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Substitution of animal-based with plant-based foods on cardiometabolic health and all-cause mortality: a systematic review and meta-analysis of prospective studies

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Abstract

Background There is growing evidence that substituting animal-based with plant-based foods is associated with a lower risk of cardiovascular diseases (CVD), type 2 diabetes (T2D), and all-cause mortality. Our aim was to summarize and evaluate the evidence for the substitution of any animal-based foods with plant-based foods on cardiometabolic health and all-cause mortality in a systematic review and meta-analysis.

Methods We systematically searched MEDLINE, Embase, and Web of Science to March 2023 for prospective studies investigating the substitution of animal-based with plant-based foods on CVD, T2D, and all-cause mortality. We calculated summary hazard ratios (SHRs) and 95% confidence intervals (95% CI) using random-effects meta-analyses. We assessed the certainty of evidence (CoE) using the GRADE approach.

Results In total, 37 publications based on 24 cohorts were included. There was moderate CoE for a lower risk of CVD when substituting processed meat with nuts [SHR (95% CI): 0.73 (0.59, 0.91), *n* = 8 cohorts], legumes [0.77 (0.68, 0.87), *n* = 8], and whole grains [0.64 (0.54, 0.75), *n* = 7], as well as eggs with nuts [0.83 (0.78, 0.89), *n* = 8] and butter with olive oil [0.96 (0.95, 0.98), *n* = 3]. Furthermore, we found moderate CoE for an inverse association with T2D incidence when substituting red meat with whole grains/cereals [0.90 (0.84, 0.96), *n* = 6] and red meat or processed meat with nuts [0.92 (0.90, 0.94), *n* = 6 or 0.78 (0.69, 0.88), *n* = 6], as well as for replacing poultry with whole grains [0.87 (0.83, 0.90), *n* = 2] and eggs with nuts or whole grains [0.82 (0.79, 0.86), *n* = 2 or 0.79 (0.76, 0.83), *n* = 2]. Moreover, replacing red meat for nuts [0.93 (0.91, 0.95), *n* = 9] and whole grains [0.96 (0.95, 0.98), *n* = 3], processed meat with nuts [0.79 (0.71, 0.88), *n* = 9] and legumes [0.91 (0.85, 0.98), *n* = 9], dairy with nuts [0.94 (0.91, 0.97), *n* = 3], and eggs with nuts [0.85 (0.82, 0.89), *n* = 8] and legumes [0.90 (0.89, 0.91), *n* = 7] was associated with a reduced risk of all-cause mortality.

Conclusions Our findings indicate that a shift from animal-based (e.g., red and processed meat, eggs, dairy, poultry, butter) to plant-based (e.g., nuts, legumes, whole grains, olive oil) foods is beneficially associated with cardiometabolic health and all-cause mortality.

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Keywords Diet, Cardiovascular disease, Type 2 diabetes, Mortality, Substitution, Plant-based food, Animal-based food

Background

The current food system has been shown to be detrimental to planetary health by depleting Earth's resources and contributing to climate change, thus decreasing the quality and sufficiency of food [1, 2]. Furthermore, noncommunicable diseases related to dietary choices such as cardiovascular diseases (CVD) and type 2 diabetes (T2D) highly contribute to deaths worldwide [3]. Therefore, the food system and current dietary habits negatively impact both planetary and human health [2]. Consequently, one of the approaches to address these problems is to change dietary habits [2, 4]. Plant-based diets are the focus of recent studies suggesting that increased intake of plant-based foods is not only beneficial for planetary health [2, 4], but also reduces the risk of T2D, CVD, and premature death [5, 6]. In contrast, the production and consumption of animal-based foods, especially red and processed meat, pose a high burden on the environment [2] and have been linked to increased risk for CVD, T2D, and mortality [7–9]. Such findings contribute to recommendations to reduce the intake of red and processed meat. However, to keep energy intake constant, other foods need to be consumed instead and the association with disease risks may depend on this substitution [10]. A promising option is the replacement of animal-based with plant-based foods. In this context, epidemiological studies investigated the substitution of animal-based foods with other protein sources and indicated that such a replacement is associated with reduced risk of CVD, T2D, and mortality [11–14]. A recent systematic review and meta-analysis found a lower risk for coronary heart disease (CHD) when replacing red meat with poultry, dairy, eggs, nuts, or legumes and a lower risk of all-cause mortality when substituting red meat with fish/seafood, poultry, eggs, or nuts [15]. However, the authors did not investigate further cardiometabolic endpoints, including CVD or T2D. Furthermore, the substitution of any animal based-foods with only plant-based foods has yet to be investigated in a systematic review and meta-analysis. Therefore, to clarify the strength and certainty of the overall evidence on this topic, there is an urgent need for a systematic review and meta-analysis examining the association between substituting animal-based with purely plant-based foods and cardiometabolic health outcomes, including CVD, stroke, myocardial infarction (MI), T2D, and mortality. Thus, it was our aim to summarize and evaluate the meta-evidence on the substitution of animal-based with plant-based foods regarding cardiometabolic health outcomes and all-cause mortality.

Methods

Our protocol was pre-registered at PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022302982). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement 2020 [16]. All steps were conducted by at least two investigators, independently. Disagreements were solved by consensus.

Deviations from the protocol

There were no deviations in methods, but we added all-cause mortality to our outcomes since cardiovascular disease and type 2 diabetes highly contribute to deaths worldwide [3].

Search strategy and selection criteria

A systematic literature search was conducted on MEDLINE via Ovid, Embase via Ovid, and Web of Science (Clarivate) up to December 2021 using predefined search terms (Additional file 1: Search terms) applying no restrictions or filters. Additionally, we screened the reference lists of relevant publications for further studies and conducted a PubMed Similar Articles search. Moreover, an update of the literature search was performed in March 2023.

