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Association of supplemental calcium and dairy milk intake with all-cause and cause-specific mortality in the UK Biobank: a prospective cohort study

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Abstract

Excessive Ca intakes have been proposed to associate with vascular calcification and a higher risk of prostate cancer. We investigated the associations of supplemental and dietary Ca intake with mortality using data from 497 828 UK Biobank participants. The average follow-up was 4·2 years and 14 255 participants died, 8297 from cancer, 2959 from CVD and 572 from respiratory disease. The use of Ca supplements and milk consumption were associated with differences in mortality in younger (≤65 years) but not in older participants (>65 years, $P_{interaction} \leq 0{\cdot}04$ for all comparisons). Among participants <65 years, there was an inverse association between Ca supplementation (OR 0·91, 95 % CI 0·83, 0·99) and milk consumption (OR 0·93, 95 % CI 0·86, 1·00) with respect to all-cause mortality. In the same age group, milk drinkers had lower odds of cancer mortality (OR 0·89, 95 % CI 0·80, 0·98) but Ca supplement use was associated with increased odds of respiratory mortality (OR 1·69, 95 % CI 1·16, 2·74). All associations in participants aged ≥65 years were null after full adjustment. In sensitivity analyses stratified by hormone replacement therapy, Ca supplement use was associated with decreased odds of cancer mortality in users but increased risk in other women (OR 0·81, 95 % CI 0·69, 0·94 *v.* OR 1·17, 95 % CI 1·01, 1·35, respectively). To conclude, we saw little evidence for harm with dietary or supplemental Ca. Further studies are required to confirm the proposed interaction with hormone replacement therapy and to exclude reverse causation as a determinant in the association between Ca supplements and increased risk of respiratory diseases.

Key words: Calcium supplements: Dairy milk: All-cause mortality: Cancer mortality: Cardiovascular mortality: Respiratory mortality

Ca is recognised as a key nutrient for human health. Dairy products, including milk, are a major food contributor of Ca due to their high bioavailability[1]. Where recommended daily intakes of Ca cannot be obtained through food sources, or for populations at risk of deficiency, Ca supplements are often advised to prevent osteoporosis[2]. However, in the last decade, several studies have linked dietary and supplemental Ca with a number of adverse health outcomes. In particular, the literature has indicated a potential link between Ca supplementation and adverse cardiovascular events[3]. It has been suggested that excessive Ca supplementation accelerates vascular calcification[4], which is an independent predictor of cardiovascular mortality[5,6]. There have also been reports of increased risk of prostate cancer in men with use of Ca supplements[7,8], proposed to be due to the down-regulation of calcitriol levels, which in turn may increase cell proliferation in the prostate[9]. However, meta-analyses of both interventional and observational studies have failed to demonstrate this association[10,11]. To our knowledge, the relationship between Ca supplements and respiratory mortality has not been investigated in adults, although parenteral Ca administration to critically ill patients has been associated with an increased risk of acute respiratory failure[12]. In line with supplementation, evidence on the association between milk consumption with disease risk and mortality has produced conflicting results. Some studies have reported an increased risk between milk consumption and mortality[13,14], while others found an inverse relationship[15,16] or no evidence for an association[17–22]. Overall, the relationship between supplemental and dietary Ca and mortality risk in the general population remains unclear and is likely to depend on the underlying pathology. In this prospective study, we used information from nearly 500 000 participants in the UK Biobank to examine the associations of supplemental Ca and dairy milk consumption with all-cause and cause-specific mortality.

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Methods

Study design and participants

The study design has been previously described elsewhere[23]. Briefly, between March 2006 and July 2010, the UK Biobank recruited 502 316 men and women from across England, Scotland and Wales. Inclusion criteria included being aged 40–69 years and living within a reasonable travelling distance (10 miles) from one of the twenty-two assessment centres. Participants attended their closest assessment centre and provided baseline information, physical measures and biological samples. In the present study, we included all participants in the UK Biobank who provided information on Ca supplementation or milk intake during the baseline assessment (n 497 828). This research was conducted under UK Biobank application 20175. The UK Biobank study was approved by the National Information Governance Board for Health and Social Care and North West Multicentre Research Ethics Committee (11/NW/0382).

Outcomes

Mortality data were obtained from the National Death Registries through linkage to records held by the Office for National Statistics for England and Wales and the Registrar General's Office for Scotland[24]. At the time of analysis, information on mortality outcomes was available up to July 2016, with the latest death date recorded in February 2016. Information on hospitalisations after the baseline data collection was identified through linkage to Hospital Episode Statistics for participants from England and Wales and through Scottish morbidity records for participants from Scotland[25]. Primary causes of death were defined using the International Classification of Diseases edition 10[26] for cancer (code C00-D48), CVD (code I00-I89) and respiratory disease (J09-J22, J40-J47). Respiratory hospital admissions were further categorised as acute and infectious respiratory conditions (code J09-J22), chronic obstructive pulmonary diseases (code J40-J44) and asthma (code J45-J46).

Exposures and covariates

Information on supplemental Ca and dairy milk consumption was self-reported at baseline using computer-based touchscreen questionnaires[23]. Use of Ca supplements referred to current use ('Do you take any of the following [mineral supplements]?'). Dairy milk consumption was based on the question asking about the use and type of milk typically used (full cream, semi-skimmed, skimmed, soya, other type of milk, never/rarely have milk). Participants who answered 'Do not know' or 'Prefer not to answer' were coded as missing. Data on dietary Ca intake were available for a subsample that completed the 24-h recall questionnaire (web-based)[23]. Participants were presented with 200 commonly consumed foods and drinks and reported the amount of each food consumed in the preceding 24-h period.

Covariate data were also self-reported via the touchscreen questionnaire[23]. We considered demographic, socio-economic, lifestyle and health factors as potential confounders based on their known associations with mortality and Ca intake. Demographic variables included sex, age group (<65 or ≥65 years), ethnicity (White British, Asian/Asian British, Black/Black British or Mixed/Other) and BMI, which was calculated based on height and weight (categorised as underweight (<18·5 kg/m^2), normal weight (18·5 to <25·0 kg/m^2), overweight (25·0 to <30·0 kg/m^2) or obese (≥30 kg/m^2). BMI was based on measures obtained during the baseline visit. Key socio-economic determinants of health were considered, including highest education qualification (none, high school, National Vocational Qualification/Certificate of Secondary Education/Advanced levels or university degree or higher) and Townsend deprivation index (divided into five quintiles). Smoking status (never, former smoker or current smoker), alcohol consumption (daily or almost daily, 3–4 times/week, 1–2 times/week, 1–3 times/month or special occasions only) and physical activity intensity (none, light/moderate, vigorous) were regarded as confounding lifestyle factors. Health-related confounders included the number of treatments or medication taken (none, 1–2, 3–4 or ≥5) and self-reported assessment of general health (self-rated as excellent, good, fair or poor). Use of hormone replacement therapy was also considered in sensitivity analyses.

