**Article 1: Red and Processed Meat and Mortality in a Low Meat Intake Population**

Author: **Saeed Mastour Alshahrani**

**Study cohort size:** 96000+ (Adventist Health Study-2), after exclusion 72149.

**Exclusion criteria:** (1) missing dietary variables (2) bad or inadequate data (3) missing more than 69 responses in dietary section (4) Canadian resident (5) extreme values of total energy (6) missing age, sex, or race (7) age younger than 25 years at baseline (8) Prevalent diseases related to mortality outcomes or prevalent CVD defined as previous coronary bypass, angioplasty/stent, carotid artery surgery, myocardial infarction, stroke, or transient ischemic attack, or angina pectoris or congestive heart failure treated in the past 12 month.

**Definition of unprocessed red meat:** Unprocessed red meat intake was reported as two items in the FFQ: “hamburger, ground beef (in casserole, meatballs, etc.)” and “beef or lamb as a main dish (e.g., steak, roast, stew, and pot pies)”.

**Definition of processed meat:** Processed meat was reported as: “processed beef, lamb (e.g., sausage, salami, and bologna)” and “processed chicken or turkey (e.g., turkey bologna, and turkey ham)”. Pork was classified as processed meat because most of the pork products listed in the single pork question in the FFQ were processed (i.e., “pork (bacon, sausage, ham, chops, ribs, and lunch-meat)”).

**Assessment of exposure:** The frequency of intake ranged from “never or rarely” to “2+ per day”, and serving sizes consisted of three levels (a half serving, standard serving (3–4 oz.), and one-and-a-half servings). The assigned weights for frequency and serving size in the FFQ used in AHS-2 have been previously described [12]. **The intake in grams per day was calculated using the product-sum method** [[12](https://www.mdpi.com/2072-6643/11/3/622/htm#B12-nutrients-11-00622),[13](https://www.mdpi.com/2072-6643/11/3/622/htm#B13-nutrients-11-00622)].

**Assessment of mortality:** Mortality outcome data were obtained from the National Death Index and were available through December 2015. International Statistical Classification of Diseases, 10th Revision (ICD-10) codes were used to determine the underlying cause of death. Individuals who died due to unnatural causes such as motor vehicle accidents and homicides (ICD-10 letters U, V, W, X, and Y) were censored at their time of death (i.e., they were not considered as cases in the analysis of all-cause mortality). ICD-10 codes for CVD mortality ranged from I00 to I78; cancer mortality ranged from C00 to C97.

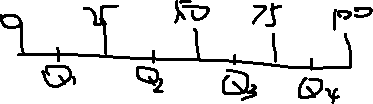
**Variables considered:**

Age, Sex, Race, Marital status, educational level, Multivitamin use, Smoking status, alcohol use, exercise, sleep, current HRT users, Diabetes, Hypertension, Hypercholesterolemia, aspirin use, BMI, Total energy intake, statin use, blood pressure medications, menopausal status (premenopausal, postmenopausal), and hormone therapy, previous screening for colon, prostate, or breast cancers during the last four years, Cruciferous vegetables, fruits, whole grain, legumes, nuts and seeds, total dairy, eggs, unprocessed poultry, processed meat, fish

**Adjusting variables:**

age (attained age as time variable), sex, race, and total energy intake, marital status, educational level, multivitamin use, smoking status, alcohol use, exercise, sleep, body mass index, aspirin use, having ever been diagnosed with or received treatment in the last 12 months for diabetes (yes/no), having been diagnosed in the last 5 years with or received treatment in the last 12 months for hypertension or hypercholesterolemia (yes/no), the use of statin for at least 2 years in the last 5 years, the use of blood pressure medications for at least 2 years in the last 5 years (yes/no), Cruciferous vegetables, fruits, whole grain, nuts and seeds, total dairy, menopausal status (premenopausal, postmenopausal), and hormone therapy (in postmenopausal women) , fish, and unprocessed poultry. Also, for model 3 in unprocessed red meat, processed meat was adjusted for (0 intake and quartiles of intake) and vice versa, previous screening for colon, prostate, or breast cancers during the last four years.

**Analytical model: Time-dependent Cox-proportional hazards regression with attained age as the time variable and left truncation by age at study entry, controlling for potential confounding covariates, was used to assess the association between the consumption of red and processed meat and all-cause**, CVD, and cancer mortality. We used **multiple imputation**, guided where possible, for missing data [14,15], in which the estimates were calculated from five imputed datasets, and then Rubin’s formula was applied to obtain the average estimates and corrected standard errors. We analyzed intakes of **unprocessed red and processed meats as continuous (log-transformed) variables measured in grams per day (g/day) comparing the 90th percentile of intake with zero-intake.** To assess for possible common associations of unprocessed red and processed meats (which were highly correlated; R = 0.56), **we combined both variables by summing the daily intakes from unprocessed red meat and processed meat together to create one single variable.** **Regression calibration** of the exposures was used, where reported, to minimize the possible bias in the association estimates due to measurement error. Only exposures of interest (red and processed meat) were calibrated, not all dietary covariates. (In this procedure, a shortened version of the main questionnaire (limited to the dietary/FFQ portion), was administered to a 1000-subject (equal allocation for Whites and Blacks) subsample of the AHS-2 cohort. The subsample was approximately representative of the AHS-2 cohort in terms of gender, age, education, and vegetarian status [19]. Six 24-h dietary recalls were also collected from the subsample. From this data, a linear model was produced, regressing the intakes of red and processed meats from dietary recalls on the corresponding intakes from the food frequency questionnaire, controlling for the respective covariates present in each analytic model. The coefficients of the exposures of interest (red and processed meats) from the linear model were used to predict calibrated intake values from the intake values obtained from the FFQ of the original cohort. That is, predicted 24-h recall intake values produced by a linear model regressing intake values from the 24-h recalls against those from the FFQ, adjusted for the analytic covariates, are used in the analytic models to produce calibrated effect estimates. These calibrated intake variables were then used in the analytic models to produce calibrated hazard ratios.) **A 4000-round bootstrap was used to produce bias-corrected and accelerated (BCa) confidence intervals for these hazard ratios.** We also conducted analyses using five categories of intake (i.e., a zero-intake group plus quartiles of consumers). Linear trends across the categories were tested by assigning the medians of intake in each quartile to all participants in that quartile and analyzing them as continuous variables. Also, we assessed the linearity of the relationship between the exposures and mortality outcomes using 4-knot restricted cubic spline regression. Dietary exposures and covariates were energy-adjusted using the residual method [20]. **We tested for interaction of the exposures of interest with age, sex, and race.** Other covariates were also tested for possible interactions with the exposures, and for possible interactions with each other where suspected. **We separately conducted subgroup analyses by sex and race**, in which we used sex- and race-specific ranges and values of intakes for the exposures. Further, we conducted separate analyses on those who reported they never smoked in order to address the effect of residual confounding by smoking in the original models. **The proportional hazards assumption of the model was assessed using log(−log) plots, Schoenfeld residuals, and attained-age interaction terms; there was no violation.** We also calculated population attributable risk comparing the 90th percentile of the combined intake of red and processed meat (~49 g/day) with zero-intake (assuming causality) [21].



