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Serum 25-hydroxyvitamin D level in relation to weight change and the risk of weight gain in adults of normal weight at baseline: the Norwegian HUNT cohort study

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ABSTRACT

Objective We sought to investigate the relationship of serum 25-hydroxyvitamin D (25(OH)D) level with weight change and the risk of weight gain in an adult population who had normal weight at baseline and were followed up for 11 years.

Design A population-based prospective cohort study.

Setting Nord-Trøndelag, Norway.

Participants The study included 1501 adults who participated in the second and third surveys of the Nord-Trøndelag Health Study (HUNT2 (1995–1997) and HUNT3 (2006–2008)) and had a normal body mass index ≥18.5 and <25.0 kg/m² at baseline.

Primary and secondary outcome measures Relative weight change (%) was calculated as ((HUNT3 weight–HUNT2 weight)/HUNT2 weight×100). Relative annual weight change (%) was calculated as (relative weight change/follow-up years×100). Clinical weight gain was defined as relative weight change ≥5% over the 11 years, while annual weight gain was defined as relative annual weight change >1.25%.

Methods Multiple regression models were used to estimate adjusted coefficients for the relative annual weight change and risk ratios (RRs) for the risk of clinical weight gain and of annual weight gain.

Results Each 25 nmol/L increase in season-standardised serum 25(OH)D level at baseline was associated with a reduction of 0.05% (95% CI −0.11 to 0.01) for relative annual weight change, a 10% (RR 0.90, 95% CI 0.82 to 0.97) reduced risk of clinical weight gain, and a 19% (RR 0.81, 95% CI 0.65 to 1.00) reduced risk of annual weight gain. A statistically significant trend was evident for the risk of clinical weight gain when 25(OH)D levels were treated as a categorical variable (p=0.006).

Conclusions The findings suggested an inverse association of serum 25(OH)D level with the risk of clinical weight gain in adults who had normal weight at baseline over 11 years' follow-up.

INTRODUCTION

The prevalence of overweight and obesity has increased rapidly in the past several decades, accounting for four million deaths worldwide in 2015 alone.[1][2] Meanwhile, vitamin

Strengths and limitations of this study

► This study was one of the few cohort studies that only followed up adults of normal weight at baseline.

► The 11-year follow-up period allowed us to evaluate the influence of vitamin D on the long-term weight change in the study population.

► We defined the risk of clinical weight gain and the risk of annual weight gain based on cut-off values established in previous research instead of using arbitrary cut-off values.

► The sample size was sufficient to perform stratified analyses by age, sex and leisure time physical activity.

► Residual confounding due to unknown or unmeasured factors cannot be excluded, for instance, information on dietary factors was not collected in the Nord-Trøndelag Health Study 2 Questionnaire.

D deficiency is also a global health issue.[3] There may exist a bidirectional relationship between vitamin D deficiency and obesity. Obese individuals tend to have a lower level of vitamin D compared with normal weight individuals.[4] Possible explanations for this association include volumetric dilution of serum vitamin D levels in obese individuals[5] and sequestration of vitamin D in adipose tissue.[6] It has also been hypothesised that low vitamin D status may contribute to the development of obesity.[7]

Prospective studies on the vitamin D and adiposity association in adults have yielded inconsistent results.[8–12] A 4-year follow-up study of Spanish adults found a significant association between low 25-hydroxyvitamin D [25(OH)D] and an increased risk of obesity.[9] An 11-year follow-up study of young-to-middle-aged Norwegian adults showed a similar association between 25(OH)D and the risk of obesity.[10] However, other studies

found no association of serum 25(OH)D level with body mass index (BMI) change in adult Hispanic and African Americans[8] or with weight change in elderly women.[11] In the latter study, however, women with higher serum 25(OH)D concentrations tended to gain less weight in a subgroup of normal weight at baseline.[11]

There is evidence that adults with normal body weight at baseline tend to experience a greater weight gain than those being overweight or obese.[13] Vitamin D may have a preventive effect on adiposity for individuals of normal weight but no treatment effect for the already overweight or obese individuals.[14–18] Thus, the objective of this study was to investigate the relationship of serum 25(OH)D level with weight change and the risk of weight gain among adults with normal weight at baseline who participated in the Nord-Trøndelag Health Study (HUNT) and were followed up for over 11 years.