With regard to respiratory disease, we deemed inhaled corticosteroids, combination of inhaled corticosteroids and long-acting β-2 agonists, as potential confounders by indication, based on the known influence on bone metabolism[27]. Medications were coded by a trained nurse via a standardised computer-assisted personal interview and validated by linking with the participants' past medical records.

Statistical methods

Our primary analyses examined associations between Ca supplementation and dairy milk intake with mortality from all causes, cancer, CVD and respiratory disease using logistic regression. Effect modification by demographic variables was tested by adding an interaction term to the logistic regression model. Due to the observed effect modification by age, main analyses and results were stratified by age group (<65 and ≥65 years). OR and 95 % CI were estimated, with P values <0·05 considered statistically significant. Crude analyses adjusted for sex, age, ethnicity and assessment centre. In multivariate analyses, the models were further adjusted for potential confounders at baseline, including BMI, education level, deprivation quintile, smoking status, alcohol consumption, physical activity intensity, number of treatments or medications taken and self-reported health.

Several sensitivity analyses were conducted to determine the influence of our assumptions on resulting associations. First, we examined associations between supplementation with nutrients other than Ca on mortality outcomes, with reference to individuals who used no supplements at all. With respect to respiratory mortality, we adjusted models for use of inhaled corticosteroids. Cross-sectional regression was also performed to determine trends between Ca supplementation and use of inhaled corticosteroids. In *post hoc* analyses, we investigated the association between Ca supplementation and hospital admissions for cause-specific respiratory diseases. We

performed these analyses twice, with participants with mild to severe airflow limitation (FEV1:FVC ratio <70 %) or other chronic lower respiratory conditions at baseline both included then excluded from the control groups. All analyses were performed using STATA, version 14.1[28].

Results

After an average follow-up time of 4·2 years, we documented 14 255 total deaths, of which 8297 were due to cancer, 2959 attributed to CVD and 572 related to respiratory diseases. Baseline characteristics of the study sample are shown in Table 1. A total of 34 906 participants reported use of Ca supplements, and 454 756 participants were consumers of dairy milk (7·56 % full cream; 70·48 % semi-skimmed; 21·96 % skimmed). Compared with participants who did not use Ca supplements, users tended to be female, aged ≥65 years, underweight, never smoke or consume alcohol, engage in light or moderate physical activity and have a degree or professional qualification. Ca supplement use was also associated with taking more total treatments or medications and poor self-reported health. Participants who consumed dairy milk were more likely to be male, of White or Asian descent and never consume alcohol. Rates of all-cause mortality were highest in males, participants aged ≥65 years and those of White ethnicity. In addition, participants that died from all causes were more likely to be underweight, current smokers at baseline, never consume alcohol, more materially deprived and less likely to engage in physical activity or have higher degree education. As expected, mortality was also associated with higher use of treatments or medications and worse self-reported health.

The association between Ca supplementation and milk consumption with mortality varied by age group ($P_{interaction} \leq 0{\cdot}04$) but not by sex or ethnicity ($P_{interaction} \geq 0{\cdot}06$). In simple models adjusted for age, sex, ethnicity and assessment centre, supplementation was associated with an increased risk of all-cause mortality in the full sample and in younger participants (<65 years), but this association was abolished or reversed after full adjustment for social, behavioural and health-related characteristics (Table 2). There was no evidence for an association between Ca supplementation with mortality from cancer or CVD after full adjustment. In contrast, mortality from respiratory diseases was elevated in participants who were aged younger than 65 years (fully adjusted OR 1·69, 95 % CI 1·16, 2·47) (Table 2). Multivariate analyses for the association between Ca supplementation and respiratory mortality in younger participants remained elevated and significant when controlling further for the use of inhaled corticosteroids ($P = 0{\cdot}006$, data not shown). There was some evidence for an association between dairy milk intake and lower mortality risk in the simple models (Table 2). A borderline association remained after full adjustment in participants <65 years old with respect to all-cause mortality and cancer mortality (Table 2). In participants aged ≥65 years, there were no associations between milk intake and all-cause or cause-specific mortality before or after multivariate adjustment (Table 2). Dietary Ca intake was not associated with all-cause or cause-specific mortality in the sub-sample, using information available from the 24-h dietary recall (*n* 68 795, Table 2).

Sensitivity analysis

In further analyses, we compared the patterns observed with Ca supplementation with those seen with the use of any other supplements. We found statistically significant decreases by the intake of other supplements (excluding Ca) in the odds of mortality from all causes, cancer and CVD ($P < 0{\cdot}01$ for all comparisons), while no associations were seen for respiratory mortality (online Supplementary Table S2).

Due to the suggested association between Ca supplementation and mortality from respiratory diseases, analyses were undertaken to establish any related evidence with respect to hospitalisations for cause-specific respiratory conditions. As shown in Table 3, Ca supplementation was not associated with the odds of hospital admission for acute and infectious respiratory conditions, chronic obstructive pulmonary diseases or asthma ($P > 0{\cdot}10$) after full confounder adjustment, despite observed increases in mortality. Cross-sectional analysis demonstrated that participants who used Ca supplements were slightly more likely to use inhaled corticosteroids (8·86 *v.* 6·97 %).

In further interaction analyses, we found evidence for a differential effect of Ca supplementation on cancer mortality based on the previous use of hormone replacement therapy ($P_{interaction} = 0{\cdot}0003$). After full adjustment for covariates, Ca supplement use was associated with a decreased odds of cancer mortality in women using hormone replacement therapy but an increased risk in other women (fully adjusted OR 0·81, 95 % CI 0·69, 0·94 *v.* OR 1·17, 95 % CI 1·01, 1·35, respectively) (Table 4). This interaction was reflected in the relation between Ca supplementation and total mortality ($P_{interaction} = 0{\cdot}015$), while associations with CVD or respiratory disease mortality were not modified by hormone replacement therapy use.

