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Cod liver oil consumption at different periods of life and bone mineral density in old age

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Abstract

Cod liver oil is a traditional source of vitamin D in Iceland, and intake is recommended partly for the sake of bone health. However, the association between lifelong consumption of cod liver oil and bone mineral density (BMD) in old age is unclear. In this study associations between intake of cod liver oil in adolescence, midlife, and current old age, and hip BMD in old age, as well as associations between current cod liver oil intake and serum 25-hydroxyvitamin D (25(OH)D) concentration was assessed. Participants of the AGES-Reykjavik Study (age 66–96 years; N=4798), reported retrospectively cod liver oil intake during adolescence and midlife, as well as intake in current old age, using a validated food frequency questionnaire. BMD of femoral neck and trochanteric region was measured by volumetric quantitative computed tomography, serum 25(OH)D concentration was measured by means of a direct, competitive chemiluminescence immunoassay. Associations were assessed using linear regression models. No significant association was seen between retrospective cod liver oil intake and hip BMD in old age. Current intake for men was also not associated with hip BMD, while women with daily intakes had Z-scores on average 0.1 higher compared with those with intake of <once/week. Although significant, this difference is slight and clinical relevance is questionable. Current intake was positively associated with serum 25(OH)D, individuals with intake of <once/week, 1–6 times/

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Conflict of interest

None

Authorship

TE drafted the manuscript and handled basic statistical analysis. TIH handled more complex statistical analysis and interpretation of data. IT, IG and LS participated in the conception and design of the study and revision of the manuscript. Other authors contributed to material supply and construction of the study. All authors have read and approved the final manuscript.

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week and daily intake having concentrations of approximately 40nmol/L, 50nmol/L, and 60nmol/L respectively (P for trend <0.001).

Keywords

Cod liver oil; lifelong consumption; bone density; elderly individuals

Introduction

Vitamin D is important for bone health through the actions of its hormonal form, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), elevating serum calcium and phosphorus levels necessary for bone mineralization.

Cod liver oil is a traditional source of vitamin D in Iceland. As the country lies at 62–67°N, little or no vitamin D is synthesized in the skin from approximately October to April (1). Dietary sources are also limited, and milk and dairy products are generally not fortified with vitamin D. Supplements are therefore especially important, and the intake of cod liver oil or other vitamin D containing supplements, is recommended for people of all ages (2).

However, whether, and then to what extent, cod liver oil intake at different periods of life is related to variations in bone mineral density (BMD) in old age is not clear as there are few studies focusing on this relationship. Findings from a Norwegian follow-up study suggested that childhood cod liver oil intake may be associated with adverse effects on BMD in elderly women, supposedly due to the high vitamin A (in the form of retinol) content of cod liver oil in earlier times (3). However, as studies are few, it is still not clear what effect cod liver oil intake during childhood, supplying high amounts of both retinol and vitamin D, has on bone health.

The association between cod liver oil intake in adulthood or old age and bone density has not been studied in detail either. Two studies on intake by elderly women have found no adverse effects on BMD (4,5) while one study found an association with lower overall fracture risk (6). However, these studies did not involve intake in childhood or adolescence, and it is possible that the growing bone may be differently affected than adult bone. Furthermore, studies on cod liver oil intake and BMD of elderly men are completely lacking.

It is of public health importance to assess possible effects of cod liver oil intake at different periods of life on bone, particularly as bone health is the primary justification for recommending and taking cod liver oil.

The aim of this study was to assess whether retrospective self-reports of cod liver oil intake during adolescence and midlife, are associated with hip BMD in old age. Further, the association between intake of cod liver oil in current old age and hip BMD, among participants of the Age, Gene/Environment Susceptibility – Reykjavik (AGES-Reykjavik) Study was investigated, as well as the association between current cod liver oil intake and serum 25-hydroxyvitamin D (25(OH)D) concentration. The AGES-Reykjavik Study is a large epidemiological study, including 5,764 elderly participants with extensive health

related data for all participants, including that on bone health and serum 25(OH)D concentrations, as well as data on dietary intake in adolescence, midlife and old age.

