 (5.23) 6.91 (2.14) 9.57 (4.66)	 0.12 (502) 0.01 0.06	 22.03 (9.39) 0.87 (2.77) -1.79 (6.18)	 0.04 (290) 0.76 0.77	 -2.08 (5.53) -0.92 (1.32) 6.40 (1.98) 7.14 (3.25) 9.332 (5.52)	 0.71 (1894) 0.50 0.008 0.05 0.12
Waist circumference cm	-0.32 (0.16)	0.07 (502)	0.09 (0.18)	0.63 (289)	-0.24 (0.072)	0.006 (1890)
Milk Times/year	0.01 (0.0028)	**0.001** (502)	0.016 (0.0041)	0.003 (290)	0.01 (0.0015)	**<** **0.0001** (1925)
Fish Times/year	2.58 (0.86)	0.01 (502)	0.77 (1.51)	0.62 (290)	0.69 (0.36)	0.08 (1925)
Sunshine Ref = <1 hr / day	-9.92 (5.81)	0.12 (502)	-3.96 (6.15)	0.53 (290)	-5.17 (1.10)	**0.0006** (1922)
Sunscreen Ref = never	-6.47 (2.75)	0.04 (473)	-3.78 (4.6 0)	0.43 (259)	-6.05 (1.66)	0.004 (1418)
Season Ref = winter	-7.23 (6.23)	0.27 (502)	-5.04 (5.66)	0.39 (290)	-4.32 (2.44)	0.10 (1925)
Any prescription Ref=no	-2.80 (5.04)	0.59 (502)	-13.73 (4.37)	0.01 (290)	-7.53 (1.12)	**< 0.0001** (1925)
Any over the counter Ref = no	-6.69 (2.89)	0.04 (502)	-3.12 (3.49)	0.39 (290)	-4.88 (2.00)	0.03 (1925)
Any vitamin Ref = no	-4.81 (2.71)	0.10 (502)	6.82 (4.67)	0.17 (290)	-4.79 (1.73)	0.02 (1925)
Any drug Ref = no	-8.57 (2.99)	0.01 (502)	-6.11 (5.40)	0.28 (290)	-12.92 (3.67)	0.005 (1925)
Age Years	-2.11 (0.75)	0.02 (502)	-0.22 (0.97)	0.82 (290)	0.072 (0.060)	0.25 (1925)
Education Ref = highschool graduation	3.18 (7.82)	0.69 (491)	-4.79 (6.68)	0.49 (280)	-4.44 (3.27)	0.20 (1880)
Household Income Ref < 20 000	-11.60 (4.44)	0.02 (490)	-13.43 (11.23)	0.26 (257)	-6.89 (2.64)	0.02 (1846)

Table 9: Crude associations between various factors and vitamin D levels in females with vitamin D < 150 nmol/L, stratified by age, continued

	<=12 years		12-18 years		>=18 years	
	n=502		n=290		n = 1925	
	Coefficient (standard error)	p value* (n)	Coefficient (standard error)	p value* (n)	Coefficient (standard error)	p value* (n)
Ethnicity Ref = not white	-24.34 (5.75)	0.01 (483)	-27.33 (3.24)	**<0.0001** (280)	-21.59 (1.93)	**< 0.0001** (1878)
Smoking category Ref = never Ex smoker Current smoker			 6.36 (19.52) 8.39 (9.25)	 0.75 (289) 0.38	 -4.97 (1.11) 2.97 (1.97)	 **0.0009** (1922) 0.16

*Bolded p values are statistically significant at p <0.001

** For children and adolescents, BMI is categorized into underweight, normal weight, overweight and obese. For adults, BMI is categorized into underweight, normal weight, overweight, obese I, obese II and obese III.

In crude regression for males with vitamin D < 150 nmol/L, stratified by age, statistically significant relationships between BMI in the obese III group with vitamin D were seen. (Table 10) Waist circumference was not significant in any age group. Frequency of milk intake was positively associated with vitamin D while sunshine exposure and any legal drug use were inversely associated with vitamin D in adult men. Nonwhite ethnicity had a lower vitamin D than white ethnicity, in adult men.

Table 10: Crude associations between various factors and vitamin D levels in males with vitamin D < 150 nmol/L stratified by age

	>=12 years		12-18 years		>=18 years	
	n=521		n = 323		n=1697	
	Coefficient (standard error)	P value*	Coefficient (standard error)	P value*	Coefficient (standard error)	P value*
BMI category Ref = normal Underweight Overweight Obese/ObeseI** Obese II Obese III	 -9.45 (3.51) 2.68 (2.92) 10.80 (4.11)	 0.02 (521) 0.38 0.02	 4.08 (7.38) 4.51 (4.84) 17.16 (4.30)	 0.59 (323) 0.37 0.002	 0.41 (8.50) -5.08 (1.87) 2.48 (1.26) 10.00 (2.69) 16.91 (3.43)	 0.96 (1696) 0.02 0.07 0.003 **0.0004**
Waist circumference cm	-0.35 (0.14)	0.0031 (521)	-0.49 (0.10)	0.0007 (322)	-0.081 (0.06)	0.21 (1694)
Milk Times/year	0.0080 (0.0035)	0.04 (521)	0.015 (0.0030)	0.0003 (323)	0.0096 (0.0021)	**0.0008** (1697)
Fish Times/year	0.18 (0.86)	0.84 (521)	0.071 (0.96)	0.94 (323)	0.47 (0.63)	0.47 (1697)
Sunshine Ref = <1 hr / day	-8.58 (2.88)	0.01 (520)	-10.09 (5.35)	0.09 (322)	-8.72 (1.34)	**<0.0001** (1696)
Sunscreen Ref = never	-2.71 (3.35)	0.44 (501)	-8.05 (3.07)	0.02 (300)	0.40 (1.60)	0.81 (1428)
Season Ref = winter	-2.22 (6.26)	0.73 (521)	-15.40 (6.06)	0.03 (323)	-3.69 (3.48)	0.31 (1697)
Any prescription Ref=no	 1.25 (2.92)	0.68 (520)	 -0.96 (4.79)	0.84 (323)	 -5.56 (1.73)	0.008 (1697)
Any over the counter Ref = no	 -4.78 (3.32)	0.18 (520)	 -4.20 (3.93)	0.31 (323)	 -3.97 (1.60)	0.03 (1697)
Any vitamin Ref = no	2.23 (2.50)	0.39 (520)	-2.39 (5.52)	0.67 (323)	-4.22 (1.99)	0.06 (1697)
Any drug Ref = no	-0.73 (3.82)	0.85 (521)	-0.55 (5.03)	0.91 (323)	-6.33 (1.36)	**0.0007** (1697)
Age years	-1.31 (0.67)	0.07 (521)	-0.50 (1.20)	0.68 (323)	0.29 (0.07)	0.0015 (1697)
Education Ref = highschool graduation			-3.87 (20.29)	0.85 (316)	0.13 (2.96)	0.97 (1647)
Household Income Ref < 20 000	-9.87 (5.45)	0.097 (507)	9.31 (10.19)	0.38 (286)	-9.23 (2.67)	0.005 (1624)

Table 10: Crude associations between various factors and vitamin D levels in males with vitamin D < 150 nmol/L stratified by age, continued

	>=12 years		12-18 years		>=18 years	
	n=521		n = 323		n=1697	
	Coefficient (standard error)	P value*	Coefficient (standard error)	P value*	Coefficient (standard error)	P value*
Ethnicity Ref = not white	-10.95 (7.58)	0.18 (501)	-16.15 (4.90)	0.007 (310)	-20.25 (2.48)	**<0.001** (1654)
Smoking category Ref = never Ex-smoker Current smoker			 -22.81 (16.73) -3.67 (7.08)	 0.20 (323) 0.61	 -4.66 (2.38) 3.73 (1.86)	 0.08 (1691) 0.07

*Bolded p values are statistically significant at p <0.001.

** For children and adolescents, BMI is categorized into underweight, normal weight, overweight and obese. For adults, BMI is categorized into underweight, normal weight, overweight, obese I, obese II and obese III.