METHODS
Study population
HUNT is a large and comprehensive health study in Norway; it has previously been described in detail.[19] Data from the second and third surveys of HUNT, HUNT2 (1995–1997) and HUNT3 (2006–2008) were used for this study. All residents aged ≥20 years in the Nord-Trøndelag region of Norway were invited to participate in each of the surveys. Of the approximately 93 000 individuals (>97% were ethnic Norwegians) invited to participate in HUNT2, 65 229 took part in the study (response rate 70%) and a 10% random sample (n=6613) was selected for measurement of serum 25(OH)D levels. Baseline 25(OH)D levels were available for 6377 participants with sufficient blood sample volume, of which 3671 (57.6%) participated in HUNT3 for an average 11-year follow-up and had complete data on the exposure and outcome variables. The general response rate for the HUNT3 survey was 54%. Among the 3671 participants, those of normal weight at baseline were included in the final analytical sample (n=1501) (figure 1). Normal weight at baseline was defined as having a BMI of ≥18.5 and <25 kg/m² in HUNT2 using the standard WHO cut-off points.[20]

Serum 25(OH)D level in HUNT2 as exposure variable
Blood samples were collected from the HUNT2 participants and stored in −70°C freezers. LIAISON 25-OH Vitamin D TOTAL assay (DiaSorin, Saluggia, Italy) was used to determine baseline serum 25(OH)D levels. This fully automated chemiluminescent immunoassay has a detection range of 10–375 nmol/L and intraassay and interassay coefficients of variation of 4% and 8%, respectively. Because seasonal fluctuations in 25(OH)D levels were expected due to the high-latitude geographical position of Norway (online supplemental figure 1A), a cosinor model based on month of blood draw was used to calculate season-standardised 25(OH)D level (nmol/L) that represents the annual average value of 25(OH)D for each participant. The standardised 25(OH)D levels were highly
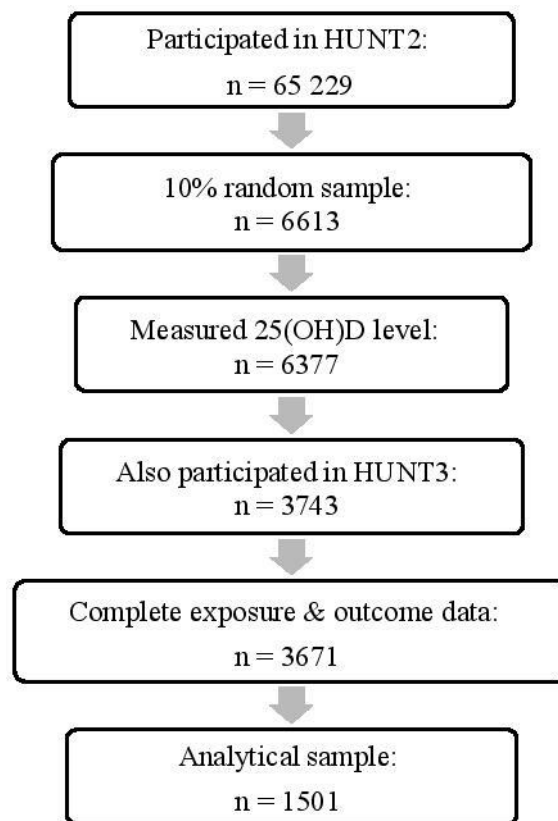
Figure 1 Selection of the study population and analytical sample, Nord-Trøndelag Health Study (HUNT). Analytical sample comprised of participants with normal weight (body mass index ≥18.5 and <25 kg/m²) at baseline and complete data on serum 25-hydroxyvitamin D level (25(OH)D), height and body weight.