Methods

Subjects - Design

The AGES–Reykjavik Study originates from the Reykjavik Study, a large population-based cohort study which was launched in 1967. All men and women born in 1907–1935 (n=30,795) and residing in Reykjavik and nearby communities in 1967 were selected, 27,281 were invited to participate and 19,381 attended (7–10). Of the 11,549 previously examined Reykjavik Study cohort members still alive when AGES–Reykjavik examinations began in 2002, 8,030 individuals were randomly chosen and invited to participate. When AGES– Reykjavik examinations concluded in 2006, 5,764 individuals (72%) had been enrolled and examined (42% male). Participants were 66–96 years old at time of examinations, average age being 76 years.

The AGES–Reykjavik examination was completed in three clinic visits within a 4- to 6-week time window. Extensive data were collected during clinical examinations, e.g. on physical and cognitive function, anthropometry, health history, and food history during adolescence, midlife and in current old age. Participants also underwent quantitative computerized tomography (QCT-scans) and were asked to bring to the clinic all medications and supplements used in the previous two weeks, representing current usage (8,11).

Of the 5,764 participants, 933 individuals did not undergo the QCT scanning, and additional 33 individuals did not give adequate dietary information. Therefore data from 4,798 individuals (44% male) was used in the present study.

The AGES-Reykjavik Study was approved by the Icelandic National Bioethics Committee (VSN: 00-063) and the MedStar IRB for the Intramural Research Program, Baltimore, MD.

Measurements of serum 25-hydroxyvitamin D - 25(OH)D

Blood samples were drawn at recruitment into the AGES Study, i.e., in current old age. Measurement of 25(OH)D was conducted by means of a direct, competitive chemiluminescence immunoassay using the Liaison “Flash” Chemiluminescence Immunoassay from DiaSorin 25(OH)D TOTAL assay (DiaSorin, Inc., Stillwater, Minnesota). The interassay coefficient of variation was < 6.5% when calculated data are from measurements using a frozen serum pool as the control sample and < 12.7% when calculated data is from measurements using Liaison quality controls.

Bone mineral density/ Bone variables

Quantitative computed tomography (QCT) measurements, providing true volumetric density, were performed on the left hip using a 4-detector CT system (Sensation, Siemens Medical Systems, Erlangen Germany). Scans were acquired using a standardized protocol and encompassed the proximal femur from a level 1cm above the acetabulum to a level 5mm inferior to the lesser trochanter with 1mm slice thickness. Further procedures and quality assessments have been described in detail elsewhere (8,12).

The variables used in the present study are volumetric integral BMD (g/cc), reflecting both trabecular and cortical bone mass, of femoral neck and trochanteric region, encompassing both trochanters. Reasons for exclusion from the QCT were inability to lie supine or weight over 150kg. Furthermore, hip scans were not performed on individuals that had undergone hip replacement surgery.

Dietary information

Dietary data were gathered using a short food frequency questionnaire (AGES-FFQ) designed for the AGES-Reykjavik Study. The questionnaire is divided into three parts, including 16 questions on adolescent intake (14–19y), 17 questions on midlife intake (40–50y) and 30 questions on current intake. Foods and food groups were selected for the questionnaire on the basis of their contribution to the absolute food intake of elderly Icelanders according to former National Nutrition Surveys (13), as well as unique nutritional qualities and possible connection to the development of various diseases in later life. The questionnaire has been described previously (14,15). Frequency of cod liver oil intake was measured by posing a question in each part of the AGES-FFQ. The response categories were: 1) Never, 2) Less than once a week, 3) 1–2 times a week, 4) 3–4 times a week, 5) 5–6 times a week or 6) Daily.

