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Relevance of physical function in the association of red and processed meat intake with all–cause, cardiovascular, and cancer mortality

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Abstract *Background and aims:* Intake of red and processed meat has been associated with a higher risk of morbidity and mortality; it is unknown whether these associations are modified by overall physical health. This study examined the associations of red and processed meat consumption with all–cause, cardiovascular, and cancer mortality and investigated whether markers of physical function modified the associations.
Methods and results: This observational cohort study used UK Biobank data derived from 419,075 participants free from cancer and cardiovascular disease. Cox models assessed the association of red and processed meat consumption (obtained from a baseline food frequency questionnaire) with mortality, adjusted for potential confounders. Objectively measured handgrip strength and self-reported walking pace were used as interaction terms. The median age was 57 (interquartile range, 49–63) years and 54.9% were women. Over 7 years of follow–up, 8586 all–cause, 1660 cardiovascular, and 4812 cancer deaths occurred. Each additional serving per week of red and processed meat was associated with a hazard ratio (HR) of 1.037 (95% CI: 1.028–1.047) for all–cause; 1.030 (1.009–1.051) for cardiovascular; and 1.029 (1.016–1.042) for cancer mortality. The association of red and processed meat consumption was modified by walking pace, with brisk walkers having the lowest risk per additional serving for all–cause and cancer mortality (HR 1.025; 1.006–1.045 and 1.015; 0.990–1.040, respectively); no interaction was observed for handgrip strength.
Conclusion: The known risk of mortality associated with red and processed meat consumption may be lower in those with high physical function.

Introduction

Red and processed meat are recognised carcinogens and risk factors for cardiovascular disease. In 2015 the International Agency for Research on Cancer (the cancer agency of the World Health Organization) classified processed meat as a Class 1 carcinogen and red meat as a Class 2A carcinogen to humans [1,2]. The latest report of the World Cancer Research Fund International/American Institute for Cancer Research (September 2017) highlights that there is strong evidence to support that red and processed meat consumption increase the risk of bowel and stomach cancers [3]. The American Heart Association

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and American College of Cardiology, along with the European Society of Cardiology, also recognise processed and red meat as risk factors for cardiovascular disease, recommending that processed meat is avoided and the intake of red meat should be limited [4,5]. Evidence for a dose–response association between processed/red meat intake and risk of mortality and morbidity including cancer and stroke has been further established in recent studies and meta–analyses [6–17]. However, red and processed meat consumption remains high across the globe, particularly in developed countries [18].

Despite consistent evidence for associations between processed/red meat intake and health outcomes, important questions remain. For example, it is unclear whether association are consistent across levels of overall health status. Markers of physical function and fitness are established markers of cardiometabolic health status and are considered a cardiovascular vital sign [19]. Those with good functional and fitness status have greater physiological flexibility in responding to other physiological stressors, such as obesity, whereas those with low functional and fitness status have reduced flexibility and reserve [20,21]. For example, subjects with low levels of physical function or who undertake low levels of physical activity display particularly strong associations of sedentary time, alcohol intake, smoking, type 2 diabetes and body mass index (BMI) with both disease biomarkers and mortality, whereas associations are partially or fully attenuated in those with high levels of fitness or physical activity [22–29].These observations suggest that low levels of physical function may help identify individuals who are particularly susceptible to the harmful associations of some lifestyle behaviours. However, the importance of functional status as a potential modifier of the association between meat consumption and mortality outcomes has not been well researched.

The aim of this study was to examine and quantify the associations of self–reported red and processed meat consumption with all–cause, cardiovascular, and cancer mortality in a contemporary population using data from the UK Biobank cohort and to evaluate whether markers of physical fitness and function (walking pace and handgrip strength) modify these associations. We hypothesise that the association of red and processed meat consumption with mortality outcomes will be attenuated in people with high physical function.

Methods

UK biobank

This analysis used data from 502,621 participants within UK Biobank. The UK Biobank study is an ongoing large prospective cohort study in the UK. The study recruited volunteers aged 40–69 years from 22 recruitment centres throughout England, Wales, and Scotland between March 2006 and July 2010. UK Biobank has approval from the North West Multi–centre Research Ethics Committee (MREC), which covers the UK. In Scotland, UK Biobank has approval from the Community Health Index Advisory Group (CHIAG). The methods and aim of UK Biobank have been reported elsewhere [30]. Baseline questionnaires, physical measures, and biological samples were collected from the recruited individuals. Data field (DF) identification numbers are reported below for each variable included in this analysis and can be used to search for detailed information about measurement procedures within the UK Biobank data showcase [31].

