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# Theoretical substitutions between dairy products and all-cause and cause-specific mortality. Results from the Danish diet, cancer and health cohort

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## Abstract

A daily intake of dairy products is recommended in many countries in order to maintain optimal health throughout life. However, evidence regarding the association between intake of individual dairy products and mortality is limited. We therfore, explored associations between intake of different dairy products and all-cause and cause-specific mortality using specified theoretical substitution analyses. We analysed data from 55 775 Danish men and women aged 50–64 years between 1993 and 1997. Information about dairy product intake at baseline was collected using a validated food frequency questionnaire. Information about vital status and causes of death was obtained through national registers. Measures of associations were calculated using Cox proportional hazards regression. During a median follow-up of 19·0 years, 11 586 participants died. For all-cause mortality, we observed that the intake of low-fat milk, whole-fat milk or low-fat yogurt products in place of cheese was associated with a higher rate of death (hazard ratios between 1·03 and 1·12 per serving/d substituted). The same pattern was present for CVD mortality. For cancer mortality, whole-fat milk and low-fat yogurt products in place of cheese were also associated with a higher rate of death for men while for women, whole-fat milk in place of buttermilk was associated with a higher cancer mortality rate. The results appeared robust in several sensitivity analyses. Our results suggest that intake of low-fat milk, whole-fat milk or low-fat yogurt products in place of cheese is associated with a higher rate of all-cause and cause-specific mortality.

**Key words: Dairy products: Mortality: Substitution analysis: Cohort studies**

A daily intake of dairy products is part of dietary recommendations for the general adult population in many Western countries[1] and often low-fat in place of high-fat varieties are promoted[2,3]. These dietary guidelines aim to promote a diet optimal for human health throughout the lifespan. However, results from cohort studies on dairy product intake and mortality remain inconclusive[4–13]. Although a meta-analysis concluded that the intake of milk was not associated with all-cause mortality[14], more recent studies have suggested that milk intake, particularly whole-fat, may be adversely associated with all-cause mortality[5,15] and that skim or low-fat milk may be associated with lower total cancer or colorectal cancer mortality but not with all-cause mortality[13,15]. In the meta-analysis[14] and later studies[5,11], the intake of fermented dairy products was inversely associated with all-cause mortality. However, there was substantial heterogeneity between the studies included in the meta-analysis[14], and many studies used broad categories such as low-fat and whole-fat dairy products which do not acknowledge that fermented dairy products, e.g. yogurt and non-fermented dairy products, e.g. milk may have unique nutritional properties irrespective of their fat contents. Even among the studies that have investigated individual dairy product subgroups, only few studies distinguished between products with different fat contents[5,6].

Most individual studies on dairy product intake and mortality investigated differences in dairy product intake while adjusting for confounding from total energy intake, i.e. keeping total energy constant within the analyses. Adjustment for total energy may partly account for measurement error in the assessment of the intake of the food of interest[16,17], but this adjustment also implies that a higher intake of a specific type of dairy product is compared with a lower intake of other non-specified energy-providing foods in the analysis. In other words, a non-specified theoretical food substitution is introduced by adjusting for total energy intake. Results from studies with non-specified theoretical substitutions may not be comparable across cohorts,

**Abbreviation:** HR, hazard ratio.

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as people may substitute dairy products differently within and between populations. Thus, in order to better approach the question of how to compose one's dairy product intake, research must focus on comparing individual dairy product subgroups with each other, which can be done using specified theoretical substitution analyses[18].

Furthermore, several previous studies only reported results for all-cause mortality[5,7,11,14], but as diet may be differently associated with different causes of death, analyses of cause-specific mortality provide additional insight into the relationship between dairy product intake and mortality.

In this study, we aim to contribute to the existing literature on dairy product intake and all-cause and cause-specific mortality by investigating replacements between different types of dairy products using specified theoretical substitution analyses.

## Subjects and methods

### Study population

The present study was based on data from the Danish cohort study Diet, Cancer and Health[19]. All men and women aged 50–64 years, born in Denmark, without a registered cancer diagnosis and residing in the greater Copenhagen and Aarhus areas were invited from December 1993 through May 1997. Of 160 725 invited men and women, 57 053 gave informed consent to participate (online Supplementary Fig. 1). The Diet, Cancer and Health study obtained ethical approval from the local medical review boards in Aarhus and Copenhagen as well as from the Danish Data Protection Agency. The participants filled in self-administered questionnaires on lifestyle and dietary habits before attending a physical examination at one of two study centres. The questionnaires were self-administered but checked for completeness at the visit to the study centre. Unclear or missing information was clarified with the participant during a computer-assisted interview conducted by study personnel[19].

### Dietary assessment

Information regarding intake of dairy products was collected using a 192-item semi-quantitative FFQ administered once at baseline[20]. The questionnaire was designed to reflect average daily food intake during the preceding year and the pre-defined responses ranged from never, to several times a day and for some items; a standard serving size was given[20]. The standard serving sizes given in the FFQ as well as those used in the subsequent quantification of food intake were derived from the survey Dietary Habits in Denmark, 1985[21,22].The information from the FFQ was converted into daily intakes of foods and nutrients using FoodCalc version 1.3[23]. In a validation study, the FFQ was validated against two 7-d food records[24]. For Ca and saturated fat, for which dairy products are important sources, the two instruments classified 81 % of men and 61 % of women into the same quintile (±1) for Ca and 64 % of men and 71 % of women into the same quintile (±1) for saturated fat. The questions addressing dairy product intake included milk (skimmed, 0·3 % fat; semi-skimmed, 1·5 % fat; whole-fat, 3·5 % fat and buttermilk, 0·5 % fat), yogurt products (semi-skimmed yogurt products, 1·5 % fat (low-fat yogurt products) with and without added fruit and whole-fat yogurt products, 3·5 % fat, with and without added fruit) and cheese (semi-hard cheese, soft matured cheese, blue cheese, cottage cheese and cream cheese). Due to a limited intake of skimmed milk, skimmed and semi-skimmed milk were categorised together as low-fat milk. We expressed dairy product intake in servings/d. For milk and yogurt products, the serving size was 200 g, for cheese it was 20 g.

