**Supplemental Materials**

for

Safety profile of vitamin D supplements using real-world data from 445,493 participants of the UK Biobank: Slightly higher hypercalcemia prevalence but neither increased risks of kidney stones nor atherosclerosis

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## 

## **Supplemental Table 1. Complete list of baseline characteristics of the population analyzed (N=445,493)**

| **Variables** | **N (%) a/  Median (IQR)** |
| --- | --- |
| **SOCIO-DEMOGRAPHIC/ -ECONOMIC FACTORS** | |
| **Age (years), median (IQR)** | 58 (50; 63) |
| **Sex, n (%)** |  |
| Female | 238,942 (53.6) |
| Male | 206,551 (46.4) |
| **Education (years), median (IQR)** | 11 (10; 17) |
| **Townsend deprivation index (points),  median (IQR)** | -0.3 (-0.7; 0.4) |
| **No. of individuals in household, n (%)** |  |
| 1 | 81,563 (18.3) |
| 2 | 206,572 (46.4) |
| 3-4 | 130,470 (29.3) |
| ≥ 5 | 23,885 (5.3) |
| **Annual household income (***£***), n (%)** |  |
| < 18,000 | 85,742 (19.2) |
| 18,000 - < 30,999 | 96,749 (21.7) |
| 31,000- < 51,999 | 100,058 (22.5) |
| 52,000 - < 100,000 | 78,640 (17.7) |
| ≥ 100,000 | 21,000 (4.7) |
|  |  |
| **LIFE-STYLE FACTORS** |  |
| **Smoking, n (%)** |  |
| Never | 244,481 (54.9) |
| Occasionally | 63,247 (14.2) |
| Regularly | 137,621 (30.9) |
| **Alcohol consumption (g ethanol/d), n (%)** |  |
| Abstainer | 137,944 (31.0) |
| Women 0 - < 20 / men 0 - < 40 | 178,258 (40.0) |
| Women 20 - < 40 / men 40 - < 60 | 75,677 (17.0) |
| Women ≥ 40 / men ≥ 60 | 53,614 (12.0) |
| **Venturesome personality, n (%)** |  |
| No | 313,093 (70.3) |
| Yes | 115,706 (26.0) |
| **Total physical activity (hours/day), n (%)** |  |
| ≤ 1 | 63,786 (14.3) |
| ≤ 2 | 140,699 (31.6) |
| > 2 | 142,047 (31.9) |
| **Frequency of visiting friends/family, n (%)** |  |
| Almost daily | 59,760 (13.4) |
| 2-4 times/week | 158,268 (35.5) |
| Once/week | 136,111 (30.6) |
| Once every few months/rare | 51,555 (11.6) |
| **Oily fish consumption, n (%)** |  |
| Never/ less than once a week | 195,508 (43.9) |
| At least once a week | 247,484 (55.6) |
| **Cereal consumption (bowls/week), n (%)** |  |
| Never | 75,841 (17.0) |
| < 7 | 198,082 (44.5) |
| ≥ 7 | 170,066 (38.2) |
| **Processed meat intake, n (%)** |  |
| Never/ less than once a week | 176,398 (39.6) |
| At least once a week | 268,147 (60.2) |
| **Milk consumption, n (%)** |  |
| Never/rarely | 14,590 (3.3) |
| Occasionally/regularly | 430,583 (96.7) |
| **Spread consumption, n (%)** |  |
| Never/rarely | 48,201 (10.8) |
| Butter | 160,664 (36.1) |