Validity of the parts of the AGES-FFQ relating to midlife and present intake has been assessed in previous papers (14,15). Cod liver oil was among the items showing the highest validity in the questionnaire. When assessing validity of questions on midlife diet, frequency of intake reported in the AGES-FFQ by 56–72-year old individuals was compared with detailed dietary data, gathered from the same individuals 18–19 years previously, i.e. in midlife, as a part of a national dietary survey (13). Correlation using Spearman's rho was r=0.53, p=<0.001; r=0.56, p=<0.001 for men and women respectively (14). Validity of questions on current intake was assessed among elderly individuals (65years and older) by comparing answers of the AGES-FFQ to 3-day weighed food records completed by the same individuals. Correlation using Spearman's rho was r=0.51, p<0.001; r=0.42, p <0.001 for men and women respectively (15).

Covariates

For examining the association between intake of cod liver oil through different periods of life and hip BMD we selected *a priori* the following set of covariates: physical activity both current and in midlife, current alcohol intake, current and previous smoking, education, oral oestrogen intake (current and previous) for women, age, body mass index (BMI), and milk consumption at the same period of life. Midlife BMI was chosen as a covariate for the retrospective data, and current BMI for current data.

Participants were asked about level of moderate or vigorous physical activity, both at present time and past activities, and split into categories (never, rarely, occasionally, moderate or high). Education was categorized into primary school, secondary school, college or university. Current consumption of alcohol was converted into grams per week (g/w) using 14g of alcohol as a standard drink and was divided into <25g/w, 25–50g/w, and >50g/w. Midlife data on BMI had been collected in the Reykjavik-Study (7).

For early life most of these covariates can only be considered surrogate measures of corresponding early life characteristics. On the other hand for midlife and in current old age covariates selected are potential predictors of both bone health and dietary habits.

Data analysis – Statistical analysis

Characteristics of study participants were described using mean and standard deviation (SD) of normal variables, median and interquartile range (IQR) for skewed variables and percentages for dichotomous variables.

Due to the approximate normal distribution of the source BMD variables in our population they were transformed into sex-specific z-scores, reflecting the number of SD from the mean BMD in our population of 66–96 years of age. Univariate and multivariate linear regression was then used for examining the association between intake of cod liver oil and BMD variables.

Intake of cod liver oil according to the AGES-FFQ was categorized into three groups; never or <once/week, 1–6 times a week, and daily intake. The lowest intake group (never or <once/week) was in all cases used as referent and results represented as difference in z-scores (Δ) with higher frequency of consumption compared to the referent. Student's t-test was used to test whether BMD was linearly related to cod liver oil intake (ordinal values). Visual inspection of model residual suggested that use of z-scores was justifiable.

Data are presented unadjusted and adjusted for age, midlife or current BMI, past and present physical activity, alcohol consumption, milk consumption at the same period of life.

For stability analyses individuals taking medication known to affect bone health at the time of AGES examinations, 435 men (21%) and 992 women (37%), were excluded. The list of medications that resulted in exclusion for this secondary analysis was antiepileptic medication, calcium supplements, oral estrogens, glucocorticoids, osteoporosis drugs, prostate disease drugs, proton pump inhibitors, oral steroids and thyroid agonists). Statistical analyses were conducted in SAS (version 9.2; SAS Institute Inc., Cary, NC, USA).

Results

Potential confounding factors in relation to cod liver oil intake at different periods of life are shown in Table 1. Intake of cod liver oil was fairly common, with the proportion of participants reporting daily intake increasing with age, from around 30% in adolescence to midlife around 60% at old age. For both sexes the correlation between intake of cod liver oil in adolescence and at older age was relatively weak (spearman $r=0.20$, $p<0.0001$) while the correlation between intake in midlife and old age was stronger (Spearman $r=0.49$, $p<0.0001$). A total of 16% of participants reported no intake of cod liver oil from adolescence to older age while 21% of subjects reported daily intake at all three time points.