### Ascertainment of vital status and cause-specific mortality

We used the Danish Civil Registration System[25] to determine the participants' vital status and potential emigration during follow-up. The primary causes of death were identified in the Danish Causes of Death register[26]. We used the 10th revision of the international classification of diseases-10 to categorise the primary causes of death. Cancer mortality encompassed codes C00 to C97, and cardiovascular mortality encompassed codes I00 to I99. We followed participants from baseline until death, emigration or 13 July 2015, whichever came first.

### Assessment of covariates

Baseline information about educational attainment, smoking habits, physical activity, hypertension, hypercholesterolaemia and diabetes was collected using a self-administered questionnaire. Educational attainment was expressed as the total length of primary and secondary education (≤7 years, 8–10 years, >10 years). Smoking habits were categorised as never, former, current <15 g tobacco daily, current 15–25 g tobacco daily and current >25 g tobacco daily. Physical activity included leisure time activities and active transportation. Participants reported the number of h/week, during summer and winter, spent on a variety of activities including walking, biking (including for transportation), other types of sports, doing house chores and gardening. We used the sum of time spent biking and participating in sports to classify participants as being active <30 min/d or ≥30 min/d, i.e. meeting the recommendations or not[27]. Hypertension was defined as having a history of hypertension or taking antihypertension medication (yes, no, do not know). Hypercholesterolaemia was defined as having a history of hypercholesterolaemia or taking lipid-lowering medication (yes, no, do not know). Diabetes was defined as having a history of diabetes or taking insulin (yes, no, do not know). Weight, height and waist circumference were measured at the physical examination. BMI was expressed as weight (kg) divided by height (m) squared. Information about alcohol intake and intake of the food groups fruit, vegetables, red meat, processed meat and fish was obtained with the FFQ.

### Statistical analyses

We used Cox proportional hazards regression models to estimate associations for specified theoretical substitutions between dairy product subgroups with the rate of all-cause and cause-specific mortality for cancer and CVD. Because of sex differences in the underlying overall risk of death, we performed the analyses for men and women separately. We used age as the underlying timescale. All analyses were adjusted for total energy intake (continuous) and further for date of inclusion (tertiles) in order to satisfy the assumption of independent delayed entry.

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Furthermore, because of delayed entry and the 14-year age range of the invited participants, the 'age' of the exposure and covariate information could be very different between individuals contributing to a given risk set. Therefore, the analyses were also adjusted for baseline age (tertiles) in order to account for this potential difference. Date of inclusion and baseline age were included in the models as stratum variables.

Our primary substitution model (Model 1a) included intake of all subgroups of dairy products (servings/d), except for the dairy product subgroup to be replaced, as well as a variable representing the combined total intake of dairy products (servings/d)[18]. An example where whole-fat milk is being substituted is presented below:

$$\log(h(t;x)) = \log(h1(t)) + \beta_1 \mathrm{low-fat\ milk} + \beta_2 \mathit{buttermilk} + \beta_3 \mathrm{low-fat\ yogurt} + \beta_4 \mathrm{whole-fat\ yogurt} + \beta_5 \mathit{cheese} + \beta_6 \mathit{total\ dairy} + \beta_7 \mathit{covariates}$$

It follows that the interpretation of the hazard ratios for each of the dairy product subgroups in the model is the estimated difference in rates of death associated with a one serving higher intake of the subgroups included in the model and a simultaneously lower intake of the subgroup left out of the model (whole-fat milk in the shown example). This type of substitution model can be referred to as 'the leave-one-out' model and is mathematically equivalent to the partition model, in which all dairy product subgroups are included simultaneously and the substitution calculated by subtraction of coefficients for the foods to be substituted[18]. Model 1b was further adjusted for the non-dietary risk factors educational attainment (categorical), residuals of waist circumference regressed on BMI (BMI-adjusted waist circumference) (continuous), BMI (continuous, 4 knot spline), smoking habits (categorical), physical activity (categorical) and alcohol intake (continuous, 5 knot spline). Model 2 was further adjusted for the dietary factors fruit, vegetables, red meat, processed meat and fish (all continuous, servings/d). Because hypertension and hypercholesterolaemia may be considered mediators rather than potential confounders, we adjusted for these conditions in a separate model (Model 3).

The linearity of the models was assessed by means of martingale residuals plotted against the exposure variables along with a lowess smoother. The models were deemed sufficiently linear. We tested the proportional hazards assumption using Schoenfeld residuals and found no appreciable violations of the assumption.

We performed several sensitivity analyses. First, we reran the analyses for CVD mortality after excluding participants with a diagnosis of myocardial infarction (708 men and 164 women) or stroke (297 men and 229 women) at baseline. This was done because participants with these diseases may have changed their diet as a consequence of diagnosis, and therefore, the diet may systematically differ between individuals with and without the disease at baseline. To investigate the potential influence of energy misreporting, we excluded the top and bottom 0·5 % of the ratio of reported energy intake to estimated energy requirement. The basal metabolic rate was estimated using equations applicable for a Scandinavian population based on information about sex, age and weight[28]. The physical activity level value was set to 1·6 for participants being moderately active <30 min/d and 1·8 for participants being active ≥30 min/d. Due to a large percentage of non-consumers of particularly low-fat yogurt products and buttermilk, we also investigated the robustness of the results in analyses where we excluded participants with non-consumption of any dairy product subgroup. We also investigated potential residual confounding by smoking by excluding smokers from the analyses. Finally, we restricted the follow-up to 10 years to investigate potential exposure misclassification during follow-up by using only one measurement of diet.

We performed non-specified substitution analyses to complement the specified substitution analyses. These analyses included the dairy product of interest, total energy intake plus covariates (models 1a and 1b) and were mutually adjusted for intake of the remaining dairy products in subsequent models.

All analyses were performed using Stata 13.1 (College Station).