| Margarine/others | 235,855 (52.9) |
| **Preferred bread type, n (%)** |  |
| White | 113,435 (25.5) |
| Wholemeal/wholegrain/brown | 316,220 (70.9) |
|  |  |
| **DISEASES & DISEASE SYMPTOMS** |  |
| **Diabetes, n (%)** |  |
| No | 423,131 (94.9) |
| Yes | 22,264 (5.1) |
| **Stroke, n (%)** |  |
| No | 439,410 (98.6) |
| Yes | 5,984 (1.3) |
| **CHD, n (%)** |  |
| No | 424,553 (95.3) |
| Yes | 20,841 (4.7) |
| **COPD, n (%)** |  |
| No | 443,907 (99.6) |
| Yes | 1,487 (0.3) |
| **Hypertension, n (%)** |  |
| No | 325,480 (73.1) |
| Untreated hypertension | 33,253 (7.5) |
| Treated hypertension | 86,671 (19.5) |
| **Asthma, n (%)** |  |
| No | 393,732 (88.4) |
| Yes | 51,662 (11.6) |
| **Osteoporosis, n (%)** |  |
| No | 434,431 (97.5) |
| Yes | 10,963 (2.5) |
| **Fracture in last 5 years, n (%)** |  |
| No | 401,340 (90.1) |
| Yes | 41,918 (9.4) |
| **Arthritis, n (%)** |  |
| No | 398,918 (89.5) |
| Yes | 46,476 (10.4) |
| **Gout, n (%)** |  |
| No | 438,211 (98.4) |
| Yes | 7,183 (1.6) |
| **Parkinson, n (%)** |  |
| No | 444,460 (99.8) |
| Yes | 934 (0.2) |
| **Depressed mood in last 2 weeks, n (%)** |  |
| ≤ half the days | 404,447 (90.8) |
| > half the days | 21,023 (4.7) |
| **Tiredness/lethargy in last 2 weeks, n (%)** |  |
| ≤ half the days | 377,274 (84.7) |
| > half the days | 54,403 (12.2) |
| **Chronic fatigue syndrome, n (%)** |  |
| No | 443,479 (99.5) |
| Yes | 1,915 (0.4) |
| **Hypothyroidism, n (%)** |  |
| No | 423,940 (95.2) |
| Yes | 21,454 (4.8) |
| **Dementia, n (%)** |  |
| No | 442,754 (99.4) |
| Yes | 2,640 (0.6) |
| **Cancer, n (%)** |  |
| No | 410,621 (92.2) |
| Yes | 33,570 (7.5) |
| **Hyperparathyroidism, n (%)** |  |
| No | 444,910 (99.9) |
| Yes | 583 (0.1) |
|  |  |
| **BIOMARKERS** |  |
| **BMI (kg/m2), n (%)** |  |
| Underweight, < 18.5 | 2,285 (0.5) |
| Low normal weight, 18.5 - <20 | 8,188 (1.8) |
| High normal weight, 20 - < 25 | 137,420 (30.8) |
| Overweight: 25 - < 30 | 188,111 (42.2) |
| Obesity class I: 30 - < 35 | 77,278 (17.3) |
| Obesity class II: 35 - < 40 | 22,021 (4.9) |
| Obesity class III: ≥ 40 | 8,515 (1.9) |
| **Waist circumference (cm), median (IQR)** | 90 (80; 99) |
| **eGFR (ml/min/1.73 m2), n (%)** |  |
| ≥ 90 | 264,715 (59.4) |
| < 90 | 180,237 (40.5) |
| **HbA1c, (%), n (%)** |  |
| < 6 | 411,465 (92.4) |
| 6 - < 6.5 | 17,488 (3.9) |
| 6.5 - < 7 | 6,204 (1.4) |
| 7 - < 8 | 5,972 (1.3) |
| ≥ 8 | 4,364 (1.0) |
| **HDL cholesterol (mg/dl), n (%)** |  |
| < 40 | 89,800 (20.1) |
| ≥ 40 | 355,693 (79.8) |
| **SBP (mmHg), n (%)** |  |
| < 140 | 236,879 (53.2) |