Main exposure

A touchscreen food frequency questionnaire (FFQ), reflect the average frequency of consumption of foods and food groups over the past year, captured diet related data fields using the Assessment Centre Environment system. The FFQ used in UK Biobank has been shown to have reasonable reliability and validity for red and processed meat and for the other dietary variables used in the models of this study [32].

Red meat was assessed through three variables: beef (DF-1369), lamb/mutton (DF-1379), and pork (DF-1389) intake. Processed meat (DF-1349) was defined through a single variable assessing any intake of bacon, ham, sausages, meat pies, kebabs, burgers, and nuggets. For each variable, participants were asked about their frequency of consumption through selecting one of the following: never, less than once a week, once a week, 2–4 times a week, 5–6 times a week, once or more daily. The frequency of response in UK Biobank for each category of red and processed meat consumption are displayed in Table S1.

For this analysis, frequency categories were converted to a continuous measure of consumption, as follows: a value of 0 was allocated to “never”, 0.5 for “less than once a week”, 1 for “once a week”, 3 for “2–4 times a week, 5.5 for “5–6 times a week” and 7 for “once or more daily”. Servings for the three red meat variables and the processed meat variable were summed to create the frequency of red and processed meat consumption with values ranging from a minimum of 0 (participant does not eat any red or processed meat) to a maximum of 28 (participant eats 28 servings each week). We analytically evaluated the appropriateness of combining red and processed meat in a single overall frequency of consumption (see Statistical analysis section).

Measures of physical function

Objectively assessed handgrip strength and self–reported walking pace were assessed at baseline. Both left and right handgrip strengths (DF-46 and DF-47) were measured using a hydraulic hand dynamometer (Jamar J00105). Participants were instructed to remain seated, placing their forearms on armrests during the measurement. The elbow of the arm holding the dynamometer was placed against the side of the body and bent to a 90° angle so that the participant’s forearm was

facing forward. Participants were instructed to squeeze the handle of the dynamometer as hard as they could for 3 s. In this study, an average of the right and left hand was used. The UK Biobank touchscreen questionnaire was used to capture usual walking pace (DF-924). Participants were asked to answer the following question: "How would you describe your usual walking pace? (a) Slow, (b) Steady/average, and (c) Brisk". Within the subsample of UK Biobank that undertook a graded exercise test, responses for walking pace have been shown to be highly associated with cardiorespiratory fitness [33]; thus brisk walkers are likely to have high cardiorespiratory fitness and good physical functionality.

Other variables

At baseline, data were also captured for other diet related fields, including weekly frequency consumption of poultry (DF-1359), oily-fish (DF-1329), non-oily fish (DF-1339), fresh fruit (DF-1309), dried fruit (DF-1319), salad/raw vegetable (DF-1299), cooked vegetable (DF-1289), and salt added to food (DF-1478) and for: age (DF-21003; years); BMI (DF-21001; kg/m^2; the weight and height of UK Biobank participants were objectively measured during the initial Assessment Centre visit); ethnicity (DF-2100; white, non−white); Townsend deprivation index (DF-189); sex (DF 31); smoking status (DF-20116; current, previous, never); alcohol use (DF-20117; current, previous, never); physical activity [number of days/week walked 10 + minutes (DF-864); number of days/week of moderate physical activity 10 + minutes (DF-884); number of days/week of vigorous physical activity 10 + minutes (DF-904)]; time spent watching television (hours/day; DF-1070); qualifications (DF-3138; college or university degree, no college or university degree); and employment (DF-6142; in paid employment or self−employed, retired, unable to work because of sickness or disability, doing unpaid or voluntary work, looking after home and/or family, unemployed, full or part−time student).