## Results

Of the 57 053 study participants, 569 had an existing cancer diagnosis at baseline due to delayed entry into the Danish Cancer Registry. These participants were excluded along with forty-two participants who did not attend the baseline examination. We further excluded 667 participants with missing values on any exposure or covariate variable leaving 55 775 (26 614 men and 29 161women) participants for analysis (online Supplementary Fig. 1). During a median follow-up of 19·0 years, 6812 men and 4774 women died. Due to emigration, 305 participants (0·5 %) could not be followed up for vital status in the Danish Civil Registration System and were, thus, lost to follow-up. Cancer accounted for 4643 (2538 men, 2105 women) deaths, and CVD accounted for 2159 (1491 men, 668 women) deaths. Other causes accounted for 4784 deaths. For both men and women, cases were older, less well educated, more likely to be smokers and less physically active compared with the cohort (Table 1). Moreover, cases were more likely to have had a history of hypertension, hypercholesterolaemia, diabetes, myocardial infarction or stroke at baseline compared with the cohort (Table 1). Participant characteristics across quintiles of intake of the substituted dairy product subgroups are given in Supplementary Tables 1–6. There were no consistent differences across quintiles of low-fat milk (online Supplementary Table 1). Compared with the lowest quintile, those with the highest intake of whole-fat milk were more likely to be men, be older, to have low educational attainment, to be more active, drink less alcohol and less likely to have a history of hypertension, hypercholesterolaemia, diabetes or myocardial infarction (online Supplementary Table 2). For cheese, those with the highest intake compared with the lowest were more likely to have high educational attainment, to be non-smokers, to be physically active and not having a history of hypertension, hypercholesterolaemia or myocardial infarction (online Supplementary Table 6). The percentage of non-consumers of the individual dairy product subgroups ranged from zero to 62·3 % (low-fat yogurt among men) (online Supplementary Table 7). Generally, the highest percentages

**Table 1.** Participant characteristics of the Danish Diet, Cancer and Health cohort (Median and ranges, percentages)

| | All | | | | Women | | | | Men | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cohort (55 775) | | Cases (11 586) | | Cohort (29 161) | | Cases (4774) | | Cohort (26 614) | | Cases (6812) | |
| Characteristics | Median | Range | Median | Range | Median | Range | Median | Range | Median | Range | Median | Range |
| Age (years) | 56·2 | 51·2–63·2 | 59·0 | 52·0–64·2 | 56·3 | 51·2–63·2 | 59·3 | 52·1–64·2 | 56·0 | 51·2–63·2 | 58·9 | 52·0–64·1 |
| BMI (kg/m$^2$) | 25·5 | 21·4–31·2 | 26·0 | 21·3–32·1 | 24·8 | 20·8–31·2 | 25·1 | 20·3–32·3 | 26·2 | 22·5–31·1 | 26·5 | 22·2–32·1 |
| Waist circumference (cm) | 89·0 | 72·0–105·0 | 92·0 | 74·0–109·0 | 80·0 | 69·0–97·0 | 82·0 | 69·0–101·0 | 95·0 | 84·0–109·0 | 97·0 | 84·5–112·0 |
| Educational attainment >10 years | | | | | | | | | | | | |
| % | 21·0 | | 16·7 | | 18·5 | | 14·2 | | 23·8 | | 18·5 | |
| Current smoker | | | | | | | | | | | | |
| % | 36·0 | | 54·4 | | 32·8 | | 52·8 | | 39·6 | | 55·6 | |
| Physical inactivity <30 min/day % | 60·6 | | 66·5 | | 59·1 | | 65·1 | | 62·1 | | 67·0 | |
| Alcohol consumption (g/d) | 12·9 | 1·6–47·4 | 7·6 | 0·6–36·5 | 9·3 | 1·0–34·5 | 7·6 | 0·6–36·5 | 19·4 | 3·6–62·5 | 21·1 | 2·4–76·7 |
| Hypertension | | | | | | | | | | | | |
| % | 16·3 | | 21·8 | | 17·3 | | 22·7 | | 15·1 | | 21·1 | |
| Hypercholesterolaemia | | | | | | | | | | | | |
| % | 7·5 | | 9·7 | | 6·4 | | 8·4 | | 8·7 | | 10·6 | |
| Diabetes | | | | | | | | | | | | |
| % | 2·1 | | 4·9 | | 1·5 | | 3·4 | | 2·7 | | 5·9 | |
| Myocardial infarction | | | | | | | | | | | | |
| % | 1·6 | | 4·1 | | 0·6 | | 1·8 | | 2·7 | | 5·7 | |
| Stroke | | | | | | | | | | | | |
| % | 1·0 | | 2·5 | | 0·8 | | 2·2 | | 1·2 | | 2·8 | |
| Habitual food consumption (g/d) | | | | | | | | | | | | |
| Total energy intake (kJ/d) | 8895 | 6123–12 561 | 9043 | 6110–12 986 | 8037 | 5661–11 158 | 7966 | 5474–11 338 | 9876 | 7097–13 565 | 9817 | 6936–13 745 |
| Total dairy products | 303 | 82–783 | 308 | 77–831 | 306 | 83–771 | 308 | 78–802 | 299 | 80–800 | 307 | 76–861 |
| Low-fat milk | 42 | 6–513 | 36 | 6–515 | 36 | 5–510 | 28 | 5–510 | 70 | 7–516 | 40 | 7–519 |
| Whole-fat milk | 10 | 3–104 | 11 | 3–205 | 9 | 3–91 | 10 | 3–119 | 10 | 3–203 | 11 | 3–209 |
| Buttermilk | 6 | 0–88 | 6 | 0–88 | 6 | 0–91 | 6 | 0–91 | 6 | 0–34 | 6 | 0–42 |
| Low-fat yogurt products | 3 | 0–160 | 0 | 0–160 | 7 | 0–200 | 3 | 0–200 | 0 | 0–89 | 0 | 0–89 |
| Whole-fat yogurt products | 13 | 1–200 | 9 | 1–190 | 16 | 1–201 | 12 | 1–201 | 10 | 1–175 | 8 | 1–169 |
| Cheese | 29 | 10–69 | 27 | 9–68 | 30 | 10–69 | 27 | 9–69 | 28 | 10–68 | 27 | 9–67 |
| Butter | 9 | 0–30 | 11 | 0–32 | 7 | 0–26 | 9 | 0–27 | 13 | 0–33 | 13 | 0–33 |
| Fruit | 143 | 33–378 | 127 | 24–359 | 171 | 48–415 | 155 | 35–404 | 116 | 26–325 | 106 | 20–321 |
| Vegetables | 148 | 58–288 | 127 | 46–269 | 159 | 63–307 | 139 | 49–288 | 138 | 55–266 | 120 | 45–252 |
| Red meat | 78 | 41–141 | 84 | 43–152 | 63 | 34–104 | 64 | 35–109 | 100 | 57–164 | 101 | 58–169 |
| Processed meat | 25 | 8–60 | 29 | 9–69 | 18 | 6–40 | 20 | 7–46 | 35 | 13–73 | 37 | 14–80 |
| Fish | 38 | 16–76 | 39 | 16–81 | 35 | 15–70 | 36 | 15–72 | 42 | 18–82 | 43 | 17–86 |