| 140 - < 160 | 140,521 (31.5) |
| 160 - < 180 | 53,988 (12.1) |
| ≥ 180 | 14,105 (3.2) |
| **DBP (mmHg), n (%)** |  |
| < 90 | 339,609 (76.2) |
| 90 - < 100 | 80,476 (18.1) |
| ≥ 100 | 25,408 (5.7) |
| **C-reactive protein (mg/L), n (%)** |  |
| < 1 | 177,546 (39.9) |
| ≥ 1 | 267,947 (60.1) |
| **FEV1 (L), median (IQR)** | 2.8 (2.3; 3.3) |
| **Hand grip strength (Kg), median (IQR)** | 31 (24; 40) |
|  |  |
| **GENERAL HEALTH** |  |
| **Disability (%)** |  |
| No | 416,119 (93.4) |
| Yes | 25,799 (5.8) |
| **General self-reported health, n (%)** |  |
| Excellent | 73,626 (16.5) |
| Good | 257,527 (57.8) |
| Fair | 92,895 (20.9) |
| Poor | 19,507 (4.4) |
| **No of chronic diseases, median (IQR)** | 2 (1; 3) |
| **No of drugs, median (IQR)** | 2 (0; 4) |
| **Low-dose aspirin use, n (%)** |  |
| No | 382,319 (85.8) |
| Yes | 63,075 (14.2) |
| **Lipid-lowering drugs use, n (%)** |  |
| No | 365,816 (82.1) |
| Yes | 79,585 (17.9) |
| **Anti-depressants use, n (%)** |  |
| No | 416,037 (93.4) |
| Yes | 29,357 (6.6) |
| **VITAMIN D SPECIFIC FACTORS** |  |
| **Latitude of study center (per 1°),  median (IQR)** | 53.0 (51.5; 53.8) |
| **Month of attending the study center  (month of blood draw)** |  |
| 1 | 30,516 (6.8) |
| 2 | 35,121 (7.9) |
| 3 | 43,433 (9.7) |
| 4 | 38,830 (8.7) |
| 5 | 46,372 (10.4) |
| 6 | 46,028 (10.3) |
| 7 | 38,137 (8.6) |
| 8 | 33,952 (7.6) |
| 9 | 32,617 (7.3) |
| 10 | 38,241 (8.6) |
| 11 | 37,335 (8.4) |
| 12 | 24,911 (5.6) |
| **Time spent outdoors in summer (h/day), n (%)** |  |
| <1 | 18,616 (4.2) |
| 1-2 | 130,269 (29.2) |
| 3-4 | 138,749 (31.1) |
| 5-6 | 84,309 (18.9) |
| ≥ 7 | 48,338 (10.9) |
| **Time spent outdoors in winter (h/day), n (%)** |  |
| <1 | 83,763 (18.8) |
| 1-2 | 238,767 (53.6) |
| 3-4 | 63,525 (14.3) |
| ≥ 5 | 34,082 (7,6) |
| **Skin color, n (%)** |  |
| Very fair | 34,021 (7.6) |
| Fair | 299,581 (67.2) |
| Olive | 81,675 (18.3) |
| Brown | 8,248 (1.9) |
| Black | 12,428 (2.8) |
| Unknown | 3,364 (0.8) |
| **Ease of skin tanning, n (%)** |  |
| Very tanned | 94,016 (21.1) |
| Moderately tanned | 173,061 (38.8) |
| Mildly/occasionally tanned | 91,909 (20.6) |
| Never tan, only burn | 74,631 (16.8) |
| **Sun screen/UV protection use, n (%)** |  |
| Never/rarely | 44,849 (10.1) |
| Sometimes | 148,262 (33.3) |
| Most of times | 157,360 (35.3) |
| Always | 91,671 (20.6) |
| Do not go out in sunshine | 2,666 (0.6) |
| **Solarium/sunlamp use (times per  year), n (%)** |  |
| Never | 399,596 (89.7) |
| < 1 | 21,586 (4.8) |
| 1 - 6 | 10,720 (2.4) |
| 7 - 12 | 4,624 (1.0) |
| > 12 | 4,390 (1.0) |