Studies were included if (1) substitution analyses of any animal-based foods (including red and processed meat, poultry, fish, shellfish, eggs, dairy, and dairy products) with any plant-based foods (including legumes, nuts, whole and refined grains, fruit, vegetables, soy, seeds, and oils) that specified the substitution were conducted; (2) cardiometabolic health outcomes, including CVD mortality; incidence of CVD, CHD, stroke, MI, and T2D; and all-cause mortality, were investigated; (3) they were prospective observational studies; and (4) the study was conducted among the general healthy population. The detailed exclusion criteria are displayed in Additional file 2: Table S1. If multiple publications reported results regarding the same association based on data from the same cohort, the study with more cases and/or a longer follow-up was included in order to avoid duplication. Thus, each cohort is only included once in each respective meta-analysis. In addition to the single outcomes, we investigated composite outcomes, such as total CVD, including CVD mortality, CVD incidence, CHD incidence, MI, and stroke, as well as total diabetes, including T2D incidence and mortality.

Relevant study characteristics were extracted (Additional file 2: Table S2).

Risk of bias and certainty of evidence assessment

A risk of bias assessment for each study was conducted using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool [17]. It includes seven domains of bias due to (1) confounding, (2) selection of participants, (3) exposure assessment, (4) misclassification of exposure during follow-up, (5) missing data, (6) measurement of the outcome, and (7) selective reporting of the results (Additional file 2: Table S3).

The certainty of evidence for each association was evaluated using the updated Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach [18]. In this updated approach, the initial certainty of evidence level is "high" for observational studies. However, the certainty of evidence is downgraded (up to three levels) unless the study design reduces confounding, selection, and information bias, as evaluated by ROBINS-I. Additionally, indication for inconsistency (as measured by the similarity of the point estimates, overlap of 95% confidence intervals, and statistical tests, such as I^2), indirectness (e.g., substantial differences in population or exposure), imprecision (wide 95% confidence interval and/or small number of events), and publication bias can lead to a downgrading, while large effects (SHR < 0.5 or > 2.0) and a dose–response gradient can lead to an upgrading [18, 19]. High and moderate certainty of evidence mean that it is very likely or probable that the true effect lies close to the estimated effect. Our confidence in the result is limited, if the certainty of evidence is rated as low or very low [19].

Data analysis

For each substitution meta-analysis, we calculated summary hazard ratios (SHR) and 95% confidence intervals (95% CIs) using a random-effects model by DerSimonian and Laird, taking into account both within- and between-study variability [20, 21].

To ensure comparability of the results, we converted hazard ratios (HRs) and 95% CIs for standardized food portions, as previously applied, for the substituted foods [7–9]. To ensure that the adaption of the HRs and 95% CIs was not only correct for the substituted food but also for the replacement, we recalculated the portion size of the substitute according to the conversion of the replaced food. For example, if a study substituted 100 g/day of red meat by 30 g nuts/day, we calculated the HR and 95% CI for a substituted portion of 50 g/day of red meat by 15 g of nuts.

Moreover, we calculated I^2 and tau^2 (τ^2) as measures of inconsistency and between-study variability, respectively, as well as 95% prediction intervals (95% PIs), which show the range in which the true effect of future studies will lie with 95% certainty [22, 23].

For some associations, single publications provided only pooled risk estimates of multiple cohorts and did not show risk estimates for the single studies separately. When we did not identify further relevant studies, we extracted the pooled risk estimates from these publications [11, 14, 24–29]. Furthermore, three studies reported risk estimates based on changes over time rather than the baseline consumption or a cumulative average [11, 29, 30]. Those risk estimates were not pooled and reported separately.

We planned to conduct sensitivity analyses, by excluding studies with a high risk of bias as well as leaving out one study at a time, and subgroup analyses by sex, region, dietary assessment method, or level of adjustment. However, due to the low number of studies, only the sensitivity analyses excluding one study at a time could be conducted.

Publication bias and small study effects were assessed using funnel plots and Egger's test [31, 32], if at least ten studies were available [33]. Potential publication bias was indicated by the asymmetry of the funnel plot and a p-value of < 0.1 for Egger's test [32].

All statistical analyses were conducted using the STATA version 14.1.

Results

Of the 1216 studies identified in our search after the removal of duplicates, 158 fulltext articles were considered for inclusion. Out of these, 126 publications were excluded, leaving 32 studies to be included in our analyses. A list of the excluded studies with reasons is provided in Additional file 2: Table S4 [12, 34–157]. Additionally, five relevant studies were identified via hand search. Thus, 37 studies were included in our final meta-analyses (Fig. 1). All identified publications were prospective cohort studies. No randomized controlled trials (RCTs) analyzed as observational studies were included.

Twenty-two publications including 12 cohorts were conducted in the USA [11, 13, 14, 24–29, 138, 154, 158–168], ten publications including seven cohorts in Europe [30, 156, 157, 169–175], and four studies including three cohorts in Asia [155, 176–178]. One publication included one US and one European cohort [179]. In all cohorts except for three (using consecutive 24-h recalls [173, 177, 178]), diet was assessed using validated food frequency questionnaires. The mean follow-up duration was 19 years. All cohorts except for five included both men and women. One cohort (Health Professionals' Follow-up Study (HPFS)) only included men [11, 13, 24–29, 138, 154, 162, 163, 166] and four cohorts (Nurses' Health Study (NHS), NHS II, Women's Health Initiative (WHI),