The association between retrospective intake of cod liver oil and difference in Z-scores, calculated from hip BMD in old age (using <once/week as a referent) is shown in Table 2. Data are shown separately for men and women and both unadjusted and adjusted for confounders. Individuals taking cod liver oil more frequently in adolescence and/or midlife

did not have significantly different hip BMD in old age compared with those with the lowest frequency of intake. This was seen for both men and women, and for femoral neck and trochanter.

The association between cod liver oil intake in current old age and hip BMD was also assessed (Table 3), excluding supplement users from the analysis, that is, individuals taking vitamin and/or mineral supplements (other than cod liver oil). There was no significant difference in hip BMD in relation to cod liver oil intake for men, while women with daily intake had significantly higher Z-scores on average (0.10 for femoral neck and 0.09 for trocanther) compared to those with the lowest frequency of intake (<once/week). Analysing the associoation between lifetime cod liver oil consumption (three time periods amalgamated through an overall score) and old age BMD showed similar results as for BMD and current consumption (data not shown).

There was a clear association between current intake of cod liver oil and serum 25(OH)D concentrations (Table 4). Median concentrations for men and women with the lowest frequency of intake being 40.2 and 37.8nmol/L respectively, compared to 61.9 and 56.4nmol/L for those with daily intake. When excluding supplement users from the analysis, median serum 25(OH)D concentrations for those with the lowest cod liver oil intake were 37.2 and 31.9nmol/L for men and women respectively, compared with 60.6 and 55.2nmol/L for those with daily intake of cod liver oil. Both men and women with intake of 1–6 times/week or daily intake of cod liver oil had significantly higher serum levels than those with the lowest frequency of intake.

Almost one third of the participants were taking medications known to be able to affect bone health. Proton pump inhibitors were most common (13%), followed by thyroid agonists, osteoporosis related drugs, oral estrogens for women, and prostate disease drugs for men. We therefore also performed analysis without these individuals, reaching the same conclusions as in our primary analysis where these subjects were included.

Discussion

No significant association was found between retrospective intake of cod liver oil in adolescence or midlife and hip BMD among participants of the AGES-Reykjavik Study. Current intake was also not associated with hip BMD in men. Women with daily intake had slightly higher Z-scores of both femoral neck and trochanteric region compared to those with the lowest frequency of consumption. Current cod liver oil intake of both sexes was positively associated with serum 25(OH)D concentration.

Adequate vitamin D is important in adolescence for bone accretion associated with rapid growth (16). Still, intervention studies are limited, with some studies showing that vitamin D supplementation can increase bone mineral content and BMD of young adolescent girls (17,18), while other studies show no significant effect (19).

In the mid 20th century, when our participants were in adolescence, cod liver oil was given to children in most schools. At that time the concentrations of both retinol and vitamin D, the two major vitamins in the oil, probably reflected that of cod liver, 83:1 (20). Until 2002, cod

liver oil in Iceland still contained high amounts of retinol (30.000μg/100g), and the recommended daily spoonful (8g) supplied approximately 2400μg retinol and 20μg vitamin D. Today an 8g spoonful contains 400μg retinol and 16μg vitamin D. Average intake of vitamin A was approximately three times the recommended daily intake in 1990 (13), but has since decreased, both as a result of decreased concentration of retinol in cod liver oil, but also changes in food intake, including decreased intake of whole milk, margarine, and other vitamin A rich foods (21,22). While fish intake has also decreased considerably, this has resulted in minimal changes in vitamin A and D intake, as lean fish, containing minimal amounts of these vitamins constituted about 80% of total fish intake (22,23). Changes in milk intake are mirrored in our AGES-FFQ data (24)".

Cod liver oil is a traditional source of vitamin D in other Nordic countries as well as Iceland. In a follow-up study of 50–70 year old women in the Norwegian Nord-Trøndelag Health Study elderly women reporting any intake of cod liver oil in childhood had significantly lower current forearm BMD than those with no intake (3). The researchers concluded that the previously high concentration of vitamin A in cod liver oil, when added to an already vitamin A rich diet, may have led to total intake reaching harmful levels, as high intakes of retinol have been linked to adverse effects on bone health and even increased risk of osteoporosis and osteoporotic fractures (25–29).