Abbreviations: BMI: body mass index CHD: coronary heart disease, COPD: chronic obstructive pulmonary disease, DBP: diastolic blood pressure, eGRF: estimated Glomerular filtration rate, FEV1: Forced expiratory volume in 1-second, IQR: interquartile range, SBP: systolic blood pressure

a Denominators in proportion calculations contain missing values.

## **Supplemental Table 2. Overviews of baseline characteristics for study population in the four analytical datasets**

|  | **Dataset for analysis of** | | | |
| --- | --- | --- | --- | --- |
|  | **Hypercalcemia**  **N=407,185** | **Kidney stone**  **N=** **439,189** | **PASI**  **N=150,117** | **CIMT**  **N=43,958** |
| **Variables** | **N (%) a /Median (IQR)** | | | |
| **Sex,** n (%) |  |  |  |  |
| Female | 216,671 (53.2) | 237,079 (54.0) | 80,118 (53.4) | 22,710 (51.7) |
| Male | 190,514 (46.8) | 202,110 (46.0) | 69,999 (46.6) | 21,248 (48.3) |
| **Age (years)** |  |  |  |  |
| Mean (SD) | 56.5 (8.1) | 56.4 (8.1) | 56.7 (8.2) | 55.1 (7.6) |
| Median (IQR) | 58 (50; 63) | 58 (50; 63) | 58 (50; 63) | 56 (49; 61) |
| **BMI,** n (%) |  |  |  |  |
| < 18.5 | 2,092 (0.5) | 2,268 (0.5) | 768 (0.5) | 195 (0.4) |
| 18.5 - <25 | 132,408 (32.5) | 144,148 (32.9) | 49,001 (32.7) | 17,241 (39.3) |
| 25 - < 30 | 172,089 (42.3) | 185,336 (42.2) | 63,333 (42.2) | 18,834 (42.8) |
| ≥30 | 99,049 (24.3) | 105,802 (24.1) | 36,838 (24.5) | 7631 (17.3) |
| **Smoking,** n (%) |  |  |  |  |
| Never | 223,218 (54.8) | 241,248 (54.9) | 83,003 (55.3) | 26,626 (60.6) |
| Ever | 183,833 (45.0) | 197,799 (45.1) | 67,050 (44.7) | 17,327 (39.4) |
| **Alcohol consumption b,** n (%) |  |  |  |  |
| Abstainer | 126,017 (30.9) | 135,739 (30.9) | 49,074 (32.7) | 10,442 (23.8) |
| Low | 163,194 (40.1) | 175,571 (40.0) | 59,889 (39.9) | 19,244 (43.8) |
| Medium | 69,070 (17.0) | 74,854 (17.0) | 23,981 (16.0) | 8,559 (19.5) |
| High | 48,904 (12.0) | 53,025 (12.1) | 17,173 (11.4) | 5,713 (13.0) |
| **Hypertension,** n (%) | 109,824 (27.0) | 117,488 (26.7) | 40,838 (27.2) | 8,554 (19.4) |
| **Diabetes,** n (%) | 20,356 (5.1) | 21,662 (4.9) | 8,209 (5.5) | 1,092 (2.5) |
| **CHD,** n (%) | 19,089 (4.7) | 20,311 (4.6) | 6,774 (4.5) | 1,051 (2.4) |
| **eGFR (ml/min/1.73 m2),** n (%) |  |  |  |  |
| ≥ 90 | 242,500 (59.6) | 261,252 (59,5) | 87,250 (58.1) | 27,130 (61.7) |
| 60-< 90 | 155,290 (38.1) | 167,534 (38.1) | 59,184 (39.4) | 16,232 (36.9) |
| < 60 | 9,157 (2.2) | 9,868 (2.2) | 3,487 (2.3) | 539 (1.2) |
| **Hypercalcemia** | 6,325 (1.6) | - | - | - |
| **kidney stones during follow-up,** n (%) | - | 5,097 (1.2) | - | - |
| **PASI,** Median (IQR) | - | - | 9.0 (6.9; 11.1) | - |
| **Adversely high PASI c,** n (%) | - | - | 11,473 (7.6) | - |
| **Average of mean CIMT,** Median (IQR) | - | - | - | 0.67 (0.60; 0.76) |
| **Adversely high CIMT > 0.9 mm,** n (%) | - | - | - | 2,713 (6.2) |
| **No. of chronic diseases,** Median (IQR) | 2 (1;3) | 2 (1;3) | 2 (1;3) | 1 (0;2) |
| **25(OH)D concentration (nmol/L),** Median (IQR) | 46.8 (32.3; 62.4) | 46.9 (32.4; 62.5) | 48.5 (33.7; 64.0) | 48.1 (33.9; 63.4) |
| **Vitamin D status,** n (%) |  |  |  |  |
| Deficiency (<30 nmol/L) | 85,776 (21.1) | 92,063 (21) | 28,842 (19.2) | 8091 (18.4) |
| Insufficiency (30- <50 nmol/L) | 140,013 (34.4) | 150,657 (34.3) | 49,880 (33.2) | 15,327 (34.9) |
| Sufficiency (50 - < 100 nmol/L) | 175,302 (43.1) | 189,875 (43.2) | 68,827 (45.8) | 19,844 (45.1) |
| High status (≥ 100 nmol/L) | 6,094 (1.5) | 6,594 (1.5) | 2,568 (1.7) | 696 (1.6) |
| **Regular vitamin supplements use,** n (%) |  |  |  |  |
| No | 306,849 (75.4) | 330,625 (75.3) | 112,249 (74.8) | 32,925 (74.9) |
| Multivitamins +/-minerals | 82,793 (20.3) | 89,638 (20.4) | 30,863 (20.6) | 9,246 (21.0) |
| Vitamin D | 17,543 (4.3) | 18,926 (4.3) | 7,005 (4.7) | 1,787 (4.1) |