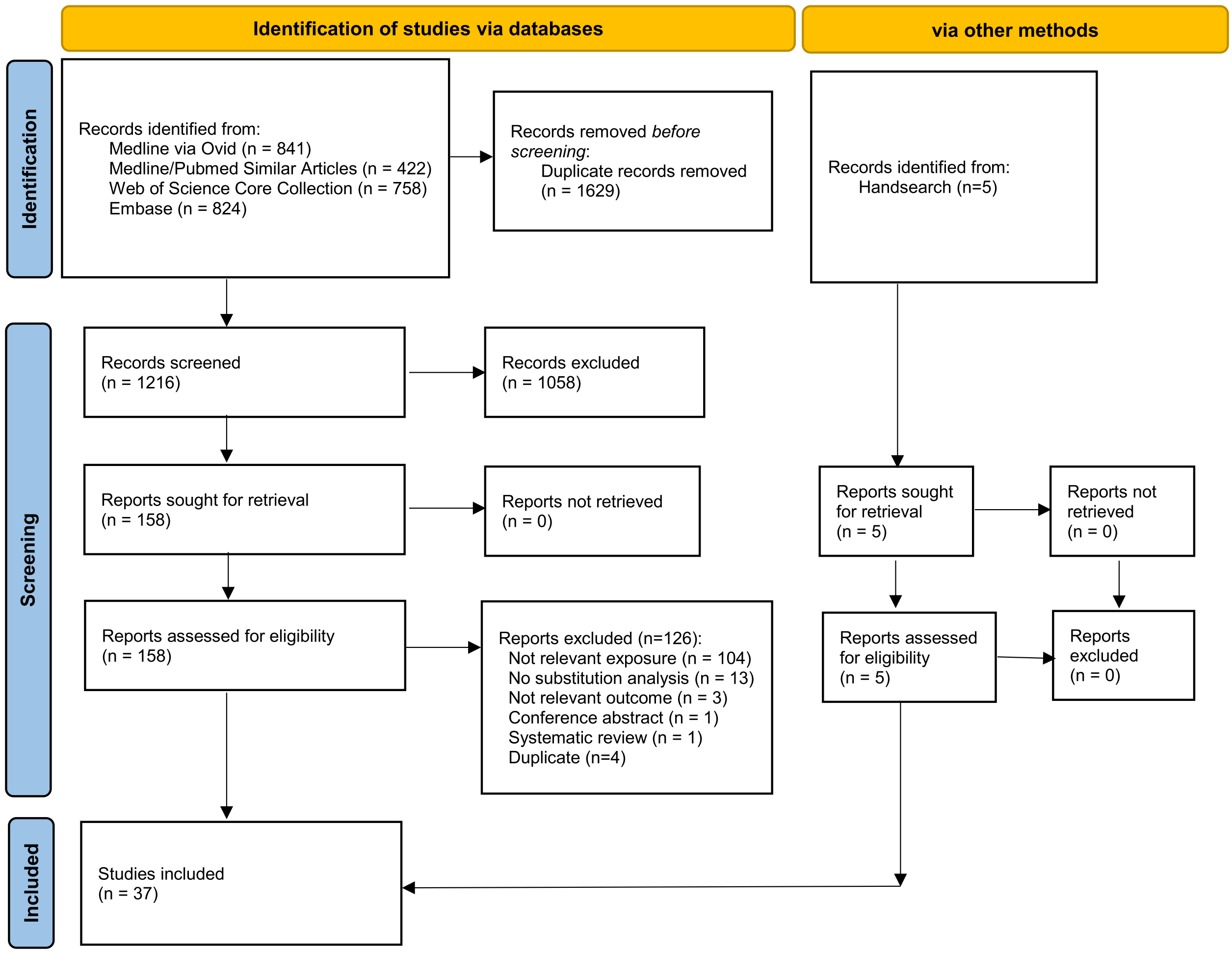

Fig. 1 Study selection

and Black Women's Health Study (BWHS)) only women [11, 24–29, 138, 154, 158, 159, 161–166, 179] (Additional file 2: Table S2).

All publications were judged as moderate risk of bias, except for one [169] (Additional file 3: Fig. S1), which was judged as serious risk of bias due to insufficient adjustment of confounders (Additional file 3: Fig. S2). No study was judged as low risk of bias due to the possibility of residual confounding in observational studies and the possibility of measurement error in the dietary assessment.

Total CVD

The meta-analyses on total CVD are shown in Fig. 2 and Additional file 3: Fig. S3.

We observed an association with a lower incidence of total CVD for the substitution of processed meat (50 g/day) with nuts (28–50 g/day) [SHR (95% CI): 0.73 (0.59, 0.91), $I^2=68\%$, $n_{cohorts}=8$], legumes (50 g/day) [SHR (95% CI): 0.77 (0.68, 0.87) $I^2=0\%$, $n_{cohorts}=8$], or whole grains (30 g/day) [SHR (95% CI): 0.64 (0.54,0.75), $I^2=38\%$, $n_{cohorts}=7$]; one egg/day with nuts (25–28 g/day) [SHR (95% CI): 0.83 (0.78, 0.89), $I^2=54\%$, $n_{cohorts}=8$]; and butter (5 g/day) with olive oil (5 g/day) [SHR (95% CI): 0.96 (0.95, 0.98), $I^2=0\%$, $n_{cohorts}=3$] with moderate certainty of evidence. There was also an indication that replacing red meat with nuts, unprocessed red meat with nuts or legumes, poultry with nuts, and eggs with legumes was associated with a lower risk of total CVD; however, the certainty of evidence for these associations was low. There were no clear associations for the other meta-analyses, and the certainty of evidence was rated as low and very low (Additional file 2: Table S5).

Single CVD outcomes

Figure 3 and Additional file 3: Figs. S4 and S5 show the findings on CVD mortality and CHD incidence.

Regarding CVD mortality, there was moderate certainty of evidence that replacing one egg/day with nuts (25 g/day) was associated with lower CVD mortality