In the light of the results from the Nord-Trøndelag Health Study, we set out to explore whether those findings could be replicated using Icelandic data. In short, we did not find any indication that the intake of cod liver oil during adolescence or midlife was associated with adverse effects on BMD of either femoral neck or trochanter. It should be noted that different methods were used for measuring BMD in the two studies. Also, the Nord-Trøndelag Health Study measured forearm BMD, while we use hip BMD, and it is possible that these bones respond differently to cod liver oil intake. Finally, we cannot rule out that misclassification of previous intake or lack of some relevant confounder adjustment, contribute to our findings.

Intervention studies among elderly individuals have shown that increased intake of vitamin D can be associated with increased BMD (30,31), decreased bone loss (31–33), and lower risk of osteoporotic fractures (31–35). However, many of the intervention studies include calcium supplements parallel to the vitamin D and according to recent reviews the effect of vitamin D supplementation alone on BMD and fracture risk is minimal, while vitamin D given alongside calcium can have significant effect (36,37).

Previous studies of elderly women have not shown any association between current cod liver oil intake and BMD (5,38). While our results showed no such association for men, there was a slight positive association for women. It has been estimated that a 1 SD decrease in hip BMD is associated with approximately 2.5 fold increased risk of hip fracture (39,40). In our study the difference between women with daily intake versus <once/week was 0.1 Z-scores for femoral neck and 0.09 Z-scores for the trochanteric region (equal to 0.1 and 0.09 SD respectively). The clinical relevance of our finding is therefore most likely minimal and may even be a case of a chance finding.

The weak or insignificant association between current cod liver oil intake and hip BMD in our study may possibly be explained by the relatively adequate serum 25(OH)D levels in our population. Even in those individuals with no intake of cod liver oil or less than <once/week, median serum levels were approximately 40nmol/L, which is close to the 50nmol/L considered adequate for bone health by the Institute of Medicine (16). In previous Icelandic studies, serum parathyroid hormone (PTH) levels levelled off at approximately 45–50nmol/L in healthy adults and elderly individuals, suggesting vitamin D sufficiency with respect to bone health (41,42).

Steingrimsdottir et al (43) found that only levels below 30nmol/L were associated with significantly lower BMD of the femoral neck in this same population, and more than double the risk of hip fracture compared with referent (50–75nmol/L). Intake of cod liver oil may therefore mostly benefit individuals with the lowest serum 25(OH)D concentrations.

The association between current frequency of intake and serum 25(OH)D concentrations may be considered as further validation of the question on cod liver oil in the AGES-FFQ. Participants with intake of <once a week, 1–6 times a week and daily intake had serum levels of approximately 40nmol/L, 50nmol/L and 60nmol/L respectively.

The AGES-Reykjavik study, with its large number of participants, provided a unique opportunity to assess the association between cod liver oil intake in different periods of life and bone health in old age of both sexes. Also, extensive data gathered in the AGES-Study, and midlife data received from the Reykjavik-Study, allowed for adjustments of various confounding factors.

The main limitation of the study is that we are partly using retrospective data with 60 years of temporal separation on average, which is always going to be imprecise and is likely to mask any potential modest or weak association. However, according to Dwyer & Coleman, (44) foods with special characteristics (such as cod liver oil), can be recalled particularly well, and the question on midlife cod liver oil intake showed the highest validity of any food item in our FFQ. Also, midlife milk intake, an important covariate in our study, was among the foods showing the highest correlation in validation studies of the FFQ (14,15,24). Another limitation is that, although the most common portion of cod liver oil is the recommended spoonful, we do not have absolute amount consumed.

As we did not have any information on supplement use during midlife we do not know if an analysis excluding midlife supplement users might have yielded different results.