correlated with the measured 25(OH)D levels (correlation coefficient=0.96, online supplemental figure 1B). This model was based on the 10% random sample of the HUNT2 participants who had available serum 25(OH)D levels (n=6377). It has been suggested that use of annual average 25(OH)D levels is a more effective method of controlling for season of blood draw than inclusion of season in adjusted models because it appears to minimise mean squared error.[21] The season-standardised 25(OH)D levels were used as a continuous variable and were also treated as a categorical variable classified by the following cut-off values (nmol/L):<30.0, 30.0–49.9, 50.0–74.9 and ≥75.0. These categories were established based on the Institute of Medicine of the National Academies.[22]

Covariates
Information on covariates at baseline was collected via questionnaires. Smoking status was categorised as never, former and current smokers. Education was categorised as <10, 10–12 and ≥13 years. The presence of economic difficulties (yes/no) was defined using the following question: 'During the last year, has it at any time been difficult to meet the costs of food, transportation, housing and such?' Alcohol consumption was categorised as 0 (abstainer), 1–4 and ≥5 times/month. Leisure time

physical activity level was classified into four categories based on reported average hours of light (no sweating or not being out of breath) and hard (sweating or out of breath) physical activity: inactive, low, moderate or high. Categorisation of physical activity in the HUNT study has been described in detail previously.[23] Total sitting time was used as a marker for sedentary lifestyle and was categorised as <4, 5–7 and ≥8 hours/day. Chronic illness was a variable generated from responses to several questions on major somatic diseases (Have you had or do you have any of the following diseases: myocardial infarction (heart attack)/angina pectoris (chest pain)/stroke (brain haemorrhage)/diabetes/cancer? yes/no). Separate 'unknown' categories were generated and included in primary analyses for participants with missing information for smoking status, education, economic difficulties, alcohol consumption, leisure time physical activity, sedentary lifestyle and chronic illness. These categorisations have been used in previous HUNT publications.[23–25]

Outcome variables

Measurement of body height and weight were performed at clinical examinations in both HUNT2 and HUNT3 by trained health professionals. Participants wore light clothing and no shoes during the measurements. Height was measured to the nearest 1.0 cm and weight to the nearest 0.5 kg. Quality assurance was performed to check for outliers for the measurements of weight and height. The height variable was checked between the HUNT surveys and there were no obvious errors. We calculated relative weight change instead of absolute weight change to take the baseline body weight into account. Relative weight change (%) was calculated as [(HUNT3 weight–HUNT2 weight)/HUNT2 weight×100] (online supplemental table 1). Relative annual weight change (%) was calculated as (relative weight change/follow-up years×100). Clinical weight gain was defined as a relative weight change ≥5% over the 11-year follow-up period. Annual weight gain was defined as a relative annual weight change >1.25%. These cut-off values were established in previous publications.[26 27] Annual weight gain redefined as a relative annual weight change >1.5% and absolute weight change were also used as outcomes for sensitivity analyses.

Statistical analysis

Descriptive statistics were calculated for the analytical sample of the normal weight adults (n=1501) and stratified by the categories of serum 25(OH)D level for the following covariates at baseline: age, sex, smoking status, education, economic difficulties, alcohol consumption, leisure time physical activity, total sitting time and chronic illness. All covariates were retained in adjusted models due to plausible confounding relationships with the exposure and outcome variables. Differences in distribution of baseline covariates between the 25(OH)D level categories were assessed using analysis of variance for continuous variables and the Pearson χ^2 test for categorical variables.

Multivariable linear regression was used to evaluate the association between baseline 25(OH)D levels and the relative annual weight change between HUNT2 and HUNT3; crude and adjusted coefficients and 95% CI were estimated. Poisson regression with robust error variance was used to investigate the relationship between baseline serum 25(OH)D levels and risk of clinical weight gain as well as risk of annual weight gain as they were common outcomes[28]; crude and adjusted risk ratios (RRs) and 95% CIs were estimated. The linear association was tested by treating serum 25(OH)D categories as an ordinal variable versus as a categorical variable using the likelihood ratio test (LRT). As the LRT did not show deviation from a linear association with the relative annual weight change (p=0.90), the lowest serum 25(OH)D category (<30.0 nmol/L) was used as the referent group and the 25(OH)D level was also used as a continuous variable in the analyses.