Numbers are median (80 % central range), unless otherwise indicated.
Cases include all deaths occurring during follow-up.

**Table 2.** Associations for 1-serving/d substitutions between dairy products with the rate of all-cause mortality among men in the Danish Diet, Cancer and Health cohort (26614/6812) (Hazard ratio (HR) and 95 % confidence interval)

| | Model 1a* | | Model 1b† | | Model 2‡ | | Model 3§ | |
|---|---|---|---|---|---|---|---|---|
| Substitution | HR | 95 % CI | HR | 95 % CI | HR | 95 % CI | HR | 95 % CI |
| Low-fat milk for | | | | | | | | |
| Whole-fat milk | 0·93 | 0·90, 0·96 | 0·98 | 0·95, 1·01 | 0·97 | 0·94, 1·01 | 0·97 | 0·94, 1·00 |
| Buttermilk | 1·07 | 1·01, 1·14 | 1·04 | 0·98, 1·10 | 1·04 | 0·98, 1·11 | 1·04 | 0·97, 1·10 |
| Low-fat yogurt products | 1·10 | 1·01, 1·19 | 0·94 | 0·87, 1·02 | 0·94 | 0·86, 1·01 | 0·95 | 0·88, 1·03 |
| Whole-fat yogurt products | 1·24 | 1·15, 1·33 | 1·07 | 1·00, 1·15 | 1·04 | 0·97, 1·12 | 1·03 | 0·96, 1·11 |
| Cheese | 1·07 | 1·05, 1·10 | 1·04 | 1·02, 1·07 | 1·03 | 1·01, 1·06 | 1·04 | 1·01, 1·06 |
| Whole-fat milk for | | | | | | | | |
| Buttermilk | 1·15 | 1·08, 1·23 | 1·06 | 0·99, 1·13 | 1·07 | 1·00, 1·14 | 1·07 | 1·00, 1·14 |
| Low-fat yogurt products | 1·18 | 1·08, 1·28 | 0·96 | 0·89, 1·04 | 0·96 | 0·88, 1·04 | 0·98 | 0·90, 1·06 |
| Whole-fat yogurt products | 1·33 | 1·23, 1·44 | 1·10 | 1·01, 1·18 | 1·07 | 0·99, 1·15 | 1·06 | 0·98, 1·15 |
| Cheese | 1·15 | 1·11, 1·19 | 1·07 | 1·03, 1·10 | 1·06 | 1·03, 1·10 | 1·07 | 1·03, 1·11 |
| Buttermilk for | | | | | | | | |
| Low-fat yogurt products | 1·02 | 0·93, 1·13 | 0·91 | 0·83, 1·00 | 0·90 | 0·81, 0·99 | 0·92 | 0·83, 1·01 |
| Whole-fat yogurt products | 1·16 | 1·05, 1·27 | 1·04 | 0·94, 1·14 | 1·00 | 0·91, 1·10 | 1·00 | 0·91, 1·10 |
| Cheese | 1·00 | 0·94, 1·07 | 1·01 | 0·95, 1·07 | 0·99 | 0·93, 1·06 | 1·00 | 0·94, 1·06 |
| Low-fat yogurt products for | | | | | | | | |
| Whole-fat yogurt products | 1·13 | 1·02, 1·26 | 1·14 | 1·02, 1·26 | 1·11 | 1·00, 1·23 | 1·08 | 0·98, 1·21 |
| Cheese | 0·98 | 0·90, 1·06 | 1·11 | 1·02, 1·20 | 1·11 | 1·02, 1·20 | 1·09 | 1·01, 1·18 |
| Whole-fat yogurt products for | | | | | | | | |
| Cheese | 0·85 | 0·79, 0·91 | 0·97 | 0·90, 1·04 | 1·01 | 0·94, 1·09 | 1·02 | 0·95, 1·10 |

HR, hazard ratio.
Serving sizes: Milk & yogurt, 200 g, cheese, 20 g.
* Model 1a was adjusted for age and date of inclusion (as stratum variables) and total energy intake.
† Model 1b was further adjusted for educational attainment, BMI, waist circumference adjusted for BMI, smoking, physical activity and alcohol intake.
‡ Model 2 was further adjusted for intakes of fruit, vegetables, red meat, processed meat and fish.
§ Model 3 was further adjusted for hypertension and hypercholesterolaemia.

of non-consumers were for low-fat yogurt products, butter and buttermilk.