Our associations between current cod liver oil intake and serum 25(OH)D concentrations are cross-sectional, and thus we remain cautious in our interpretation as influence of other unmeasured confounders, e.g. outdoor activities and the amount of sunlight exposure, cannot be excluded. However, the seasonal variation observed in this study was small, or 3.9nmol, suggesting that sun exposure is a relatively small confounding factor here.

Also, we do not have accurate enough information in order to calculate total vitamin D intake. The AGES-FFQ only includes simple global questions, such as frequency of fish intake, without specifying different types of fish, e.g., fatty fish and lean fish. However, fish

intake in Iceland during the whole study period was characterized by lean fish species, containing minimal amount of vitamin D. Also, milk was not fortified with vitamin D during the study period In a recent INDS the portion of the oldest age group (61–80y), not taking cod liver oil, had an average intake of 5.3μg/d of vitamin D from food (22). Assuming comparable intake of our participants, it indicates that 5 to 6μg/d of vitamin D might be sufficient to keep average serum levels of approximately 40nmol/L. This is however lower than has previously been reported, where approximately 9μg/d of vitamin D have been required to achieve average serum 25(OH)D concentrations of 50nmol/L (45).

Conclusion

In conclusion, we found no evidence that cod liver oil intake at any age might be harmful to hip BMD in old age. For current intake a slight positive association was seen for hip BMD among women. Possibly, the relatively high median serum 25(OH)D concentration in our study population, even among those not taking cod liver oil or other vitamin D containing supplements, may mask any putative, more profound relationship between current intake and hip BMD. Current daily intake of cod liver oil was associated with an increase of approximately 20nmol/L in 25(OH)D concentration, compared to no intake or less than once a week.

The significance of cod liver oil intake at various ages for bone health in old age warrants further study, especially intake during childhood and adolescence, as cod liver oil is supplied in several schools and child care centers in Iceland for public health purposes.

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Table 1

Possible confounding factors in relation to cod liver oil intake in adolescence (14–19y), midlife (40–50y) and current old age. Data shown as mean (SD) / median (IQR [*]), or proportion (%).

	Men				Women			
	<once/week	1–6 times/week	Daily	P[†]	<once/week	1–6 times/week	Daily	P[†]
Adolescence		**(n=2092)**				**(n=2691)**		
No. (%)	943 (45)	508 (24)	641 (31)		1318 (49)	432 (16)	941 (35)	
Age, years	76.6 (5.5)	76.0 (5.3)	76.6 (5.1)	0,06	76.1 (5.7)	75.6 (5.3)	76.4 (5.4)	0.05
Midlife BMI, kg/m^2	25.4 (3.0)	25.7 (3.3)	25.5 (3.1)	0.36	25.2 (4.0) [*]	24.1 (3.3) [*]	25.0 (3.7) [*]	<0.001
Current BMI, kg/m^2	26.7 (3.8)	27.0 (4.0)	26.7 (3.7)	0.39	27.5 (5.0) [*]	26.5 (4.5) [*]	27.3 (4.7) [*]	0.001
Alcohol, grams/week	6.4 (26.4) [*]	8.0 (26.4) [*]	4.8 (24.1) [*]	0.20	1.6 (8.0) [*]	1.6 (8.0) [*]	1.6 (8.0) [*]	0.21
Not physically active at follow-up, %	45	32	41	0.001	52	43	46	<0.001
Not physically active at midlife, %	30	18	23	<0.001	30	20	25	<0.001
Current smoker, %	12	13	11	0.49	13	11	13	0.52
University education, %	15	21	21	<0.001	5	7	6	0.43
Daily milk consumption, %	78	73	85	<0.001	71	72	84	<0.001
Medications [†], %	21	19	21	68	37	36	37	0.86
Midlife		**(n=2089)**				**(n=2687)**		
No. (%)	745 (36)	429 (21)	915 (44)		1102 (41)	428 (16)	1157 (43)	
Age, years	76.9 (5.6)	75.4 (5.3)	76.6 (5.1)	<0.001	76.1 (5.6)	75.6 (5.3)	76.3 (5.5)	0.12
Midlife BMI, kg/m^2	25.7 (3.3)	25.4 (3.1)	25.4 (3.0)	0.09	25.4 (4.1) [*]	24.4 (3.4) [*]	24.8 (3.7) [*]	<0.001
Current BMI, kg/m^2	27.1 (4.0)	27.0 (3.8)	26.4 (3.6)	0.002	27.8 (5.1) [*]	26.6 (4.5) [*]	27.0 (4.6) [*]	<0.001
Alcohol, grams/week	4.8 (26.4) [*]	8.0 (26.4) [*]	6.4 (26.4) [*]	0.06	1.6 (8.0) [*]	3.2 (8.0) [*]	1.6 (8.0) [*]	<0.001
Not physically active at follow-up, %	49	36	37	<0.001	56	41	44	<0.001
Not physically active at midlife, %	33	19	21	<0.001	33	19	24	<0.001
current smoker, %	14	12	10	0.03	13	12	13	0.07
University education, %	14	19	21	0.002	4	11	5	<0.001
Daily milk consumption, %	59	53	69	<0.001	54	52	60	0.001
Medications [†], %	21	20	21	0.86	36	38	36	0.75