Effect modification by age, sex and leisure time physical activity for the risk of clinical weight gain was evaluated using the Wald test. Age and physical activity were categorised as dichotomous variables with similar numbers of participants in each stratum to maintain statistical power. Age was categorised as <45 and ≥45 years, and the four physical activity categories were collapsed into less active (physical activity level being inactive or low) and more active (physical activity level being moderate or high) groups. All statistical analyses were conducted using Stata/MP V.15.1 (StataCorp LP, College Station, Texas).

Patient and public involvement

There was no patient or public involvement in the design or data analysis of this study.

RESULTS

Study participants were on average 43.4 years of age at baseline (table 1). There were more women (61.4%) than men (38.7%). The distribution of participants in the four baseline serum 25(OH)D categories was 8.1% in <30.0 nmol/L, 41.5% in 30.0–49.9 nmol/L, 41.8% in 50.0–74.9 nmol/L and 8.6% in ≥75.0 nmol/L. Higher serum 25(OH)D levels were associated with older age, higher education and higher physical activity as well as being male and never smokers compared with 25(OH)D<30.0 nmol/L.

In general, a lower mean of relative annual weight change was present in all categories with higher 25(OH)D levels compared with the <30.0 nmol/L category (table 2). Every 25-unit increase in serum 25(OH)D was associated with a reduction of relative annual weight change by 0.05% (95% CI −0.11 to 0.01), which corresponds to a reduction of 369 g in absolute weight change during the 11 years' follow-up for a person with the average weight of 67 kg in HUNT2. Similar but weaker associations were observed for absolute weight change compared with the relative annual weight change (online supplemental table 2).

Table 1 Baseline characteristics of subjects overall and by baseline serum 25(OH)D levels in the HUNT2 study, 1995–1997

| Characteristic | Overall N=1501 | Baseline seasonal-standardised serum 25(OH)D level (nmol/L) | | | | P value* |
		<30.0 n=121	30.0–49.9 n=623	50.0–74.9 n=628	≥75.0 n=129	
Weight (kg)	66.9±8.5	66.6±8.6	67.0±8.5	66.8±8.4	67.1±8.6	0.92
Weight range (kg)	41.5–96.0	48.0–86.0	41.5–96.0	46.0–91.5	46.5–87.5	
Age (years)	43.4±13.2	39.5±12.0	43.0±12.2	44.2±14.0	45.3±14.6	<0.001
Sex						0.04
Male	579 (38.7%)	37 (30.6%)	249 (40.0%)	232 (36.9%)	61 (47.3%)	
Female	922 (61.4%)	84 (69.4%)	374 (60.0%)	396 (63.1%)	68 (52.7%)	
Smoking status						0.004
Never	689 (45.9%)	47 (38.8%)	272 (43.7%)	308 (49.0%)	62 (48.1%)	
Former	332 (22.1%)	22 (18.2%)	124 (19.9%)	150 (23.9%)	36 (27.9%)	
Current	461 (30.7%)	50 (41.3%)	218 (35.0%)	163 (26.0%)	30 (23.3%)	
Unknown	19 (1.3%)	2 (1.7%)	9 (1.4%)	7 (1.1%)	1 (0.8%)	
Education (years)						<0.001
<10	377 (25.1%)	36 (29.8%)	170 (27.3%)	147 (23.4%)	24 (18.6%)	
10–12	522 (34.8%)	40 (33.1%)	214 (34.3%)	217 (34.6%)	51 (39.5%)	
≥13	573 (38.2%)	39 (32.2%)	222 (35.6%)	259 (41.2%)	53 (41.1%)	
Unknown	29 (1.9%)	6 (5.0%)	17 (2.7%)	5 (0.8%)	1 (0.8%)	
Economic difficulties						0.02
No	911 (60.7%)	60 (49.6%)	359 (57.6%)	406 (64.6%)	86 (66.7%)	
Yes	333 (22.2%)	34 (28.1%)	154 (24.7%)	123 (19.6%)	22 (17.1%)	
Unknown	257 (17.1%)	27 (22.3%)	110 (17.7%)	99 (15.8%)	21 (16.3%)	
Alcohol consumption (times/month)						0.001
0 (abstainer)	397 (26.5%)	46 (38.0%)	172 (27.6%)	153 (24.4%)	26 (20.2%)	
1–4	814 (54.2%)	51 (42.1%)	350 (56.2%)	345 (54.9%)	68 (52.7%)	
≥5	195 (13.0%)	13 (10.7%)	65 (10.4%)	89 (14.2%)	28 (21.7%)	
Unknown	95 (6.3%)	11 (9.1%)	36 (5.8%)	41 (6.5%)	7 (5.4%)	
Leisure time physical activity						<0.001
Inactive	278 (18.5%)	28 (23.1%)	132 (21.2%)	104 (16.6%)	14 (10.9%)	
Low	289 (19.3%)	17 (14.0%)	124 (19.9%)	121 (19.3%)	27 (20.9%)	
Moderate	413 (27.5%)	25 (20.7%)	165 (26.5%)	185 (29.5%)	38 (29.5%)	
High	159 (10.6%)	7 (5.8%)	51 (8.2%)	81 (12.9%)	20 (15.5%)	
Unknown	362 (24.1%)	44 (36.4%)	151 (24.2%)	137 (21.8%)	30 (23.3%)	
Total sitting time (hours/day)						0.05
<4	417 (27.8%)	26 (21.5%)	172 (27.6%)	179 (28.5%)	40 (31.0%)	
5–7	375 (25.0%)	33 (27.3%)	139 (22.3%)	172 (27.4%)	31 (24.0%)	
≥8	437 (29.1%)	31 (25.6%)	184 (29.5%)	182 (29.0%)	40 (31.0%)	
Unknown	272 (18.1%)	31 (25.6%)	128 (20.5%)	95 (15.1%)	18 (14.0%)	
Chronic illness						0.59
No	1389 (92.5%)	112 (92.6%)	576 (92.5%)	581 (92.5%)	120 (93.0%)	
Yes	72 (4.8%)	5 (4.1%)	33 (5.3%)	31 (4.9%)	3 (2.3%)	
Unknown	40 (2.7%)	4 (3.3%)	14 (2.2%)	16 (2.5%)	6 (4.7%)	