Discussion

In this large-scale prospective study, we found little evidence to support the expressed concerns for possible adverse effects of Ca on mortality risk. In majority of these analyses, significant associations appeared to be due to confounding. However, we observed an association between Ca supplementation and elevated odds of mortality from respiratory diseases in participants aged younger than 65 years, with this association being robust to adjustment for social, lifestyle and health-related confounders, including the use of inhaled corticosteroid medications. However, the suggested increase in respiratory disease risk by Ca supplementation was not replicated in the analyses using data from hospital admissions, suggesting that independent data are required to confirm our findings.

Parenteral Ca administration to critically ill patients has been reported to more than double the mortality risk and the risk of acute respiratory failure[12]. These observations are in line with animal studies and may be related to pro-inflammatory actions by Ca[29]. However, the evidence for an association between oral Ca supplementation and mortality from respiratory diseases was unexpected. To our knowledge, no study has specifically

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Table 1. Characteristics of the UK Biobank participants
(Numbers and percentages)

	Total		Other supplementation			Ca supplementation			Dairy milk drinkers			All-cause mortality		
	n	%	*n*	%	*P*	*n*	%	*P*	*n*	%	*P*	*n*	%	*P*
Sex														
Male	227 086	45·62	101 477	44·89	$<1·0 \times 10^{-300}$	6055	2·68	$<1·0 \times 10^{-300}$	211 397	93·22	$<1·0 \times 10^{-300}$	8655	3·81	$2·8 \times 10^{-295}$
Female	270 742	54·38	150 862	55·84		28 851	10·68		243 359	89·83		5600	2·07	
Age (years)														
<65	403 040	80·96	195 943	48·77	$<1·0 \times 10^{-300}$	26 390	6·57	$<1·0 \times 10^{-300}$	367 218	91·20	$<1·0 \times 10^{-300}$	8738	2·17	$<1·0 \times 10^{-300}$
≥65	94 788	19·04	56 396	59·71		8516	9·02		87 538	92·41		5517	5·82	
Ethnicity														
White/White British	469 204	94·25	237 401	50·72	$1·3 \times 10^{-30}$	31 921	6·82	$8·5 \times 10^{-158}$	430 319	91·78	$<1·0 \times 10^{-300}$	13 737	2·93	$4·5 \times 10^{-32}$
Asian/Asian British	12 202	2·45	6101	50·99		1346	11·25		11 053	90·96		200	1·64	
Black/Black British	9054	1·82	5084	56·98		847	9·49		7212	79·96		132	1·46	
Mixed/other	5616	1·13	2899	52·34		652	11·77		4704	84·15		118	2·10	
Missing	1752	0·35	854	50·03		140	8·20		1468	84·66		68	3·88	
BMI (kg/m^2)														
Underweight	2471	0·50	1337	54·28	$5·4 \times 10^{-250}$	416	16·89	$<1·0 \times 10^{-300}$	2074	84·17	$1·1 \times 10^{-256}$	159	6·43	$1·3 \times 10^{-93}$
Normal	158 723	31·88	85 116	53·74		15 013	9·48		142 149	89·64		3847	2·42	
Overweight	211 479	42·48	106 862	50·69		12 937	6·14		195 029	92·29		5711	2·70	
Obese	122 465	24·60	57 689	47·31		6288	5·16		113 117	92·46		4304	3·51	
Missing	2690	0·54	1335	51·17		252	9·66		2387	89·20		4304	8·70	
Education														
None	85 048	17·08	43 204	51·17	$4·0 \times 10^{-4}$	5404	6·40	$1·2 \times 10^{-47}$	92·79	92·79	$1·6 \times 10^{-113}$	4359	5·13	$<1·0 \times 10^{-300}$
NVQ/CSE/A-levels	173 693	34·89	87 436	50·47		11 434	6·60		159 720	92·02		4475	2·58	
Degree/professional	233 714	46·95	119 007	51·00		17 676	7·57		211 467	90·53		5199	2·22	
Missing	5373	1·08	2692	52·07		392	7·58		4806	90·22		222	4·13	
Townsend deprivation index quintiles														
Q1 Lowest	99 636	20·01	52 038	52·30	$1·2 \times 10^{-82}$	6947	6·98	$2·1 \times 10^{-100}$	92 228	92·60	$1·7 \times 10^{-244}$	2404	2·41	$3·9 \times 10^{-112}$
Q2	99 565	20·00	51 597	51·90		6835	6·88		91 988	92·43		2425	2·44	
Q3	99 481	19·98	50 971	51·36		6847	6·90		91 601	92·13		2651	2·66	
Q4	99 429	19·97	49 878	50·32		7032	7·09		90 385	90·98		2913	2·93	
Q5 Highest	99, 098	19·91	47 583	48·39		7206	7·33		87 991	89·00		3848	3·88	
Missing	619	0·12	272	44·23		39	6·34		563	90·95		14	2·26	
Smoking														
Never smoker	271 575	54·55	137 947	50·95	$<1·0 \times 10^{-300}$	20 035	7·40	$<1·0 \times 10^{-300}$	248 437	91·55	$5·3 \times 10^{-8}$	5283	1·95	$<1·0 \times 10^{-300}$
Former smoker	171 734	34·50	90 966	53·10		12 108	7·07		156 419	91·14		5987	3·49	
Current smoker	52 595	10·56	22 435	42·90		2634	5·04		48 184	91·81		2889	5·49	
Missing	1924	0·39	991	53·39		129	6·95		1716	90·65		96	4·99	
Alcohol intake														
Daily or almost daily	101 156	20·32	50 966	50·48	$1·8 \times 10^{-11}$	6463	6·40	$7·7 \times 10^{-225}$	92 822	91·83	$3·1 \times 10^{-250}$	3237	3·20	$2·8 \times 10^{-122}$
3–4 times/week	114 638	23·03	58 313	50·97		7169	6·27		105 877	92·40		2642	2·30	
1–2 times/week	128 297	25·77	64 723	50·60		8180	6·40		118 370	92·32		3323	2·59	
1–3 times/month	55 415	11·13	27 773	50·25		4068	7·36		50 405	91·02		1355	2·45	
Special occasions	57 546	11·56	29 887	52·18		5053	8·82		51 556	89·70		1959	3·40	
Never	40 298	8·09	20 431	51·16		3936	9·86		35 321	87·88		1710	4·24	
Missing	478	0·10	246	57·21		37	8·60		405	89·80		29	6·07	

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Table 1. (*Continued*)