Model 1 adjusted for age (attained age as time variable), sex (male and female), race (Black and non-Black), and total energy intake (continuous).

Model 2 adjusted for age (attained age as time variable), sex (male and female), race (Black and non-Black), total energy intake (continuous), marital status (married/common-law and single/widowed/divorced/separated), educational level (up to high school graduate, trade school/some college/associate degree, bachelor degree, and graduate degree), multivitamin use (current use), smoking status (current smoker, quit <1 year, quit 1–4 years, quit 5–9 years, quit 10–19 years, quit 20–29 years, quit ≥30 years, and never smoked), alcohol use (none, rarely, monthly, weekly, and daily), exercise (none, ≤20 min/week, 21–60 min/week, 61–150 min/week, and ≥151 min/week), sleep (≤4 h/night, 5–8 h/night, and ≥9 h/night), body mass index (<18.5, 18.5–24.9, 25.0–29.9, and ≥30.0), aspirin use (yes/no: used weekly for at least two years in the last five years), having ever been diagnosed with or received treatment in the last 12 months for diabetes (yes/no), having been diagnosed in the last 5 years with or received treatment in the last 12 months for hypertension or hypercholesterolemia (yes/no), the use of statin for at least 2 years in the last 5 years, the use of blood pressure medications for at least 2 years in the last 5 years (yes/no), and dietary variables (each variable has 5 levels in g/day) as follows. Cruciferous vegetables (Quintiles: <9.6, 9.6–16.7, >16.7–26.1, >26.1–45.2, >45.2), fruits (Quintiles: <130, 130–224.4, >224.4–322, >322–464.2, >464.2), whole grain (Quintiles: <65, 65–109.9, >109.9–170.3, >170.3–252.2, >252.2), legumes (Quintiles: <17, 17–29.7, >29.7–45.9, >45.9–77.1, >77.1), nuts and seeds (Quintiles: <6.4, 6.4–12.8, >12.8–21.6, >21.6–35.1, >35.1), total dairy (0 intake, quartiles of intake: >0–36, >36–108.1, >108.1–240.9, >240.9), eggs (0 intake, quartiles of intake: >0–3.6, >3.6–7.3, >7.3–20.1, >20.1); and in women, the model also adjusted for menopausal status (premenopausal, postmenopausal), and hormone therapy (in postmenopausal women) (not taking hormone therapy, taking hormone therapy).

Model 3: In addition to covariates in model 2, also adjusted for other meat variables such as fish (0 intake, quartiles of intake: >0–7, >7–12.6, >12.6–21.4, >21.4), and unprocessed poultry (0 intake, quartiles of intake: >0–4.8, >4.8–10.4, >10.4–32.5, >32.5). Also, for model 3 in unprocessed red meat, processed meat was adjusted for (0 intake and quartiles of intake) and vice versa. Models in these analyses are correspondents to models 1, 2, and 3, except energy-adjusted log-transformed continuous dietary variables were used instead of five-level adjustment (90th percentile for unprocessed red meat: 46.5 g/day; for processed meat: 11 g/day; and for combined intake of red and processed meats: 49.1 g/day). 5 Also adjusted for previous screening for colon, prostate, or breast cancers during the last four years.

**Article 2: Mortality in vegetarians and comparable nonvegetarians in the United Kingdom**

**Author: Paul N Appleby**

**Study cohort size:** 60,310 persons pooled mortality data from 2 prospective studies in the United Kingdom, the Oxford Vegetarian Study (OVS) (10) and the EPIC-Oxford cohort

**Definition of meat eaters:** meat eaters (participants who ate meat, irrespective of whether they ate fish, dairy products, or eggs), fish eaters (participants who did not eat meat but did eat fish), vegetarians (participants who did not eat meat or fish, but did eat either or both dairy products and eggs), and vegans (participants who did not eat meat, fish, eggs, or dairy products). **creating 4 diet groups: regular meat eaters (who reported eating meat ≥5 times/wk on average), low meat eaters (who ate meat but did so <5 times/wk), fish eaters, and vegetarians and vegans.**

**Definition of mortality:** The 18 common underlying causes of death for which HRs were calculated were as follows: **malignant cancer** [International Classification of Diseases (ICD)-10 codes C00–97 and equivalent ICD-9 codes], including **colorectal cancer** (ICD-10 C18–20**), pancreatic cancer** (C25), **lung cancer** (C34), **female breast cancer (**C50), **ovarian cancer** (C56), and **cancers of the lymphatic/hematopoietic tissue** (C81–96); **mental and behavioral disorders** (F00–99); **diseases of the nervous system** (G00–99); **circulatory disease** (I00–99), including **ischemic heart disease** (IHD) (I20–25), **cerebrovascular disease** (I60–69), and **other circulatory disease** (I00–15, I26–52, and I70–99); **diseases of the respiratory system** (J00–99); **diseases of the digestive system** (K00–93); **injury, poisoning and external causes** (S00–T98 and V01–Y98); **all other causes** (ICD-10 codes beginning with A, B, D, E, H, and L–R); and **all causes combined**.

**Exclusion criteria:** Participants were excluded from the analysis if they were aged <20 or >89 y at recruitment, or had a previous (registered or self-reported) malignant neoplasm before recruitment; a previous self-reported stroke, heart attack, or angina; uncertain follow-up; or had no information for ≥1 of the factors age, sex, smoking, and diet group at recruitment. EPIC-Oxford participants who did not complete the main questionnaire were also excluded because data on several important factors were thereby unavailable.

**Variable considered:**

Age, Smoking, alcohol consumption, physical activity, marital status, regular use of nutritional supplements, diabetes, blood pressure, receiving long term medical treatment, BMI, Energy, protein, animal protein, plant protein, carbohydrates, total fat, saturated fat, dietary fibers, total meat, red meat, poultry meat, total processed meat, total fish, oily fish, fresh fruit, fresh vegetables

**Adjusting variables:**

Smoking, alcohol consumption, physical activity, marital status, regular use of nutritional supplements, with optional further adjustment for BMI.

**Analytical model: In the main analysis of mortality before age 90 y**,HRs (95% CIs) for 18 common causes of death, including all causes combined, were calculated by **Cox proportional hazards regression with age as the underlying time variable**, with the use of a clustered sandwich variance estimator to allow for intraparticipant correlation among individuals contributing person-years to >1 of the 5 possible phases of follow-up, including OVS recruitment to the earlier of EPIC-Oxford recruitment (if applicable) or death/censoring, EPIC-Oxford recruitment to the earliest of FU1/FU2/FU3 completion (if applicable) or death/censoring, FU1 completion (if applicable) to the earliest of FU2/FU3 completion (if applicable) or death/censoring, FU2 completion (if applicable) to the earlier of FU3 completion (if applicable) or death/censoring, and FU3 completion (if applicable) to death/censoring. For the small number of participants whose diet group was unknown at FU1, FU2, or FU3 completion (∼30 participants at each stage), diet group was deemed to be the same as at EPIC-Oxford recruitment or at the most-recently completed follow-up questionnaire, as appropriate. For the 6 most common causes of death (malignant cancer, circulatory disease, IHD, cerebrovascular disease, diseases of the respiratory system, and all causes combined), **subgroup analyses** were also conducted for men; women; participants with BMI <20 (underweight), BMI 20–24.9 (normal weight), and BMI ≥25 (overweight); never smokers, former smokers and current smokers; **We also conducted the mortality analyses for all 18 causes of death after excluding participants known to have changed diet group at least once during follow-up**. **We also examined mortality before age 75 y.**