Data are given as number of subjects (column percentage) or mean±SD; percentages (%) may not add up to 100% due to rounding.
*Comparisons between baseline serum 25(OH)D level categories; p values reported using Pearson χ^2 tests for categorical covariates or analysis of variance tests for continuous covariates.
HUNT2, Nord-Trøndelag Health Study 2; 25(OH)D, 25-hydroxyvitamin D.

Overall, the risk of clinical weight gain was 47.2% and the risk of annual weight gain was 13.4% for the 11-year study period (table 3). There was an inverse association of the other 25(OH)D categories with the risk of clinical weight gain and the risk of annual weight gain compared with the 25(OH)D <30.0 nmol/L category, and a statistically

Table 2 Association between baseline seasonal-standardised serum 25(OH)D level and relative annual weight change from 1995–1997 to 2006–2008

Seasonal-standardised serum 25(OH)D (nmol/L)	Participants (n)	Crude model		Adjusted model*	
		Mean (%)	Coefficient (95% CI) (%)	Mean (%)	Coefficient (95% CI) (%)
Categorical					
<30.0	121	0.60	0 (reference)	0.50	0 (reference)
30.0–49.9	623	0.51	−0.09 (−0.25 to 0.07)	0.49	−0.01 (−0.16 to 0.14)
50.0–74.9	628	0.40	−0.20 (−0.35 to −0.04)	0.43	−0.07 (−0.22 to 0.09)
≥75.0	129	0.34	−0.26 (−0.46 to −0.06)	0.40	−0.10 (−0.29 to 0.10)
P for trend			0.001		0.12
Continuous	1501		−0.11 (−0.17 to −0.05)		−0.05 (−0.11 to 0.01)

For categorical 25(OH)D, 'mean' is the mean value of relative annual weight change in percentage in the 25(OH)D categories; 'coefficient' is the mean difference in the relative annual weight change in percentage among the other 25(OH)D categories compared with the reference category (<30.0).