	Total		Other supplementation			Ca supplementation			Dairy milk drinkers			All-cause mortality		
	n	%	*n*	%	*P*	*n*	%	*P*	*n*	%	*P*	*n*	%	*P*
Physical activity intensity														
None	32 582	6·54	13 749	42·51	$9·3 \times 10^{-210}$	2110	6·52	$3·6 \times 10^{-249}$	29 399	90·49	$5·0 \times 10^{-9}$	1809	5·55	$3·8 \times 10^{-286}$
Light/moderate	409 374	82·23	209 700	51·38		29 426	7·21		374 344	91·49		11 337	2·77	
Strenuous	49 749	9·99	25 729	51·77		2854	5·74		45 456	91·40		649	1·30	
Missing	6123	1·23	3161	52·65		516	8·59		5557	92·57		460	7·51	
Number of treatments or medications taken														
None	136 473	27·41	49 862	36·63	$<1·0 \times 10^{-300}$	5016	3·69	$<1·0 \times 10^{-300}$	125 111	91·77	$4·6 \times 10^{-30}$	2169	1·59	$<1·0 \times 10^{-300}$
1–2	170 957	34·34	84 503	49·57		9945	5·83		156 687	91·73		3559	2·08	
3–4	99 176	19·92	58 888	58·58		8330	8·43		90 480	91·30		3024	3·05	
≥5	90 720	18·22	58 864	65·17		11 574	12·81		82 028	90·51		5470	6·03	
Missing	502	0·10	222	48·68		41	8·99		450	90·18		33	6·57	
Self-reported health														
Excellent	81 303	16·33	40 385	49·72	$2·0 \times 10^{-47}$	5451	6·71	$9·3 \times 10^{-117}$	74 472	91·64	$3·8 \times 10^{-47}$	1252	1·54	$<1·0 \times 10^{-300}$
Good	286 902	57·63	148 187	51·77		19 670	6·87		262 827	91·67		6267	2·18	
Fair	104 591	21·01	51 641	49·62		7443	7·15		95 344	91·28		4324	4·13	
Poor	22 585	4·54	11 073	49·43		2146	9·58		20 013	88·86		2256	9·99	
Missing	2447	0·49	1053	46·41		196	8·64		2100	87·14		156	6·38	

NVQ, National Vocational Qualification; CSE, Certificate of Secondary Education; A-levels, Advanced level.

investigated the effect of Ca supplementation on respiratory diseases. Given the lack of reliable literature to support this finding, one possibility is that the observed association between Ca supplementation and respiratory mortality was due to confounding by indication. Theoretically, people with pre-existing respiratory conditions may have intentionally taken Ca supplements to prevent osteoporosis, which is a well-known complication of chronic inflammatory airway diseases[27,30–33]. This is due to the systemic inflammatory response of the disease itself, as well as from chronic use of inhaled corticosteroids to control the disease[27]. Although we are unable to fully discount possible influences by confounding or reverse causation, the association between Ca supplementation and mortality from respiratory diseases remained significant even when we controlled for use of inhaled corticosteroids in multivariate models, in addition to the broad range of social, behavioural and health-related covariates.

There are some biologically plausible mechanisms which might contribute to the suggestive association between Ca supplementation and increased respiratory mortality. Exacerbations of obstructive lung diseases such as chronic obstructive pulmonary diseases and asthma are characterised by airway obstruction, mucus hypersecretion and inflammation[34]. The distinctive narrowing of the bronchi and bronchioles in chronic obstructive pulmonary diseases may result from contraction of the airway smooth muscle[34], which may be initiated by increases in intracellular Ca[35]. An increase in cytosolic concentrations of free Ca must also develop to trigger mucous gland secretion, vagal nerve activity (which constricts the bronchi), mast cell mediator release (which induces inflammation) and the movement of inflammatory cells into the walls of the airways[36]. Thus, a possible action of Ca supplements on the respiratory system may be related to the acute increase in serum Ca, which has been observed after ingestion of Ca supplements, but not after consuming Ca-rich foods[37]. Such a mechanism is plausible, as the 'Calcium hypothesis of asthma' suggests that Ca channel blocking agents may have a beneficial effect in asthma by inhibiting these actions[38]. However, bronchoprovocation studies to support this theory have been inconsistent[39–41]. Overall, more mechanistic studies are needed to understand the true effects of Ca on the respiratory system.

Previous research is generally consistent with our results on Ca supplementation and mortality from all causes, cancer and CVD. Our results correspond to those of Avenell *et al.*[42], who conducted a randomised controlled trial examining supplementation with 1000 mg calcium carbonate *v.* placebo in 5292 people residing within the UK. They reported no significant increase in total, cancer or cardiovascular mortality with Ca supplementation. The participants are alike in terms of geographical location and that users were predominantly female (85 % women), but they were generally older (mean age 77 years old) than participants within the UK Biobank.

With regard to cancer-specific mortality, a meta-analysis of ten randomised controlled trials investigating Ca supplementation also reported null findings, although cancer was not a primary outcome of any included study[10].

Oestrogen therapy has been suggested to be a modifier of the effect of Ca (+vitamin D) supplementation on colorectal cancer[43], and in line with this suggestion, we found some evidence for a differential association between Ca supplementation

Table 2. Calcium supplementation, dairy milk consumption, dietary calcium and mortality (Odds ratios and 95 % confidence intervals)