**Article 3: High red meat intake and all-cause cardiovascular and cancer mortality: is the risk modified by fruit and vegetable intake?**

**Author:** Andrea Bellavia

**Study cohort size:** 74,645 participants from the Cohort of Swedish Men (COSM) (NCT01127711) and the Swedish Mammography Cohort (SMC)

**Exclusion criteria:** we excluded participants who reported an incorrect national personal identification number or who did not report their personal number (n = 540), those who died before the start of follow-up (n = 97), and those with any history of CVD (n = 6994) or cancer (n = 4390). We further excluded participants with an unlikely extreme value of total energy intake (3 SDs from the log-transformed mean energy intake; n = 709) and those with unlikely high daily red meat consumption (>300 g/d; n = 305) or missing information on red meat consumption (n = 397).

**Definition of Nonprocessed red meat**: fresh and minced pork, beef, and veal. The total intake of red meat, **assessed in g/d,** **was calculated by combining information on the amount and frequency of the consumption of different types of red meat.**

**Definition of Processed red meat:** sausages, hot dogs, salami, ham, processed meat cuts, liver pate, and blood sausage. All reported information was combined to derive continuous variables of total, processed, and nonprocessed meat intake.

**Definition of fruit and vegetables:** Information on daily FV intake was obtained with the use of 14 questions on vegetable consumption (carrots, beetroots, lettuce, cabbage, cauliflower, broccoli, tomatoes, peppers, spinach, green peas, onion, garlic, pea soup, other vegetables), 5 on fruit (oranges, apples, bananas, berries, other fruits), and 1 on orange juice. Total FV consumption was summarized into a single variable, expressed as servings/d, that was obtained by converting the questionnaire responses to a mean daily intake of each item and adding the intake of all items together. To assess the association between red meat consumption and mortality across levels of FV consumption, **the main variable of FV consumption was categorized into 3 predefined levels (low FV intake: <2 servings/d; medium FV intake: 2–4 servings/d; and high FV intake: >4 servings/d).**

**Definition of mortality:** deaths

**Variables considered:**

Sex, age, bmi, total physical activity, smoking status, alcohol consumption, education, diabetes, fruit and vegetable consumption, fish consumption, energy intake

**Adjusting variables:**

sex, pack-years of smoking, physical activity, educational status, BMI (in kg/m2), alcohol consumption, diabetes, fish consumption, and total energy, grain intake and soft drink and soda consumption

**Analytical model: Total, processed, and nonprocessed red meat intakes were then categorized into quintiles and investigated as categorical covariates.** **Cox proportional hazard regression with attained age at the event as the primary time scale was used** to assess the association between red meat and FV consumption and the risk of total, CVD, and cancer-specific mortality. **The assumption of proportionality of the hazards was tested by calculating Schoenfeld residuals, regressed against survival time, and tested for a nonzero slope**. No evidence of departure from this assumption was observed in all the reported models. **The lowest quintile of either total, processed, and nonprocessed meat was used as reference category.** **We first assessed the association between quintiles of total red meat consumption and overall mortality, estimating HRs of death in the overall population and across amounts of FV consumption.** **The statistical interaction between red meat and FVs was assessed by testing the product terms of the categorical indicators jointly equal to 0. We next replicated the main analysis over levels of fruit consumption and vegetable consumption, investigated as 2 independent covariates.** Both fruit and vegetable consumption were categorized into 3 predefined groups to reflect low, medium, and high intakes. We also evaluated processed and nonprocessed red meat consumption as 2 distinct exposures in a mutually adjusted model. HRs of death were estimated in the overall population and across levels of FV consumption, testing for the presence of an interaction between processed and nonprocessed meat and FVs in predicting mortality.

**Article 4: Higher Diet Quality Is Inversely Associated with Mortality in African-American Women**

**Author:** Deborah A Boggs

**Study cohort size:** 59,000 women Black Women's Health Study (BWHS). After exclusion, 37001 women.

**Exclusion criteria:** The present analysis excluded women who at baseline were <30 y of age (n = 12,812); had a history of cancer (except nonmelanoma skin cancer) (n = 1488), myocardial infarction (n = 620), stroke (n = 439), or diabetes (n = 2378); left >10 items blank on the FFQ (n = 1510); had implausible energy intake values (<400 or >3800 kcal) (n = 1783); were pregnant at baseline (n = 482) or were missing height or weight (n = 442); or had an implausible BMI (<15 or ≥60 kg/m2) (n = 46).

**Definition of Dietary Approaches to Stop Hypertension (DASH) scores:** We evaluated a DASH score created by Fung et al. (14) that ranks participants based on intake of 8 food and nutrient components. Participants were categorized into quintiles for each component. For fruits (including fruit juice), vegetables, nuts and legumes, whole grains, and low-fat dairy, the lowest quintile was assigned 1 point and the highest quintile was assigned 5 points. For sodium, red and processed meats, and sugar-sweetened beverages, scores were reversed such that the lowest quintile was assigned 5 points and the highest quintile was assigned 1 point. DASH scores can range from 8 to 40; in the present study the scores ranged from 8 to 38. We categorized the scores into quintiles (quintiles 1 and 5 represent low and high adherence, respectively).

**Definition of Prudent and Western dietary patterns:** Prudent and Western dietary patterns were derived with the use of factor analysis of 35 individual foods or food groups, as described previously (15). Factor scores for each pattern were calculated by summing intakes of each food group weighted by that food group's factor loading. The prudent dietary pattern is characterized by high intake of vegetables and fruits, whereas the Western dietary pattern is characterized by high intake of red and processed meat and fried foods. Quintiles 1 and 5 represent low and high adherence, respectively, to each dietary pattern.

**Definition of death:** Deaths through 31 December 2011 were identified through linkage with the National Death Index for all participants who had not completed the 2011 questionnaire. **The International Classification of Diseases, Tenth Revision, was used to classify underlying cause of death as death from cardiovascular disease (I00–I99), cancer (C00–C97), or all other causes [excluding “external” causes of death, S00–Y98 (e.g., accidents and homicides)].**

**Variables considered:** age, BMI, education, marital status, exercise, television watching, smoking, alcohol use, total energy intake

**Adjusting variables:** age, total energy intake, education, marital status, vigorous exercise, television watching, smoking, and alcohol intake. health insurance status, visits to a physician. **Optional adjusting for BMI**

**Analytical model:** **Cox proportional hazards models were used** to estimate HRs and 95% CIs for the association between diet quality and mortality. Participants contributed to the analysis from 1995 until death, loss to follow-up, or the end of follow-up in 2011, whichever occurred first. Time-varying covariates were updated with the use of the Andersen-Gill data structure (26); this structure creates a new record for each follow-up cycle in which a participant is at risk, and assigns the covariate value for that cycle. **missing data for covariates were modeled as indicator variables**. **The primary analyses did not adjust for BMI, which is considered to be an intermediate between dietary pattern and illness/death.** We conducted **subgroup analyses** within strata of BMI, age, smoking, vigorous exercise, and years of education. **Tests for interaction** were performed by using the likelihood ratio test comparing models with and without crossproduct terms between the variable of interest (e.g., **BMI) and the diet quality score.**