For continuous 25(OH)D, 'coefficient' is the difference in the relative annual weight change in percentage per 25 nmol/L increase in 25(OH)D.

*Adjusted for age, sex, smoking status, education, economic difficulties, alcohol consumption, leisure time physical activity, total sitting time and chronic illness.

25(OH)D, 25-hydroxyvitamin D.

significant trend was evident for the risk of clinical weight gain (p=0.006). The adjusted RR for 25(OH)D ≥75.0 nmol/L versus <30.0 nmol/L was 0.77 (95% CI 0.59 to 1.01) for the risk of clinical weight gain and was 0.52 (95% CI 0.26 to 1.07) for the risk of annual weight gain. Per 25 nmol/L increase in the 25(OH)D level was associated with a 10% (RR 0.90, 95% CI 0.82 to 0.97) reduced risk of clinical weight gain and a 19% (RR 0.81, 95% CI 0.65 to 1.00) reduced risk of annual weight gain. In one of the sensitivity analyses, 132 (8.8%) individuals were defined as a relative annual weight change >1.5%. Similar results were demonstrated for serum 25(OH)D level as a categorical or continuous variable associated with the risk of relative annual weight change >1.5% (online supplemental table 3).

We also evaluated the association between serum 25(OH)D as a continuous variable and the risk of clinical weight gain stratified by age, sex and leisure time physical activity (table 4). The risk of clinical weight gain over the 11-year follow-up period was higher among participants <45 years of age (58.2%) than older counterparts (32.8%), and in males (49.9%) than females (45.4%). However, the risk was not different between those who were less active and those who were more active. As shown in table 4, a significant reduction in the risk of clinical weight gain per 25 nmol/L increase in serum 25(OH)D was observed among female participants (RR 0.84, 95% CI 0.75 to 0.94) but not in males (p for interaction=0.04). Each 25 nmol/L increase in serum 25(OH)D was associated with a 18% reduced risk of clinical weight gain among participants who were less active, but there appeared no association for those who were more active (p for interaction=0.07). Age did not modify the association between 25(OH)D and the risk of clinical weight gain (p for interaction=0.67).

DISCUSSION

Based on data from 1501 adults who had normal weight at baseline and were followed up for 11 years, we found that each 25-unit increase in serum 25(OH)D level was associated with a small reduction of 0.05% in relative annual weight change, a 10% reduced risk of clinical weight gain, and a 19% reduced risk of annual weight gain. The associations showed a statistically significant trend for the risk of clinical weight gain when serum 25(OH)D levels were used as a categorical variable. The association between 25(OH)D and risk of clinical weight gain seemed to be modified by sex and leisure time physical activity but not by age.

Several prospective studies have investigated the association of serum vitamin D level with adiposity in adults and shown inconsistent results.[8–12] The inconsistencies among studies could be partly explained by differences in choice and categorisation of exposure and outcome variables. Different cut-off values were used to categorise the vitamin D groups[9–11] or vitamin D level was treated solely as a continuous variable.[8 12] The outcome variables varied including the risk of obesity,[9 10] change in BMI, body weight and waist circumference,[8 9 12] or alternative adiposity measures.[8] Additionally, difference in follow-up duration may contribute to the discrepancy among studies. Vitamin D might have a preventive effect on adiposity but no treatment effect on overweight and obesity.[14–18] Therefore, our study only selected adults who had a normal weight at baseline. Our findings of the inverse associations in adults of normal weight were consistent with those of a previous study of 4659 elderly women; in that study, women with higher baseline 25(OH)D level gained less weight over 4.5 years of follow-up in a subgroup of predominately normal weight at baseline.[11]

Table 3 Association between baseline seasonal-standardised serum 25(OH)D level and risk of clinical weight gain and annual weight gain from 1995–1997 to 2006–2008