Abbreviations: 25(OH)D: 25-hydroxyvitamin D, BMI: body mass index, CHD: coronary heart disease, CIMT: carotid intima-medial thickness, eGFR: estimated glomerular filtration rate, IQR: interquartile range, PASI: pulse wave arterial stiffness index, SD: standard deviation.

a Denominators in proportion calculations contain missing values.

b Alcohol consumption: Low: Women > 0-19.99 grams of ethanol per day (g/d) or men > 0-39.99 g/d; Medium: Women 20-39.99 g/d or men 40-59.99 g/d; High: Women ≥ 40g/d or men ≥ 60 g/d.

c Based on calculated age specific cut-off values.

## **Supplemental Table 3. Cross-sectional associations of vitamin D serum status and vitamin supplements use with hypercalcemia, subgroup analysis by age groups**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Vitamin D exposure** | **Age, 40 - 59 years a**  N=231,560 | | |  | **Age, 60 - 69 years b**  N=175,625 | | |  | **p-interaction c** |
|  | **Ntotal** | **Ncase (%)** | **OR (95%CI)** |  | **Ntotal** | **Ncase (%)** | **OR (95%CI)** |  |  |
| **Vitamin D serum status,  (25[OH]D, nmol/L)** |  |  |  |  |  |  |  |  |  |
| **Deficiency (<30)** | 55,930 | 676(1.2) | 0.94(0.84,1.05) |  | 29,846 | 538(1.8) | 0.95(0.85,1.06) |  | 0.93 |
| **Insufficiency (30-<50)** | 81,079 | 1060(1.3) | 1.00(0.92,1.10) |  | 58,934 | 1084(1.8) | 0.96(0.89,1.05) |  | 0.97 |
| **Sufficiency (50-<100)** | 91,177 | 1237(1.4) | Ref |  | 84,125 | 1634(1.9) | Ref |  | - |
| **High status (≥100)** | 3,374 | 37(1.1) | 0.80(0.58,1.12) |  | 2,720 | 59(2.2) | 1.13(0.87,1.48) |  | 0.36 |
|  |  |  |  |  |  |  |  |  |  |
| **Vitamin supplements use** |  |  |  |  |  |  |  |  |  |
| **Non-users** | 175,023 | 2141(1.2) | Ref |  | 131,826 | 2329(1.8) | Ref |  | - |
| **Multivitamin user** | 48,331 | 679(1.4) | **1.12(1.02,1.22)** |  | 34,462 | 695(2.0) | **1.10(1.01,1.20)** |  | 0.21 |
| **Vitamin D user** | 8,206 | 190(2.3) | **1.55(1.33,1.82)** |  | 9,337 | 291(3.1) | **1.39(1.22,1.58)** |  | 0.26 |

Abbreviations: 25(OH)D: 25-hydroxyvitamin D, CI: confidence interval, HR: hazard ratio, Ref: reference.

Bold print: statistically significant (p<0.05).

All covariates were adjusted in the model (see the legend of Table 2)

a including as small minority of study participants aged 37-39 years (n=6)

b including as small minority of study participants aged 70-73 years (n=1,947)

c Age was considered as continuous variable when calculating interaction terms.