Examining the data for children with vitamin D less than 150 nmol/L stratified by BMI showed waist circumference was not statistically significantly associated with vitamin D ($p<0.001$). (Table 11) In underweight children, age was inversely associated with vitamin D level. In normal weight children, frequency of milk intake was positively associated with vitamin D level. In normal weight children, nonwhite ethnicity had a lower vitamin D level than white ethnicity. In overweight children, no statistically significant relationships were seen with vitamin D. In obese children, nonwhite ethnicity had a lower vitamin D level than white ethnicity.

Table 11: Crude associations between various factors and vitamin D levels in children (< 18 years) with vitamin D < 150 nmol/L stratified by BMI

	Measured BMI category underweight <5.0 %		Measured BMI category normal weight 5.0 – 84.9 %		Measured BMI category Overweight 85.0 – 94.9 %		Measured BMI category Obese > =95.0 %	
	n=55		n = 1173		n=225		n=183	
	Coefficient (standard error)	*p value (n)	Coefficient (standard error)	*p value (n)	Coefficient (standard error)	*p value (n)	Coefficient (standard error)	*p value (n)
Waist circumference cm	-1.57 (0.41)	0.0029 (54)	-0.33 (0.19)	0.11 (1173)	-0.47 (0.18)	0.03 (224)	-0.29 (0.16)	0.10 (183)
Milk Times/year	0.025 (0.0069)	0.004 (55)	0.013 (0.0018)	**<0.0001** (1173)	0.010 (0.0038)	0.02 (225)	0.02 (0.0061)	0.02 (183)
Fish Times/year	2.18 (2.84)	0.46 (55)	0.52 (0.65)	0.44 (1173)	-1.08 (1.47)	0.48 (225)	2.68 (1.64)	0.13 (183)
Sunshine Ref = <1 hr / day	15.39 (8.97)	0.11 (55)	-12.04 (3.67)	0.007 **(**1172)	1.64 (7.09)	0.82 (225)	-2.55 (6.98)	0.72 (182)
Sunscreen Ref = never	-19.37 (5.38)	0.0041 (49)	-4.55 (1.79)	0.03 (1111)	-6.12 (3.03)	0.07 (216)	-12.42 (3.44)	0.004 (147)
Season Ref = winter	6.95 (11.72)	0.56 (55)	-8.23 (5.11)	0.13 (1173)	-6.89 (5.76)	0.26 (225)	-10.66 (6.45)	0.13 (183)
Any prescription Ref=no	-10.15 (7.24)	0.19 (55)	-6.76 (2.32)	0.01 (1173)	0.53 (5.13)	0.92 (225)	5.63 (6.29)	0.39 (183)
Any over the counter Ref = no	3.86 (10.75)	0.73 (55)	-3.73 (1.76)	0.06 (1173)	-3.87 (4.26)	0.38 (224)	-2.41 (5.60)	0.67 (183)
Any vitamin Ref = no	12.31 (11.85)	0.32 (55)	-0.73 (2.26)	0.75 (1173)	0.31 (3.28)	0.93 (225)	4.45 (5.93)	0.47 (183)
Any drug Ref = no	8.43 (7.28)	0.27 (55)	-4.83 (2.10)	0.04 (1173)	-0.04 (3.12)	0.99 (225)	6.48 (6.24)	0.32 (183)
Age years	-3.53 (0.80)	**0.001** (55)	-1.08 (0.53)	0.07 (1173)	-1.40 (0.51)	0.02 (225)	-1.07 (0.68)	0.14 (183)
Sex Ref = male	7.15 (10.01)	0.49 (55)	3.28 (2.32)	0.18 (1173)	1.95 (3.00)	0.53 (225)	-6.98 (4.70)	0.17 (183)

Table 11: Crude associations between various factors and vitamin D levels in children (< 18 years) with vitamin D < 150 nmol/L stratified by BMI, continued

	Measured BMI category underweight <5.0 %		Measured BMI category normal weight 5.0 – 84.9 %		Measured BMI category Overweight 85.0 – 94.9 %		Measured BMI category Obese >= 95.0 %	
	n=55		n = 1173		n=225		n=183	
	Coefficient (standard error)	*p value (n)	Coefficient (standard error)	*p value (n)	Coefficient (standard error)	*p value (n)	Coefficient (standard error)	*p value (n)
Education Ref = highschool graduation	9.82 (9.52)	0.32 (53)	-1.86 (7.23)	0.80 (1145)	-8.32 (6.13)	0.20 (221)	10.50 (3.99)	0.02 (177)
Household Income Ref < 20 000			-11.99 (6.43)	0.09 (1105)	-11.85 (8.03)	0.17 (217)	19.94 (11.62)	0.11 (168)
Ethnicity Ref = not white	-22.09 (9.44)	0.04 (55)	-19.18 (2.98)	**<0.0001** (1135)	-18.91 (7.76)	0.03 (213)	-19.28 (4.38)	**0.001** (171)
Smoking category Ref = never Ex smoker Current	 -36.25 (16.07)	 0.02 (25)	 -16.13 (14.38) 3.37 (7.90)	 0.29 (522) 0.68	 6.97 (4.66)	 0.16 (103)	 15.13 (9.92) 13.64 (10.82)	 0.16 (85) 0.23

*Bolded p values are statistically significant at p < 0.001

Stratifying the data by BMI category in adults with vitamin D levels less than 150 nmol/L showed waist circumference was not significant in any group, $p<0.001$ (Table 12) No statistically significant relationships were seen in the underweight group, the obese II group or the obese III group. The normal weight group showed statistically significant inverse relationships between vitamin D and sunshine, any legal drug use, ethnicity and ex-smoker status. The overweight category showed statistically significant positive relationships between vitamin D and frequency of milk intake and age and a statistically significant inverse relationship between vitamin D and ethnicity. The obese I category showed a statistically significant inverse association between vitamin D and ethnicity.

Table 12: Crude associations between various factors and vitamin D levels in adults (>= 18 years) with vitamin D < 150 nmol/L stratified by BMI