Seasonal-standardised serum 25(OH)D (nmol/L)	Clinical weight gain				Annual weight gain			
	Cases	Risk	Crude RR (95% CI)	Adjusted RR* (95% CI)	Cases	Risk	Crude RR (95% CI)	Adjusted RR* (95% CI)
Categorical								
<30.0	69	57.0%	1.00 (reference)	1.00 (reference)	25	20.7%	1.00 (reference)	1.00 (reference)
30.0–49.9	319	51.2%	0.90 (0.76 to 1.07)	0.96 (0.81 to 1.14)	91	14.6%	0.71 (0.48 to 1.05)	0.92 (0.62 to 1.37)
50.0–74.9	271	43.2%	0.76 (0.63 to 0.90)	0.85 (0.71 to 1.02)	76	12.1%	0.59 (0.39 to 0.88)	0.83 (0.55 to 1.25)
≥75.0	49	38.0%	0.67 (0.51 to 0.87)	0.77 (0.59 to 1.01)	9	7.0%	0.34 (0.16 to 0.69)	0.52 (0.26 to 1.07)
P for trend			<0.001	0.006			0.001	0.07
Continuous	708	47.2%	0.85 (0.78 to 0.92)	0.90 (0.82 to 0.97)	201	13.4%	0.69 (0.55 to 0.87)	0.81 (0.65 to 1.00)

Clinical weight gain was defined as the relative weight change ≥5% over 11 years between HUNT2 and HUNT3.
Annual weight gain was defined as the relative annual weight change >1.25%.
For continuous 25(OH)D, RR is associated with per 25 nmol/L increase in 25(OH)D.
*Poisson regression adjusted for age, sex, smoking status, education, economic difficulties, alcohol consumption, leisure time physical activity, total sitting time and chronic illness.
HUNT, Nord-Trøndelag Health Study; 25(OH)D, 25-hydroxyvitamin D; RR, risk ratio.

Randomised controlled trials (RCT) have in general shown no effect of vitamin D supplementation on weight change over time.[14–18] These trials have mostly been conducted in overweight or obese individuals. Only one large RCT showed that participants of normal weight who received a daily supplement of calcium and vitamin D experienced significantly lower average annual weight gain and a lower risk of weight gain over 7 years of follow-up.[29] However, it is impossible to isolate the effects of calcium and vitamin D on weight change in this study.

The exact mechanisms by which serum 25(OH)D might affect change in body weight have not been well established. Several plausible pathways have been proposed. High vitamin D and calcium, and the consequent low level of parathyroid hormone, may play a regulatory role in adipocytes by promoting lipolysis and inhibiting lipogenesis.[30 31] High level of vitamin D and calcium may increase whole body fat oxidation and faecal fat excretion. Emerging evidence suggests that vitamin D has a potential to improve insulin sensitivity that would reduce food intake.[30] In addition, in vitro and animal studies have shown that the bioactive form of vitamin D, 1,25-dihydroxyvitamin D can induce mature adipocytes death by apoptosis[32]; in a high-fat diet-induced obesity mouse model, an increased intake of vitamin D is associated with a decreased weight of white adipose tissue due to induction of apoptosis.

Our study demonstrated possible effect modification by sex. Female participants had a 16% reduction in risk of clinical weight gain per 25 nmol/L increase in serum 25(OH)D, whereas there was no association in males. These findings indicated that low vitamin D could be a more important risk factor for long-term clinical weight gain for women than men. Women have been reported to be at increased risk for both vitamin D deficiency and obesity.[3 33] In the current study, 9.1% of women had serum 25(OH)D level <30.0 nmol/L compared with 6.4% in men. A recent Finnish study reported that sufficient vitamin D level (≥50 nmol/L) may be a protective factor for weight gain in men but not in women.[34] This Finnish study, however, included a general population rather than adults of normal weight at baseline. Our finding was consistent with results from a German cohort of older adults in which higher vitamin D status was associated with a lower odds ratio for body fat gain in women but not in men in a 3-year follow-up study.[35]

Our results were also indicative of potential effect modification by leisure time physical activity. Participants who were less active had a 18% reduced risk of clinical weight gain per 25 nmol/L increase in serum 25(OH)D, while the association was much weaker for participants who were more active. These results are consistent with the findings from a previous RCT on vitamin D supplementation.[29] Women taking the vitamin D supplement experienced smaller average annual weight gain in the lowest physical activity group, whereas annual weight gain did not differ between women taking the supplement and placebo who had higher physical activity. Since high level of physical activity is an important preventive factor for weight gain and is associated with elevated serum 25(OH)D,[36 37] it might cancel out the harmful effect of low vitamin D on the risk of weight gain.