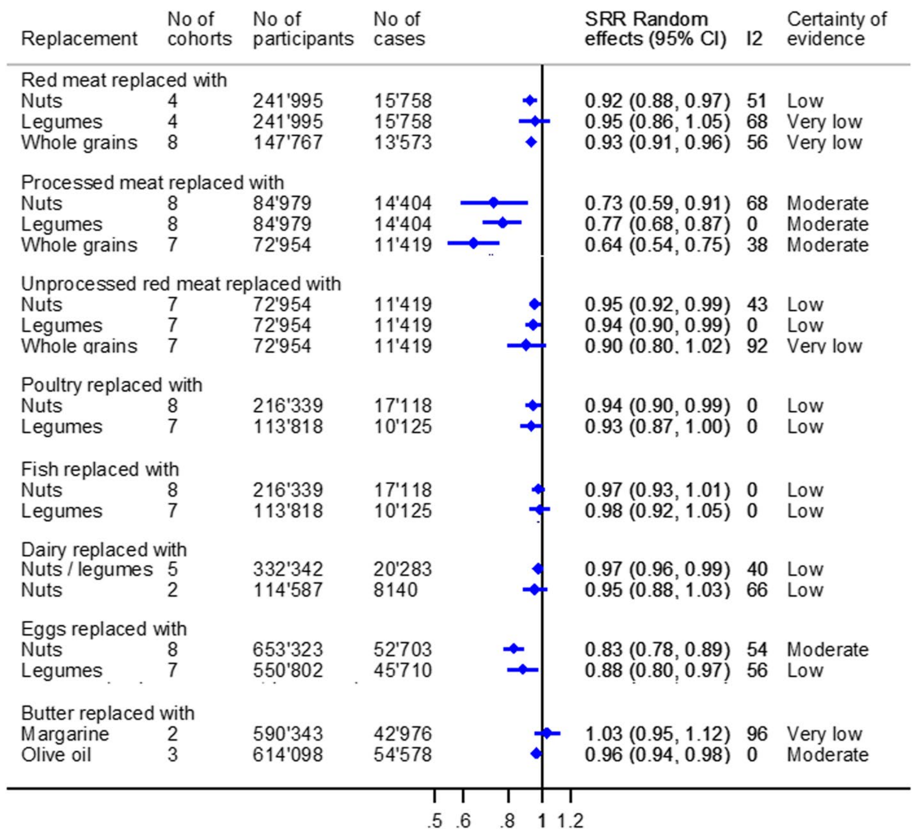

Fig. 2 Substitution meta-analyses replacing animal-based foods with plant-based foods regarding total CVD (including incidence of CVD, CHD, MI, and CVD mortality). Portion sizes: red meat/(un)processed meat/poultry/fish/dairy: 50 g/day; eggs: 1 egg/day; nuts: 10–50 g/day; legumes: 13–50 g/day; whole grains: 10–30 g/day; butter: 5 g/day; olive oil: 5 g/day; and margarine: 5 g/day

[SHR (95% CI): 0.84 (0.79, 0.90), I^2=61%, $n_{cohorts}$=2], as did replacing butter (5 g/day) with olive oil (5 g/day) [SHR (95% CI): 0.96 (0.94, 0.98), I^2=0%, $n_{cohorts}$=3]. The other associations were rated as low and very low certainty of evidence (Additional file 2: Table S6).

There was moderate certainty of evidence that substituting processed meat (50 g/day) with nuts (28 g/day) was associated with a lower CHD incidence [SHR (95% CI): 0.87 (0.80, 0.95), I^2=4%, $n_{cohorts}$=2] and that replacing poultry (50 g/day) with nuts (11–14 g/day), as well as fish/seafood (50 g/day) with nuts (7 g/day) or legumes (12.5 g/day), was not associated with CHD incidence. There was an indication that replacing red meat with nuts or legumes, as well as processed meat with legumes, was associated with a lower CHD risk, but the certainty of evidence for these associations was low (Additional file 2: Table S7).

Type 2 diabetes

The meta-analyses regarding total T2D (incidence and mortality combined) and T2D incidence are shown in Fig. 4 and Additional file 3: Figs. S6 and S7.

There was moderate certainty of evidence for a lower risk of total T2D associated with replacing butter (5 g/day) with olive oil (5 g/day) [SHR (95% CI): 0.94 (0.91, 0.98), I^2=12%, $n_{cohorts}$=3] (Additional file 2: Table S8). Moreover, we observed an association with a lower T2D incidence with moderate certainty of evidence when substituting red meat (50 g/day) with nuts (10 g/day) [SHR (95% CI): 0.92 (0.90, 0.94), I^2=25%, $n_{cohorts}$=6] or whole grains/cereals (11–30 g/day) [SHR (95% CI): 0.90 (0.84, 0.96), I^2=93%, $n_{cohorts}$=6], as well as processed meat (50 g/day) with nuts (10–28 g/day) [SHR (95% CI): 0.78 (0.69, 0.88), I^2=88%, $n_{cohorts}$=6] and poultry (50 g/day) with whole grains (30 g/day) [SHR (95% CI): 0.87 (0.84, 0.91), I^2=0%, $n_{cohorts}$=2]. Furthermore, replacing one egg/day with nuts (10 g/day) or whole grains (30 g/day) was also inversely associated with T2D incidence [SHR (95% CI): 0.82 (0.79, 0.86), I^2=0%, $n_{cohorts}$=2, or 0.79 (0.76, 0.83), I^2=4%, $n_{cohorts}$=2]. The remaining associations were rated as low or very low (Additional file 2: Table S9).

All-cause mortality

The meta-analyses regarding all-cause mortality are shown in Fig. 5 and Additional file 3: Fig. S8.