	Measured BMI category underweight < 18.5 kg/m^2		Measured BMI category normal weight 18.5 – 24.9 kg/m^2		Measured BMI category Overweight 25.0 – 29.9 kg/m^2		Measured BMI category Obese I 30.0 – 34.9 kg/m^2		Measured BMI category Obese II 35.0 – 39.9 kg/m^2		Measured BMI category Obese III >=40.0 kg/m^2	
	n=48		n=1323		n=1329		n=556		n=210		n=124	
	Coefficient (standard error)	*p value (n)	Coefficient (standard error)	*p value (n)	Coefficient (standard error)	*p value (n)	Coefficient (standard error)	*p value (n)	Coefficient (standard error)	*p value (n)	Coefficient (standard error)	*p value (n)
Waist circumference cm	1.12 (1.51)	0.47 (48)	-0.19 (0.17)	0.28 (1322)	-0.10 (0.11)	0.38 (1328)	0.036 (0.23)	0.88 (555)	0.33 (0.19)	0.11 (208)	-0.31 (0.19)	0.13 (122)
Milk Times/year	0.028 (0.014)	0.06 (48)	0.012 (0.0031)	0.003 (1323)	0.009 (0.0019)	**0.0007** (1329)	0.0095 (0.0065)	0.17 (556)	0.0063 (0.0036)	0.11 (210)	0.016 (0.008)	0.06 (124)
Fish Times/year	1.85 (4.84)	0.71 (48)	0.02 (0.55)	0.09 (1323)	0.48 (0.55)	0.40 (1329)	-0.57 (0.46)	0.25 (556)	2.10 (1.82)	0.27 (210)	-0.58 (1.58)	0.72 (124)
Sunshine Ref = <1 hr / day	-19.30 (6.21)	0.01 (48)	-8.82 (1.94)	**0.0008** (1320)	-2.92 (1.81)	0.13 (1328)	-4.56 (2.47)	0.09 (556)	1.84 (4.69)	0.70 (210)	-3.76 (5.21)	0.48 (124)
Sunscreen Ref = never	-16.42 (12.22)	0.21 (40)	-4.56 (2.65)	0.11 (1042)	-3.60 (1.63)	0.05 (1074)	-0.49 (2.92)	0.87 (426)	-9.28 (5.89)	0.14 (153)	-2.57 (6.00)	0.68 (86)
Season Ref = winter	-20.38 (10.13)	0.07 (48)	-5.95 (3.79)	0.14 (1323)	-2.08 (3.43)	0.56 (1329)	-3.55 (3.08)	0.27 (556)	-9.67 (3.81)	0.03 (210)	-1.26 (7.45)	0.87 (124)
Any prescription Ref=no	-13.91 (13.91)	0.34 (48)	-11.62 (2.97)	0.002 (1323)	-5.17 (2.09)	0.03 (1329)	-5.90 (2.58)	0.04 (556)	-8.08 (3.91)	0.06 (210)	-6.09 (6.51)	0.37 (124)
Any over the counter Ref = no	1.04 (7.54)	0.89 (48)	-7.65 (2.95)	0.02 (1323)	-2.35 (1.73)	0.20 (1329)	-4.58 (3.36)	0.22 (556)	-2.17 (2.83)	0.46 (210)	-13.28 (6.37)	0.06 (124)
Any vitamin Ref = no	-17.73 (8.31)	0.06 (48)	-5.22 (2.07)	0.03 (1323)	-5.16 (2.12)	0.03 (1329)	-4.49 (2.85)	0.14 (556)	-1.46 (5.34)	0.79 (210)	-3.37 (6.34)	0.60 (124)
Any drug Ref = no	-7.53 (15.29)	0.63 (48)	-12.46 (2.73)	**0.0008** (1323)	-5.77 (2.17)	0.02 (1329)	-9.77 (2.98)	0.007 (556)	-1.47 (6.94)	0.84 (210)	-16.83 (17.86)	0.37 (124)
Age years	0.042 (0.24)	0.86 (48)	0.14 (0.077)	0.10 (1323)	0.27 (0.059)	**0.0008** (1329)	0.32 (0.09)	0.0045 (556)	0.22 (0.15)	0.17 (210)	0.076 (0.22)	0.74 (124)
Sex Ref = male	-7.74 (8.29)	0.37 (48)	-8.52 (2.02)	0.0015 (1323)	-3.11 (1.81)	0.11 (1329)	-1.74 (3.06)	0.58 (556)	-8.21 (3.45)	0.04 (210)	-12.87 (6.76)	0.08 (124)
Education Ref = highschool graduation	-21.84 (28.30)	0.46 (48)	-0.66 (5.25)	0.90 (1280)	-5.78 (1.99)	0.01 (1302)	3.84 (3.41)	0.28 (542)	3.76 (5.78)	0.53 (202)	2.72 (9.17)	0.77 (121)

Table 12: Crude associations between various factors and vitamin D levels in adults (>= 18 years) with vitamin D < 150 nmol/L stratified by BMI, continued

	Measured BMI category underweight < 18.5 kg/m^2		Measured BMI category normal weight 18.5 – 24.9 kg/m^2		Measured BMI category Overweight 25.0 – 29.9 kg/m^2		Measured BMI category Obese I 30.0 – 34.9 kg/m^2		Measured BMI category Obese II 35.0 – 39.9 kg/m^2		Measured BMI category Obese III >=40.0 kg/m^2	
	n=48		n=1323		n=1329		n=556		n=210		n=124	
	Coefficient (standard error)	*p value (n)	Coefficient (standard error)	*p value (n)	Coefficient (standard error)	*p value (n)	Coefficient (standard error)	*p value (n)	Coefficient (standard error)	*p value (n)	Coefficient (standard error)	*p value (n)
Household Income Ref < 20 000	-5.04 (10.76)	0.65 (44)	-7.51 (2.31)	0.008 (1262)	-6.60 (3.56)	0.09 (1275)	-9.56 (3.88)	0.03 (538)	-2.79 (5.43)	0.62 (202)	-4.81 (8.16)	0.57 (120)
Ethnicity Ref = not white	-27.84 (8.70)	0.008 (45)	-24.89 (3.06)	**<0.0001** (1295)	-20.65 (2.46)	**<0.0001** (1298)	-22.22 (2.62)	**<0.0001** (542)	-12.81 (4.55)	0.02 (205)	-10.36 (11.16)	0.37 (116)
Smoking category Ref = never												
Ex smoker	-23.52 (14.35)	0.13 (47)	-9.29 (2.71)	0.005 (1322)	-4.17 (2.16)	0.08 (1326)	-0.093 (2.57)	0.97 (552)	1.29 (4.52)	0.78 (210)	-13.17 (6.31)	0.06 (124)
Current	2.09 (13.13)	0.88	3.49 (2.78)	0.24	3.36 (1.80)	0.09	4.70 (3.46)	0.20	8.67 (5.34)	0.13	9.63 (9.43)	0.33

*Bolded p values are statistically significant at $p < 0.001$

Stratifying participants with vitamin D < 150 nmol/L by any vitamin or herbal supplement use showed a small difference between the two groups (Table 13). Waist circumference, sunshine, sunscreen and any over the counter drug use were significantly inversely associated with vitamin D in the non-supplement users and not in the supplement users. In both groups, frequency of milk intake showed a positive association. Nonwhite ethnicity had a lower vitamin D level than white ethnicity.

Table 13: Crude associations between various factors and vitamin D levels in participants with vitamin D < 150 nmol/L stratified by supplement use

	Non supplement user		Supplement user	
	n=3447		n=1809	
	Coefficient (standard error)	p value *	Coefficient (standard error)	p value*
BMI category Ref = normal Underweight	-0.93 (4.16)	0.83 (3429)	-3.81 (6.99)	0.60 (1795)
Overweight	-0.71 (1.41)	0.62	-1.63 (2.04)	0.44
Obese/ObeseI***	5.02 (1.37)	0.004	5.78 (1.93)	0.01
Obese II	7.10 (3.06)	0.04	10.13 (4.07)	0.03
Obese III	11.20 (5.12)	0.05	12.02 (3.14)	0.003
Waist circumference cm	-0.23 (0.045)	**0.0003** (3425)	-0.18 (0.06)	0.02 (1791)
Milk Times/year	0.011 (0.0017)	**<0.0001** (3447)	0.012 (0.0012)	**<0.0001** (1809)
Fish Times/year	0.16 (0.23)	0.50 (3447)	1.13 (0.49)	0.04 (1809)
Sunshine Ref = <1 hr / day	-6.87 (1.03)	**<0.001** (3443)	-5.10 (1.24)	0.002 (1807)
Sunscreen Ref = never	-4.91 (1.15)	**0.001** (2869)	-4.10 (1.34)	0.01 (1508)
Season Ref = winter	-5.71 (3.25)	0.11 (3447)	-2.88 (3.79)	0.46 (1809)
Any prescription Ref=no	-3.11 (1.01)	0.01 (3447)	-9.73 (2.59)	0.003 (1809)
Any over the counter Ref = no	-6.19 (0.86)	**<0.0001** (3447)	-1.67 (1.94)	0.41 (1809)
Average activity Steps / day	0.00017 (0.00032)	0.60 (3447)	0.00059 (0.00046)	0.23 (1809)
Age years	-0.0013 (0.039)	0.97 (3447)	0.12 (0.06)	0.09 (1809)
Sex Ref = male	-3.37 (1.04)	0.008 (3447)	-4.09 (2.02)	0.07 (1809)
Education Ref = highschool graduation	-1.82 (2.20)	0.42 (3349)	-2.77 (3.12)	0.39 (1773)
Household income Ref < 20 000	-6.31 (1.71)	0.004 (3271)	-8.70 (3.58)	0.03 (1737)

Table 13: Crude associations between various factors and vitamin D levels in participants with vitamin D < 150 nmol/L stratified by supplement use, continued

	Non supplement user		Supplement user	
	n=3447		n=1809	
	Coefficient (standard error)	p value *	Coefficient (standard error)	p value*
Ethnicity Ref = not white	-20.62 (2.13)	**<0.0001** (3342)	-21.08 (2.46)	**<0.0001** (1762)
Smoking category Ref = never				
Ex smoker	-2.97 (1.94)	0.15 (2801)	-5.12 (2.19)	0.04 (1547)
Current	1.53 (1.67)	0.38	6.76 (2.49)	0.02

*Bolded p values are statistically significant at p<0.001

** For children and adolescents, BMI is categorized into underweight, normal weight, overweight and obese. For adults, BMI is categorized into underweight, normal weight, overweight, obese I, obese II and obese III.