	Men				Women			
	<once/week	1–6 times/week	Daily	P†	<once/week	1–6 times/week	Daily	P†
Current		(n=2092)				(n=2679)		
No. (%)	586 (28)	237 (11)	1270 (61)		832 (31)	227 (9)	1620 (60)	
Age, years	76.6 (5.6)	75.4 (5.1)	76.6 (5.3)	0.003	76.1 (5.6)	75.4 (5.2)	76.2 (5.5)	0.09
Midlife BMI, kg/m^2	25.6 (3.5)	25.3 (3.0)	25.5 (3.0)	0.36	25.4 (4.1)*	24.8 (3.8)*	24.7 (3.6)*	<0.001
Current BMI, kg/m^2	27.2 (4.1)	26.9 (3.5)	26.6 (3.7)	0.004	27.9 (5.2)*	27.3 (5.2)*	26.9 (4.6)*	<0.001
Alcohol, grams/week	4.8 (26.4)*	13.2 (24.8)*	6.4 (26.4)*	0.009	1.6 (6.4)*	3.2 (9.7)*	1.6 (8.0)*	<0.001
Use of dietary supplements, %	19	21	28	<0.001	27	28	36	<0.001
Not physically active at follow-up, %	49	41	37	<0.001	57	42	45	<0.001
Not physically active at midlife, %	30	21	23	0.003	32	25	24	<0.001
current smoker, %	15	14	10	0.02	14	12	12	0.44
University education, %	16	17	19	0.11	4	8	6	0.007
Daily milk consumption, %	49	48	55	0.02	42	38	51.0	<0.001
Medications††, %	18	21	22	0.15	39	34	36	0.23

*interquartile range

†F-test (Type III) for continuous variables, Chi-square test for dichotomous variables

††Medications: Reported intake of medication known to affect bone density: antiepileptic medication, calcium supplements, oral estrogens, glucocorticoids, osteoporosis drugs, prostate disease drugs, proton pump inhibitors, oral steroids and thyroid agonists

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Table 2

Difference in hip BMD in old age, presented as Z-scores, between individual with retrospective cod liver oil intake of 1–6 times/week or daily intake, compared to <once/week.

