

Supplements

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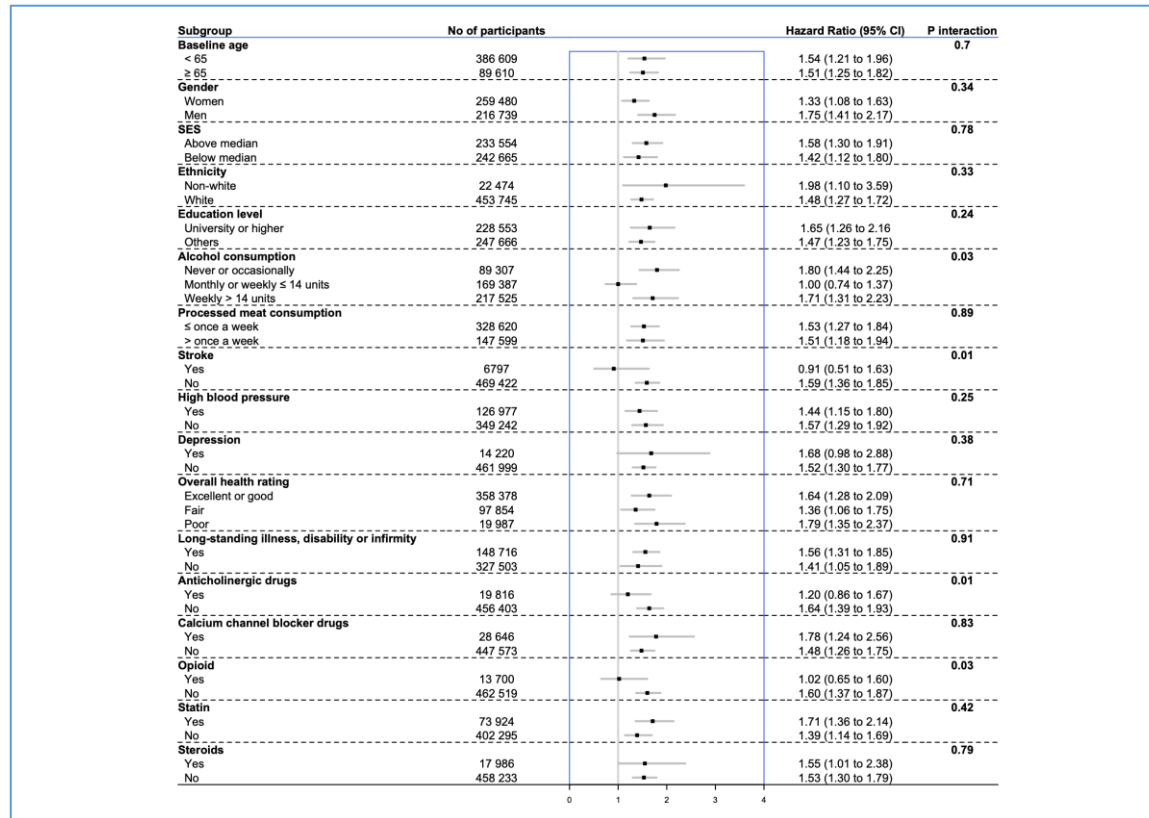
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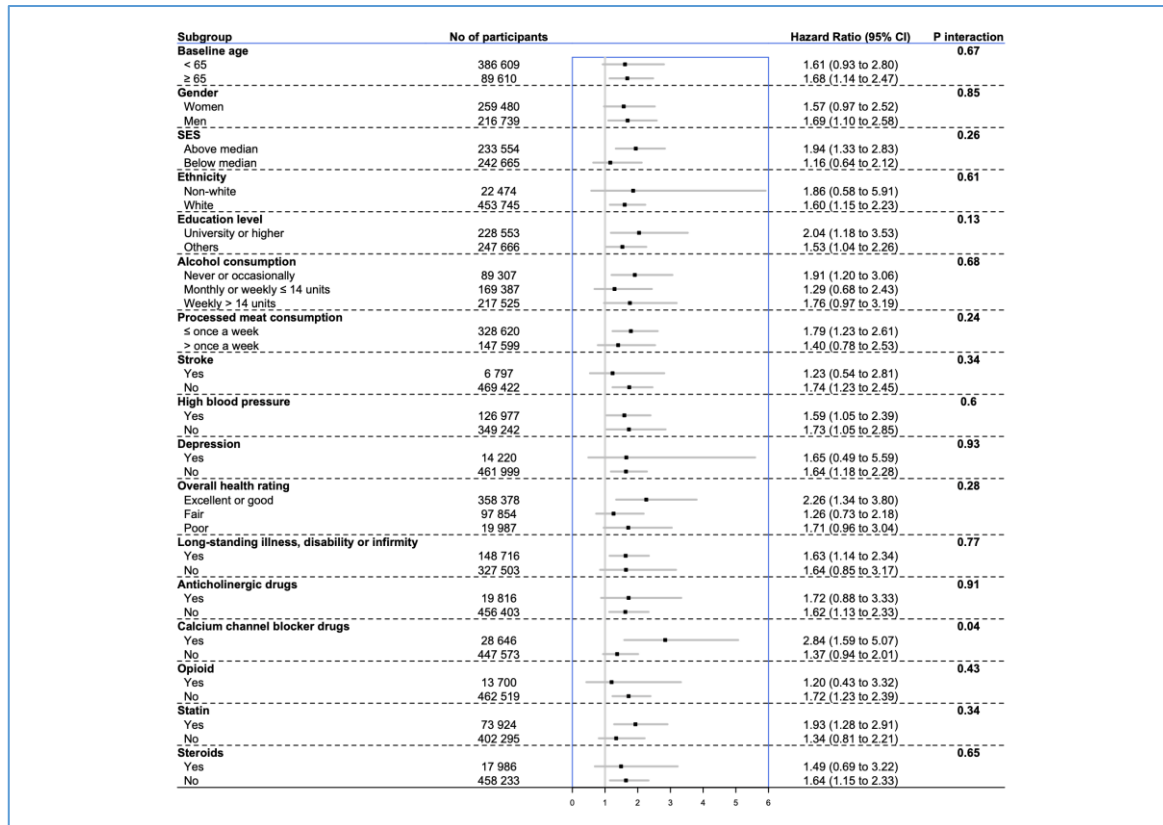
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eFigure 1. Subgroup analysis, association between laxative use and the risk of all-cause dementia