5.3 Multivariate association between vitamin D and various factors

Multivariate regression was performed using the full data set (n = 5298) with all ages and both sexes together using backwards, forwards, and stepwise regression. (Box 1) The multivariate relationship showed waist circumference was inversely associated with vitamin D level in two of the models (backwards and stepwise regression). In the backwards regression, frequency of milk intake, summer sunshine exposure, white vs not white ethnicity, income, any drug use, and supplement use were significantly positively associated with vitamin D level.

Box 1: Multivariate regression of vitamin D with various factors

Backward elimination:

Vitamin D = 57.08 + 0.011 milk + 5.10 sunshine + 20.91 ethnicity + 5.72 income + 11.11 any drug use + 5.95 supplement use - 0.32 waist circumference

Forward selection:

Vitamin D = 46.82 + 0.011 milk + 23.77 ethnicity

Stepwise regression:

Vitamin D = 55.69 + 0.0099 milk + 23.31 ethnicity + 8.16 any drug use + 5.45 income – 0.27 waist circumference

5.4 Sun exposure, sunscreen use and milk intake by obesity

Table 14 shows that obese and non-obese adults do not differ in exposure to summer sunshine: 65% of obese adults and 65% of non-obese adults receive greater than an hour of sunshine per day in summer.

Table 14: Sun exposure by obesity in adults

	Sunshine < 1 hr/ day	Sunshine > 1 hr / day
Not obese	470	917
Obese (BMI >= 30 kg/m^2)	774	1453

Table 15 shows overweight and non-overweight children do not differ in exposure to summer sunshine: 85% of overweight children and 88% of non-overweight children receive greater than an hour of sunshine per day.

Table 15: Sun exposure by overweight in children

	Sunshine < 1 hr/ day	Sunshine > 1 hr / day
Not overweight	148	1091
Overweight (BMI >= 85th %)	59	348

Table 16 shows a small difference in use of sunscreen between obese and non-obese adults: 36% of non-obese adults use sunscreen whereas 29% of obese adults use sunscreen.

Table 16: Sunscreen use by obesity in adults

	Sunscreen Never, Rarely	Sunscreen Always, Sometimes
Not obese	695	404
Obese (BMI >= 30 kg/m^2)	1225	521

.

Table 17 shows overweight children do not differ from non-overweight children in sunscreen use: 50% versus 48%.

Table 17: Sunscreen use by overweight in children

	Sunscreen Never, Rarely	Sunscreen Always, Sometimes
Not overweight	586	586
Overweight (BMI >= 85th %)	193	180

Table 18 shows frequency of milk intake varies by BMI category and is lowest in the largest BMI group in adults. Vitamin D levels are lowest in the largest BMI group.

Table 18: Mean frequency of milk intake (per year) and median vitamin D level by BMI category in adults

<18.5 Underweight Mean milk intake (standard error) n Median vitamin D (standard error)	18.5 – 24.9 Normal weight Mean milk intake (standard error) n Median vitamin D (standard error)	25.0 – 29.9 Overweight Mean milk intake (standard error) n Median vitamin D (standard error)	30.0-34.9 Obese I Mean milk intake (standard error) n Median vitamin D (standard error)	35.0 – 39.9 Obese II Mean milk intake (standard error) n Median vitamin D (standard error)	>=40 Obese III Mean milk intake (standard error) n Median vitamin D (standard error)
483 (63) 48 60.70 nmol/L (10.90)	363 (15) 1342 66.65 nmol/L (1.64)	356 (17) 1337 66.79 nmol/L (1.35)	322 (26) 557 61.33 nmol/L (2.56)	415 (92) 210 57.62 nmol/L (2.45)	276 (26) 124 52.11 nmol/L (5.96)

Table 19 shows frequency of milk intake varies by BMI category and is lowest in the smallest BMI group in children. Vitamin D levels are lowest in the largest BMI group.

Table 19: Mean frequency of milk intake (per year) and median vitamin D level by BMI category in children

< 5% Underweight	5.00– 84.99% Normal weight	85.00 – 94.99% Overweight	>=95.0% Obese
Mean milk intake (standard error) n Median vitamin D (standard error)	Mean milk intake (standard error) n Median vitamin D (standard error)	Mean milk intake (standard error) n Median vitamin D (standard error)	Mean milk intake (standard error) n Median vitamin D (standard error)
582 (60) 56 69.21 nmol/L (4.62)	685 (28) 1184 72.74 nmol/L (1.80)	695 (43) 225 66.39 nmol/L (1.98)	637 (43) 183 58.85 nmol/L (3.70)

6. Discussion

This work examined the relationship between vitamin D level and BMI and waist circumference in the CHMS. Vitamin D level is lower in the larger BMI categories. Obese persons may be different from non-obese persons behaviorally. Less frequent milk intake may be one reason obese persons have lower vitamin D in the CHMS. Within the CHMS, obese and non-obese do not differ in exposure to summer sunshine. Further, obese persons are not more likely to use sunscreen.

Waist circumference was inversely associated with vitamin D level in crude analysis and after adjustment for covariates. The obese BMI category was positively associated with vitamin D levels in crude analysis only. Stratification of the data by age, sex, and supplement use showed frequency of milk intake was positively associated with vitamin D status, and people of nonwhite ethnicity had lower vitamin D than people of white ethnicity.

6.1 Strengths

The major strength of work with the CHMS is that it has direct measurements of height, weight and vitamin D. (151-155) It is a nationally representative survey and includes both adults and children. Participants are not selected on the basis of vitamin D status or obesity, therefore the results are generalizable. Further, a consistent and valid method was used to measure vitamin D for all samples. (3) The CHMS measured many determinants of vitamin D status including self-reported sun exposure, sunscreen use, supplement use, frequency of milk & fish intake and ethnicity.

6.2 Limitations

6.2A Reverse Causation

The cross sectional nature of this study design does not allow causation or reverse causation to be delineated between vitamin D and obesity because temporality and directionality are lacking. However, given the lack of results in randomized controlled trials where vitamin D therapy did not affect weight, it is likely that obesity leads to low vitamin D. (129-130) This conclusion is reinforced by a study of short-term effects of whole body ultra-violet B radiation on serum vitamin D and accompanying *in vitro* findings (131) and a study of genetic markers as instrumental variables for both BMI and vitamin D. (131A)

6.2B Validity

Multiple testing was a potential concern. For example, if one considers Table 5 alone, there were 48 linear regressions. However, a conservative p value of 0.001 was set. Moreover, there is a debate in the literature about whether it is appropriate to adjust p values for multiple testing. (169A-D)

The CHMS has 11 degrees of freedom. This is a limitation in the multivariate analysis where more than 10 categories were included in that the stability of estimates may be compromised.

At first sight the data are contradictory: (1) vitamin D levels are lower in persons with higher BMI yet BMI category obese shows a positive regression coefficient with vitamin D; (2) waist circumference has an inverse relationship whereas BMI category

obese has a positive relationship with vitamin D; (3) sunshine has an inverse regression coefficient; (4) season shows no relationship yet sunscreen shows an inverse relationship with vitamin D.

The positive regression coefficient of BMI category obese and vitamin D levels being lower in persons with higher BMI is puzzling. It may be that the number of persons in the category of high BMI is small enough that it does not affect the regression coefficient. A curvilinear relationship may be another explanation. We considered the possibility of illness in the large BMI group. We also considered outliers disturbing the relationship; however, the bubble plots did not demonstrate severe outliers. This may be a finding due to chance; however, it is worth noting that the size of this group is larger than that of other studies.