Table 4 Association between baseline seasonal-standardised serum 25(OH)D level and risk of clinical weight gain over 11-year follow-up, stratified by age, sex and leisure time physical activity level

	Participants (n)	Cases	Risk	Adjusted RR* (95% CI)	P for interaction
Age (years)					
<45	851	495	58.2%	0.90 (0.82 to 0.99)	0.67
≥45	650	213	32.8%	0.87 (0.72 to 1.06)	
Sex					
Male	579	289	49.9%	0.99 (0.88 to 1.13)	0.04
Female	922	419	45.4%	0.84 (0.75 to 0.94)	
Leisure time physical activity					
Less active	567	280	49.4%	0.82 (0.71 to 0.94)	0.07
More active	572	286	50.0%	0.96 (0.85 to 1.09)	

Clinical weight gain was defined as relative weight change ≥5% over 11 years between HUNT2 and HUNT3.
Less active referred to physical activity level being inactive or low; more active referred to physical activity level being moderate or high.
*Risk ratio per 25 nmol/L increase in 25(OH)D; poisson regression adjusted for age, sex, smoking status, education, economic difficulties, alcohol consumption, leisure time physical activity, total sitting time and chronic illness.
HUNT, Nord-Trøndelag Health Study; 25(OH)D, 25-hydroxyvitamin D; RR, risk ratio.

To our knowledge, this prospective cohort study is one of the few to investigate the relationship of serum 25(OH)D with weight change and risk of weight gain in adults of normal weight. We mainly assessed the relative instead of absolute weight change to take the baseline body weight into account. We also defined the risk of clinical weight gain and the risk of annual weight gain based on cut-off values established in previous research instead of using arbitrary cut-off values.[26 27] The sample size was sufficient to perform stratified analyses by age, sex and leisure time physical activity. Inclusion of comprehensive information on relevant covariates minimised confounding in adjusted models. Use of seasonal-standardised serum 25(OH)D as opposed to adjustment for season of blood draw allowed for minimisation of mean squared error, as mentioned previously.[21] This helped provide more accurate estimates of association measures. Furthermore, the 11-year follow-up period allowed us to evaluate the influence of vitamin D on the long-term weight change in the study population.

There were several limitations related to our study. Data on lifestyle factors were self-reported, which were subject to misclassification. Our analysis did not account for changes in the serum 25(OH)D level or lifestyle factors that might have taken place over the course of follow-up. Although an inverse association of serum 25(OH)D with the risk of weight gain was observed, residual confounding due to missing data of the covariates or unknown or unmeasured factors cannot be excluded. For instance, information on dietary factors was not collected in the HUNT2 Questionnaire. Socioeconomic status can reasonably be used as a proxy for dietary factors due to the observation that diet quality tends to vary by socioeconomic status.[38] Our results would have been confounded if the dietary factors were not associated with any of the covariates adjusted in the models. Thus, caution should be taken when we draw conclusions owing to the possibilities of residual confounding and some of the results at borderline statistical significance. Moreover, based on the estimate size

for relative annual weight change or absolute weight change per 25 units increase in 25(OH)D, the role of vitamin D in weight change is likely far less important than dietary factors and physical activity. Additionally, in the stratified analysis, serum 25(OH)D could only be evaluated as a continuous variable due to concerns about statistical power. Evaluation of leisure time physical activity as an effect modifier could only be performed in 1139 of the 1501 participants due to missing data on baseline physical activity. Thus, possible effect modification by age, sex and physical activity should be confirmed in different populations with a larger sample size.

In summary, our 11-year follow-up study suggested that higher serum 25(OH)D level was associated with a reduced risk of weight gain in adults who had normal weight at baseline, more evidently with the risk of clinical weight gain. The potential causal role of vitamin D in weight gain warrants further investigation in Norwegian and other ethnic populations.

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