## **Supplemental Table 4. Cross-sectional associations of vitamin D serum status and vitamin supplements use with hypercalcemia, subgroup analysis by sex**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Vitamin D exposure** | **Female** | | |  | **Male** | | |  | **p-interaction** | |
|  | **Ntotal** | **Ncase (%)** | **OR (95%CI)** |  | **Ntotal** | **Ncase (%)** | **OR (95%CI)** |  |  | |
| **Vitamin D serum status,  (25[OH]D, nmol/L)** |  |  |  |  |  |  |  |  |  | |
| **Deficiency (<30)** | 45,362 | 794 (1.8) | **0.89 (0.81, 0.98)** |  | 40,414 | 420 (1.0) | 1.02 (0.88, 1.17) |  | **<.001** | |
| **Insufficiency (30-<50)** | 74,311 | 1492 (2.0) | 0.96 (0.90, 1.03) |  | 65,702 | 652 (1.0) | 1.00 (0.90, 1.12) |  | 0.19 | |
| **Sufficiency (50-<100)** | 93,904 | 2065 (2.2) | Ref |  | 81,398 | 806 (1.0) | Ref |  | - | |
| **High status (≥100)** | 3,094 | 67 (2.2) | 1.02 (0.79, 1.31) |  | 3,000 | 29 (1.0) | 0.93 (0.64, 1.36) |  | 0.97 | |
|  |  |  |  |  |  |  |  |  |  | |
| **Vitamin supplements use** |  |  |  |  |  |  |  |  |  | |
| **Non-users** | 154,733 | 2983 (1.9) | Ref |  | 152,116 | 1487 (1.0) | Ref |  | - | |
| **Multivitamin user** | 49,521 | 1017 (2.1) | **1.10 (1.02, 1.18)** |  | 33,272 | 357 (1.1) | **1.14 (1.01, 1.28)** |  | 0.63 |  | |
| **Vitamin D user** | 12,417 | 418 (3.4) | **1.50 (1.34, 1.67)** |  | 5,126 | 63 (1.2) | 1.20 (0.93, 1.56) |  | 0.59 | |

Abbreviation: 25(OH)D: 25-hydroxyvitamin D, CI: confidence interval, HR: hazard ratio, Ref: reference.

Bold print: statistically significant (p<0.05).

All covariates were adjusted in the model (see the legend of Table 2)

## **Supplemental Table 5. Cross-sectional associations of vitamin D serum status as well as vitamin supplements use with hypercalcemia, subgroup analyses by kidney function**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Vitamin D exposure** | **eGFR < 60 ml/min/1.73m2** | |  | **eGFR 60-<90** **ml/min/1.73m2** | |  | **eGFR ≥ 90 ml/min/1.73m2** | |  | **p-interaction** |
| **Ncase (%)** | **OR (95%CI) a** |  | **Ncase (%)** | **OR (95%CI) a** |  | **Ncase (%)** | **OR (95%CI) a** |  |  |
| **Vitamin D serum status,  (25[OH]D, nmol/L)** |  |  |  |  |  |  |  |  |  |  |
| **Deficiency** | 42 (2.2) | **0.64 (0.43; 0.96)** |  | 469 (1.7) | 0.97 (0.86; 1.10) |  | 701 (1.2) | 0.95 (0.86; 1.06) |  | 0.72 |
| **Insufficiency** | 103 (3.3) | 1.03 (0.78; 1.37) |  | 892 (1.7) | 0.96 (0.88; 1.05) |  | 1,146 (1.4) | 1.00 (0.92; 1.09) |  | 0.27 |
| **Sufficiency** | 130 (3.3) | Ref |  | 1,338 (1.8) | Ref |  | 1,394 (1.4) | Ref |  | - |
| **High status** | 5 (2.3) | 0.67 (0.26; 1.70) |  | 43 (1.7) | 0.93 (0.68; 1.27) |  | 47 (1.4) | 1.05 (0.78; 1.42) |  | 0.75 |
|  |  |  |  |  |  |  |  |  |  |  |
| **Vitamin supplements use** |  |  |  |  |  |  |  |  |  |  |
| **Non-users** | 216 (3.0) | Ref |  | 1,961 (1.7) | Ref |  | 2,284 (1.3) | Ref |  | - |
| **Multivitamin user** | 44 (3.1) | 1.00 (0.71; 1.41) |  | 588 (2.0) | **1.15 (1.04; 1.26)** |  | 736 (1.4) | 1.08 (0.99; 1.18) |  | 0.21 |
| **Vitamin D user** | 20 (4.3) | 1.09 (0.66; 1.79) |  | 193 (2.9) | **1.35 (1.15; 1.58)** |  | 268 (2.6) | **1.59 (1.39; 1.82)** |  | 0.15 |

Abbreviation: 25(OH)D: 25-hydroxyvitamin D, CI: confidence interval, eGRF: estimated Glomerular filtration rate, OR: odds ratio, Ref: reference.