Note: The model is fully adjusted for sociodemographic variables, lifestyle factors, medical conditions and status of regular medication use. The Bonferroni-corrected significance level is 0.003 (original $\alpha = 0.05$, number of tests = 17). Difference between subgroups is statistically significant only when the P-interaction is lower than 0.003.

eFigure 2. Subgroup analysis, association between laxative use and the risk of vascular dementia



Note: The model is fully adjusted for sociodemographic variables, lifestyle factors, medical conditions and status of regular medication use. The Bonferroni-corrected significance level is 0.003 (original $\alpha = 0.05$, number of tests = 17). Difference between subgroups is statistically significant only when the P-interaction is lower than 0.003.

eTable 1. Description of covariates used in the present study.

Measure	Description	Reference group
<i>Sociodemographic variables</i>		
Sex	Female vs. male (Field 31)	Male
Ethnicity	White vs. non-white (Field 21000)	White
Education	University degree or higher vs. degree lower than university (Field 6138)	Degree lower than university
Socio-economic status	Townsend deprivation score, based on the preceding national census output areas. Each participant is assigned a score corresponding to the output area in which their postcode is located. It combines information on social class, employment, car availability and housing: categorized as quintiles 1 (Low), 2 to 4 (Intermediate), and 5(High) (Field 189)	Low
<i>Lifestyle factors</i>		
Smoking status	Touchscreen question: self-reported as never, ex-smoker, or current smoker (Field 20116)	Never
Alcohol consumption	Touchscreen question: categorized as never or occasionally, monthly or weekly lower than 14 units, weekly and more than 14 units (Fields in category 100051)	Never or occasionally
Living alone	Touchscreen question: Including yourself, how many people are living together in your household? (Include those who usually live in the house such as students living away from home during term, partners in the armed forces or professions such as pilots) (Field 709)	Not living alone