Outcomes

All−cause mortality was defined for all participants as any death recorded between baseline and censoring dates (31 January 2016 for England and Wales and 30 November 2015 for Scotland) [30]. Date and cause of death were obtained from the NHS Information Centre for participants, from England and Wales, and from the NHS Central Register, for participants from Scotland. Survival time was defined as the difference between the date of death or censoring and baseline visit at the UK Biobank assessment centres. Cause of death was classified using DF-40001 and the International Classification of Diseases (ICD) code assigned to the underlying (primary) cause of death. We defined cancer mortality using ICD−10 C00−C97 and cardiovascular disease (CVD) death using ICD−10 I00−I79.

Study population

From the initial sample of 502,621 participants, we excluded people with prevalent cancer [number of self−reported cancers (DF-134); n = 41 706] or prevalent cardiovascular disease [defined as peripheral vascular disease, angina, heart attack/myocardial infarction, heart failure/pulmonary oedema, stroke, and transient ischaemic attack (DF-20002); n = 28,078]. From the remaining sample, subjects with information available for all covariates were included: missing data were less than 2% for all included covariates and 6.7% in total, leaving 419,075 for the analysis conducted in 2018 (Fig. S1).

Statistical analysis

Linearity in the association between the combined red and processed meat consumption (exposure) and mortality outcomes was assessed graphically by plotting the HR estimated within quartiles of baseline red and processed meat frequency consumption relative to the bottom quartile versus the mean frequency consumption value in each quartile using floating absolute risks [34]. We further confirmed linearity by comparing with the likelihood ratio test models including linear vs non-linear (i.e., cubic splines) exposure. As linearity was confirmed for all outcomes, results are reported as differences in risk per one unit increase of frequency of red and processed meat consumption, i.e., per 1 serving per week.

Cox proportional hazards models were used to investigate the associations of red and processed meat consumption with cardiovascular, cancer, and all−cause mortality. We progressively adjusted estimations accounting for possible confounders: model 1 was unadjusted; model 2 was adjusted for age, sex, ethnicity, Townsend score, employment, number of medications; model 3 additionally adjusted for smoking status, alcohol use, diet (fresh fruit, dried fruit, cooked and raw vegetable consumption; poultry, oily-fish, non-oily fish and salt added to food), and education; model 4 further adjusted for time spent TV viewing, physical activity (walking, moderate, and vigorous), and BMI; finally, model 5 adjusted for measures of physical function [walking pace (model 5a) or handgrip strength (model 5b)].

In order to confirm the appropriateness of adding red and processed meat together into a single score, an analysis was carried out using model 4 to investigate the association between red meat only or processed meat only with mortality, which confirmed similar HRs with overlapping 95% CIs between the two exposures (Table S2).

Interaction terms were fitted to models 5a for walking pace and 5b for handgrip strength to assess whether handgrip strength (as tertiles) or walking pace (brisk vs steady/average or slow) modified the association of red and processed meat consumption with cancer, cardiovascular, and all−cause mortality. For walking pace, slow and steady/average categories were combined due to the small number reporting a slow walking pace (n = 29,904).

Interactions at the P < 0.10 level were further explored in stratified analysis [35].

E–values were calculated, using model 4 and comparing top vs bottom quartiles of red and processed meat consumption for the three mortality outcomes. E–value represents the minimum strength of association that an unmeasured confounder needs to have with both the exposure and outcome to fully explain away the association (i.e., null true effect) [36]. It is therefore a measure of potential causality: the higher the E-value, the less likely an investigated associated is confounded by an unmeasured factor (i.e., non–causal).

All analyses were conducted using Stata MP 14.1 (Stata Corporation, College Station, TX, USA), with the exception of the calculation of E–values, performed with R, Version 0.99.491 [37]. Statistical significance was set at P < 0.05 and results are reported with robust 95% confidence interval (CI).

Sensitivity analysis

In a landmark analysis, we exclude participants who died during the first year of follow-up to limit the potential of reverse causation.

Results

Table S3 displays the baseline characteristics of the 419 075 included participants overall and when stratified by quartile of red and processed meat consumption. The median (interquartile range, IQR) age of was 57 (49–63) years and 229 885 (54.9%) were women. There were 8586 (2.05%) all–cause, 1660 (0.40%) cardiovascular, and 4812 (1.15%) cancer deaths during a median (IQR) of 6.97 (6.29–7.63) years follow–up and 2,906,217 person-years. The median (IQR) for red and processed meat frequency of consumption was 3 (2–5) servings per week.