	Total sample							Participants < 65 years							Participants ≥ 65 years						
	Case/non-case	OR_{crude}*	95 % CI	*P*	OR_{adj}†	95 % CI	*P*	Case/non-case	OR_{crude}*	95 % CI	*P*	OR_{adj}†	95 % CI	*P*	Case/non-case	OR_{crude}*	95 % CI	*P*	OR_{adj}†	95 % CI	*P*
Ca supplementation‡																					
All-cause mortality																					
No	12 129/431 621	Ref		$1{\cdot}0 \times 10^{-3}$	Ref		0·6	7458/354 274	Ref		$1{\cdot}0 \times 10^{-4}$	Ref		0·04	4671/77 347	Ref		0·5	Ref		0·4
Yes	953/32 396	1·12	1·05, 1·20		1·02	0·95, 1·09		579/24 676	1·19	1·09, 1·30		0·91	0·83, 0·99		374/7720	1·04	0·93, 1·16		0·95	0·85, 1·07	
Cancer mortality																					
No	7221/431 621	Ref		0·9	Ref		0·5	4461/354 274	Ref		0·4	Ref		0·9	2760/77 347	Ref		0·6	Ref		0·3
Yes	561/32 396	1·01	0·92, 1·10		0·97	0·89, 1·06		344/24 676	1·05	0·94, 1·18		1·01	0·90, 1·13		217/7720	0·96	0·83, 1·11		0·93	0·81, 1·08	
Cardiovascular mortality																					
No	2526/431 621	Ref		0·8	Ref		0·3	1487/354 274	Ref		0·2	Ref		0·9	1039/77 347	Ref		0·3	Ref		0·06
Yes	147/32 396	1·11	0·78, 1·22		0·91	0·77, 1·08		87/24 676	1·17	0·93, 1·46		1·02	0·81, 1·27		60/7720	0·87	0·67, 1·14		0·77	0·59, 1·01	
Respiratory mortality																					
No	439/429 072	Ref		$3{\cdot}3 \times 10^{-6}$	Ref		0·05	233/345 638	Ref		$7{\cdot}9 \times 10^{-7}$	Ref		0·01	206/76 784	Ref		0·1	Ref		0·9
Yes	58/32 214	1·97	1·48, 2·61		1·33	1·00, 1·78		35/23 864	2·55	1·76, 3·69		1·69	1·16, 2·47		23/7671	1·44	0·92, 2·25		0·97	0·62, 1·54	
Dairy milk consumption‡																					
All-cause mortality																					
No	1155/39 561	Ref		$1{\cdot}5 \times 10^{-6}$	Ref		$8{\cdot}0 \times 10^{-3}$	777/33 121	Ref		$2{\cdot}3 \times 10^{-7}$	Ref		0·046	378/6440	Ref		0·3	Ref		0·9
Yes	11 968/425 281	0·86	0·81, 0·91		0·92	0·86, 0·98		7285/346 465	0·82	0·76, 0·88		0·93	0·86, 1·00		4683/78 816	0·94	0·85, 1·05		0·99	0·89, 1·11	
Cancer mortality																					
No	694/39 561	Ref		$1{\cdot}0 \times 10^{-3}$	Ref		0·02	466/33 121	Ref		$5{\cdot}0 \times 10^{-4}$	Ref		0·02	228/6440	Ref		0·3	Ref		0·6
Yes	7106/425 281	0·87	0·80, 0·94		0·91	0·84, 0·98		4348/346 465	0·84	0·76, 0·93		0·89	0·80, 0·98		2758/78 816	0·93	0·81, 1·07		0·96	0·84, 1·11	
Cardiovascular mortality																					
No	222/39 561	Ref		0·04	Ref		0·3	142/33 121	Ref		0·02	Ref		0·2	80/6440	Ref		0·6	Ref		0·96
Yes	2463/425 281	0·87	0·75, 0·99		0·93	0·81, 1·07		1439/346 465	0·82	0·69, 0·97		0·89	0·74, 1·06		1024/78 816	0·95	0·75, 1·19		0·99	0·79, 1·26	
Respiratory mortality																					
No	47/39 331	Ref		0·09	Ref		0·9	31/31 457	Ref		0·02	Ref		0·3	16/6398	Ref		0·96	Ref		0·4
Yes	453/422 779	0·77	0·57, 1·04		0·97	0·72, 1·32		239/338 634	0·64	0·44, 0·93		0·83	0·57, 1·21		214/78 248	1·01	0·61, 1·69		1·25	0·74, 2·11	
Dietary Ca intake§																					
All-cause mortality																					
Q1‖	304/16 779	Ref		0·3	Ref		0·9	203/14 148	Ref		0·2	Ref		0·6	101/2631	Ref		0·4	Ref		0·3
Q2¶	301/16 938	0·90	0·77, 1·06		0·99	0·84, 1·17		176/13 986	0·89	0·72, 1·09		0·89	0·72, 1·09		123/2952	1·07	0·82, 1·40		1·22	0·92, 1·60	
Q3**	298/16 953	0·86	0·73, 1·01		0·95	0·81, 1·12		189/13 880	0·94	0·77, 1·15		0·94	0·77, 1·15		109/3073	0·87	0·66, 1·15		0·98	0·74, 1·31	
Q4††	310/16 912	0·90	0·77, 1·06		0·99	0·84, 1·16		199/13 899	0·99	0·81, 1·21		0·99	0·81, 1·21		111/3013	0·90	0·68, 1·18		1·00	0·75, 1·32	
Cancer mortality																					
Q1	189/16 779	Ref		0·7	Ref		0·96	137/13 138	Ref		0·2	Ref		0·4	52/2631	Ref		0·4	Ref		0·2
Q2	192/16 938	0·93	0·76, 1·14		0·99	0·80, 1·21		113/13 986	0·82	0·64, 1·05		0·82	0·64, 1·05		79/2952	1·33	0·93, 1·89		1·44	1·01, 2·06	
Q3	192/16 953	0·90	0·73, 1·10		0·96	0·78, 1·17		123/13 880	0·87	0·68, 1·12		0·87	0·68, 1·12		69/3073	1·08	0·75, 1·55		1·17	0·81, 1·69	
Q4	189/16 912	0·90	0·73, 1·11		0·95	0·78, 1·17		117/13 899	0·85	0·66, 1·09		0·85	0·66, 1·09		72/3013	1·14	0·80, 1·64		1·24	0·86, 1·78	
Cardiovascular mortality																					
Q1	59/16 779	Ref		0·8	Ref		0·97	29/14 148	Ref		0·8	Ref		0·6	30/2584	Ref		0·5	Ref		0·8
Q2	54/16 938	0·83	0·57, 1·20		0·96	0·66, 1·40		27/13 986	0·99	0·58, 1·68		0·99	0·58, 1·68		27/2926	0·77	0·46, 1·31		0·94	0·55, 1·60	
Q3	59/16 953	0·85	0·59, 1·22		1·01	0·70, 1·46		32/13 880	1·15	0·69, 1·92		1·15	0·69, 1·92		27/3064	0·71	0·42, 1·21		0·88	0·51, 1·50	
Q4	63/16 912	0·90	0·63, 1·29		1·05	0·73, 1·51		38/13 899	1·33	0·81, 2·18		1·33	0·81, 2·18		25/2988	0·67	0·39, 1·14		0·77	0·45, 1·34	
Respiratory mortality																					
Q1	9/15 071	Ref		0·8	Ref		0·9	5/9398	Ref		0·9	Ref		0·8	4/2376	Ref		0·8	Ref		0·9
Q2	9/16 120	0·87	0·34, 2·19		1·19	0·46, 3·08		6/9874	1·71	0·49, 5·93		1·71	0·49, 5·93		3/2741	0·63	0·14, 2·82		0·88	0·18, 4·19	
Q3	8/16 258	0·72	0·28, 1·87		1·06	0·40, 2·84		4/9818	1·09	0·28, 4·26		1·09	0·28, 4·26		4/2844	0·79	0·20, 3·19		1·12	0·26, 4·80	
Q4	12/16 012	1·08	0·45, 2·57		1·41	0·58, 3·46		6/9559	1·49	0·44, 5·12		1·49	0·44, 5·12		6/2767	1·18	0·33, 4·19		1·55	0·40, 5·95	