Vegetable consumption (servings)	Touchscreen question: total servings of cooked and raw vegetable intake (Field 1289, 1299). One serving of vegetable is defined as 1 cup of raw leafy vegetables; ½ cup of cut-up raw vegetables, cooked vegetables, or 100% vegetable juice.	--
Fruit consumption (servings)	Touchscreen question: total servings of fresh and dried fruit intake (Field 1309, 1319). One serving of fruit consumption is defined as 1 medium-sized fruit; ½ cup of fresh, frozen, or unsweetened canned fruit; ½ cup of dried fruit; ½ cup of 100% juice.	--
Fish consumption	Touchscreen question: frequency of oily and non-oily fish intake (Field 1329, 1339)	Less than twice a week
Processed meat consumption	Touchscreen question: frequency of processed meat intake (Field 1349)	More than once a week
Unprocessed red meat consumption	Touchscreen question: frequency of beef, lamb and pork intake (Field 1369, 1379, 1389)	More than once a week
Physical activities	Touchscreen question: duration of moderate, vigorous activities and number of days/week of moderate or vigorous physical activity 10+ minutes. (Field 894, 914, 884, 904), activity strength was categorized according to World Health Organization recommendations: low = activity less than moderate; moderate activity = 2.5 hr/week moderate or 75 minutes/week vigorous, or > once per week, or equivalent; high activity (for additional health benefits) = 300 minutes/week moderate or 150 minutes/week vigorous, or equivalent.	High

Body mass index	Physical measures: BMI value was constructed from height and weight measured in the initial Assessment Centre visit. (Field 21001)	--
<i>Medical conditions</i>		
Cognitive function (reaction time)	The mean duration to first press of snap-button summed over rounds in which both cards matched. It gives a crude measure of the raw processing and reaction speed of a participant. (Field 20023)	--
Diabetes	Touchscreen question and verbal interview: self-reported regular use of insulin, or at nurse interview, reported diagnosis or taking of a diabetes-related medication (Field 6177, 6153, 20002, 20003)	No diabetes
Heart attack		No heart attack
Stroke	Touchscreen question: has a doctor ever told you that you have had any of the following conditions (heart attack, stroke, high blood pressure, etc.) at baseline assessment (Field 6150)	No stroke
High blood pressure		No high blood pressure
Parkinson's disease	Whether one had records in Parkinson's disease at baseline, using UK Biobank algorithmically-defined outcome. (Field 42030)	No Parkinson's disease
Inflammatory bowel disease	Verbal interview: self-reported non-cancer illness at baseline. (Field 20002)	No inflammatory bowel disease

Depression	Touchscreen question: A combined score of .3 on the first two items of the Patient Health Questionnaire (PHQ-2) that assess the two core criteria of depression experienced in the previous two weeks, or whether participant ever visited a GP for depression or anxiety. (Field 2050, 2060, 2090)	No depression
Family history of dementia	Touchscreen question: self-reported father/mother/sibling with dementia diagnosis Alzheimer's disease/dementia. (Field 20107, 20110, 20111)	No family history of dementia
Overall health rating	Touchscreen question: in general, how would you rate your overall health, with options of poor, fair, good and excellent. (Field 2178)	Excellent
Long-standing illness, disability or infirmity	Touchscreen question: do you have any long-standing illness, disability or infirmity. (Field 2188)	No long-standing illness, disability nor infirmities
<i>Status of regular medication use</i>		
Anticholinergic drugs		No regular use
Calcium channel blocker drugs	Verbal interview: among participants who reported regularly taking other prescription medications (Field 2492), whether one has reported anticholinergic, calcium channel blocker, opioid, statin, antidiarrhoeal or steroids in verbal interview (Field 20003). Medications were categorized according to British National Formula.	No regular use
Opioid		No regular use
Statin		No regular use
Antidiarrhoeal		No regular use
Steroids		No regular use

eTable 2. Baseline characteristics of data used for primary analysis and data excluded.