Red and processed meat consumption was associated with a higher risk of all–cause, cardiovascular, and cancer mortality in models progressively adjusted for confounders (Fig. 1 and Table S4): in the unadjusted model, the HR per weekly serving of red and processed meat consumption was 1.087 (95% CI, 1.079–1.096) for all-cause; 1.109 (1.090–1.129) for cardiovascular; and 1.069 (1.057–1.081) for cancer mortality. Upon inclusion of possible confounders (model 4), the HR per weekly serving of red and processed meat consumption was 1.037 (1.028–1.047); 1.030 (1.009–1.051); and 1.029 (1.016–1.042) for all-cause, cardiovascular, and cancer mortality, respectively. Further inclusion of physical function markers did not materially change the estimates (Fig. 1 and Table S4).

Linearity between the frequency of red meat and processed meat consumption and HR for all-cause, cardiovascular, and cancer mortality was confirmed using quartile data (Fig. 2); in the fully adjusted model HR comparing quartile 4 vs reference (quartile 1) was 1.252 (1.172–1.338) for all-cause, 1.238 (1.062–1.442) for cardiovascular and 1.183 (1.082–1.293) for cancer mortality. Furthermore, there was no evidence of model differences comparing linear vs the cubic splines transformation of red meat and processed meat consumption for all-cause (P = 0.864), cardiovascular (P = 0.773) and cancer mortality (P = 0.493).

Interaction analyses revealed the association between meat consumption and all–cause mortality was modified by walking pace (P = 0.046), with brisk walkers having the weakest association (HR 1.025, 1.006–1.045; Fig. 3 and Table S5) while slow-average pace walkers had a stronger association (HR 1.040, 1.029–1.051). Similarly, the association between red and processed meat consumption and cancer mortality was modified by walking pace (P = 0.062), with brisk walkers having no association (HR 1.015, 0.990–1.040) while HR for slow-average pace was 1.034 (1.018–1.050). Handgrip strength was not found to modify associations for all-cause (P = 0.201), cardiovascular (P = 0.420) and cancer mortality (P = 0.571).

The 95% lower CI of E-values for red and processed meat frequency of consumption and all–cause, cardiovascular, and cancer mortality were 1.621, 1.301, and 1.383, respectively (Table S6).

The results were consistent in the analysis excluding participants who died during the first year of follow-up (445 people; 174 cardiovascular and 138 cancer deaths), including the interactions of walking pace with all-cause mortality (P = 0.062) and cancer mortality (P = 0.065).

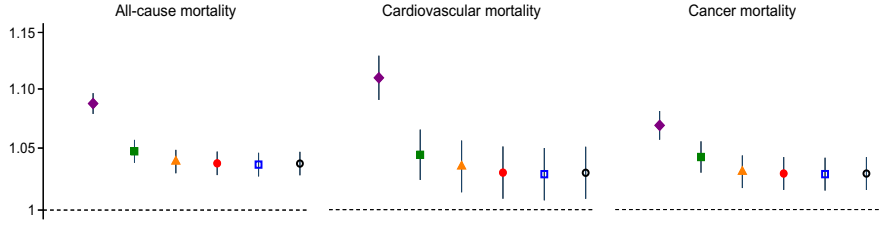

Figure 1 Association of red and processed meat intake (servings per week) with all–cause, cancer, and cardiovascular mortality. Model adjustment: ◆ Model 1: Unadjusted. ■ Model 2: Age, gender, ethnicity, Townsend score, employment, number of medications. ▲ Model 3: Model 2 + education, smoking status, alcohol use, diet (fresh fruit, dried fruit, cooked and raw vegetable consumption; poultry, oily-fish, non-oily fish, salt added to food). ● Model 4: Model 3 + time TV viewing, physical activity (walking, moderate and vigorous), Body Mass Index. □ Model 5a: Model 4 + walking pace. ○ Model 5b: Model 4 + handgrip strength (average of right and left hand measures). References (hazard ratio 1, dotted lines). Results are presented per 1- weekly serving of red and processed meat intake (processed meat + beef + lamb/mutton + pork). Spikes indicate 95% CI. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