**Article 5: Lifestyle Determinants and Mortality in German Vegetarians and Health-Conscious Persons: Results of a 21-Year Follow-up**

**Author:** Jenny Chang-Claude

**Study cohort size:** 1,904 German vegetarian study

**Definition of meat eaters:** The study participants were classified **into vegetarian** (vegan (those who avoid meat, fish, eggs, and dairy products), lacto-ovo vegetarian (those who avoid meat and fish but eat eggs and/or dairy products)), **and nonvegetarian** (those who occasionally or regularly eat meat and/or fish). **Or, Meat consumption (Never ≤Once a month ,>Once a month,≥3 times/wk), meat product consumption (Never ≤Once a month ,>Once a month), fish consumption (Never ≤Once a month ,>Once a month).**

**Definition of death:** The underlying cause of death was coded by a trained nosologist according to the ninth revision of the International Classification of Diseases and Causes of Death. All causes: ICD-9 001-999

**Variables considered:**

Gender, age group, education, bmi, exercise, smoking, alcohol consumption,

**Adjusting variables:**

Age, gender, smoking, exercise, alcohol, dietary group (vegetarian/nonvegetarian), BMI, education

**Analytical models:** **Standardized mortality ratios (SMR)** were calculated by comparison of observed deaths with those expected based on the age- and sex-specific mortality rates of Germany between 1975 and 1999. Within the total cohort, **Poisson regression was used to investigate possible determinants of mortality by comparing death rates among study participants for various factors simultaneously including vegetarian status, age, sex, education, and BMI.** The highest educational level of the parents was used for subjects under the age of 20 years who had not yet finished schooling. Multiplicative models were fitted to appropriately cross-classified data using PROC GENMOD (SAS System version 8.0). The person-years at risk were used as offset. Maximum likelihood estimates of rate ratios (RR) for exposure variables and 95% confidence intervals (95% CI) based on exact Poisson probabilities were calculated.

**Article 6: Should we recommend reductions in saturated fat intake or in red/processed meat consumption? The Sun prospective cohort study**

**Author**: Ligia J.Dominguez

**Study cohort size: 22,476 participants initially**, after exclusion, **18,540 participants of the SUN (Seguimiento Universidad de Navarra)**

**Exclusion criteria:** We recruited participants who had spent enough time in the study as to be able to complete and return at least the 2-year follow-up questionnaire (>2 years and additional 9 months to account for the lag time in returning the questionnaires) and we excluded 798 participants for this reason. Participants were also excluded from the analyses if they reported total energy intake out of pre-defined limits (800–6000 kcal/d for men and 500–5500 kcal/d for women) or if they left 20 or more items in blank from the FFQ (n = 1512) [35] or they were lost to follow up (n = 1626).

**Definition of meat:** In the semi-quantitative FFQ we explicitly included serving sizes (in grams) according to the typical **serving size** of each food in the Spanish population, corresponding to **125 g of red meat, 125 g of white meat, 50 g of processed meat, and 100 g of total meat.** **The meat variables included consumption of white meat (chicken, turkey, and rabbit), red meat (veal, pork, lamb, liver, viscera (offal), hamburger), and processed meat (dry cured ham [Serrano ham type], cooked ham [York ham type], sausages [salami, mortadella, blood sausage, spicy pork sausage, würstel], bacon, pancetta, paté), as well as total meat considering together all types of meat.** **They treat baseline categories of meat consumption (less than 3 servings per week as reference category, 3–6 servings per week, 7 servings per week [once a day], and more than 7 servings per week) as categorical variable and also treat it as continuous variable examine one additional serving for HR. They considered red meat, total meat, processed meat, and red + processed meat consumption.**

**Definition of death:**

We also checked the National Death Index every six months to confirm the vital status of our participants and to request and complete the data regarding mortality, including the cause of death in our cohort.

**Variables considered:**

Gender, martial status, age, education, BMI, Alcohol, activity, television watching, history of depression, hypertension, hypercholesterolemia, history of cardiovascular disease, history of cancer, history of diabetes, total energy intake, adoption of special diet, between meal snacking, vegetables, fruits, legumes, cereals, whole bread, nuts, olive oil, eggs, fish and other seafood, whole dairy product, low-fat dairy product, coffee, carbohydrates, protein, total fat, MUFAs, SFAs, PUFAs (% of total energy), Vitamin C, Vitamin D, Iron from haem sources, Folate, Dietary fiber

**Adjusting variables:**

Age, sex, year of entering the cohort, years of university education, BMI, smoking, alcohol, physical activity, hours per day watching television, history of hypercholesterolemia, hypertension, and/or depression, CV disease, cancer, and/or diabetes, following special diets at baseline, snacking between meals, and total energy intake (continuous). **age examined as interaction term.**

**Analytical model:**

**We calculated HR and 95% CI by means of Cox proportional hazards models using the lowest category of consumption as the reference category (less than 3 servings per week).** **Age was the underlying time variable, and different degrees of adjustment were used: 1) adjusted for sex and age (in 10 categories); 2) additional adjustments for year of entering the cohort (4 categories), BMI (continuous), years of university education (continuous), alcohol use (in 5 categories), smoking (in 3 categories), physical activity (MET-h/week) (continuous), hours per day spent watching television (continuous), history of hypercholesterolemia, hypertension, and/or depression, CV disease, cancer, and/or diabetes, following special diets at baseline, snacking between meals, and total energy intake (continuous). We also performed all the analyses using as exposure a 1-serving per day increment (as a continuous variable) in the different types of meat consumption**. Trend tests were calculated using meat consumption as a continuous variable. Multivariable-adjusted estimates for restricted cubic splines were used to calculate dose–response association between SFA intake or red meat consumption and total mortality. **We assessed interactions with age using likelihood ratio tests in fully adjusted Cox models. We introduced a product-term with both age and meat servings/d (or SFA intake) as continuous variable in this term.** We also performed multivariable analyses to examine the HRs for mortality when we did isocaloric replacements of MUFA, PUFA, and carbohydrates by SFA, and replaced 100 g of fish, potatoes, poultry, eggs, vegetables, fruits and nuts, and cereals by 100 g of red meat. These variables were incorporated in the same fully-adjusted model as continuous variables, and the differences in their beta-coefficients, variances and covariance were used to calculate the beta-coefficient ± SE for the substitution effect. Subsequently, we used these parameters to estimate the HRs and 95% CIs. **We performed diverse sensitivity analyses by estimating the fully adjusted HR for a 1-serving increment in red meat consumption and total meat consumption after changing several assumptions: 1) including only men or women; 2) considering different allowed limits for total energy intake; 3) adopting allowed limits for total energy intake from percentile 1 to 99; 4) excluding participants with history of diabetes at baseline; 5) Excluding prevalent cancer, CVD, and diabetes; 6) excluding participants with diagnosis of hypertension and hypercholesterolemia at baseline; 7) censoring the follow-up time of participants at 6 or 8 years; 8) excluding early deaths (within the first 2 years of follow-up); 89) adjusting for the Mediterranean diet score calculated as proposed by Trichopoulou et al. [45], excluding meat and alcohol to avoid redundancy (maximum score = 7 points); 10) including only deaths occurring at 60 years of age and over; 11) including only cancer deaths; 12) including only CV deaths.**