Q, quartile.
* Crude OR with the adjustment of age, sex, ethnicity and assessment centre.
† Adjusted OR with the adjustment of age, sex, ethnicity, assessment centre, education level, deprivation index quintile, smoking, alcohol use, physical activity intensity, BMI, number of treatments or medications taken and self-reported health.
‡ Using data gathered via touchscreen questionnaire.
§ Using data gathered via 24-h recall.
‖ Quartile 1 = 0–689 mg.
¶ Quartile 2 = 690–914 mg.
** Quartile 3 = 915–1187 mg.
†† Quartile 4 = 1188–8012 mg.

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Table 3. Calcium supplementation and incident respiratory diseases (Odds ratios and 95 % confidence intervals)

Ca supplementation	Total sample							Participants < 65 years							Participants ≥ 65 years						
	Case/non-case*	OR_{crude}†	95 % CI	*P*	OR_{adj}‡	95 % CI	*P*	Case/non-case*	OR_{crude}†	95 % CI	*P*	OR_{adj}‡	95 % CI	*P*	Case/non-case*	OR_{crude}†	95 % CI	*P*	OR_{adj}‡	95 % CI	*P*
Any respiratory diseases																					
No	14 269/380 517	Ref		$2{\cdot}1 \times 10^{-12}$	Ref		0·07	10 227/315 700	Ref		$7{\cdot}7 \times 10^{-9}$	Ref		0·2	4042/64 817	Ref		$1{\cdot}1 \times 10^{-5}$	Ref		0·08
Yes	1308/28 376	1·24	1·17, 1·31		1·06	0·996, 1·13		865/21 925	1·24	1·15, 1·33		1·05	0·97, 1·13		443/6451	1·26	1·14, 1·40		1·10	0·99, 1·23	
Acute and infectious respiratory diseases																					
No	12 532/380 517	Ref		$5{\cdot}8 \times 10^{-11}$	Ref		0·07	9007/315 700	Ref		$1{\cdot}5 \times 10^{-7}$	Ref		0·2	3525/64 817	Ref		$1{\cdot}6 \times 10^{-5}$	Ref		0·07
Yes	1132/28 376	1·24	1·16, 1·32		1·06	0·996, 1·13		747/21 925	1·23	1·14, 1·33		1·05	0·97, 1·14		385/6451	1·28	1·14, 1·43		1·11	0·99, 1·25	
Chronic obstructive pulmonary disease																					
No	1465/390 036	Ref		$2{\cdot}9 \times 10^{-3}$	Ref		0·2	919/322 793	Ref		$2{\cdot}0 \times 10^{-3}$	Ref		0·07	546/67 143	Ref		0·3	Ref		0·8
Yes	144/29 165	1·31	1·10, 1·56		1·12	92/22 459			1·42	1·14, 1·76		1·24	0·98, 1·55		52/6702	1·15	0·86, 1·55		0·95	0·70, 1·29	
Asthma																					
No	781/389 503	Ref		$2{\cdot}9 \times 10^{-3}$	Ref		0·3	593/322 360	Ref		$4{\cdot}6 \times 10^{-3}$	Ref		0·3	188/67 143	Ref		0·3	Ref		0·7
Yes	94/29 148	1·39	1·12, 1·74		1·13	0·91, 1·41		67/22 446	1·45	1·12, 1·88		1·16	0·89, 1·50		27/6702	1·28	0·84, 1·93		1·09	0·71, 1·65	

* Among non-cases, participants with the FEV1:FVC ratio greater than 70 % were removed from analyses.
† Crude OR with the adjustment of age, sex, ethnicity and assessment centre.
‡ Adjusted OR with the adjustment of age, sex, ethnicity, assessment centre, education level, deprivation index quintile, smoking, alcohol use, physical activity, intensity, BMI, number of treatments or medications taken and self-reported health.

and cancer mortality in women based on the use of hormone replacement therapy. However, in the earlier study, women who did not receive oestrogen therapy but who were randomised to receive Ca and vitamin D were at suggestively decreased risk of developing colorectal cancer, while in our study, Ca supplementation was associated with an increased cancer risk in those who did not use hormone replacement therapy (and a decreased risk in those who did). While we cannot discount the role of methodological differences or chance, this discrepancy might have a biological explanation as variant in the *CYP24A1* gene (involved in the regulation of Ca homeostasis) has been shown to interact with hormone replacement therapy effects on colorectal cancer[44].

Our findings are consistent with the European Prospective Investigation into Cancer and Nutrition study, where researchers found no evidence for an association between Ca supplementation and cardiovascular mortality[45].

On the contrary, in the prospective NIH-AARP Diet and Health Study (*n* 388 229), Ca supplementation was associated with an increased risk of cardiovascular mortality in men (but not women)[46], while we found no evidence for interaction by sex. The proportion of men reporting the use of Ca supplements in the UK Biobank was notably lower compared with this earlier study (2·7 *v.* 23 %, respectively), which may explain the discrepancy.

Our findings are relatively comparable with previous observational studies on milk consumption and mortality. A meta-analysis of twelve prospective studies found no consistent association between milk intake and mortality from all causes, cancer or CVD[19]. However, similar to our analyses, when studies were stratified by age, results in younger cohorts (≤55 years) suggested a borderline inverse association with all-cause mortality. We were unable to locate published studies examining the effects of milk consumption on respiratory mortality, which highlights a gap in the literature. It could also reflect a lack of causal effect of Ca on respiratory diseases, as non-significant findings tend to be less likely to be published[47].

Overall, findings on milk consumption differed from those on Ca supplements, with weak inverse associations observed for all-cause and cancer mortality, and null associations for respiratory mortality. It seems pertinent to note that sensitivity analyses demonstrated null or protective effects of supplementation with nutrients besides Ca and mortality outcomes. Thus, differences between Ca supplements and dairy milk may be attributable to the presence of other micronutrients in milk.