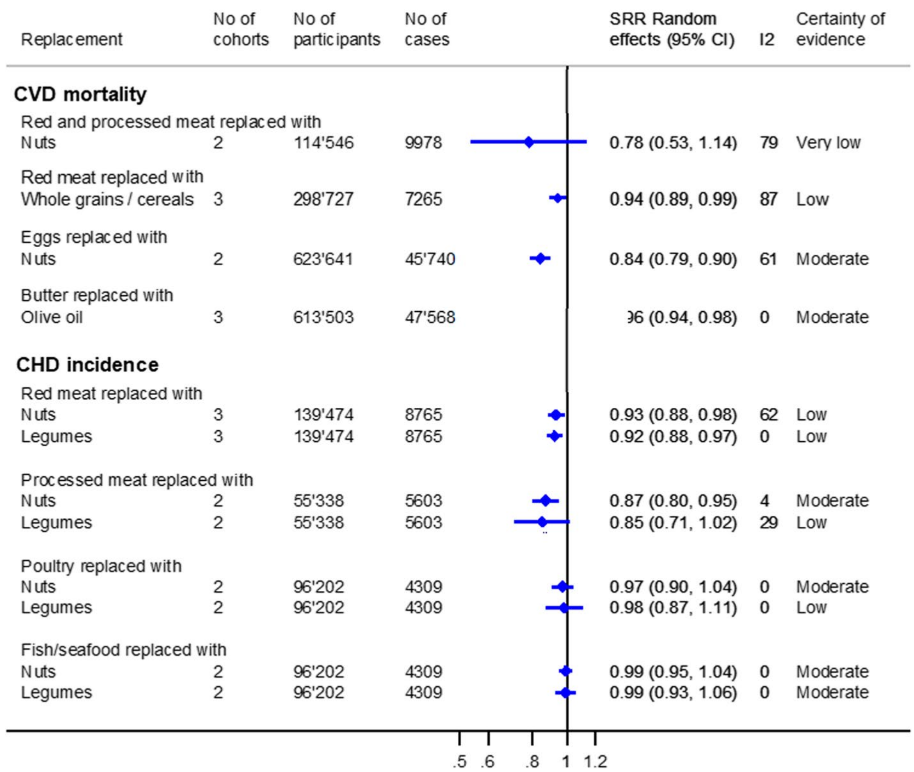

Fig. 3 Substitution meta-analyses replacing animal-based foods with plant-based foods regarding single CVD outcomes. Portion sizes: red meat/processed meat/poultry/fish and seafood: 50 g/day; eggs: 1 egg/day; nuts: 10–28 g/day; legumes: 12.5–50 g/day; whole grains/cereals: 15–30 g/day; butter: 5 g/day; and olive oil: 5 g/day

We found moderate certainty of evidence for an association with a lower risk of all-cause mortality, when replacing red meat (50 g/day) with nuts (10–50 g/day) or whole grains (11–15 g/day) [SHR (95% CI): 0.93 (0.91, 0.95), $I^2=0\%$, $n_{cohorts}=9$, or 0.96 (0.95, 0.98), $I^2=34\%$, $n_{cohorts}=3$], processed meat (50 g/day) with nuts (28–50 g/day) or legumes (50 g/day) [SHR (95% CI): 0.79 (0.71, 0.88), $I^2=48\%$, $n_{cohorts}=9$ or 0.91 (0.85, 0.98), $I^2=9\%$, $n_{cohorts}=9$], and unprocessed red meat (50 g/day) with nuts (10–16 g/day) [SHR (95% CI): 0.93 (0.92, 0.94), $I^2=0\%$, $n_{cohorts}=8$]. Furthermore, replacing dairy (50 g/day) with nuts/legumes (7–50 g/day) or nuts only (7–50 g/day) [SHR (95% CI): 0.94 (0.92, 0.97), $I^2=65\%$, $n_{cohorts}=6$, or 0.94 (0.91, 0.97), $I^2=67\%$, $n_{cohorts}=3$], one egg/day with nuts (25–28 g/day) or legumes (25–50 g/day) [SHR (95% CI): 0.85 (0.82, 0.89), $I^2=67\%$, $n_{cohorts}=8$, or 0.90 (0.89, 0.91), $I^2=0\%$, $n_{cohorts}=7$], and butter (5 g/day) with olive oil (5 g/day) [SHR (95% CI): 0.94 (0.92, 0.97), $I^2=87\%$, $n_{cohorts}=3$] was also associated with a lower risk of all-cause mortality. The other associations were rated as low or very low certainty of evidence (Additional file 2: Table S10).

Single study findings

A pooled analysis (based on two cohorts, only the pooled effect estimate was reported, and new meta-analysis was not possible) showed that replacing processed meat, yogurt, cheese, eggs, and butter with avocado was associated with a lower incidence of CVD (Additional file 3: Fig. S9) and CHD (Additional file 3: Fig. S10) [25]. Furthermore, the substitution of poultry, fish, and eggs with peanuts and peanut butter or with whole grain was associated with a lower T2D incidence (pooled analysis, based on three cohorts) [28]. The estimates on change over time were pooled from three cohorts, and the findings showed an inverse association with T2D when substituting red meat, as well as unprocessed and processed red meat with nuts and legumes (Additional file 3: Fig. S11) [11]. In addition, replacing processed meat, unprocessed red meat, dairy, and eggs with whole grains was associated with a lower risk of all-cause mortality (pooled analysis, based on six cohorts) [14, 24]. Furthermore, the estimates on change over time were pooled from two cohorts and showed that replacing red meat, processed meat, and unprocessed meat with nuts or whole grains