### *All-cause mortality*

Tables 2 and 3 present results from the minimally and multivariable adjusted analyses, while Fig. 1 only shows multivariable adjusted analyses (model 2). Intakes of low-fat milk, whole-fat milk or low-fat yogurt products in place of cheese were associated with a higher rate of death among both men and women with hazard ratios ranging between 1·03 and 1·12 serving/d substituted (Fig. 1, Tables 2 and 3, model 2). Whole-fat milk in place of buttermilk was also associated with a higher rate of death (men: hazard ratio (HR) = 1·07, 95 % CI (1·00, 1·14), women: HR = 1·08, 95 % CI (1·01, 1·16)) (Fig. 1, Tables 2 and 3, model 2). Among men only, buttermilk in place of low-fat yogurt products was associated with a lower rate of death (HR = 0·90, 95 % CI (0·81, 0·99)) (Fig. 1 top panel and Table 2, model 2). Among women only, intake of low-fat milk in place of whole-fat milk was associated with a lower rate of death (HR = 0·93, 95 % CI (0·88, 0·97)) (Fig. 1 bottom panel and Table 3, model 2).

### *Cancer mortality*

After adjustment for lifestyle and dietary covariates, intakes of whole-fat milk or low-fat yogurt products in place of cheese were associated with a higher rate of death from cancer among men (whole-fat milk: HR = 1·07, 95 % CI (1·01, 1·13), low-fat yogurt: HR = 1·17, 95 % CI (1·03, 1·33), serving/d substituted) (Fig. 2, top panel, and online Supplementary Table 8, model 2). For women, intakes of whole-fat milk in place of buttermilk or cheese (although this estimate was imprecise) were associated with a higher rate of death (buttermilk: HR = 1·16, 95 % CI (1·03, 1·30), cheese: HR = 1·07, 95 % CI (0·99, 1·16)) (Fig. 2, bottom panel, and online Supplementary Table 9, model 2).

### *CVD mortality*

Among men, intakes of low-fat milk, whole-fat milk or low-fat yogurt products in place of cheese were associated with a higher rate of death after adjustment for lifestyle and dietary covariates (hazard ratios between 1·07 and 1·17 serving/d substituted) (Fig. 3, top panel and online Supplementary Table 10, model 2). Among women, data suggested a higher rate of cardiovascular mortality for intakes of low-fat milk, whole-fat milk or buttermilk in place of cheese, although estimates were imprecise (Fig. 3, bottom panel, and online Supplementary Table 11, model 2).

### *Sensitivity analyses*

Our results did not materially change in the sensitivity analyses where we excluded participants with a diagnosis of myocardial infarction or stroke at baseline (online Supplementary Tables 12 and 13). Excluding the top and bottom 0·5 % of the ratio of reported energy intake to estimated energy requirement yielded similar estimates for all-cause and cause-specific mortality as the main analyses (online Supplementary Table 14). When we restricted the analyses to participants who consumed all dairy product subgroups, the results were not appreciably different to the main results, albeit the precision was severely reduced (online Supplementary Table 15). Among men, the rate of CVD mortality

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**Table 3.** Associations for 1-serving substitutions between dairy products with the rate of all-cause mortality among women in the Danish Diet, Cancer and Health cohort (29161/4774) (Hazard ratio (HR) and 95 % confidence interval)

| | Model 1a* | | Model 1b† | | Model 2‡ | | Model 3§ | |
|---|---|---|---|---|---|---|---|---|
| Substitution | HR | 95 % CI | HR | 95 % CI | HR | 95 % CI | HR | 95 % CI |
| Low-fat milk for | | | | | | | | |
| Whole-fat milk | 0·86 | 0·82, 0·90 | 0·93 | 0·89, 0·98 | 0·93 | 0·88, 0·97 | 0·93 | 0·88, 0·97 |
| Buttermilk | 1·04 | 0·98, 1·10 | 1·00 | 0·94, 1·06 | 1·00 | 0·95, 1·06 | 1·00 | 0·95, 1·06 |
| Low-fat yogurt products | 1·04 | 0·97, 1·13 | 0·95 | 0·88, 1·03 | 0·94 | 0·87, 1·01 | 0·95 | 0·88, 1·02 |
| Whole-fat yogurt products | 1·09 | 1·00, 1·18 | 1·00 | 0·92, 1·08 | 0·98 | 0·91, 1·06 | 0·97 | 0·90, 1·06 |
| Cheese | 1·07 | 1·03, 1·10 | 1·05 | 1·02, 1·08 | 1·04 | 1·01, 1·08 | 1·04 | 1·01, 1·08 |
| Whole-fat milk for | | | | | | | | |
| Buttermilk | 1·21 | 1·13, 1·30 | 1·07 | 1·00, 1·15 | 1·08 | 1·01, 1·16 | 1·08 | 1·01, 1·16 |
| Low-fat yogurt products | 1·21 | 1·12, 1·32 | 1·02 | 0·94, 1·11 | 1·01 | 0·93, 1·10 | 1·02 | 0·94, 1·11 |
| Whole-fat yogurt products | 1·27 | 1·16, 1·39 | 1·08 | 0·98, 1·18 | 1·06 | 0·97, 1·16 | 1·05 | 0·96, 1·15 |
| Cheese | 1·24 | 1·18, 1·31 | 1·13 | 1·07, 1·19 | 1·12 | 1·07, 1·18 | 1·12 | 1·07, 1·18 |
| Buttermilk for | | | | | | | | |
| Low-fat yogurt products | 1·00 | 0·91, 1·10 | 0·95 | 0·87, 1·04 | 0·94 | 0·85, 1·02 | 0·94 | 0·86, 1·03 |
| Whole-fat yogurt products | 1·05 | 0·95, 1·16 | 1·00 | 0·91, 1·10 | 0·98 | 0·89, 1·08 | 0·97 | 0·88, 1·07 |
| Cheese | 1·03 | 0·97, 1·09 | 1·05 | 0·99, 1·11 | 1·04 | 0·98, 1·10 | 1·04 | 0·98, 1·10 |
| Low-fat yogurt products for | | | | | | | | |
| Whole-fat yogurt products | 1·04 | 0·94, 1·16 | 1·05 | 0·95, 1·16 | 1·05 | 0·95, 1·16 | 1·03 | 0·93, 1·14 |
| Cheese | 1·02 | 0·95, 1·10 | 1·10 | 1·02, 1·19 | 1·11 | 1·03, 1·20 | 1·10 | 1·02, 1·19 |
| Whole-fat yogurt products for | | | | | | | | |
| Cheese | 0·98 | 0·90, 1·07 | 1·05 | 0·97, 1·14 | 1·06 | 0·98, 1·15 | 1·07 | 0·99, 1·16 |