**Article 7: Mortality from different causes associated with meat, heme iron, nitrates, and nitrites in the NIH-AARP Diet and Health Study: population-based cohort study**

**Author: Arash Etemadi**

**Study cohort:** 617 119 originally, after exclusion, **536 969 AARP** members aged 50-71 at baseline

**Exclusion criteria:** We excluded people who moved out of the study areas before returning the baseline questionnaire, requested to be withdrawn, died before study entry, indicated that they were not the intended respondent, did not answer substantial portions of the questionnaire, or had more than 10 recording errors; people whose questionnaire was filled in by someone else on their behalf; those reporting extreme daily total energy intake; people with a prevalent cancer before the study entry; and those who had zero person years of follow-up.

**Definition of meat:** Items included in the red meat intake were unprocessed red meat (beef and pork, hamburger, liver, steak, and meats in foods such as chili, lasagna, and stew) and processed red meat (bacon, beef cold cuts, ham, hotdogs, and sausage). White meat included unprocessed chicken, turkey, and fish, canned tuna, and processed white meat (poultry cold cuts, low fat sausages, and low fat hotdogs made from poultry**). We divided all nutritional variables by the daily calorie intake (the nutritional density method) and categorized the calorie adjusted values into fifths for the entire cohort. Calculate g/1000kcal.**

**Definition of death:** Cancer mortality included ICD-10 (international classification of diseases, 10th revision) codes C00-C44, C45.0, C45.1, C45.7, C45.9, C48-C97, and D12-D48. Cardiovascular disease mortality was subdivided into diseases of the heart (ICD-10 codes I00-I09, I10-I13, I20-I51, and I70-I78), and stroke or cerebrovascular diseases (ICD-10 codes I60-I69). We also studied death from respiratory disease (ICD-10 codes J10-J18 and J40-J47), diabetes mellitus (ICD-10 codes E10-E14), infections (ICD-10 codes A00-B99), Alzheimer’s disease (ICD-10 code G30), kidney disease (ICD-10 codes N00-N07, N17-N19, N25-N27), chronic liver disease (ICD-10 codes K70, K73-K74), and all other causes.

**Variables considered:**

Total death (cancer, heat disease, respiratory disease, stroke, diabetes, infections, alzheimer’s disease, chronic kidney disease, chronic liver disease, other causes), gender, age, previous cancer, heart diease, stoke, diabetes, health status, race, smoking, socioeconomic status, education, physical activity, body mass index, alcohol intake, vegetable intake, fruit intake, heme iron intake, nitrate intake, nitrite intake.

**Adjusting variables:**

sex, age at entry to study, marital status, ethnicity, education, fifths of a composite deprivation index as an indicator of socioeconomic status, perceived health at baseline, self-reported history of heart disease, stroke, diabetes, and cancer at baseline, cigarette smoking, body mass index, vigorous physical activity, usual activity throughout the day, alcohol consumption, fruit and vegetable intakes (both pyramid servings per day), and total energy intake. vitamin supplement use, family history of cancer (for cancer mortality), and the use of hormone replacement therapy (for women).

**Analytical models:** **We estimated hazard ratios and 95% confidence intervals with time since entry into the study as the underlying time metric, by using Cox proportional hazards regression models with the lowest fifth of the calorie adjusted intakes as the reference categories,** after checking the violation of the proportional hazard assumption. **As the differences between the lowest and the highest fifths were different among various types of meat, we also analyzed the effects of a fixed intake increase (20 g/1000 kcal/day) on the outcomes.** As our main hypothesis was to test the change in mortality risk by substituting different meat products without changing the overall meat intake, the main model was a “**substitution model**.” **This model was adjusted for total meat intake, so that increases in the meat variable of interest reflected reductions in other meat types and the total meat intake remained constant.** **We also tested another series of models in which each meat variable was adjusted for all other forms of meat, so that all meat types in the model added up to total meat (addition model); increase in any individual meat variable resulted in an increase in the person’s total meat intake.** In all the models, we used median values of each fifth to test for linear trends. We also stratified the population by important potential effect modifiers and tested the interaction between these variables and the main variables of exposure. **We did several sensitivity analyses: excluding people who reported a previous diagnosis of heart problem, stroke, diabetes, or cancer at baseline; stratifying by the duration of follow-up; including the 2010 Healthy Eating Index as an independent variable in the model (to adjust for the potentially confounding effect of the overall healthiness of the diet) 21; and using the residual method for calorie adjustment instead of the nutritional density.** We also did a **calibration analysis** to correct the estimates of daily red meat intake in the entire cohort for measurement error, using data from a subset of participants with two non-consecutive 24 hour dietary recalls (n=1877).

**Article 8: Dietary Protein Sources and All-Cause and Cause-Specific Mortality: The Golestan Cohort Study in Iran**

**Author: Maryam S. Farvid PhD**

**Study cohort: 49,112 initially**, after exclusion, **42,403** Golestan Cohort Study in Iran.

**Exclusion criteria:** Participants were excluded owing to loss of follow up ( n =63); extreme total energy intake (<600 or >4,200 kcal/day, n =436); or prior diagnosis of chronic disease, including cancer, diabetes, CHD, or stroke ( n =6,210)

**Definition of meat:** Total red meat items listed on the food frequency questionnaire included unprocessed (beef or lamb, hamburger) and processed (sausage) red meat; poultry included chicken; fish included tuna, stellate sturgeon, carp, smoked fish, salted fish, and other fish; and legumes included soybeans, beans, lentils, peas, and split peas. Participants were asked about the frequency of food item consumption per day, week, month, or year. The standard serving sizes for these food items were 85 g for cooked beef, lamb, hamburger, chicken, and fish; 45 g for sausage; 100 g for cooked beans, lentils, peas, split peas, and soybeans; and 54 g for eggs. **Participants were divided into quintiles according to food group intake. serving/day calculated**

**Definition of death:** All collected documents were reviewed, and the cause of death was coded according to the ICD-10. In this analysis, deaths were classified as due to CVD (ICD-I00–I99); CHD (ICD-I20–I52); stroke (ICD-I60–I69); cancer (ICD-C00–D48); gastrointestinal cancers (ICD-C15–26); and other cancers (ICD-C00–14, ICD-C30–97, and ICD-D00–48).

**Variables considered:**

Age, BMI, gender, ethnicity, martial status, current smokers, opium use, place of residence (rural), physical activity, total red meat intake, poultry intake, fish intake, egg intake, legume intake, total dairy food intake, total grain intake, total fruit intake, total vegetable intake, total energy intake.