Characteristics	Total	Kept in primary analysis		SMD*
		Yes	No	
No of participants (prevalence)	502 229	476 219 (94.8)	26 010 (5.2)	
Mean (SD) baseline age (years)	56.5 (8.1)	56.5 (8.1)	57.4 (8.3)	0.11
Women	273 251 (54.4)	259 480 (54.5)	13 771 (52.9)	0.03
Non-white	27 017 (5.4)	22 474 (4.7)	4543 (17.5)	0.42
University degree or higher	234 905 (46.8)	228 553 (48.0)	6352 (24.4)	0.51
Socio-economic status:				0.45
Low	100 607 (20.1)	97 781 (20.5)	2826 (11.1)	
Intermediate	300 702 (59.9)	287 875 (60.5)	12 827 (50.5)	
High	100 297 (20.0)	90 563 (19.0)	9734 (38.3)	
Smoking status:				0.18
Never	273 384 (54.8)	261 141 (54.8)	12 243 (53.1)	
Former	172 949 (34.6)	166 056 (34.9)	6893 (29.9)	
Current	52 951 (10.6)	49 022 (10.3)	3929 (17.0)	
Alcohol consumption:				0.42
Never or occasionally	98 565 (19.7)	89 307 (18.8)	9258 (38.0)	
Monthly or weekly \leq 14 units	176 809 (35.3)	169 387 (35.6)	7422 (30.5)	
Weekly $>$ 14 units	225 209 (45.0)	217 525 (45.7)	7684 (31.5)	
Living alone	92 858 (18.5)	87 033 (18.3)	5825 (22.4)	0.10
Mean (SD) Vegetable consumption (servings)	4.9 (3.4)	4.9 (3.3)	5.0 (4.3)	0.02
Mean (SD) Fruit consumption (servings)	3.1 (2.6)	3.1 (2.6)	3.1 (3.3)	0.01
Fish consumption \geq twice a week	259 955 (51.8)	248 273 (52.1)	11 682 (44.9)	0.15
Processed meat consumption \leq once a week	345 012 (68.7)	328 620 (69.0)	16 392 (63.0)	0.13
Unprocessed red meat consumption \leq once a week	341 201 (67.9)	324 820 (68.2)	16 381 (63.0)	0.11

Physical activities:				0.16
Low	207 775 (42.4)	201 789 (42.4)	5986 (43.6)	
Moderate	124 399 (25.4)	120 178 (25.2)	4221 (30.7)	
High	157 778 (32.2)	154 252 (32.4)	3526 (25.7)	
Mean (SD) cognitive function (reaction time)	559.6 (117.9)	557.8 (115.8)	603.4 (154.7)	0.33
Diabetes	26 057 (5.2)	23 456 (4.9)	2601 (10.0)	0.19
Heart attack	11 588 (2.3)	10 592 (2.2)	996 (3.8)	0.09
Stroke	7647 (1.5)	6797 (1.4)	850 (3.3)	0.12
High blood pressure	135 662 (27.0)	126 977 (26.7)	8685 (33.4)	0.15
Parkinson's disease	936 (0.2)	851 (0.2)	85 (0.3)	0.03
Inflammatory bowel disease	4227 (0.8)	4030 (0.8)	197 (0.8)	0.01
Mean (SD) body mass index	27.4 (4.8)	27.4 (4.8)	28.7 (5.4)	0.26
Depression	15 980 (3.2)	14 220 (3.0)	1760 (6.8)	0.18
Family history of dementia	58 308 (11.6)	55 978 (11.8)	2330 (9.0)	0.09
Overall health rating:				0.49
Excellent	81 842 (16.4)	80 099 (16.8)	1743 (7.7)	
Good	288 913 (57.9)	278 279 (58.4)	10 634 (47.2)	
Fair	105 274 (21.1)	97 854 (20.5)	7420 (32.9)	
Poor	22 719 (4.6)	19 987 (4.2)	2732 (12.1)	
Long-standing illness, disability or infirmity	159 704 (31.8)	148 716 (31.2)	10 988 (42.2)	0.23
Anticholinergic drugs	21 846 (4.3)	19 816 (4.2)	2030 (7.8)	0.15
Calcium channel blocker drugs	30 973 (6.2)	28 646 (6.0)	2327 (8.9)	0.11
Opioid	15 355 (3.1)	13 700 (2.9)	1655 (6.4)	0.17
Statin	79 463 (15.8)	73 924 (15.5)	5539 (21.3)	0.15
Antidiarrhoeal	383 (0.1)	358 (0.1)	25 (0.1)	0.01
Steroid	19 044 (3.8)	17 986 (3.8)	1058 (4.1)	0.02

The numbers in the parenthesis are column percentages, unless stated otherwise.

* SMD is standardized mean differences shown as an absolute value, which indicates meaningful imbalance if its value is greater than 0.1.

eTable 3. Association of regular use of specific types of laxatives with the risk of all-cause dementia (comparison with bulk-forming).

Laxative class	All-cause dementia	
	cases/total	HR (95% CI)
Bulk-forming	19/2339 (0.8)	1 (ref)
Softening	6/315 (1.9)	1.57 (0.59 to 4.17)
Osmotic	44/2051 (2.1)	2.10 (1.20 to 3.69)**
Stimulant	18/1095 (1.6)	1.25 (0.62 to 2.53)

Note: *P<0.05, **P<0.01, ***P<0.001.