HR, hazard ratio.
Serving sizes: Milk & yogurt, 200 g, cheese, 20 g.
* Model 1a was adjusted for age and date of inclusion (as stratum variables) and total energy intake.
† Model 1b was further adjusted for educational attainment, BMI, waist circumference adjusted for BMI, smoking, physical activity and alcohol intake.
‡ Model 2 was further adjusted for intakes of fruit, vegetables, fresh red meat, processed red meat and fish.
§ Model 3 was further adjusted for hypertension and hypercholesterolaemia.

for substitutions with whole-fat yogurt products appeared somewhat different, but in both the full cohort and the restricted sample, the associations for those substitutions were too imprecise to draw conclusions from. When restricting the analyses to non-smokers, the precision decreased. However, among men, the same patterns of associations were observed among non-smokers as in the full sample (online Supplementary Table 16). Among women, the associations for all-cause and cancer mortality were attenuated but of similar direction, while for CVD mortality, associations with buttermilk were reversed; intake of milk in place of buttermilk was associated with a higher rate and buttermilk in place of yogurt product or cheese was associated with lower rate of mortality (online Supplementary Table 16). When we restricted follow-up to 10 years after baseline, the results were largely similar for women, albeit less precise, but were slightly different for men (online Supplementary Table 17). For cancer mortality, whole-fat milk intake in place of cheese was no longer associated with a higher rate, whereas low-fat milk in place of cheese was. For CVD mortality, substitution of low-fat yogurt products with other dairy products appeared beneficial.

### *Non-specified substitution analyses*

For all-cause mortality, intake of milk, regardless of fat content, or low-fat yogurt products in place of other non-specified foods was associated with a higher rate, whereas cheese in place of other non-specified foods appeared neutral in models mutually adjusted for the remaining dairy product subgroups and for other foods (online Supplementary Table 18, model 2b). For cancer mortality, the intake of whole-fat milk or low-fat yogurt products in place of other foods was associated with a higher rate, while intake of cheese appeared neutral (online Supplementary Table 19, model 2b). For CVD mortality, intake of milk or low-fat yogurt products in place of other non-specified foods was associated with a higher rate, while intake of cheese appeared neutral (online Supplementary Table 20, model 2b). Among women only, intake of buttermilk in place of other non-specified foods was associated with a higher rate of cardiovascular mortality.

## Discussion

For all-cause and CVD mortality, we observed that intakes of low-fat milk, whole-fat milk or low-fat yogurt products in place of cheese were associated with a higher rate of death. For cancer mortality, whole-fat milk and low-fat yogurt products in place of cheese were also associated with a higher rate of death for men, while for women, whole-fat milk in place of cheese or buttermilk was associated with a higher rate. Our results appeared robust and did not appreciably differ in sensitivity analyses where we (1) restricted the sample to participants without hypertension, hypercholesterolaemia or myocardial infarction at baseline; (2) excluded the top and bottom 0·5 % of the ratio of reported energy intake to estimated energy requirement; (3) restricted the sample to consumers of all dairy products and (4) non-smokers. Of course, the precision of the sensitivity analyses decreased as a result of reducing the study sample.

### *Methodological considerations*

Methodological issues are reviewed below. All residents aged 50–64 years between 1993 and 1997 and living in two defined


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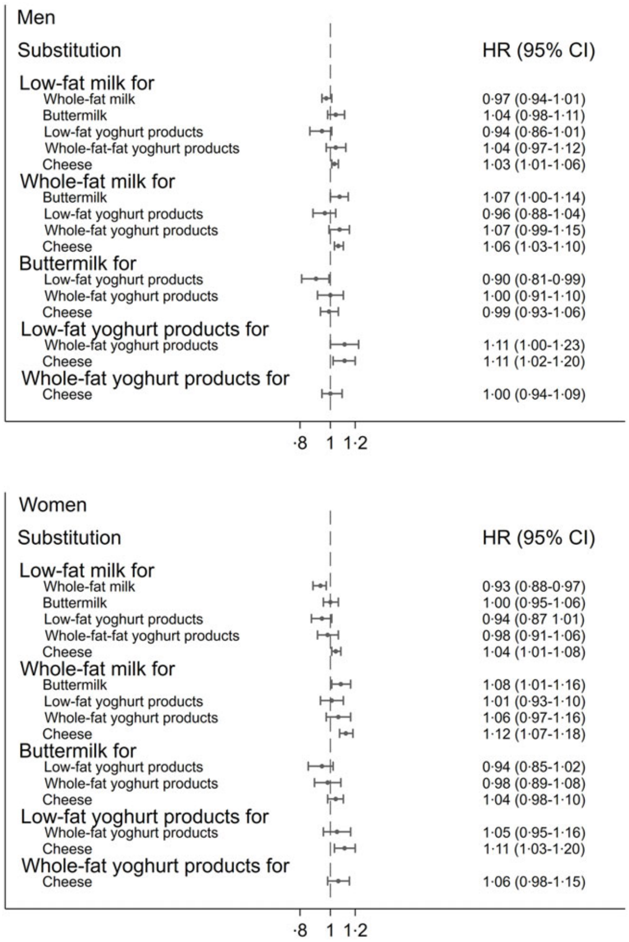


**Fig. 1.** Associations for 1-serving/d substitutions between dairy products with the rate of all-cause mortality among men (panel above) and women (panel below) in the Danish Diet, Cancer and Health cohort (Cases: 11 586 (6812 men, 4774 women)). Serving sizes: milk & yogurt, 200 g; cheese, 20 g. HR, Hazard ratio. The circles indicate hazard ratios and the whiskers indicate 95 % CI. The analyses are adjusted for age and date of inclusion (as stratum variables), total energy intake, educational attainment, BMI, waist circumference adjusted for BMI, smoking, physical activity, alcohol intake and intakes of fruit, vegetables, red meat, processed meat and fish.