**Adjusting variables:**

age, gender, place of residence, marital status, educational level, ethnicity, cigarette smoking, opium use, BMI, systolic blood pressure, family history of cancer, occupational physical activity, medication, wealth score, alcohol consumption, and total energy intake, **further adjustments for fruit and vegetable or total grain intake, low-fat dairy foods. Interaction terms: gender, age, BMI, smoking, or wealth score, and dietary protein sources**

**Analytical model:** **Cox proportional hazards regression was used to estimate age-adjusted and multivariate-adjusted hazard ratios (HRs) and 95% CIs for all-cause and disease-specific mortality in relation to total red meat, poultry, fish, egg, and legume consumption. Missing covariate data, which included five participants for BMI and eight participants for systolic blood pressure, were replaced with median values.** The effect of substituting one serving/day of poultry, fish, legumes, or eggs for one serving/day of total red meat was estimated by including these food items simultaneously as continuous variables in the multivariate-adjusted model. The HRs and 95% CIs for the **substitution effect** were estimated from the difference between the regression coefficients, variances, and covariance. **In sensitivity analyses, participants who died as a result of external events (i.e., accidents, intoxication, suicide, or other types of injury; n =217) were excluded. Further, the authors evaluated whether the association between protein-rich food intake and all-cause mortality risk was modified by gender, age, BMI, smoking, and wealth score.(interaction)**

**Article 9: Associations between diet and cancer, ischemic heart disease, and all-cause mortality in non-Hispanic white California Seventh-day Adventists**

**Author: Gary E Fraser**

**Study cohort:** 34192 California Seventh-day Adventists

**Definition of meat:** 3 categories of dietary habits were defined. These were vegetarian, those who ate no fish, poultry, or meat (29.5%); semivegetarian, those who ate fish and poultry, but <1 time/wk (21.2%); and nonvegetarian, referring to the remaining subjects (49.2%).

**Definition of death:** In addition, computerized matching with state death tapes and the National Death Index was used to identify fatal cases.

**Variables considered:**

Age, sex, beef, poultry, fish, vegetarian meat substitutes, soft margarine on bread, eggs, doughnuts, coffee, tomatoes, legumes, nuts, green salads, canned fruit, dried fruit, citrus fruit, winter fruit, other fruit, all fruit, whole-grain bread, beer or wine, hard liquor, bmi, diabetes, hypertension, rheumatoid arthritis, rheumatism, colon cancer, breast, lung, prostate, uterine

**Adjusting variables:**

Age, sex, smokig, exercise, BMI, hypertension, consumption of bread, nuts, fish, cheese, coffee, legumes, and fruit

**Analytical models: Not enough information on this paper**

**Odds ratios adjusted for age calculated for vegetarians, semi vegetarians, and nonvegetarians. Incidence and relative risk calculated between vegetarians and non-vegetarians. Regression?**

**Article 10: Meat intake and cause-specific mortality: a pooled analysis of Asian prospective cohort studies**

**Author: Jung Eun Lee**

**Study cohort: 296,721** men and women, 8 Asian prospective cohort studies in Bangladesh, China, Japan, Korea, and Taiwan

**Exclusion criteria:** We excluded participants who did not provide food-frequency questionnaires (FFQs) (n = 8177) and those for whom time under study was missing (n = 467).

**Definition of meat:** The number of items for red meat, poultry, and fish varied from 6 to 17 across studies (see Supplemental Table 1 under “Supplemental data” in the online issue). **We quantified food-group intake in grams per day or servings per day using the reported frequency of intake of each relevant food item and study-specific portion sizes.** **g/day calculated.** **Because the number of food items varied across studies, in the main analysis, we obtained HRs and 95% CIs using study- and sex-specific quartiles of grams per day of each food group.**

**Variables considered:**

Age, educational, alcohol intake, urban or rural residence, total energy intake, fruit and vegetable intake, BMI, and tobacco smoking, socioeconomic status, baseline period

**Adjusting variables:**

Baseline age (<40, 40–49, 50–59, 60–69, 70–79, and ≥80 y), educational level (less than secondary, secondary, and more than secondary school graduate), alcohol intake (continuous), urban or rural residence, total energy intake (continuous), fruit and vegetable intake (continuous), BMI (in kg/m2; <18.5, 18.5–19.9, 20.0–24.9, 25.0–29.9, and ≥30.0), and tobacco smoking (never smoked, former smoker, current with <20 pack-years of smoking, and current with ≥20 pack-years of smoking) were adjusted for as potential confounding factors in the multivariate analyses. **Interaction with BMI, baseline period, smoking status**

**Analytical models:** **Using individual-level data, we calculated study-specific HRs and 95% CIs using a Cox proportional hazards model; age was used as the time metric.** Outcomes of interest included all-cause mortality and cancer and CVD mortality. **For males and females separately, cohort-specific HRs were pooled to compute cross-cohort estimates by using a random-effects model.** The random-effects model also produced a trend test for pooled HR estimates. Tertiles rather than quartiles of poultry intake were used to ensure an adequate number of cases in each category. In supplemental analyses, we computed pooled cohort HRs from cohort-specific estimates computed by using uniform cutoffs rather than cohort-specific cutoffs to construct intake quartiles and tertiles. In other supplemental analyses, we included 2 additional cohort studies that offered nonquantitative dietary intake data: 1) the Korean Multi-Center Cancer Cohort Study (19) and 2) the Radiation Effects Research Foundation in Hiroshima and Nagasaki, the Life Span Study cohort (20), which had assessed diet by using nonquantitative FFQs (data on frequency of intake only). We tested for heterogeneity across studies using a likelihood ratio test that compared random- and fixed-effect models for pooled cohort effect estimates. **Because socioeconomic status may be related to meat intake and disease pattern in Asian populations and because meat intake varies over time, we also examined whether the associations varied by educational level**. **Also, we examined whether BMI, smoking status, or baseline period modified the associations.**

**Article 11: Meat consumption and diet quality and mortality in NHANES III**

**Author: R Kappeler**

**Study cohort: 17 611 participants** from Third National Health and Nutrition Examination Survey (NHANES III) (1986–2010)

**Exclusion critieria**: We excluded individuals who had a history of myocardial infarction, stroke, heart failure or cancer (n=2353). We further excluded individuals whose questionnaire had missing answers for meat consumption (n=86). After all exclusions, our analytic cohort consists of 8239 men and 9372 women.

**Definition of meat: Red meat intake was calculated using the frequency of consumption of all types of beef, pork, ham, liver and other organ meats**. White meat included chicken and turkey and processed meat included bacon, sausage and other processed meats. The category fish included only the item fish. ***times/week calculated with 5 groups.***

**Definition of mortality:** Based on the National Death Index, data underlying cause of death were used for case definition according to the ICD-9 through 1998, and the remainder according to ICD-10. Cardiovascular mortality was defined by any of the ICD-9 codes 390–434 and 436–459 and ICD-10 codes I00–I99. Cancer mortality was defined by ICD-9 codes 140–239 and ICD-10 codes C00–C34, C37–C41, C43–C49, C50–C52, C54–C65, C67–C80, C82–C85, C88, C90–C95 and C97. All-cause mortality included all specified causes as well as unknown cause.