Strengths and limitations

The large, prospective study design with rich data on potential confounding factors and standardised protocols for data collection were clear strengths of the present study. However, we recognise that the present study also had several limitations. Firstly, information on Ca supplementation and milk intake was based on self-report, which may have resulted in misclassification of participants with respect to the main exposure. However, any response bias is likely to be unselected, as there is no apparent reason for individuals to be more inclined to report consumption of dairy milk or use of Ca supplements. We only considered baseline exposure data, and therefore changes in diet over time may have confounded diet–disease associations. Only limited

Table 4. Calcium supplementation and mortality in women, with and without history of hormone replacement therapy use* (Odds ratios and 95 % confidence intervals)

	Hormone-replacement therapy non-users				Hormone-replacement therapy users			
Ca supplementation†	Case/non-case	OR_{adj}‡	95 % CI	*P*	Case/non-case	OR_{adj}‡	95 % CI	*P*
All-cause mortality								
No	2341/144 003	Ref		0·1	2151/83 391	Ref		0·1
Yes	319/13 779	1·11	0·98, 1·25		334/13 104	0·90	0·80, 1·01	
Cancer mortality								
No	1627/144 003	Ref		0·04	1488/83 391	Ref		0·01
Yes	226/13 767	1·17	1·01, 1·35		202/13 104	0·81	0·69, 0·94	
Cardiovascular mortality								
No	295/144 003	Ref		0·71	303/83 273	Ref		0·11
Yes	37/13 779	0·94	0·66, 1·33		39/13 097	0·75	0·54, 1·06	
Respiratory mortality								
No	65/117 965	Ref		0·7	76/70 496	Ref		0·05
Yes	11/10 575	1·14	0·59, 2·22		24/11 031	1·60	0·99, 2·59	

* *P* value for interaction by the use of hormone replacement therapy is 0·015 and 0·0003 for total and cancer mortality, respectively.
† Using data gathered via touchscreen questionnaire.
‡ Adjusted OR with the adjustment of age, sex, ethnicity, assessment centre, education level, deprivation index quintile, smoking, alcohol use, physical activity intensity, BMI, number of treatments or medications taken and self-reported health.

information on diet and supplement use was available for the whole cohort, while total Ca intakes could be estimated for a sub-sample.

It is also acknowledged that UK Biobank participants are not representative of the general population in terms of prevalence of obesity and co-morbidities[48]. There is evidence of a 'healthy volunteer' selection bias in this cohort, which is likely to have reduced the incidences of mortality. Efforts were made to control for this through multivariate adjustments[49] but, at the same time, multivariate statistical models also had the potential to 'over-adjust' for morbidity[50].

Conclusion

In conclusion, the present study suggests that Ca intake is not associated with increases in all-cause mortality. Ca supplementation, however, may modestly increase mortality from respiratory diseases, but we cannot exclude the possibility that our analysis captured a reverse causation phenomenon. Future research should be directed towards determining causality using experimental study designs. Meanwhile, dairy milk may be a safer source of attaining recommended daily intakes of Ca in terms of longevity.

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E. H. conceived and supervised the study. L. S. and A. Z. conducted data analysis, and all authors interpreted the results. L. S. drafted the manuscript with input from all authors. All authors approved the final version for submission.

There are no conflicts of interest.

Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114519003076

References

1. Beto JA (2015) The role of calcium in human aging. *Clin Nutr Res* **4**, 1–8.
2. Cosman F, de Beur SJ, LeBoff MS, *et al.* (2014) Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int* **25**, 2359–2381.
3. Bolland MJ, Avenell A, Baron JA, *et al.* (2010) Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* **341**, c3691.
4. Reid IR, Bolland MJ & Grey A (2010) Does calcium supplementation increase cardiovascular risk? *Clin Endocrinol* **73**, 689–695.
5. Wilson PW, Kauppila LI, O'Donnell CJ, *et al.* (2001) Abdominal aortic calcific deposits are an important predictor of vascular morbidity and mortality. *Circulation* **103**, 1529–1534.
6. Pletcher MJ, Tice JA, Pignone M, *et al.* (2004) Using the coronary artery calcium score to predict coronary heart disease events: a systematic review and meta-analysis. *Arch Intern Med* **164**, 1285–1292.
7. Chan JM & Giovannucci EL (2001) Dairy products, calcium, and vitamin D and risk of prostate cancer. *Epidemiol Rev* **23**, 87–92.
8. Rodriguez C, McCullough ML, Mondul AM, *et al.* (2003) Calcium, dairy products, and risk of prostate cancer in a prospective cohort of United States men. *Cancer Epidemiol Biomarkers Prev* **12**, 597–603.
9. Lokeshwar BL, Schwartz GG, Selzer MG, *et al.* (1999) Inhibition of prostate cancer metastasis *in vivo*: a comparison of 1,23-dihydroxyvitamin D (calcitriol) and EB1089. *Cancer Epidemiol Biomarkers Prev* **8**, 241–248.
10. Bristow SM, Bolland MJ, MacLennan GS, *et al.* (2013) Calcium supplements and cancer risk: a meta-analysis of randomised controlled trials. *Br J Nutr* **110**, 1384–1393.
11. Schwingshackl L, Boeing H, stelmach-mardas M, *et al.* (2017) Dietary supplements and risk of cause-specific death, cardiovascular disease, and cancer: a systematic review and meta-analysis of primary prevention trials. *Adv Nutr* **8**, 27–39.