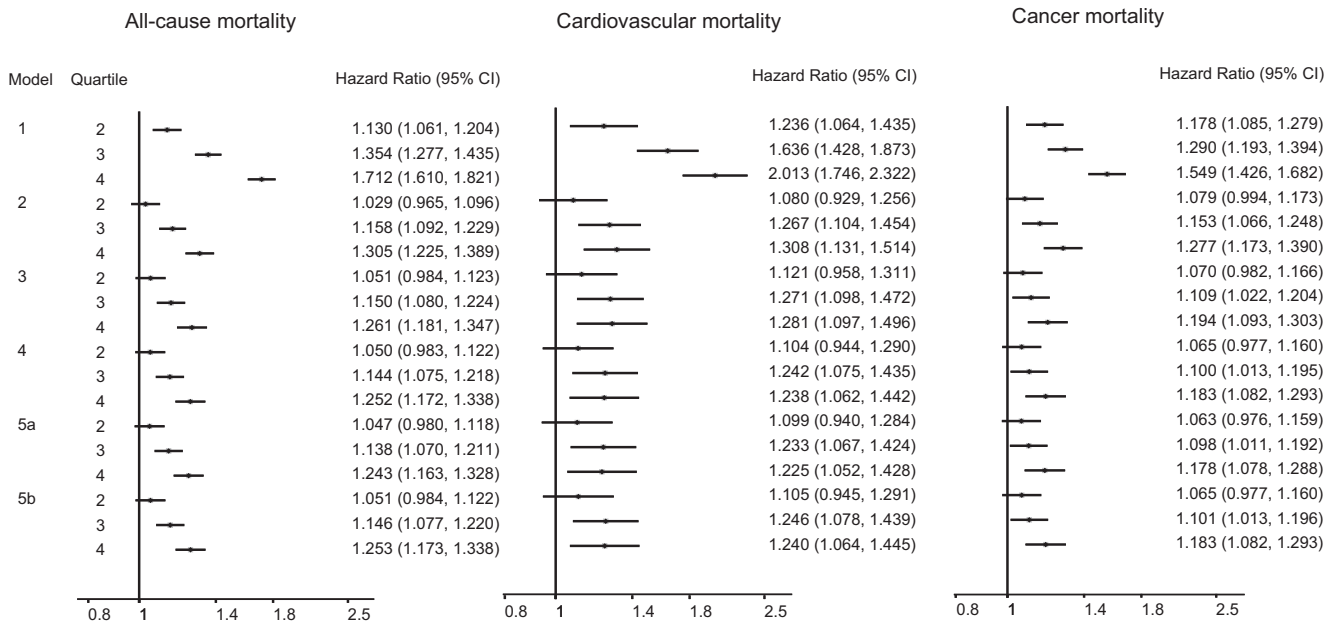

Figure 2 Association of red and processed meat frequency of consumption with all−cause, cancer, and cardiovascular mortality-in quartiles. Model 1: Unadjusted. Model 2: Age, gender, ethnicity, Townsend score, employment, number of medications. Model 3: Model 2 + education, smoking status, alcohol use, diet (fresh fruit, dried fruit, cooked and raw vegetable consumption; poultry, oily-fish, non-oily fish, salt added to food). Model 4: Model 3 + time TV viewing, physical activity (walking, moderate and vigorous), Body Mass Index. Model 5a: Model 4 + walking pace. Model 5b: Model 4 + handgrip strength (average of right and left hand measures). Reference is the lowest quartile (quartile 1). Median (IQR) frequency per week of red and processed meat of consumption by quartile: **Q1**, 1.5 (1.0−2.0); **Q2**, 2.5 (2.5−3.0); **Q3**, 4.5 (4.0−5.0); **Q4**, 7.0 (6.0−8.0).

Discussion

In this large cohort study, we showed that red and processed meat consumption is associated with a higher risk of cardiovascular, cancer, and all−cause mortality. After adjusting for multiple potential confounders (demographic characteristics, medical history, physical activity, and dietary factors), each additional serving per week of red and processed meat was associated with 3.3%, 2.4%, and 2.6% higher risk of all−cause, cardiovascular, and cancer death, respectively. Results for all-cause, cardiovascular, and cancer mortality were unaffected after further adjustment for measures of physical function. Walking pace was found to modify associations such that for those with a fast walking pace the association of meat consumption with mortality outcomes was partially (all-cause mortality) or fully (cancer mortality) attenuated. This study therefore extends the evidence around the deleterious association of red and processed meat intake using a contemporary population whilst presenting the novel finding that walking pace modifies the association of red and processed meat intake with cancer and all−cause mortality, whereby the risk related to meat consumption appeared to be lower in those reporting a brisk walking pace.