This analysis included 5800 participants who reported the use of only one type of laxatives. The model is fully adjusted for sociodemographic variables, lifestyle factors, medical conditions and status of regular medication use.

eTable 4. Association between regular laxative use and risk of all-cause dementia, Alzheimer’s disease, and vascular dementia in competing risk analysis.†

Outcomes	Regular laxative users		Cox regression	Competing risk analysis	No of competing (death)
	Yes (n = 16 703)	No (n = 459 516)	HR (95% CI)	HR (95% CI)	
All-cause dementia	218 (1.3)	1969 (0.4)	1.51 (1.30 to 1.75)***	1.52 (1.30 to 1.77)***	25 920
Alzheimer's disease	55 (0.3)	769 (0.2)	1.05 (0.79 to 1.40)	1.04 (0.78 to 1.40)	26 756
Vascular dementia	47 (0.3)	403 (0.1)	1.65 (1.21 to 2.27)**	1.62 (1.17 to 2.24)**	26 954

Note: *P<0.05, **P<0.01, ***P<0.001.

The model is fully adjusted for sociodemographic variables, lifestyle factors, medical conditions and status of regular medication use.

†Modified Fine and Gray competing risk analysis.

eTable 5. Association between regular laxative use and risk of all-cause dementia, Alzheimer’s disease, and vascular dementia after excluding 106 participants diagnosed with dementia within first two years of follow-up

Outcomes	Regular laxative users		Hazard ratio (95% CI)			
	Yes (n = 16 683)	No (n = 459 430)	Model 1†	Model 2‡	Model 3¶	Model 4§
All-cause dementia	198 (1.2)	1883 (0.4)	2.39 (2.06 to 2.77)***	2.24 (1.93 to 2.60)***	1.53 (1.31 to 1.78)***	1.45 (1.24 to 1.69)***
Alzheimer's disease	51 (0.3)	746 (0.2)	1.47 (1.11 to 1.96)**	1.39 (1.05 to 1.85)**	1.06 (0.79 to 1.42)	1.01 (0.75 to 1.35)
Vascular dementia	39 (0.2)	388 (0.1)	2.35 (1.69 to 3.28)***	2.13 (1.52 to 2.97)***	1.50 (1.07 to 2.10)*	1.44 (1.03 to 2.03)*

Note: *P<0.05, **P<0.01, ***P<0.001.

†Adjusted for sociodemographic variables: age (time scale), sex, ethnicity, education, and socio-economic status.

‡Additionally adjusted for lifestyle factors: smoking status, alcohol consumption, living alone, dietary consumption of vegetable, fruit, fish, and processed/unprocessed meat, physical activities, and body mass index.

¶Additionally adjusted for medical conditions: diabetes, heart attack, stroke, high blood pressure, Parkinson’s disease, inflammatory bowel disease, depression, cognitive test, family history of dementia, overall health rating and long-standing illness.

§Additionally adjusted for status of regular medication use: opioids, anticholinergic drugs, statins, calcium channel blockers, antidiarrheal agents, and steroids.

eTable 6. Association between regular laxative use and risk of all-cause dementia, Alzheimer’s disease, and vascular dementia after excluding 393 participants diagnosed with dementia within first four years of follow-up.

Outcomes	Regular laxative users		Hazard ratio (95% CI)			
	Yes (n = 16 655)	No (n = 459 171)	Model 1†	Model 2‡	Model 3¶	Model 4§
All-cause dementia	170 (1.0)	1624 (0.4)	2.35 (2.01 to 2.76)***	2.20 (1.88 to 2.59)***	1.53 (1.30 to 1.81)***	1.44 (1.22 to 1.71)***
Alzheimer's disease	44 (0.3)	642 (0.1)	1.48 (1.09 to 2.01)*	1.39 (1.02 to 1.89)*	1.07 (0.78 to 1.47)	1.01 (0.74 to 1.39)
Vascular dementia	32 (0.2)	335 (0.1)	2.19 (1.52 to 3.16)***	1.97 (1.36 to 2.84)***	1.42 (0.98 to 2.06)	1.35 (0.93 to 1.97)

Note: *P<0.05, **P<0.01, ***P<0.001.

†Adjusted for sociodemographic variables: age (time scale), sex, ethnicity, education, and socio-economic status.

‡Additionally adjusted for lifestyle factors: smoking status, alcohol consumption, living alone, dietary consumption of vegetable, fruit, fish, and processed/unprocessed meat, physical activities, and body mass index.