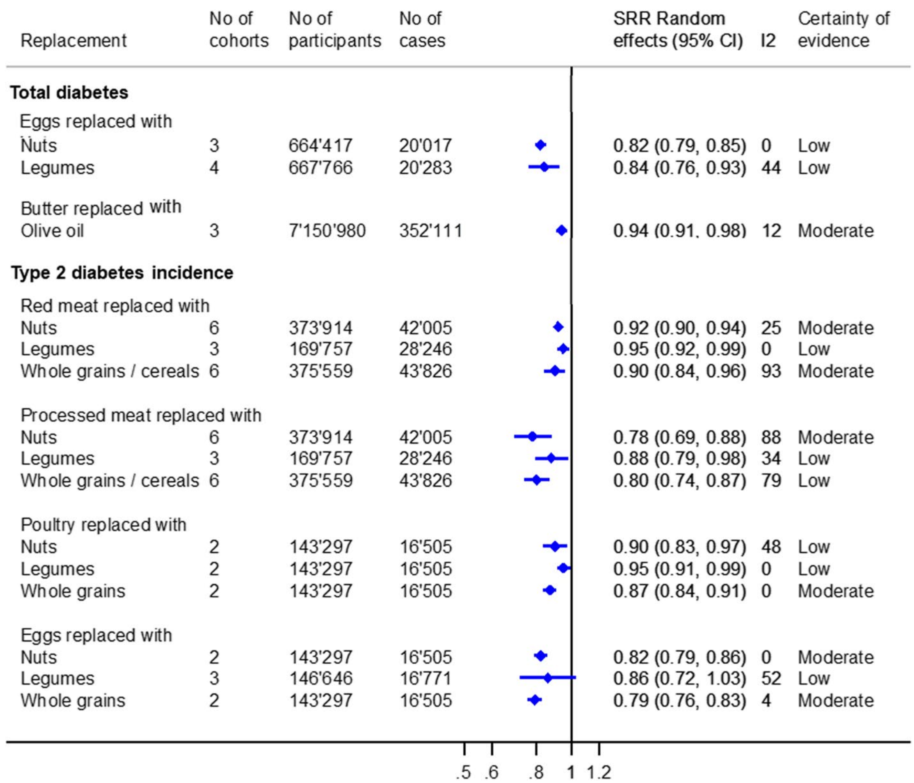

Fig. 4 Substitution meta-analyses replacing animal-based foods with plant-based foods regarding type 2 diabetes incidence and total diabetes (type 2 diabetes incidence and diabetes mortality). Portion sizes: red and processed meat/red meat/processed meat: 50 g/day; nuts: 10–28 g/day; legumes: 18–50 g/day; whole grains/cereals: 11–30 g/day; butter: 5 g/day; and olive oil: 5 g/day

was associated with a lower risk of all-cause mortality (Additional file 3: Fig. S12) [29].

Furthermore, several substitution analyses were only conducted in one single cohort. In these studies, there was an association with a lower risk of CVD mortality when substituting butter with canola oil (Additional file 3: Fig. S13) [167]. In addition, replacing butter with margarine was associated with an increased incidence of CVD (Additional file 3: Fig. S13) and CHD (Additional file 3: Fig. S14) [161]. Furthermore, there was an inverse association with T2D incidence for the substitution of milk with coffee or tea [172], as well as of sweetened milk-beverages with drinking water [173]. The study estimates based on change over time showed an inverse association with T2D for the replacement of red meat with whole grains or refined grains (Additional file 3: Fig. S15). Moreover, there were associations with a lower risk of all-cause mortality when substituting butter with margarine, corn oil, and canola oil [167], as well as animal cooking oil with plant oils other than peanut, soybean, canola, or salad oil (Additional file 3: Fig. S16) [177].

Heterogeneity, subgroup, sensitivity and bias analysis

I^2 is reported in Figs. 2, 3, 4 and 5 and, together with tau^2 and the 95% PIs, in the individual forest plots in Additional file 3: Figs. S3-S8. The only 95% PI that excluded the null value was for the association between the substitution of red meat with nuts on T2D incidence (95% PI: 0.85, 0.98), indicating that the true effects of future studies are expected to point in the same direction. All the other 95% PIs were wider and indicated that the true effect of future studies could be null or point in the opposite direction.

Since only few publications were available for the meta-analyses, which partly provided pooled risk estimates of multiple cohorts, but no single estimates [11, 14, 24, 26, 28, 29, 154, 159, 162, 163, 166], no subgroup analyses or assessment of publication bias was possible.

In sensitivity analyses leaving out one study at a time, the results remained mainly robust. The direction of the associations always remained the same; however, for several associations, the risk estimate changed in magnitude and precision. For the substitution of red and processed meat with nuts regarding CVD mortality, the SHR (95% CI) changed from 0.78 (0.53, 1.14) to 0.62 (0.44, 0.88) when excluding the study by Sun et al. [165] (WHI). Moreover, the association between the replacement of eggs with legumes regarding T2D incidence changed from an SHR (95% CI) of 0.86 (0.72, 1.03) to 0.63 (0.22,

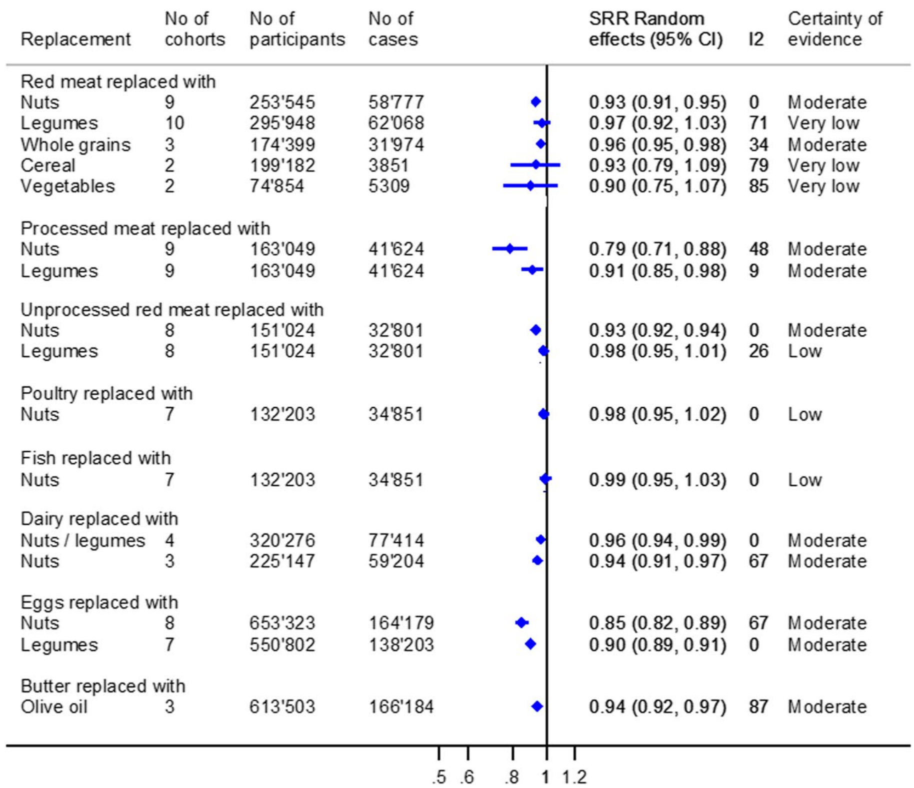

Fig. 5 Substitution meta-analyses replacing animal-based foods with plant-based foods regarding all-cause mortality. Portion sizes: red meat/(un)processed meat/poultry/fish/dairy: 50 g/day; eggs: 1 egg/day; nuts: 10–50 g/day; legumes: 13–50 g/day; whole grains: 11–30 g/day; butter: 5 g/day; and olive oil: 5 g/day

1.84) and 0.60 (0.24, 1.55) when leaving out the study by Li et al. [179] (WHI) and Li et al. [179] (UK Biobank study (UKB)), respectively (data not shown).