Bold print: statistically significant (p<0.05).

a Model adjusted for all covariates (see legend of Table 2)

## **Supplemental Table 6. Longitudinal associations of vitamin D serum status and vitamin supplements use with kidney stones, subgroup analysis by age groups**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Vitamin D exposure** | **Age, 40 - 59 years a**  N=250,696 | | |  | **Age, 60 - 69 years b**  N=188,493 | | |  | **p-interactionc** |
|  | **Ntotal** | **Ncase (%)** | **HR (95%CI)** |  | **Ntotal** | **Ncase (%)** | **HR (95%CI)** |  |  |
| **Vitamin D serum status,  (25[OH]D, nmol/L)** |  |  |  |  |  |  |  |  |  |
| **Deficiency (<30)** | 60,077 | 713 (1.2) | 1.07 (0.95, 1.20) |  | 31,986 | 459 (1.4) | 1.07 (0.94, 1.21) |  | 0.75 |
| **Insufficiency (30-<50)** | 87,610 | 1,024 (1.2) | **1.13 (1.03, 1.24)** |  | 63,047 | 835 (1.3) | 1.09 (0.99, 1.20) |  | 0.35 |
| **Sufficiency (50-<100)** | 99,329 | 954 (1.0) | Ref |  | 90,546 | 1,040 (1.2) | Ref |  | - |
| **High status (≥100)** | 3,680 | 35 (1.0) | 1.00 (0.71, 1.40) |  | 2,914 | 37 (1.3) | 1.06 (0.76, 1.47) |  | 0.78 |
|  |  |  |  |  |  |  |  |  |  |
| **Vitamin supplements use** |  |  |  |  |  |  |  |  |  |
| **Non-users** | 189,248 | 2,167 (1.2) | Ref |  | 141,377 | 1,813 (1.3) | Ref |  | - |
| **Multivitamin user** | 52,564 | 486 (0.9) | **0.89 (0.81, 0.99)** |  | 37,074 | 439 (1.3) | 1.04 (0.93,1.16) |  | 0.06 |
| **Vitamin D user** | 8,884 | 73 (0.8) | **0.77 (0.61, 0.98)** |  | 10,042 | 119 (1.2) | 1.10 (0.91,1.34) |  | 0.12 |

Abbreviation: 25(OH)D: 25-hydroxyvitamin D, CI: confidence interval, HR: hazard ratio, Ref: reference.

Bold print: statistically significant (p<0.05).

All covariates were adjusted in the model (see the legend of Table 2)

a including as small minority of study participants aged 37-39 years (n=5)

b including as small minority of study participants aged 70-73 years (n=2,088)

c Age was considered as continuous variable when calculating interaction terms.

## **Supplemental Table 7. Longitudinal associations of vitamin D serum status as well as vitamin supplements use with kidney stones, subgroup analysis by sex**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Vitamin D exposure** | **Female** | | |  | **Male** | | |  | **p-interaction** |
|  | **Ntotal** | **Ncase (%)** | **HR (95%CI)** |  | **Ntotal** | **Ncase (%)** | **HR (95%CI)** |  |  |
| **Vitamin D serum status,  (25[OH]D, nmol/L)** |  |  |  |  |  |  |  |  |  |
| **Deficiency (<30)** | 49,295 | 455 (0.9) | **1.18 (1.02, 1.35)** |  | 42,768 | 717 (1.7) | 1.02 (0.91, 1.13) |  | 0.02 |
| **Insufficiency (30-<50)** | 81,292 | 657 (0.8) | **1.15 (1.03, 1.29)** |  | 69,365 | 1,202 (1.7) | **1.09 (1.01, 1.19)** |  | 0.54 |
| **Sufficiency (50-<100)** | 103,117 | 685 (0.7) | Ref |  | 86,758 | 1,309 (1.5) | Ref |  | - |
| **High status (≥100)** | 3,375 | 28 (0.8) | 1.23 (0.84, 1.80) |  | 3219 | 44 (1.4) | 0.93 (0.69, 1.26) |  | 0.19 |
|  |  |  |  |  |  |  |  |  |  |
| **Vitamin supplements use** |  |  |  |  |  |  |  |  |  |
| **Non-users** | 169,252 | 1333 (0.8) | Ref |  | 161,373 | 2,647 (1.6) | Ref |  | - |
| **Multivitamin user** | 54,301 | 374 (0.7) | 0.91 (0.81, 1.02) |  | 35,337 | 551 (1.6) | 0.99 (0.90, 1.09) |  | 0.21 |
| **Vitamin D user** | 13,526 | 118 (0.9) | 1.05 (0.87, 1.28) |  | 5400 | 74 (1.4) | 0.82 (0.65, 1.03) |  | 0.08 |