¶Additionally adjusted for medical conditions: diabetes, heart attack, stroke, high blood pressure, Parkinson’s disease, inflammatory bowel disease, depression, cognitive test, family history of dementia, overall health rating and long-standing illness.

§Additionally adjusted for status of regular medication use: opioids, anticholinergic drugs, statins, calcium channel blockers, antidiarrheal agents, and steroids.

eTable 7. Association between regular laxative use and risk of all-cause dementia, Alzheimer’s disease, and vascular dementia after multiple imputation.

Outcomes	Regular laxative users		Hazard ratio (95% CI)			
	Yes (n = 18 235)	No (n = 483 994)	Model 1†	Model 2‡	Model 3¶	Model 4§
All-cause dementia	258 (1.4)	2244 (0.5)	2.51 (2.20 to 2.86)***	2.35 (2.06 to 2.68)***	1.60 (1.40 to 1.83)***	1.53 (1.34 to 1.76)***
Alzheimer's disease	65 (0.4)	865 (0.2)	1.56 (1.21 to 2.01)**	1.47 (1.14 to 1.89)**	1.12 (0.87 to 1.45)	1.07 (0.83 to 1.39)
Vascular dementia	59 (0.3)	466 (0.1)	2.82 (2.14 to 3.71)***	2.56 (1.94 to 3.37)***	1.72 (1.30 to 2.28)***	1.66 (1.25 to 2.20)***

Note: *P<0.05, **P<0.01, ***P<0.001.

†Adjusted for sociodemographic variables: age (time scale), sex, ethnicity, education, and socio-economic status.

‡Additionally adjusted for lifestyle factors: smoking status, alcohol consumption, living alone, dietary consumption of vegetable, fruit, fish, and processed/unprocessed meat, physical activities, and body mass index.

¶Additionally adjusted for medical conditions: diabetes, heart attack, stroke, high blood pressure, Parkinson’s disease, inflammatory bowel disease, depression, cognitive test, family history of dementia, overall health rating and long-standing illness.

§Additionally adjusted for status of regular medication use: opioids, anticholinergic drugs, statins, calcium channel blockers, antidiarrheal agents, and steroids.

eTable 8. Association between regular laxative use and early-onset dementia

Outcome	Regular laxative use		Hazard ratio (95% CI)
	Yes (n=5150)	No (n=181 593)	Fully adjusted model
Early-onset dementia	32 (0.6)	261 (0.1)	1.65 (1.09 to 2.50)*

Note: *P<0.05, **P<0.01, ***P<0.001.

This analysis included 186 643 participants aged 40-64. The model is fully adjusted for sociodemographic variables, lifestyle factors, medical conditions and status of regular medication use.

eTable 9. Association between regular laxative use and late-onset dementia

Outcome	Regular laxative use		Hazard ratio (95% CI)
	Yes (n=16 703)	No (n=459 516)	Fully adjusted model
Late-onset dementia	186 (1.1)	1708 (0.4)	1.48 (1.26 to 1.73)***

Note: *P<0.05, **P<0.01, ***P<0.001.

The model is fully adjusted for sociodemographic variables, lifestyle factors, medical conditions and status of regular medication use.

eTable 10. Negative control outcome analysis examining the association between regular laxative use and risk of hip fracture

Outcome	Regular laxative users		Hazard ratio (95% CI)			
	Yes (n = 16 651)	No (n = 458 974)	Model 1†	Model 2‡	Model 3¶	Model 4§
Hip fracture	116 (0.7)	1732 (0.4)	1.42 (1.18 to 1.72)***	1.38 (1.14 to 1.67)**	1.10 (0.91 to 1.34)	1.05 (0.87 to 1.28)

Note: *P<0.05, **P<0.01, ***P<0.001.

†Adjusted for sociodemographic variables: age (time scale), sex, ethnicity, education, and socio-economic status.

‡Additionally adjusted for lifestyle factors: smoking status, alcohol consumption, living alone, dietary consumption of vegetable, fruit, fish, and processed/unprocessed meat, physical activities, and body mass index.

¶Additionally adjusted for medical conditions: diabetes, heart attack, stroke, high blood pressure, Parkinson's disease, inflammatory bowel disease, depression, cognitive test, family history of dementia, overall health rating and long-standing illness.

§Additionally adjusted for status of regular medication use: opioids, anticholinergic drugs, statins, calcium channel blockers, antidiarrheal agents, and steroids.