As both waist circumference and BMI are measures of obesity, one might expect them to have similar relationships with vitamin D. Although waist circumference can vary within levels of BMI, (170) one would further expect that as BMI increases from category to category, waist circumference would increase and thus they would have to affect vitamin D in the same direction. However, waist circumference is a measure of abdominal obesity whereas BMI is a measure of general obesity. Collinearity between BMI and waist circumference was borderline at 69%. This is less than the 80% threshold where collinearity is regarded as "serious", meaning that the variability in each is only partially accounted for by the variability in the other, so that BMI and waist circumference have partially separate effects. (170A) It is possible that adipose tissue interacts differently with vitamin D depending on body compartment (abdominal/visceral versus subcutaneous). As Table 3 shows, the published regression

coefficients between vitamin D and BMI are highly variable. It may be the relationship is not linear, with different studies investigating different components of the range of variability in measures of obesity and vitamin D, or is affected by the size of subgroups such as the underweight. The variation in magnitude of association may also have been affected by publication bias, selection bias and differences in addressing confounding in the published studies.

The expected positive relationship between summer sun exposure and vitamin D level would likely be seen had uv dosimeters been used instead of self reporting. Indeed, cumulative solar ultraviolet radiation prior to blood draw was positively associated with vitamin D level in the CHMS. (171)

6.2C Selection bias

Selection bias may theoretically occur during recruitment or may be due to incomplete participation in the collection and analysis of exposure or biological specimens. In consequence, respondents and non-respondents may differ in a systematic way. Selection bias can be overcome with a high participation rate. The CHMS used various methods to minimize non-response including introductory letters and brochures, multiple contact times and personnel, and multiple languages (154). Moreover, clinic respondents were found to be similar to household questionnaire respondents according to region, whether the dwelling was detached or not, collection site, age group, marital status, household size, education, income, stress level, quality of life, frequency of seeing a dental professional, having a regular medical doctor, smoking, alcohol consumption, taking prescription medication in the past month, job status, body mass index class and indicators of health such as cognition, dexterity, emotional

problems, hearing problems, disability levels, mobility trouble, pain and vision. (154) This suggests that selection bias is not a major concern. Further, although the number of 20 to 39 year olds living with children is overestimated in the CHMS due to the selection method, it does not lead to bias in the overall results. (154)

To determine if the presence of obesity affected individuals decision to participate in fitness measurements, obesity estimates were compared with the 2008 Canadian Community Health Survey (CCHS), which did not include any direct measurements of participants. For adults aged 20 to 69 years, the estimated prevalence of obesity was similar in the two studies: 25.4% in CCHS data and 24.3% in CHMS data suggesting the presence of direct measurements did not affect adults participation and further suggesting that selection bias Is unlikely to have impacted the results of this study. (31) For 12 to 19 year olds, the prevalence of overweight/obesity was 30.8 % in the 2008 CCHS and 28.2% in the CHMS suggesting the presence of direct measurements may affect children's participation. (32)

6.2D Measurement bias

25(OH)D assay using Liason25-hydroxyvitamin D TOTAL assay by Diasorin has been shown to be relatively consistent between laboratories. (36) However, the Liason assay does not distinguish between vitamin D3 and vitamin D2. Vitamin D3 is obtained largely through skin synthesis and is more potent at maintaining vitamin D levels than vitamin D2, which is obtained through supplementation.

BMI measures overweight or excess weight relative to height. BMI is not able to distinguish between fat free or lean mass and fat mass. Studies show a sensitivity of 40 to 50% and specificity of 90% when compared to a gold standard diagnosis of obesity

such as dual energy X-ray absorptiometry. (81) As sensitivity decreases the number of false negatives increases. A sensitivity of 50% indicates those not labeled as obese may in fact have excess adiposity (81) This misclassification would act to move the results towards the null.

BMI also differs by age and ethnicity. Older adults are shorter and have less lean mass than younger adults. Distribution of body fat also changes with age and there is more abdominal fat and less subcutaneous fat. For a given BMI, some Asians have a higher percentage of body fat than whites. (172)

However, despite its limitations, BMI is a convenient measure and is the standard way to measure adult obesity in a population. BMI has been recommended for use in diagnosing obesity in children. (173)

Other measures of body composition also have limitations. Skin fold thickness is difficult to measure, poorly reproducible and not recommended in obese persons. (173, 174) Skin fold thicknesses may be affected by differences in fat patterns among different races. Gold standard measurements are overly expensive to use on a sample of this size. Bioelectrical impedance and dual energy X-ray absorptiometry may have large errors when used to measure children. (175, 176)

Self-report of food intake has the potential for bias (systematic error) and random error. Frequency of milk or fish intake, not amount of milk, fish, or vitamin D was obtained. Questions concerning cottage cheese, yogurt and ice cream intake were included in the CHMS; however, dairy products other than milk were not considered in this study because they are not substantial sources of vitamin D. Milk and milk products

contribute almost 50% of dietary vitamin D in Canada (177) Frequency of fish intake was measured; however this may not be equivalent to actual oily fish intake.

Sun exposure was determined by reported time spent outside and not measured with a UV dosimeter. Self-reported sun exposure diaries have been shown to agree with concurrent UV dosimeter readings. (178, 179) This may or may not be true for self-reported sun exposure in the CHMS as there may have been a significant time delay between actual summer time exposure and self-reporting (up to 6 months for some participants) and face-to-face interviews may lead to social desirability bias. "Sun holidays" (travel to warmer latitudes with stronger light) and indoor UV tanning bed use were not recorded but are unlikely to have a large effect at a population level.

Skin pigmentation was not measured. Self-reported white versus not white ethnicity was used as a proxy. This may lead to a misclassification of persons for instance, vitamin D levels are known to be different in Hispanic Americans compared to non-Hispanic white Americans. Misclassification of ethnicity would attenuate the relationship towards the null.

Any supplement use was used as a proxy for vitamin D consumption. The CHMS asks 3 yes/no questions concerning medication use: MEDD100A prescription use, MEDD200A over the counter use, and MEDD300A use of health products like vitamins or herbal remedies (Appendix Two). In the CHMS, thirty-four percent of participants reported using vitamins, herbals or supplements while thirty percent of the participants reported that they actually took vitamin D. (180) There was no difference in supplement use between white and non-white Canadians. (180)

6.2E Unresolved confounding

Several variables known to affect vitamin D status were not considered in the current study due either to lack of information in the survey or complex analysis required and low likelihood of importance at a population level. Travel to lower latitudes and indoor tanning are associated with vitamin D levels and were not evaluated in the CHMS. Medications which alter vitamin D metabolism such as anticonvulsants and corticosteroids were not taken into account in the current study. Chronic diseases such as malabsorption syndromes were not considered in the current study due to the low expected prevalence of such syndromes. Outdoor exercise was not considered and will be discussed further. Although the CHMS included self reported physical activity index and accelerometer data, neither source of information specifically addressed outdoor physical activity. There may be other unmeasured confounders. The effect of unmeasured confounders remains unknown but is probably low at a population level.

Scragg and Camargo showed the location of physical activity (outdoors) and the frequency, rather than the intensity, are related to vitamin D status. (121) Vigorous physical activity was positively associated with vitamin D in 4723 persons in a multinational study. (181) In one study of elderly Australians (27 S), physical activity was found to be the strongest positive predictor of vitamin D. (120) A study of 559 adolescents age 14 to 18, in Georgia, USA, (30 – 35 N) showed white ethnicity and summer season were positively associated with vitamin D. Fat mass was inversely associated and total physical activity was positively associated with vitamin D. (119) A study of 323 Chinese female adolescents in winter (39 N) showed BMI, milk intake,

participation in organized sports & total physical activity were positively associated with vitamin D status (107). The relationship between physical activity and sunshine was not explored in the Chinese study. Physical activity was a significant positive independent co-variate of vitamin D status in a cross sectional study of 307 adolescents in Boston (42 N). (115) Positive association with hours playing outside per week was seen with vitamin D in the Belgian arm of the Identification and prevention of dietary and lifestyle induced health effects in children and infants study (IDEFICS) (50 N) (116) A relationship was seen between low vitamin D status and sedentary activity in a Danish study of 6784 persons (56 N). (182) Within NHANES 2001-2004, a sample of 6275 children under the age of 21 showed > 4 hours of television, video, or computers per day was associated with low vitamin D. (183)

6.3 Results within the context of literature

The current study found 8% of variation in vitamin D accounted for by all measured variables (Table 6). McCullough found 30% of the variation in vitamin D concentrations accounted for. Half of this was seasonal effects in the McCullough study. (181) Season was not statistically significant in the current study. There may have been significant differences in the populations studied. The McCullough study included 4723 controls from the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers with participants from USA, Finland and China. 72% were white and the majority was over 50 years of age. In Finland and China food is not fortified with vitamin D. A Vietnamese twin study has shown up to 70% of the variation in vitamin D concentrations in winter was explained by heritable factors. (184)

6.3A BMI

In a previous examination of CHMS data, BMI and waist circumference were not considered. (3) Reports of BMI and waist circumference being associated with vitamin D are common but not universal and there is significant variability in other variables included in the model.