**Variables considered:** sex, age, race, hypertension, diabetes, Hypercholesterolemia, dietary supplement use, smoking, physical activity, social economic status, marital status, BMI, waist circumference, vegetables intake (times/month), Fruits—times/month, Processed meat—times/month, White meat—times/month, Fish—times/month

**Adjusting variables:** age (continuous), race (non-Hispanic white, non-Hispanic black, Mexican-American, other), sex, cigarette smoking (never, former, current (1–19 cigarettes/day; 20–39 cigarettes/day; 40+ cigarettes/day); missing), alcohol consumption (none, 1–4, 5–29, 30+ times/month), physical activity (none, 0 to <2 to <4 to <6, >6 times/week), socioeconomic status (poor, near poor, middle income, higher income; based on the poverty income ratio), body mass index (BMI) (continuous; calculated as weight in kilograms divided by height in meters squared), marital status (married/living together; never married/widowed; divorced/separated; missing), fruit and vegetables intake (quartiles of intake), history of hypertension, diabetes, hypercholesterolemia, use of aspirin and ibuprofen, use of mineral and vitamin supplements and family history of diabetes or hypercholesterolemia. In women, we also adjusted for hormone replacement therapy and oral contraceptive use. **Interaction with sex considered.**

**Analytical models:** For this study, **we included all participants who were 18 years of age or older at the examination and from whom mortality data were available.** **We used time-dependent Cox proportional hazards regression models** to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). **The entire cohort was divided into categories of red meat, processed meat, white meat and fish consumption, and multivariate-adjusted HRs are reported using the lowest category as the referent category.** **The cut-points for the groups were as follows: red meat: 6; 14; 29; 44 times/month;** processed meat: 0; 6; 14; 29 times/month; white meat: 0; 3; 8; 12 times/month; fish: 0; 2; 4; 8; times/month. Trend tests were performed by assigning to each subject the median value for the consumption category1, 2, 3, 4, 5 into which the subject fell and modeling this term as a continuous variable, the coefficient for which was evaluated by the Wald test. **We tested for interaction between sex and meat or fish consumption by including a cross-product term along with the main effect terms in the Cox regression model.** The statistical significance of the cross-product terms was evaluated using the Wald test.

**Article 12: Associations of Dietary Protein with Disease and Mortality in a Prospective Study of Postmenopausal Women**

**Author: Linda E. Kelemen**

**Study cohort:** 41,836 originally, after exclusion, **29,017** women were available for analysis. Iowa Women’s Health Study

**Exclusion criteria:** We excluded women who, at baseline, were premenopausal, who reported a history of cancer other than skin cancer, known heart disease, or known diabetes, and who left 30 or more food items blank or had total energy intake less than 600 kcal/day (2.5 MJ/day) or more than 5,000 kcal/day (20.9 MJ/day).

**Definition of meat:** For each food, a common unit or portion size was specified, and participants were asked how often, on average, they had consumed that amount of the item over the past year. The nine responses ranged from “never or less than once per month” to “six or more times per day.” **a percentage of total energy calculated for total protein intake.**

**Definition of death:** Deceased nonrespondents were identified through linkage with the National Death Index.

**Variables considered:** smoking, hypertension, education, postmenopausal hormone use, physical activity, multiple vitamin supplement use, daily alcohol, age, waist/hip ratio, BMI, carbohydrates (% of energy), total fat, saturated fat, polyunsaturated fat, monounsaturated fat, trans-fat, cholesterol, total fiber, methionine, processed and red meat, chicken and poultry, fish and seafood, dairy products, eggs, nuts tofu and legumes, whole grains, refined grains, white bread, rice or pasta, potatoes, sweets and desserts, fruits and vegetables (servings per 1000kcal(4.2MJ))

**Adjusting variables:** age, total energy, saturated fat, polyunsaturated fat, monounsaturated fat, and trans-fat (expressed as percentage of energy and categorized into quintiles), carbohydrates, total fiber, dietary cholesterol, dietary methionine (all quintiles are based on energy-adjusted values), alcohol (≤14 g/day vs. >14 g/day), smoking (never, former, current), activity level (active vs. not active), body mass index (<21.0, 21.0–22.9, 23.0–24.9, 25.0–28.9, ≥29.0), history of hypertension, postmenopausal hormone use, multivitamin use, vitamin E supplement use, education (high school education or less vs. post-high school), and family history of cancer.

**Analytical models: Substitution model. Macronutrients were expressed as a percentage of total energy,** and other dietary covariates were energy adjusted by the regression method (20). We examined the distribution of potential confounding and risk factors by **quintiles of total protein intake.** **Continuous variables were categorized into quintiles and treated as indicator variables in statistical models following inspection of their relation with each outcome in univariable analysis. We calculated risk ratios and 95 percent confidence intervals using Cox regression, and we modeled survival as a function of age (21), using as the referent the lowest quintile of protein intake. We assessed the relation between dietary protein and each outcome with multivariable-adjusted nutrient density models (22).** These models allow estimation of the effect on each outcome of an increase in the percentage of energy from protein intake. By forcing total energy and other intake, such as dietary fats, to be constant and by excluding carbohydrate from the model, an increase in protein intake by definition statistically results in a decrease in carbohydrate intake. Thus, the effect estimates of protein assume a **substitution interpretation** (12, 22). The percentage of energy from protein that is “substituted” for carbohydrate is the difference in median energy intake of protein between the highest and lowest quintiles**. For each endpoint, we first assessed the effect of an isoenergetic substitution of each of total, animal, and vegetable protein for total carbohydrate**. Next, we assessed the effect of an isoenergetic substitution of vegetable protein for animal protein while holding constant the intakes of carbohydrate, total energy, and potential confounding factors. Thus, the difference in the percentage of energy from protein (or protein type) between the lowest and the four remaining quintiles varied according to the comparison under study. While the use of nutrient values was necessary to evaluate our hypotheses of protein for carbohydrate substitutions on various outcomes, realistically most individuals interchange foods when implementing dietary changes. **Therefore, we also evaluated the effect of an isoenergetic substitution of various intakes of high-protein foods, standardized as servings per 1,000 kcal/day (4.2 MJ/day), for carbohydrate-dense foods while holding constant total energy, dietary fats, and other components of protein foods such as cholesterol.** This was done to better isolate the effect on our outcomes of the protein in these foods separate from the effects of other nutrients that have established associations with our outcomes.

**Article 13: The Mortality Risk of Elevated Serum Transferrin Saturation and Consumption of Dietary Iron**

**Author: Arch G. Mainous**

**Study cohort: 9,229** persons aged 35 to 70 years at baseline from NHANES II

**Exclusion criteria:** For the present study we excluded pregnant women, as well as the 2 respondents in the NHANES II who indicated that they had been told by a physician that they have hemochromatosis. These 2 respondents were excluded because they might have received treatment for their hemochromatosis.

**Definition of red meat:** Second, to provide a general estimate of heme iron intake rather than total iron, each participant was asked the weekly frequency of eating various types of meat. Red meat consumption at least 7 times per week was considered high consumption.

**Definition of mortality:** Mortality was measured as all-cause mortality. Mortality status was ascertained solely by computerized matching to national databases and evaluation of the resulting matches.