12. Dotson B, Larabell P, Patel JU, *et al.* (2016) Calcium administration is associated with adverse outcomes in critically ill patients receiving parenteral nutrition: results from a natural experiment created by a calcium gluconate shortage. *Pharmacotherapy* **6**, 1185–1190.
13. Tognon G, Rothenberg E, Petrolo M, *et al.* (2017) Dairy product intake and mortality in a cohort of 70-year-old Swedes: a contribution to the Nordic diet discussion. *Eur J Nutr* **57**, 2869–2876.
14. Michaelsson K, Wolk A, Langenskiold S, *et al.* (2014) Milk intake and risk of mortality and fractures in women and men: cohort studies. *BMJ* **349**, g6015.
15. Ness AR, Smith GD & Hart C (2001) Milk, coronary heart disease and mortality. *J Epidemiol Community Health* **55**, 379–382.
16. Wang X, Chen H, Ouyang Y, *et al.* (2014) Dietary calcium intake and mortality risk from cardiovascular disease and all causes: a meta-analysis of prospective cohort studies. *BMC Med* **12**, 158.
17. Farvid MS, Malekshah AF, Pourshams A, *et al.* (2017) Dairy food intake and all-cause, cardiovascular disease, and cancer mortality: the Golestan Cohort Study. *Am J Epidemiol* **185**, 697–711.
18. Guo J, Astrup A, Lovegrove JA, *et al.* (2017) Milk and dairy consumption and risk of cardiovascular diseases and all-cause mortality: dose–response meta-analysis of prospective cohort studies. *Eur J Epidemiol* **32**, 269–287.
19. Larsson SC, Crippa A, Orsini N, *et al.* (2015) Milk consumption and mortality from all causes, cardiovascular disease, and cancer: a systematic review and meta-analysis. *Nutrients* **7**, 7749–7763.
20. Mullie P, Pizot C & Autier P (2016) Daily milk consumption and all-cause mortality, coronary heart disease and stroke: a systematic review and meta-analysis of observational cohort studies. *BMC Public Health* **16**, 1236.
21. O'Sullivan TA, Hafekost K, Mitrou F, *et al.* (2013) Food sources of saturated fat and the association with mortality: a meta-analysis. *Am J Public Health* **103**, e31–e42.
22. Umesawa M, Iso H, Date C, *et al.* (2006) Dietary intake of calcium in relation to mortality from cardiovascular disease: the JACC Study. *Stroke* **37**, 20–26.
23. UK Biobank (2007) UK Biobank: protocol for a large-scale prospective epidemiological resource. http://www.ukbiobank.ac.uk/wp-content/uploads/2011/11/UK-Biobank-Protocol.pdf (accessed June 2018).
24. UK Biobank (2013) Mortality data: linkage from national death registries. http://biobank.ctsu.ox.ac.uk/crystal/docs/DeathLinkage.pdf (accessed November 2018).
25. UK Biobank (2013) Hospital episode statistics data in showcase. http://biobank.ctsu.ox.ac.uk/crystal/docs/HospitalEpisodeStatistics.pdf (accessed November 2018).
26. World Health Organization (2010) International statistical classification of diseases and related health problems, 10th rev. https://icd.who.int/browse10/2010/en (accessed November 2018).
27. Biskobing DM (2002) COPD and osteoporosis. *Chest* **121**, 609–620.
28. StataCorp (2015) Stata Statistical Software [computer program]. Version 14. College Station, TX: StataCorp LP.
29. Collage RD, Howell GM, Zhang X, *et al.* (2013) Calcium supplementation during sepsis exacerbates organ failure and mortality via calcium/calmodulin-dependent protein kinase kinase signaling. *Crit Care Med* **41**, e352–e360.
30. Buehring B, Viswanathan R, Binkley N, *et al.* (2013) Glucocorticoid-induced osteoporosis: an update on effects and management. *J Allergy Clin Immunol* **132**, 1019–1030.
31. Sarkar M, Bhardwaj R, Madabhavi I, *et al.* (2015) Osteoporosis in chronic obstructive pulmonary disease. *Clin Med Insights Circ Respir Pulm Med* **9**, 5–21.
32. Jorgensen NR, Schwarz P, Holme I, *et al.* (2007) The prevalence of osteoporosis in patients with chronic obstructive pulmonary disease: a cross-sectional study. *Respir Med* **101**, 177–185.
33. Weinstein RS (2011) Glucocorticoid-induced bone disease. *N Engl J Med* **365**, 62–70.
34. Cukic V, Lovre V, Dragisic D, *et al.* (2012) Asthma and chronic obstructive pulmonary disease (COPD) – differences and similarities. *Mater Sociomed* **24**, 100–105.
35. Kuo IY & Ehrlich BE (2015) Signaling in muscle contraction. *Cold Spring Harb Perspect Biol* **7**, a006023.
36. Middleton E Jr (1980) Antiasthmatic drug therapy and calcium ions: review of pathogenesis and role of calcium. *J Pharm Sci* **69**, 243–251.
37. Machado MC, Bruce-Mensah A, Whitmire M, *et al.* (2015) Hypercalcemia associated with calcium supplement use: prevalence and characteristics in hospitalized patients. *J Clin Med* **4**, 414–424.
38. Svedmyr N (1984) Szentivanyi's hypothesis of asthma. *Eur J Respir Dis Suppl* **136**, 59–65.
39. Nair N, Townley RG, Bewtra A, *et al.* (1984) Safety of nifedipine in subjects with bronchial asthma and COPD. *Chest* **86**, 515–518.
40. Patakas D, Maniki E, Tsara V, *et al.* (1987) Nifedipine treatment of patients with bronchial asthma. *J Allergy Clin Immunol* **79**, 959–963.
41. Ann Twiss M, Harman E, Chesrown S, *et al.* (2002) Efficacy of calcium channel blockers as maintenance therapy for asthma. *Br J Clin Pharmacol* **53**, 243–249.
42. Avenell A, MacLennan GS, Jenkinson DJ, *et al.* (2012) Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial). *J Clin Endocrinol Metab* **97**, 614–622.
43. Ding EL, Mehta S, Fawzi WW, *et al.* (2008) Interaction of estrogen therapy with calcium and vitamin D supplementation on colorectal cancer risk: reanalysis of Women's Health Initiative randomized trial. *Int J Cancer* **122**, 1690–1694.
44. Garcia-Albeniz X, Rudolph A, Hutter C, *et al.* (2016) CYP24A1 variant modifies the association between use of oestrogen plus progestogen therapy and colorectal cancer risk. *Br J Cancer* **114**, 221–229.
45. Li K, Kaaks R, Linseisen J, *et al.* (2012) Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). *Heart* **98**, 920–925.
46. Xiao Q, Murphy RA, Houston DK, *et al.* (2013) Dietary and supplemental calcium intakes in relation to mortality from cardiovascular diseases in the NIH-AARP Diet and Health Study. *JAMA Intern Med* **173**, 639–646.
47. Easterbrook PJ, Gopalan R, Berlin JA, *et al.* (1991) Publication bias in clinical research. *Lancet* **337**, 867–872.
48. Fry A, Littlejohns TJ, Sudlow C, *et al.* (2017) Comparison of sociodemographic and health-related characteristic– participants with those of the general population. *Am J Epidemiol* **186**, 1026–1034.
49. Suresh K, Gajendragad M & Rahman H (2014) Design and analysis of observational studies. *Int J Infertil Fetal Med* **5**, 33–39.
50. Weinberg CR (1993) Toward a clearer definition of confounding. *Am J Epidemiol* **137**, 1–8.