We also observed no significant deviation from linearity in the association between the frequency of red meat and processed meat consumption with all-cause, cardiovascular, and cancer mortality. Findings from the present study in a large cohort are consistent with increasing epidemiological evidence showing that both red and processed meat are associated with mortality [6−10]. This study also supports recent meta-analyses showing a graded dose−response association with the risk of mortality whereby the risk increases with higher consumption of red and processed meat [11,12]. The shape of association has important public health implications. For example, the second global report by the World Cancer Research Fund sets as a public health goal to limit consumption of red meat (beef, pork, lamb, and goat) to less than 500 g (cooked weight) per week for meat eaters, little if any of which should to be processed (ham, bacon, salami, hot dogs, and sausages) [38]. Our study suggests similar levels of risk between processed and red meat consumption and supports the need for more research to establish whether there is a safe upper limit of red or processed meat consumption for the general population.

There are various possible mechanistic explanations underlying the adverse associations of red and processed meat consumption with mortality risk. A number of compounds formed by high-temperature cooking of red meat, such as heterocyclic amines and polycyclic aromatic hydrocarbons, N-nitroso compounds, and endogenous N-nitroso compounds from inherent heme iron are potential carcinogens [39−41]. Open-flame cooking, the degree of doneness as well as curing and smoking meat may also result in the formation of these hazardous chemicals which could further contribute to the association between meat intake and cancer risk [42]. The generation of lipid and protein oxidation products, as a result of the thermal effect during the processing of red meat, could also initiate carcinogenic responses [41]. Moreover, meat is a major