Discussion

This is the first systematic review and meta-analysis that summarized the associations between the substitution of animal-based with plant-based foods with a wide range of cardiometabolic outcomes, such as CVD mortality; incidence of CVD, CHD, and T2D; diabetes mortality, and all-cause mortality, and evaluated the risk of bias and certainty of evidence of the meta-findings. Our results indicate that replacing animal-based with plant-based foods is beneficially associated with cardiometabolic health. The substitution of red and processed meat with nuts, legumes, and whole grains reduced the risk of total CVD, CHD, and T2D and all-cause mortality with moderate certainty of evidence. We also observed moderate certainty of evidence for the association between the replacement of eggs with nuts and a lower incidence of total CVD and all-cause mortality. Additionally, replacing butter with olive oil lowered the incidence of total CVD, CVD mortality, total diabetes, and all-cause mortality with moderate certainty of evidence.

Furthermore, we found moderate certainty of evidence for an inverse association between the substitution of poultry with whole grains and T2D incidence and for the replacement of dairy products with nuts and legumes regarding all-cause mortality. For the other associations regarding the replacement of dairy products, poultry, or fish/seafood with plant-based foods, the certainty of evidence was low. However, our results indicated an inverse association for the substitution of poultry with nuts or legumes in relation to T2D incidence but no clear association for replacing dairy products, fish/seafood, or poultry with nuts or legumes regarding total CVD. In addition, no association was observed for the substitution of fish/seafood or poultry with nuts or legumes regarding all-cause mortality.

Our results are in agreement with a previous systematic review and meta-analysis investigating the replacement of red meat with other protein sources on CHD and all-cause mortality [15]. The authors observed a lower risk of CHD, when replacing red meat, processed red meat, and unprocessed red meat with nuts or legumes, and a lower risk of all-cause mortality when substituting red meat with nuts and processed red meat with nuts or legumes [15]. The certainty of evidence was assessed using NutriGrade [180] and was also rated as moderate for these associations [15]. However, they did not investigate further cardiometabolic endpoints, such as CVD mortality, CVD incidence, or T2D. Previous meta-analyses also support our findings that higher meat intake was associated with a risk of T2D [8], CHD, and stroke [7], as well as all-cause mortality [9]. This also applies to the associations between olive oil and CVD, T2D, and all-cause mortality [181, 182]. In contrast, a higher intake of eggs and butter was not associated with these outcomes in previous studies [7–9]. However, these studies included no substitution analyses. This suggests that not only the amount of these foods consumed is important but that it also plays a role what foods they are replaced with. Furthermore, our results indicate that the replacement of dairy products with nuts and legumes is associated with a lower risk of CVD or all-cause mortality. However, dairy includes a wide range of different products (e.g., milk, yogurt, cheese) with different associations with cardiometabolic outcomes. For example, contrary to our results, a higher intake of yogurt was inversely associated with risk for all-cause and CVD mortality [183]. Thus, associations for the replacement of different subtypes of dairy products with plant-based foods might differ, and more research is needed on this aspect. A network meta-analysis of randomized controlled trials comparing different food groups and their effect on intermediate diseases markers, such as blood lipids, blood pressure, and glycaemic control parameters, also found that plant-based foods, such as nuts, legumes, and whole grains, were most beneficial for all outcomes combined [184]. Given these results, stronger associations for the replacement of animal-based foods with legumes might have been expected. However, the network meta-analysis focussed on intermediate endpoints and rather reflects short-term effects due to the inclusion of RCTs with shorter follow-up times (mainly around 8–12 weeks). Therefore, long-term effects on hard endpoints might differ. However, the certainty of evidence for the majority of the findings on legumes was low or very low, limiting our confidence in the results. Thus, future studies might provide more insight into these associations. Moreover, in line with our results, a network meta-analysis comparing different types of oils and solid fats on blood lipids confirmed a more beneficial effect of olive oil compared to butter [185].

There are different mechanisms that might explain the observed associations. First, it is likely that persons favoring plant-based foods follow a more health-conscious lifestyle in general. However, the included studies all adjusted for important lifestyle confounders such as total energy intake, physical activity, alcohol intake, and smoking, and the associations persisted. Nevertheless, residual confounding cannot be ruled out.

Furthermore, processed meat contains saturated fatty acids, such as stearic and palmitic acid, which potentially increase the risk of CVD and T2D [108, 116]. Moreover, red and processed meats contain compounds promoting oxidative stress and chronic low-grade inflammation, such as heme iron, sodium, nitrates, and nitrites that might be associated with increased risk of CVD, T2D, and mortality [54, 186]. In contrast, plant-based foods such as nuts, legumes, and whole grains, as well as olive oil, contain high amounts of anti-oxidant and anti-inflammatory compounds, including fiber, phytochemicals, vitamins and minerals, and polyphenols that show beneficial associations with cardiovascular health and, in relation to cardiovascular health, obesity [187, 188]. Thus, both the reduction of animal-based foods, especially meat, and the increase of plant-based foods simultaneously contribute to the observed beneficial associations regarding cardiometabolic health.