Adults (> 18 years) – Our finding that the obese / obese I category of BMI is positively related to vitamin D is not supported by the majority of the literature where an inverse relationship is found. In a multinational study of 4723 adults without cancer, statistically significant positive correlates of vitamin D included male sex, summer blood draw, vigorous physical activity, vitamin D intake, fish intake, multivitamin use and calcium supplement use. Significant inverse correlates were **BMI**, winter and spring blood draw, history of diabetes, sedentary behavior, smoking and black ethnicity. (181) In 153 women in Sherbrooke, Quebec, (45 N), **BMI** was inversely associated with vitamin D while travel to warmer climate and oral contraceptive use were positively associated with vitamin D (15) In the Third Generation Framingham Heart Study, an analysis of 3890 adults showed vitamin D was inversely associated with winter season, **waist circumference**, serum insulin, **BMI** and smoking status. (80) Skin tone, fish consumption, milk intake, sun exposure, tanning bed use, and nutritional supplement use were found to be independent positive predictors of vitamin D status. (16) In NHANES data from adults in the 2005 to 2006 cycle showed being from a non-white race, not college educated, **obese**, having low HDL cholesterol, poor health and no daily milk consumption were all significantly, independently associated with vitamin D deficiency, ($p<0.05$). (185) In the population based Canadian Multicentre Osteoporosis

Study (CaMos), n=1912, winter and spring season, **BMI >=30**, non white ethnicity and lower vitamin D supplementation were associated with low vitamin D status. (186) In 2621 controls, predictors of low vitamin D status were low vitamin D intake, **BMI >=30** kg/m^2, physical inactivity and low milk and calcium supplement intake. (187) In a study of 538 white Dutch adults (52 N) **lower body fatness**, more time spent on outdoor physical activity and use of fortified margarine products, fatty fish and vitamin D containing supplements were associated with better vitamin D status. Older age and female sex were associated with substantially worse vitamin D status. (188)

Conversely, an examination of 405 elderly Quebeckers (46 N) found vitamin D was not associated with BMI or physical activity, education, perception of income, and smoking status. Summer season and supplement use were strong independent positive determinants of vitamin D. (13)

Children and adolescents (<18 years) - Similarly, the literature shows an inverse relationship with BMI in adolescents and children. In a study of adolescents using NHANES III, nonwhite ethnicity, age, measured **weight**, region of the US, urban v rural, income and education were independent predictors of low vitamin D. Income was not an independent predictor after adjustment for all variables. (76) Ethnicity and season were predictive of vitamin D. **Total fat mass** was inversely associated and vigorous physical activity was positively associated with vitamin D. (119) Examination of 307 adolescents in Boston (42 N) showed summer season, white ethnicity, milk and physical activity were positive predictors of vitamin D while juice consumption and **BMI** and were negative predictors of vitamin D. Multivitamin use was confounded with ethnicity. Interaction between milk and season was found with milk being significant during

winter and spring but not summer and fall. (115) In a study of 64 obese adolescents, in the multivariate model, older age, puberty, higher value of **percentage of body fat** and the presence of *acanthosis nigricans* were all inversely associated with vitamin D. Summer season of blood draw positively correlated with vitamin D. (189) (*Acanthosis nigricans* is hyperpigmentation of the skin in body folds. It is associated with obesity and endocrinopathies such as thyroid disorders and diabetes.) A study of 382 children in the northeast USA showed vitamin D was inversely correlated with greater fat mass and higher **BMI** in crude analysis. Multivariate analysis showed older age, black ethnicity, wintertime study visit and total daily vitamin D intake < 200 IU = 5 µg were associated with low vitamin D concentrations. (190) A study of 237 Black and White American children showed nonwhite race, winter season, pubertal status and **visceral adipose tissue** were inversely associated with vitamin D status. (191) A study of 85 children in Philadelphia (39 N) showed older age, **higher BMI-Z** score and black ethnicity were inversely associated while summer season was positively associated with vitamin D. (192)

In contrast, stepwise multivariate linear regression showed no contribution by age, sex, sexual maturation stage, height, visceral adipose tissue or cardiovascular fitness in adolescents in Southern USA. (119) In a study of 263 school children in Boston, (42 N), BMI was not associated with vitamin D. (193) Some studies have shown no relationship with measured BMI but a relationship with more precise fat measures has been present. (119, 194) One study showed height and whole body surface area related positively to vitamin D. (195)

6.3B Waist circumference

Waist circumference (WC) in CHMS accounted for 1.6% of the variability in vitamin D. WC in the Shea study accounted for 3% of variability in vitamin D. (196) Although this is a small percentage of the variability in vitamin D, waist circumference is clinically important for cardiovascular disease and Metabolic Syndrome. It is an easily applied measure of abdominal obesity that could be used to identify individuals at risk of low vitamin D.

WC has been shown to be inversely associated with vitamin D in multiple studies (Table 3) including the Third Generation Framingham study. (80,197) Increased waist circumference is an indicator of Metabolic Syndrome (including diabetes) and increased serum insulin has also been associated with low vitamin D. (80) As McCullough noted, two systematic reviews and meta analyses have also shown an inverse association between vitamin D status or intake and type 2 diabetes or Metabolic Syndrome. (181, 198, 199)

6.3C Age

Age was not significantly associated with vitamin D in the current study. Age has been found to be a significant co-variate of vitamin D in NHANES children and adolescents (76, 183) although, not in other studies. (119,186) Skin synthesis of vitamin D decreases with age. (200, 201) However, with adequate outdoor physical activity, older persons can maintain adequate vitamin D stores. (121)

6.3D Sex

Sex was not statistically significantly associated with vitamin D in the current study. Sex differences were seen in the likelihood to be vitamin D deficient in children in NHANES 2001-2004. (183) In 1912 adult participants, being overweight, low sun exposure, low intake of vitamin D from milk and supplements and lack of regular activity were associated with low vitamin D in women whereas for men, the interaction between vitamin D supplementation and spring season was associated with vitamin D. (186) In a separate study, vitamin D level was determined by different variables in men and women: milk intake on cereal in men and supplement use and menopausal hormone therapy in women. (133) In NHANES III, among African American women of reproductive age, low vitamin D was associated with milk or breakfast cereal intake less than 3 times per week, no use of supplements, season, urban residence, low BMI and no use of oral contraceptives. (202) NHANES III showed women who were overweight were more likely to have low vitamin D. (203)

6.3E Sun exposure (including ethnicity)

Sunshine, season, sunscreen, and ethnicity can be considered all part of a sun exposure complex. Season was identified as important in multiple papers and yet does not show any statistical significance in the current analysis in the full data set. (13, 16, 80, 115, 119, 181, 186, 204, 205) Within the same category as sun exposure, travel to a warmer climate and tanning bed use have also been shown to be significant. These would be unmeasured confounders in the current study although perhaps unlikely to show a large effect at the population level. (15, 16)

Nonwhite ethnicity was strongly associated with lower vitamin D concentration than white ethnicity. In NHANES data on children collected in 2001-4, Mexican American or non-Hispanic Black ethnicity was significantly associated with the likelihood of being vitamin D deficient. (183) In an analyses of 4495 adults included in NHANES from 2005 to 2006, being Black or Hispanic was significantly associated with vitamin D in a multivariate model. (185) In the Canadian Multicentre Osteoporosis Study, 1912 adults showed non-white ethnicity was associated with lower vitamin D. (186) Both season and ethnicity were independently associated with vitamin D status in multivariate analysis of 307 Boston adolescents (42 N). (115) Low vitamin D was associated with higher visceral adipose tissue in whites and higher subcutaneous adipose tissue in blacks. (206) In addition to the increased melanin pigment requiring increased sun exposure, non-White ethnicity may also be associated with different eating patterns and different sun exposure behavior.