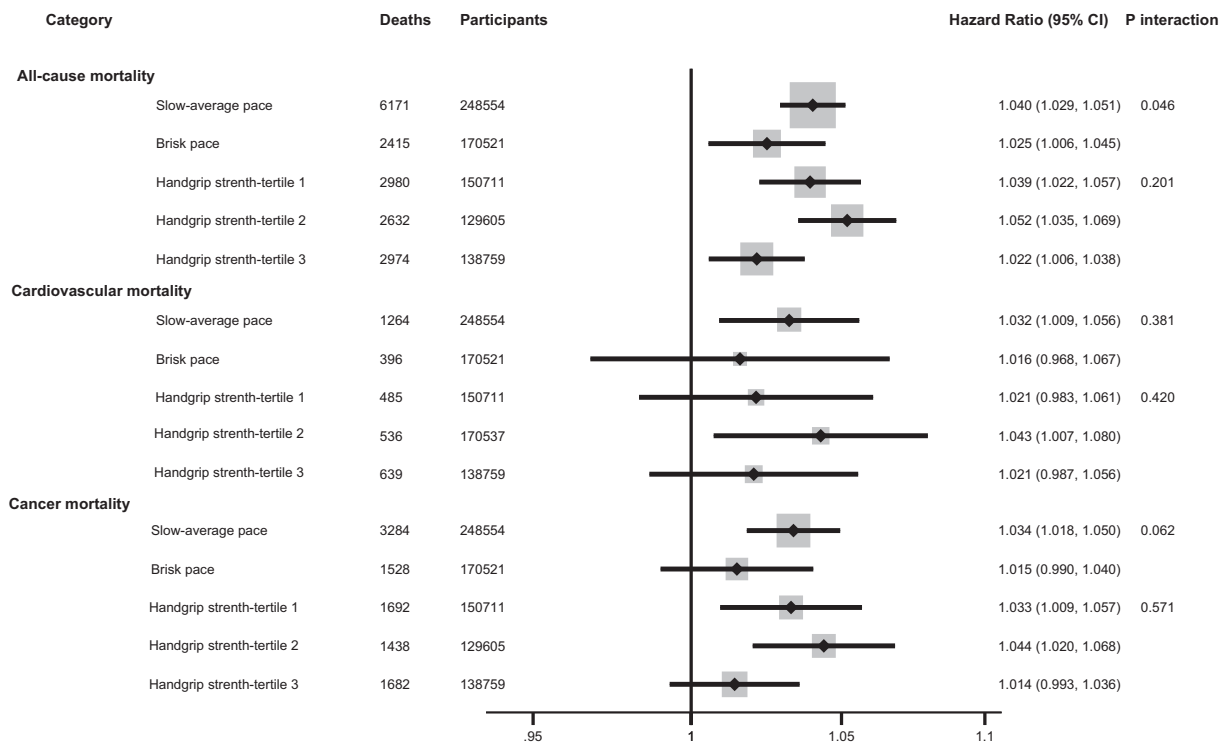

Figure 3 Interaction of red and processed meat intake with walking pace and handgrip strength on the risk of all-cause, cardiovascular and cancer mortality.

dietary source of saturated fat, which has been positively associated with numerous cancers, including breast [43] and colorectal cancer [38]. Processed meat contains high amounts of sodium which may increase the risk of heart disease through its effect on blood pressure [44,45]. Finally dietary compounds found in red and processed meat may interact with gut microbiota to create metabolites that have been associated with atherosclerosis and heart disease [46].

Self–reported walking pace is an important indicator functional status, cardiovascular health and is associated with all–cause and cardiovascular mortality [33,47]. Data from UK Biobank have also shown that self-reported walking pace is strongly associated with objectively assessed cardiorespiratory fitness [33]. Therefore, this study suggests that those with good cardiorespiratory function and fitness may gain some protection against the deleterious associations of red and processed meat intake compared to those with average or poor fitness. Specifically, those with good physical fitness and function may have greater metabolic flexibility in coping with the physiological stressors initiated by red and processed meat intake compared to those with low physical fitness and function.

This is consistent with other epidemiological and experimental studies which have shown that cardiorespiratory fitness or physical activity may modify the detrimental association between other risk factors (including sedentary time, BMI and, alcohol) and mortality [22–28]. However, it should be noted that the modifying effect of walking pace was not confirmed for handgrip strength. Handgrip strength is a measure of overall muscle strength whereas walking pace is associated with cardiorespiratory fitness [33,48]. Although handgrip strength has consistently been associated with all-cause and cardiovascular mortality [49–51], it has been suggested to be a less generalizable marker of mortality outcomes than walking pace, particularly for women [33].

E-values gave an additional epidemiological strength on this study. In order to explain the potential causality of the association, an unmeasured confounder would need to have an additional hazard ratio of a minimum of 1.621 for all-cause, 1.301 for cardiovascular, and 1.383 for cancer mortality, respectively, over and above the factors we have adjusted for.

Strengths of our study include the large sample size and a contemporary cohort. Assessing the association between lifestyle exposures and mortality outcomes in a contemporary population is important as patterns of behaviour and causes of mortality change over time [52]. This study is also novel in examining the influence of physical health (e.g. walking pace) on the strength of association between red/processed meat intake and mortality outcomes. This study also has some important limitations. The observational nature of the study limits our ability to assess causality between red and processed meat consumption and mortality outcomes and residual or unmeasured confounding remains possible, including other unmeasured dietary factors such as soft drinks. However, the estimated E-values were relatively high, increasing confidence that reported associations are not confounded by unmeasured factors. Diet was assessed using FFQ, therefore the

measure of meat consumption may have some degree of measurement error and act to increase regression dilution [53]. Finally, UK Biobank is not representative of the general population with regard to a number of lifestyle, health and sociodemographic-related characteristics and this may limit the generalizability of the findings to other populations [54].

In summary, our results showed an association of red and processed meat consumption with the risk of cancer, cardiovascular, and all−cause mortality in a contemporary population. Our study adds a novel finding that the risk of all-cause and cancer mortality with high red and processed meat intake may be lower in those with a brisk walking pace, a measure of good cardiorespiratory fitness. Therefore, red and processed meat intake may be less harmful in those with good cardiorespiratory fitness. These findings may help prioritise and tailor dietary advice around meat intake to those at greatest risk (i.e. those with low fitness). However, results need to be confirmed in further epidemiological and intervention research in order to allow for more specific, personalised recommendations to be formed on the basis of overall health status.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.06.019.

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