Our findings also highlight the need for future research. First, some of the results still show some inconsistencies. For example, both the substitution of processed and unprocessed red meat with legumes were associated with a lower risk of total CVD, while the association for the replacement of red meat with legumes was less clear. This was mainly due to an imprecise estimate of the latter association also resulting in a very low level of the certainty of evidence. Therefore, more studies on this association are needed in order to provide further insights into the consistency of these associations and to improve our confidence in the findings. In general, to increase the certainty of evidence, well-conducted prospective observational studies on the associations with low and very low certainty of evidence and on the associations only investigated in single studies are needed. This includes for example the substitution of dairy products, especially subtypes of dairy products, poultry, or fish/seafood with plant-based products, or the replacement of animal-based foods with further plant-based foods, such as fruit and vegetables. These studies should minimize the risk of bias, e.g., by using models with a sufficient level of adjustment, and use standardized portion sizes (e.g., 50 g for meat/poultry/fish/seafood, 30 g for whole grains/legumes, 5 g for butter/olive oil) for both the substituted food and the replacement in order to improve the comparability between the results and to decrease heterogeneity between the studies. Furthermore, the majority of the studies investigated a theoretical substitution. Future studies should focus more on an observed change in food intake, as was done in three recent studies [11, 29, 30]. Moreover, more research is needed on the substitution of animal-based products with meat and dairy replacement foods, which strongly gained popularity in recent years.

Strengths and limitations

This is the first systematic review and meta-analysis focussing on the association between the substitution of animal-based with plant-based foods on multiple cardiovascular outcomes, including 37 studies on CVD, CHD, T2D, related mortality, and all-cause mortality. We followed the recommended procedures (pre-registered protocol and reporting guidelines) and applied validated tools for the risk of bias and certainty of evidence assessments. Moreover, we used standardized portions for the substituted foods, which increased the comparability of the results.

However, our work also has several limitations. First, only few studies were available for some of the meta-analyses, and these findings should be interpreted with caution and more studies on this topic are needed. While some studies provided pooled risk estimates of multiple cohorts, no separate estimates for these single cohorts were available, and thus, subgroup and sensitivity analyses excluding studies with a high risk of bias or assessment of publication bias could not be conducted. Second, several substitution analyses were only investigated in one study. Therefore, no meta-analyses were possible. More prospective studies with substitution analyses for these associations are needed in order to further investigate this evidence. Third, while we increased the comparability of the results, using standardized portions for the substituted foods, this was not possible for the substitute simultaneously. We adapted the portion sizes of the replacement according to the conversion of the substituted foods. However, given the varying portion sizes between studies, the portions of the replacement still varied, leading to the comparison of different amounts of the replacement. This was considered in the indirectness domain in GRADE, contributing to the downgrading of the certainty of evidence for the respective associations. Fourth, due to the observational design of the included studies, unknown confounding cannot be ruled out. Therefore, no study could be judged as low risk of bias in ROBINS-I, leading to a downgrade in the GRADE risk of bias domain. Furthermore, given that the substitution models adjusted for total energy intake while controlling for different foods in grams per day, a residual energy substitution was introduced [10]. However, we only included prospective observational studies thus minimizing the risk of selection or recall bias. Fifth, to date, no study is available regarding meat and dairy replacement products, which have rapidly increased in popularity in recent years. Sixth, dairy products were mostly treated as one group, and more research is needed on the substitution of subtypes of dairy products with plant-based foods.

Conclusions

Our findings suggest that a shift in diet from a high consumption of animal-based foods, especially red and processed meat, to plant-based foods (e.g., nuts, legumes, and whole grains) is associated with a lower risk of all-cause mortality, CVD, and T2D. Thus, a change in dietary habits towards an increment of plant-based products appears to be important for cardiometabolic health. However, more research is needed in order to strengthen the existing evidence and to investigate new associations, especially with a focus on meat and dairy replacement products.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-023-03093-1.

Additional file 1. Search terms.

Additional file 2: Table S1. Eligibility criteria by the PICOS statement. **Table S2.** Study characteristics. **Table S3.** Description and decision criteria for each domain in ROBINS-I. **Table S4.** List of excluded studies. **Table S5.** GRADE assessment for the substitution analyses regarding total CVD. **Table S6.** GRADE assessment for the substitution analyses regarding CVD mortality. **Table S7.** GRADE assessment for the substitution analyses regarding CHD incidence. **Table S8.** GRADE assessment for the substitution analyses regarding total diabetes. **Table S9.** GRADE assessment for the substitution analyses regarding type 2 diabetes incidence. **Table S10.** GRADE assessment for the substitution analyses regarding all-cause mortality.

Additional file 3: Fig. S1. Risk of bias of each study for each domain and overall. **Fig. S2.** Risk of bias of judgements within each bias domain. **Fig. S3.** Forest plots for the substitution analyses regarding total CVD. **Fig. S4.** Forest plots for the substitution analyses regarding CVD mortality. **Fig. S5.** Forest plots for the substitution analyses regarding CHD incidence. **Fig. S6.** Forest plot for the substitution analyses regarding total diabetes. **Fig. S7.** Forest plots for the substitution analyses regarding incidence of type 2 diabetes. **Fig. S8.** Forest plots for the substitution analyses regarding all-cause mortality. **Fig. S9.** Forest plot showing the results from extracted pooled analyses regarding CVD mortality and CVD incidence. **Fig. S10.** Forest plot showing the results from extracted pooled analyses regarding CHD and stroke incidence. **Fig. S11.** Forest plot showing the results from extracted pooled analyses regarding diabetes. **Fig. S12.** Forest plot showing the results from extracted pooled analyses regarding all-cause mortality. **Fig. S13.** Forest plot showing the results from single cohorts regarding CVD mortality and CVD incidence. **Fig. S14.** Forest plot showing the results from single cohorts regarding CHD, MI and stroke incidence. **Fig. S15.** Forest plot showing the results from single cohorts regarding diabetes. **Fig. S16.** Forest plot showing the results from single cohorts regarding all-cause mortality.

Authors' contributions

SS and LS designed the research. KG conducted the literature search. MN, SS, LS, JE, and EK screened the studies for eligibility. MN, JE, and LS extracted the data. MN, JS, ES, and EK assessed the risk of bias. MN conducted the meta-analyses. MN and LS assessed the certainty of evidence. MN and SS drafted the first version of the manuscript. All authors interpreted the data. MN and SS are guarantors. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria were omitted. All authors read and approved the final manuscript.

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Availability of data and materials
This manuscript makes use of publicly available data from published studies; therefore, no original data are available for sharing.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare that they have no competing interests.

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