6.3F Milk

Frequency of milk intake was significantly positively associated with vitamin D concentration; however, its regression coefficient was near zero. Drinking fortified milk less than once per week was significantly associated with the likelihood of being vitamin D deficient in children in NHANES 2001 – 2004. (183) In NHANES from 2005 to 2006, investigation of 4495 adults showed not consuming fortified milk products daily was significantly inversely associated with vitamin D in a multivariate model. (185) Smaller studies have shown a similar relationship with milk and juice intake. (115)

6.3G Fish

Frequency of fish consumption is not significantly associated with vitamin D in the CHMS. The lack of association with the frequency of fish intake may be due to self reporting error, eating non-oily fish, or insufficient fish intake compared to other populations such as Scandinavian countries. Fish intake was associated with vitamin D status in the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers (n=4723) which included US, Finnish and Chinese participants. (181) Measured vitamin D was not associated with estimated dietary intake of vitamin D in a Danish study of 6784 persons (56 N). (182)

6.3H Supplement use

As the use of multivitamin supplements increases, vitamin D levels are not increasing. (207) Most commonly used supplements of 400 IU = 10 µg per day only increase serum vitamin D by 7 nmol/L ; thus, most supplement users are not taking enough vitamin D to significantly alter their level. (208) In the CHMS, 70% of supplement users took <= 400 IU/day (180). However, this may be different for elderly who are more likely to take larger doses of supplements for osteoporosis treatment. In the CHMS, 3% took > 1000 IU of vitamin D and were largely older females. (180) Lower vitamin D supplementation was associated with lower vitamin D status in the Canadian Multicentre Osteoporosis study, n=1912. (186) Elderly blacks and whites who did not consume a multivitamin were more likely to have low vitamin D in the Health, Aging & Body Composition study, n=2581. (209)

A variety of chronically used medications were found to be associated with low vitamin D in the Longitudinal Aging Study Amsterdam, n=2037 (52 N) (210)

Polypharmacy and low vitamin D levels may be confounded with inadequate dietary intake in the frail elderly.

6.3 I Socioeconomic variables

Household income but not education was associated with vitamin D in the current study. Perception of income and smoking status were not associated with vitamin D among 405 elderly Quebeckers. (13) However, in NHANES III, a study of adolescents showed that nonwhite ethnicity, region of the US, urban v. rural, income and education were independent covariates of vitamin D deficiency. Income did not remain significant in multivariate analysis. (76) In NHANES from 2005 to 2006, study of 4495 adults showed that no college education and not being in a good health status were significantly inversely associated with vitamin D in a multivariate model. (185) In the HUNT study (Nord-Trøndelag Health Study), education, social benefits and economic difficulties were important covariates of low vitamin D (n=2460). (128)

6.3J Smoking

Ex-smoking status was inversely associated with vitamin D levels in some groups in the current study. A relationship between smoking and vitamin D has been noted in some literature (not others) but the underlying reason has not been postulated. (13, 80, 128, 181, 182)

6.4 Conclusion

BMI was positively associated and waist circumference was inversely associated with vitamin D levels in the CHMS. An association between vitamin D and other covariates is also present. Frequency of milk intake was positively associated with

vitamin D level. Nonwhite ethnicity was associated with lower vitamin D levels than white ethnicity.

Significant differences were seen between this study and the literature. It is possible that these differences were due to differences in populations studied ie: rates of supplementation, fortification, or differences in ethnicity. CHMS is a large survey with over 5000 respondents and objective measurements which would lend credence to these findings. However, concerns with internal validity and contradictions suggest these findings, particularly the positive relationship with BMI and the inverse relationship with sunshine, merit further investigation by (1) seeking to replicate this work with a second nationally representative sample (Cycle Two of the CHMS); (2) combining data from the two cycles to have greater stability of estimates in modeling, addressing the limitation of the clustered nature of the data; and (3) conducting other types of studies such as cohort or randomized controlled trials, as outlined below.

6.5 Future directions of research

Further work may be done with the current sample including examination of skinfolds in the normal weight group, self reported physical activity and accelerometer data. Combination with Cycle Two (2009 – 2011) or NHANES will allow verification of these findings in a second nationally representative data set with more power to examine subgroups such as the underweight. Future work may determine change in vitamin D status of Canadian population over time. (128, 213, 214) Other types of studies may be conducted to determine the relationship between vitamin D and BMI or waist circumference, for example, longitudinal work within the Ontario Health Study or randomized controlled trials.

6.6 Significance

Understanding the interrelationships of vitamin D, BMI and waist circumference will inform clinical practice and research. (181) Both obesity and low vitamin D are important clinically, common, and increasing in prevalence. Hypertension and cancer might involve both obesity and vitamin D causal pathways. (211) Increasing vitamin D intake and decreasing abdominal obesity are interventions to increase vitamin D levels that do not involve sun exposure. (187) The widespread presence of suboptimal vitamin D in a population that consumes fortified milk and margarine supports increasing fortification, types of food fortified or winter supplementation. A daily intake of 1400 IU = 35 µg is needed to maintain vitamin D levels above 80 nmol/L in 90% of a healthy adult population. (212) Physicians can target vulnerable groups including non-white ethnic groups and the abdominally obese for monitoring and supplementation of vitamin D.