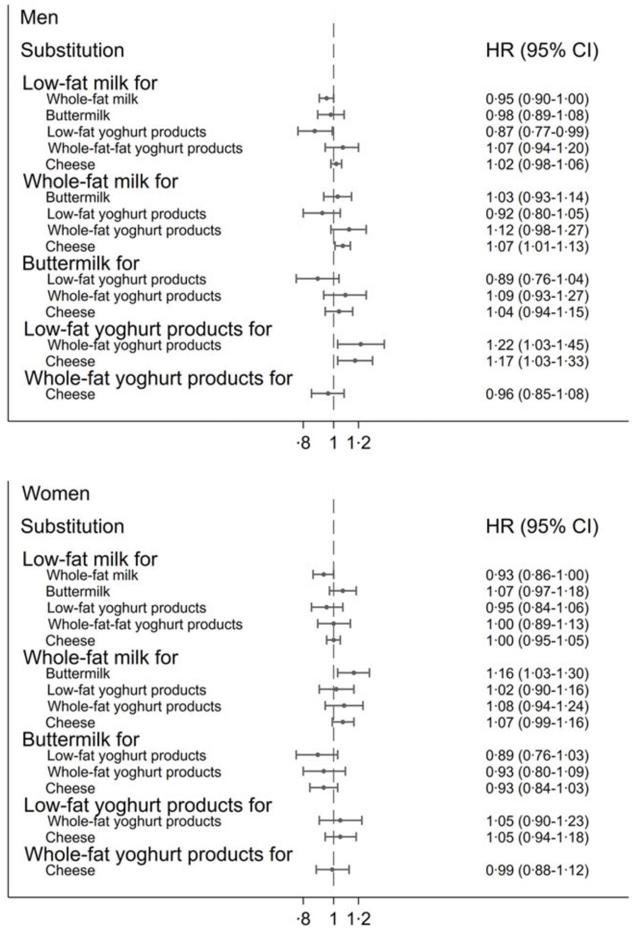


**Fig. 2.** Associations for 1-serving substitutions between dairy products with the rate of cancer mortality among men (panel above) and women (panel below) in the Danish Diet, Cancer and Health cohort (Cases: 4643 (2538 men, 2105 women)). Serving sizes: milk & yogurt, 200 g, cheese, 20 g. HR, hazard ratio. The circles indicate hazard ratios and the whiskers indicate 95 % CI. The analyses are adjusted for age and date of inclusion (as stratum variables), total energy intake, educational attainment, BMI, waist circumference adjusted for BMI, smoking, physical activity, alcohol intake and intakes of fruit, vegetables, red meat, processed meat and fish.

urban and suburban areas in Denmark were invited to participate in the cohort. Of these, 35 % accepted the invitation. Participants were generally more affluent than non-participants which may affect the generalisation of the results[19]. Because we invited persons aged 50–64 years to participate in the study, our results apply to dairy product intake in middle-aged persons. Cases were identified by linkage of each participant's civil registration number to national registers, and we therefore had complete ascertainment for vital status for 99·5 % of the participants, rendering selection bias due to loss to follow-up negligible.

Information about dairy product intake was collected using an FFQ which covered a large range of dairy foods. In order to obtain the highest quality of our exposure data, we only included dairy products that were specifically asked for in the questionnaire and disregarded dairy products with information derived solely from standard recipes used for dishes in the questionnaire, e.g. cream and ice cream. Nevertheless, non-differential measurement error of dairy product intake is expected, a potential cause of bias in unpredictable directions. To reduce the risk of biased estimates due to misreported diet, we adjusted all our analysis for total energy intake as this has been shown to provide more accurate estimates of diet–disease relationships[17]. Furthermore, we performed sensitivity analyses in which we excluded the top and bottom 0·5 % of the ratio of reported energy intake to estimated energy requirement. Results from this analysis were not materially different from the main results. However, poor reporters of energy are not easy to identify, and misreporting of energy can be present across the entire range of the ratio of reported energy intake to estimated energy requirement.

We asked participants about their average food intake during the past year, which is a snapshot of time during the lifespan that may be related to health outcomes regardless of former or future dietary habits. However, assuming causality, an exposure will continuously affect health, and because people may change dietary habits throughout life, a study using only one measurement of diet

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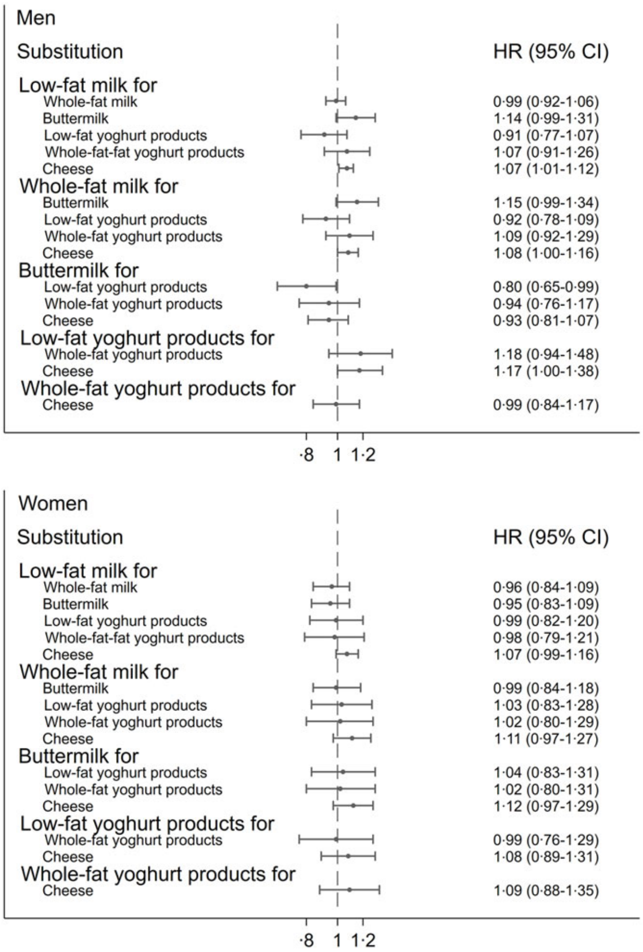