Abbreviation: 25(OH)D: 25-hydroxyvitamin D, CI: confidence interval, HR: hazard ratio, Ref: reference.

Bold print: statistically significant (p<0.05).

All covariates were adjusted in the model (see the legend of Table 2)

## **Supplemental Table 8. Longitudinal associations of vitamin D serum status as well as vitamin supplements use with kidney stones, subgroup analyses by kidney function**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Vitamin D exposure** | **eGFR < 60 ml/min/1.73m2** | |  | **eGFR 60-<90** **ml/min/1.73m2** | |  | **eGFR ≥ 90 ml/min/1.73m2** | |  | **p-interaction** |
| **Ncase (%)** | **HR (95%CI) a** |  | **Ncase (%)** | **HR (95%CI) a** |  | **Ncase (%)** | **HR (95%CI) a** |  |  |
| **Vitamin D serum status,  (25[OH]D, nmol/L)** |  |  |  |  |  |  |  |  |  |  |
| **Deficiency** | 49 (2.4) | 1.57 (0.99, 2.50) |  | 382 (1.3) | 1.01 (0.88, 1.17) |  | 740 (1.2) | 1.09 (0.98, 1.22) |  | 0.18 |
| **Insufficiency** | 57 (1.7) | 1.27 (0.86, 1.89) |  | 664 (1.2) | 1.01 (0.91, 1.12) |  | 1,136 (1.3) | **1.18 (1.08, 1.29)** |  | 0.21 |
| **Sufficiency** | 52 (1.2) | Ref |  | 866 (1.1) | Ref |  | 1,071 (1.0) | Ref |  | - |
| **High status** | 4 (1.7) | 1.42 (0.50, 4.06) |  | 36 (1.3) | 1.11 (0.79, 1.56) |  | 32 (0.9) | 0.92 (0.64, 1.31) |  | 0.23 |
|  |  |  |  |  |  |  |  |  |  |  |
| **Vitamin supplements use** |  |  |  |  |  |  |  |  |  |  |
| **Non-users** | 132 (1.7) | Ref |  | 1,535 (1.2) | Ref |  | 2,307 (1.2) | Ref |  | - |
| **Multivitamin user** | 20 (1.3) | 0.86 (0.53, 1.40) |  | 351 (1.1) | 1.03 (0.91, 1.15) |  | 553 (1.0) | 0.92 (0.84, 1.01) |  | 0.37 |
| **Vitamin D user** | 10 (2.0) | 1.42 (0.73, 2.76) |  | 62 (0.9) | 0.85 (0.66, 1.10) |  | 119 (1.1) | 0.99 (0.82, 1.19) |  | 0.60 |

Abbreviation: 25(OH)D: 25-hydroxyvitamin D, CI: confidence interval, eGRF: estimated Glomerular filtration rate, OR: odds ratio, Ref: reference.

Bold print: statistically significant (p<0.05).

a Model adjusted for all covariates (see legend of Table 2)



## **Supplemental Figure 1. Distribution of serum 25-hydroxyvitamin D concentration among regular vitamin D supplement users stratified by hypercalcemia status**

Notes: The sample sizes are as follows: n (total) =17,543, n (without hypercalcemia)=17,062, n (with hypercalcemia)=481. The Wilcoxon rank sum test for comparing the median 25-hydroxyvitamin D levels in the groups result was p=0.14.