7. Appendix One

```
*saved as G:\My SAS Files\9.3\Program17;

options nofmterr;

*LOADING FULL DATA;

libname gsas 'g:\sas';
data gsas.full;
set 'z:\data\sas\english\hclsup_e';
run;



*LOADING MEDICATION DATA;

libname gsas 'g:\sas';
data gsas.medication;
set 'z:\data\sas\english\med_e';
run;

*LOADING WEIGHT DATA:

libname gsas 'g:\sas';

data gsas.weight;

set 'z:\bootstrp\data\sas\wgt_acmo';

run;


*MERGING DATA FILES;

proc sort data = gsas.full;
by clinicid;
run;

proc sort data = gsas.activity;
by clinicid;
run;

proc sort data = gsas.medication;
by clinicid;
run;

data gsas.mergedfile;
merge gsas.full gsas.medication gsas.weight;
by clinicid;
run;


data gsas.mergedfile2;
set gsas.mergedfile;
if lab_vitD=. then delete;
```

```
run;


*SETTING VARIABLE NAMES;

data test;
set gsas.mergedfile2;

age=.;
age=clc_age;


drug1=.; *any prescription use;
if medd100A = 1 then drug1 = 1;
if medd100A = 2 then drug1 = 0;

drug2=.; *any over the counter use;
if medd200A = 1 then drug2 = 1;
if medd200A = 2 then drug2 = 0;

drug3=.; *any supplement or herbal;
if medd300A = 1 then drug3 = 1;
if medd300A = 2 then drug3 = 0;

drugs=.;
if drug1 =1 then drugs=1;
else if drug2 = 1 then drugs = 1;
else if drug3 = 1 then drugs = 1;
else drugs=0;


bmicat = .;
if hwmdbmiA = 1 or hwmdbmik =1then bmicat = 1; *under;
else if hwmdbmik = 2 or hwmdbmia=2 then bmicat = 0; *normal;
else if hwmdbmik =3   or hwmdbmia = 3   then bmicat = 2;
*over&obese;
else if hwmdbmik = 4 or hwmdbmia = 4 then bmicat=2;

if bmicat=1 then newbmicat1=1;
else if bmicat ne . then newbmicat1 = 0;
if bmicat=2 then newbmicat2 = 1;
else if bmicat ne . then newbmicat2 = 0;



bmi = .;
if hwmdbmi < 99 then bmi = hwmdbmi;


hischool = .;
if EDUDH04=1 then hischool = 0;
if EDUDH04 = 2 then hischool = 1;
if EDUDH04 = 3 then hischool = 1;
if EDUDH04 = 4 then hischool = 1;


fish=.;
```

```
fish=mfc_16;

income = .;
if inc_22 = 1 then income =0; *<20 0000;
if inc_22 = 2 then income = 1; *>20 000;

milk = .;
milk = mdcd11y;

pregnant=.;
if prs_11 = 1 then pregnant = 1; *yes;
if prs_11 = 2 then pregnant = 0;
if prs_11 = 6 then pregnant = 0;

season=.;
if 1<=v2_mth<=3 then season = 0; *winter;
else if 4<=v2_mth<=9 then season = 1; *summer;
else if 10<=v2_mth<=12 then season = 0;


sex=.;
if clc_sex = 1 then sex = 0; *male;
if clc_sex = 2 then sex =1; *female;

smoke = .;
if smkdsty=6 then smoke = 0; *never;
else if smkdsty = 4 then smoke = 1; *ex;
else if smkdsty = 5 then smoke = 1;
else if smkdsty = 1 then smoke = 2; *current;
else if smkdsty = 2 then smoke = 2;
else if smkdsty = 3 then smoke =2;

if smoke=1 then newsmoke1=1; *ex;
else if smoke ne . then newsmoke1 = 0;
if smoke=2 then newsmoke2 = 1; *current;
else if smoke ne . then newsmoke2 = 0;


sunscreen=.;
if seb_13 <=2 then sunscreen = 1; * sunscreen = always/often;
if seb_13 > = 3 then sunscreen = 0; *sometimes/rarely/never;

sunshine=.;
if SEB_12<=3 then sunshine = 0; *<= 1 hour per summer day;
if SEB_12>= 4 then sunshine = 1;

WC = .;
if HWM_14cm < 900 then wc=hwm_14cm;


white=.;
if sdc_24A=1 then white = 1; *yes;
if sdc_24A = 2 then white =0;

*SETTING UP TERMS FOR INTERACTION SUBGROUP TESTS;

if age<18 then adult = 0;
```

```
else if age >=18 then adult = 1;

if age <12 then child = 1;
else if age >=12 then child = 0;

if  12<age<18 then teen = 1;
else if age >=18 then teen = 0;



run;




*IS THERE COLINEARITY?

proc corr data =  test;
var age drug1 drug2 drug3 drugs activity bmicat srbmicat hischool
fish income milk pregnant sex smoke sunscreen sunshine wc white;
run;


*WHAT DO THE RESIDUALS LOOK LIKE?

Proc reg data=test;
Model lab_vitD = age;
Plot lab_vitD*age r.*p. r.*age;
Run;




*WHAT IS THE UNIVARIATE RELATIONSHIP?


proc surveyreg data = test varmethod = brr;

class income;

model lab_vitD = income / solution;

weight wgt_full;

repweights bsw1-bsw500/df=11;

run;

*DIVIDING THE DATA INTO SUBGROUPS;

data gsas.adult;

set test;

if age<18 then delete;
```

```
run;

data gsas.female;
set test;
where sex=1;
run;

data gsas.male;
set test;
where sex=0;
run;

data gsas.low;
set test;
where bmicat=1;
run;

data gsas.normal;
set test;
where bmicat = 0;
run;

data gsas.high;
set test;
where bmicat = 2;
run;

data gsas.drugs;
set test;
where drug3 = 1;
```

```
run;


data gsas.nodrugs;

set test;

where drug3 = 0;

run;

data gsas.girls;
set test;
if sex = 0 then delete;
if age >=12 then delete;
run;

data gsas.boys;
set test;
if sex = 1 then delete;
if age >=12 then delete;
run;

data gsas.women;
set test;
if sex = 0 then delete;
if age <18 then delete;
run;

data gsas.men;
set test;
if sex = 1 then delete;
if age <18 then delete;
run;

data gsas.teenboys;
set test;
if sex=1 then delete;
where 12<age<18;
run;

data gsas.teengirls;
set test;
if sex =0 then delete;
where 12<age<18;
run;




proc surveyreg data = gsas.adult varmethod = brr;

class income;

model lab_vitD = income /solution;
```

```
weight wgt_full;

repweights bsw1-bsw500/df=11;

run;



*LOOKING FOR MEANS;



proc surveymeans data=test varmethod=brr all;

var lab_vitD;

weight wgt_full;

repweight bsw1-bsw500/df=11;

run;

*IS THERE LEVERAGE;

proc reg data = test;
model lab_vitD = age;
output out=gsas.diagnostics cookd=cookd h=leverage r=resid;
plot lab_vitD*age age*cookd. lab_vitd*cookd. r.*h.;
run;
quit;

proc gplot data = gsas.diagnostics;
bubble resid*leverage=cookd;
run;
quit;



*ARE THERE TWO WAY INTERACTIONS (EFFECT MODIFIERS);

Proc reg;

Class ;

Model lab_vitD= age | drug1 | drug2| drug3 | drugs| activity|
newbmicat1 |newbmicat2| hischool | fish| income| milk | pregnant
| season| sex| newsmoke1 |newsmoke2 | sunscreen| sunshine| wc|
white @2;Run;

*SENSITIVITY ANALYSIS;

data gsas.mergedfile2;
set gsas.mergedfile;
if lab_vitD >150 then delete;
run;
```

8. Appendix Two

MED_Q100A In the past month, that is, from [date last month] to yesterday, did you take any prescription medications? Prescribed medications could include such things as insulin, nicotine patches and birth control (pills, patches or injections).

MED_Q200A In the past month did you take any over-the-counter medications? Over the counter medications could include such things as pain killers, antacids, allergy pills and hydrocortisone creams.

MED_Q300A There are also many health products and herbal remedies such as vitamins, minerals, fish oils and other oils, and botanical or homeopathic preparations which people use to prevent illness or to improve or maintain their health. In the past month did you take any health products or herbal remedies?

Illicit drug use was asked separately and was not considered in this study: IDU_11 Used or tried marijuana, cannabis or hashish, IDU_12 Used prescription drugs for recreational purposes, IDU_13 Used or tried street drugs; IDU_14 Ever injected drugs.

MDC_B11
How often do you drink milk or enriched milk substitutes or use them on cereal? (For example: twice a day, three times a week, once a month)

SEB_R11
The next few questions are about your exposure to the sun.

SEB_R12
For the next questions, think about a typical weekend or day off from work or school in the summer months.

SEB_Q12
About how much time each day do you spend in the sun between 11 am and 4 pm

SEB_Q13
In the summer months, on a typical weekend or day off, when you are in the sun for 30 minutes or more, how often do you use sunscreen?

People living in Canada come from many different cultural and racial backgrounds. Are you:

- SDC_Q24 Interviewer: Read categories to respondent. Mark all that apply.
    1. … White?
    2. … Chinese?
    3. … South Asian (e.g., East Indian, Pakistani, Sri Lankan)?
    4. … Black?
    5. … Filipino?
    6. … Latin American?
    7. … Southeast Asian (e.g., Cambodian, Indonesian, Laotian, Vietnamese)?
    8. … Arab?
    9. … West Asian (e.g., Afghan, Iranian)?

10. … Japanese?
11. … Korean?
12.

- INC_Q22
  Can you estimate in which of the following groups your *household* income falls? Was the total*household* income less than $20,000 or $20,000 or more?
-
- Now, think about *all* salt and freshwater fish you ate, both meals and snacks, at home and away from home. Include fresh, frozen and canned fish of all types, as well as the fish in fish and chips.

  FSF_Q12
  Have you eaten any of the following fish over the past month, that is, from [date one month ago] to today?
  DFS_Q11
  Over the past month, how many times did you eat:
  … [shellfish/fish name]?

  SMK_Q12

At the present time, do you smoke cigarettes daily, occasionally or not at all?

1. Daily
2. Occasionally
3. Not at all

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