**Fig. 3.** Associations for 1-serving substitutions between dairy products with the rate of CVD mortality among men (panel above) and women (panel below) in the Danish Diet, Cancer and Health cohort (Cases: 2159 (1491 men, 668 women)). Serving sizes: milk & yogurt, 200 g, cheese, 20 g. HR, hazard ratio. The circles indicate hazard ratios and the whiskers indicate 95 % CI. The analyses are adjusted for age and date of inclusion (as stratum variables), total energy intake, educational attainment, BMI, waist circumference adjusted for BMI, smoking, physical activity, alcohol intake and intakes of fruit, vegetables, red meat, processed meat and fish.

could fail to identify true associations if the exposure level has changed before study entry and during follow-up. When we restricted follow-up to 10 years, the results for women were not materially different, while for men substitution of low-fat yogurt products with any other dairy product subgroup appeared beneficial for CVD mortality.

We adjusted the analyses for a number of potential non-dietary and dietary confounders, but although the results did not appreciably change after adjustment, residual confounding from unmeasured and unknown confounders is still a possibility.

In our study, we applied an analytical approach where we specified theoretical substitutions[18]. In other words, we directly compared 1-serving differences in intake of two specific dairy product subgroups between individuals in the analyses. Thus, our results represent joint associations, namely choosing one product in place of the other. While the advantage of using specified theoretical substitution analysis has been well demonstrated in studies of macronutrient intake[29–31], the method is infrequently applied in studies of food intake. When we compare equal serving sizes of products with different energy contents or foods with different serving sizes, a difference in energy intake from other non-specified foods remains unexplained by the model, but this unexplained residual energy is, of course, smaller than if we had not specified a substitution.

In studies conducted in the same study population as the present study, we have previously observed that the intake of whole-fat yogurt products in place of milk, buttermilk or low-fat yogurt was associated with a lower risk of incident ischemic stroke[32] and that intake of cheese in place of milk was associated with lower risk of myocardial infarction[33]. The findings for incident ischaemic stroke are not retained in our findings for cardiovascular mortality, while the findings of substitution between milk and cheese for myocardial infarction resemble the present results for cardiovascular mortality. This discrepancy may have several causes. For instance, a given diet composition may not be similarly associated with disease incidence and progression or prognosis and, therefore, studies of disease incidence and cause-specific mortality may not be comparable. Also, CVD mortality encompasses all CVD diagnoses (international classification of diseases-10 codes I00–I99) listed as the primary cause of death. Thus, incident ischemic stroke or myocardial infarction and total CVD mortality are not identical outcomes.

### Discussion of results

Previous studies of Swedish cohorts using non-specified theoretical substitution analyses have suggested that non-fermented milk intake regardless of its fat content is associated with a higher risk of all-cause mortality[4,5]. This is in line with our results from non-specified substitution analyses, where intake of milk, regardless of fat content, in place of other non-specified foods was associated with a higher rate of all-cause mortality while intake of cheese appeared neutral. Also, a recent study of USA adults found that whole-fat milk intake in place of other non-specified foods was associated with higher all-cause, cancer and CVD mortality[15]. In contrast, a study of Danish cohorts observed no associations between milk intake in place of other non-specified foods and all-cause mortality but a potential inverse association between skim milk intake in place of non-specified foods and cancer mortality[13].

Our results imply that the biological effects of intake of dairy foods are complex and cannot be attributed to the content of individual nutrients such as saturated fatty acids or production properties such as fermentation alone as also concluded by a review of potential biological pathways underlying the health effects of dairy foods[34]. It may be more important to consider the interplay between the whole package of nutrients, processing features and physical structure. Cheese contains considerably higher amounts of fat than milk and yogurt products. The fatty acid composition of dairy products differs from the fatty acid composition of other foods, particularly by the content of short- and medium-chain saturated fatty acids, ruminant trans fatty acids and conjugated linoleic acid[35]. Several studies have reported potential benefits of these types of fatty acids; Short- and medium-chain saturated fatty acids are absorbed directly into the portal vein and preferentially oxidised and have different physiological properties than long-chain saturated fatty acids, such as modulation of tissue metabolism and mitochondrial function[34,36,37]. Furthermore, conjugated linoleic acid may be associated with improved health through effects on body fat, lipid profile and blood pressure[38,39]. Cheese is also a source of vitamin $K_2$, which is produced by bacteria during the fermentation process and has been associated with improved arterial health[34,40]. Another biological explanation for our findings may lie in the differences in the physical structures of the compared dairy products. With cheese being a solid structure, cheese may yield a slower fat digestion than liquid and gel-like dairy products such as milk and yogurt[41]. Further clinical research on the biological effects of intake of different dairy product subtypes is needed to identify potential explanations for our observations.

In conclusion, our results suggest that the intake of low-fat milk, whole-fat milk or low-fat yogurt products in place of cheese is associated with a higher rate of all-cause and cause-specific mortality. Although the results appeared robust in several sensitivity analyses, they need to be replicated in other cohorts with the use of specified theoretical substitution analyses.

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A. S. D. L., A. L. T., A. B. and M. U. J. designed the study. A. S. D. L. analysed the data. A. S. D. L., A. L. T., A. B., K. O. and M. U. J. interpreted the data and critically revised the manuscript. A. S. D. L. wrote the paper and had final responsibility of the final content.

The authors declare that they have no conflicts of interest.

## Supplementary material

For supplementary material accompanying this paper visit https://doi.org/10.1017/S0007114521002464

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