	Femoral neck				Trochanteric region			
	Men (n=2093)		Women (n=2684)		Men (n=2093)		Women (n=2684)	
	Δ Z	95% CI	Δ Z	95% CI	Δ Z	95% CI	Δ Z	95% CI
Unadjusted								
Adolescence intake								
<once/week	referent	-	-	-	-	-	-	-
1–6 week	0.09	−0.01 ; 0.20	−0.09	−0.20 ; 0.01	0.08	−0.03 ; 0.19	−0.10	−0.20 ; 0.01
daily	0.02	−0.08 ; 0.12	0.04	−0.05 ; 0.12	0.01	−0.09 ; 0.11	0.05	−0.03 ; 0.14
p-value	0.61		0.48		0.79		0.28	
Midlife intake								
<once/week	referent	-	-	-	-	-	-	-
1–6 week	0.02	−0.10 ; 0.14	−0.06	−0.17 ; 0.05	−0.01	−0.13 ; 0.11	−0.06	−0.17 ; 0.06
daily	0.01	−0.09 ; 0.11	0.01	−0.07 ; 0.10	−0.01	−0.11 ; 0.09	0.01	−0.07 ; 0.09
p-value		0.83		0.73		0.84		0.83
Adjusted *								
Adolescence intake								
<once/week	referent	-	-	-	-	-	-	-
1–6 week	0.04	−0.07 ; 0.14	−0.09	−0.19 ; 0.02	0.04	−0.07 ; 0.14	−0.08	−0.18 ; 0.02
daily	0.00	−0.10 ; 0.09	0.05	−0.02 ; 0.13	−0.02	−0.11 ; 0.08	0.08	0.00 ; 0.15
p-value	0.99		0.22		0.80		0.07	
Midlife intake								
<once/week	referent	-	-	-	-	-	-	-
1–6 week	−0.04	−0.16 ; 0.08	−0.09	−0.19 ; 0.02	−0.07	−0.18 ; 0.05	−0.07	−0.17 ; 0.03
daily	−0.02	−0.12 ; 0.07	0.02	−0.06 ; 0.10	−0.04	−0.13 ; 0.05	0.03	−0.05 ; 0.10
p-value		0.66		0.57		0.40		0.44

*Adjusted for age, past and present physical activity, midlife BMI, alcohol consumption, current and previous smoking, education, current or previous use of oral oestrogens (among women) and milk consumption at the same period

Table 3

Difference in hip BMD, presented as Z-scores, in relation to current cod liver oil intake (dietary supplement users excluded).

	Femoral neck				Trochanteric region			
	Men (n=1569)		Women (n=1784)		Men (n=1569)		Women (n=1784)	
	Δ Z	95% CI	Δ Z	95% CI	Δ Z	95% CI	Δ Z	95% CI
Unadjusted								
<once/week	referent	-	-	-	-	-	-	-
1–6 week	0.06	−0.11 ; 0.23	−0.02	−0.20 ; 0.15	0.11	−0.06 ; 0.28	−0.06	−0.23 ; 0.12
daily	−0.00	−0.11 ; 0.11	0.05	−0.05 ; 0.15	0.02	−0.09 ; 0.13	0.03	−0.08 ; 0.13
p-value	0.93		0.34		0.86		0.56	
Adjusted								
<once/week	referent	-	-	-	-	-	-	-
1–6 week	0.04	−0.13 ; 0.20	−0.07	−0.23 ; 0.10	0.09	−0.07 ; 0.26	−0.12	−0.28 ; 0.03
daily	−0.03	−0.14 ; 0.08	0.10	−0.00 ; 0.19	0.01	−0.10 ; 0.11	0.09	0.00 ; 0.19
p-value	0.52		0.04		0.98		0.03	

*Adjusted for age, past and present physical activity, current BMI, alcohol consumption, current and previous smoking, education, current or previous use of oral oestrogens (among women) and current milk consumption

Table 4

Serum 25(OH)D concentration in nmol/L in relation to current cod liver oil intake

	Men				Women			
	n	**median**	**P10**	**P90**	**n**	**median**	**P10**	**P90**
All subjects								
<once/week	642	40	20	71	933	38	17.1	68
1–6 times/week	256	48	28	86	249	45	21.6	76
daily	1375	62	35	93	1856	56	29.2	84
p-value *		<0.001				<0.001		
Without supplement users								
<once/week	518	37	20	68	669	32	15.2	64
1–6 times/week	203	49	28	87	174	44	21.3	70
daily	979	61	34	95	1168	55	27.7	86
p-value *		<0.001				<0.001		

* Test for trend