**Variables considered:**

Age, race, sex, poverty income ratio, education level, body mass index, smoking, health status, charlson comorbidity index

**Adjusting variables:**

**age, race, sex, poverty status, and education, body mass index (BMI) and current self-reported smoking status**. In an effort to control for severity of illness, we included self-reported health status as well as comorbid conditions. A variety of conditions were assessed in the NHANES II. Comorbidities were positive responses in the baseline interview to questions regarding whether a physician ever told the patient that he or she had each of the following conditions: **cirrhosis, diabetes, high blood pressure, heart failure, heart attack, stroke, hardening of the arteries, rheumatic fever, rheumatic heart disease, heart murmur, ulcer (peptic, stomach, duodenal), chronic enteritis, ulcerative colitis, spastic colon or mucous colitis, gallstones, hepatitis, yellow jaundice, pleurisy, low blood pressure, cataracts, glaucoma, thyroid disease, polio or paralysis, goiter, hiatus hernia of the diaphragm, cancer, benign tumor, trouble with blood not clotting properly, loss of blood from stomach or bowels, nervous breakdown, neck injury, back injury, anemia, arthritis, gout, asthma, chronic bronchitis, emphysema, tuberculosis, and kidney problems.** The **Charlson Comorbidity Index** was calculated from the responses to these questions. This index is a validated tool for predicting mortality in longitudinal studies.12

**Analytical models: We classified the population into 4 groups based upon normal and elevated transferrin saturation, and low and high iron intake. The criteria for high iron intake (total iron and red meat consumption) were analyzed separately**. For the analysis of the mortality, we used sampling weights to calculate prevalence estimates for the civilian noninstitutionalized US population. Because of the complex sampling design of the survey, we performed all analyses using the statistical software package SUDAAN, as recommended by the National Center for Health Statistics. Using the population estimates generated by SUDAAN, we computed Kaplan-Meier curves to show graphically the unadjusted relationship between all-cause mortality and elevated serum transferrin saturation and low or high iron ingestion. **We performed Cox proportional hazards analysis with all-cause mortality for serum transferrin saturations of greater than 55% controlling for age, race, sex, poverty status, education, BMI, smoking status, and Charlson Comorbidity Index.**

**Article 14: A traditional Sami diet score as a determinant of mortality in a general northern Swedish population**

**Author:** Nilsson, Lena Maria

**Study cohort: 77,319 subjects** from the Västerbotten Intervention Program (VIP) cohort

**Exclusion criteria:** subjects with missing data for more than 10% of the items in the FFQ and/or portion size (n=6,715); subjects lacking data for body mass index (BMI) or with BMIB10 kg/m2 (n=60); subjects with unrealistic food intake level (FIL) values, defined as a ratio of total energy intake to estimated basal metabolic rate (41) in the lowest 5th percentile or the highest 2.5th percentile, determined separately for sex and FFQ version (n=7,977); and subjects with repeated health surveys (n=21,134), in which the most recent sampling occasion was excluded from all analyses.

**Definition of meat:** Food items were recalculated into grams/ day by multiplying frequency with portion size and adjusting for validated sex- and age-specific intake levels, defined by repeated 24 hour dietary recalls. Intakes were energy adjusted by the residual method. **A traditional Sami diet score was constructed in a similar manner to the Mediterranean diet score (1), by adding 1 point for each intake above or below the median intake of several dietary items characteristic or uncharacteristic of the traditional Sami diet, respectively. The score included 1 point for each intake above the median for red meat, fatty fish, total fat, berries and boiled coffee and 1 point for each intake below the median for vegetables, bread and fibre**, all calculated separately for sex and FFQ version, **thus creating a range from 0 to 8 points for each subject.**

**Definition of mortality:**

Mortality end-points up to and including 31 December 2007, were identified by linking the VIP database with the Swedish national cause-of-death registry. 12-digit Swedish personal identification numbers were used as the linkage variable. Cancer mortality was defined as underlying cause of death, ICD-9 codes 140-208, or ICD-10 codes C00-C97. CVD mortality was defined as the main cause of death and/or underlying cause of death, ICD-9 codes 390-438, or ICD-10 codes I00-I69.

**Variables considered:** age, sex, BMI, smoking, education, sedentary lifestyle, physical activity level, low outdoor activity, energy, fat, protein, carbohydrates, sucrose, fiber, ethanol, red meat, fatty fish, berries, vegetables, bread, boiled coffee

**Adjusting variables:**

Model 1: age included as strata

Model 2: age, BMI, sedentary lifestyle, education, current smoking, intake of alcohol, total energy

Model 3: age, BMI, sedentary lifestyle, education, current smoking, intake of alcohol, total energy, red meat (>median), fatty fish (>median), fat (>median), berries (>median), Boiled coffee (>median), Blood dishes (>median), Liver/kidney (>median), vegetables (<median), bread (<median), fibre (<median)

**Analytical models:**

Likely predictors of mortality, including age, body mass index (BMI, kg/m2), current smoking (yes/no), education (lack of post-secondary, yes/no), sedentary lifestyle (no regular physical activity in exercise clothes, yes/no), and intake of alcohol (g/day), fat (g/day), saturated fat (g/day), and total energy (kcal/day), were examined for association with traditional Sami diet score categories by Kruskal-Wallis tests (Tables I and II). **Sex-specific hazard ratios (HR) for all-cause, cancer (including the most common cancer sites), and CVD mortality were calculated by Cox regression.** Though all lifestyle variables were significantly associated with traditional Sami diet score categories in at least 1 sex, none met our criterion for a confounder: altering the HR for the traditional Sami diet score by 10% or more when included in a bivariate model.

To facilitate comparison with other studies, common risk factors were kept in the multivariate Model 2, which thus included: age, BMI, current smoking, education, sedentary lifestyle, and intake of alcohol and total energy.

**Proportional hazard assumptions were confirmed by Schoenfeld's test.**

**Subgroups based on metabolic risk profile and physical activity at baseline were also analysed.** In order to ensure that dietary changes due to disease did not affect the results, we did analysis with excluding all subjects with follow-up times shorter than 2 years. Analyses were also performed after excluding low-energy reporters. In addition we replaced the sedentary lifestyle variable in the multivariate model with PAL or with a variable representing low physical activity outdoors, the latter encompassing questions on walking, biking, picking berries or mushrooms, gardening, shovelling snow, and hunting and fishing.

**Article 15: Red Meat Consumption and Mortality**

**Author: An Pan, PhD**

**Study cohort: 37 698** men from the Health Professionals Follow-up Study (1986-2008) and **83 644** women from the Nurses' Health Study

**Exclusion criteria:** We excluded 5617 men and 5613 women who had a history of CVD or cancer at baseline and 6619 men and 3211 women who left more than 9 blank responses on the baseline FFQ, had missing information about meat intake, or reported implausible energy intake levels (<500 or >3500 kcal/d).

**Definition of meat:** unprocessed red meat consumption included “beef, pork, or lamb as main dish” (pork was queried separately beginning in 1990), “hamburger,” and “beef, pork, or lamb as a sandwich or mixed dish.” The standard serving size was 85 g (3 oz) for unprocessed red meat. Processed red meat included “bacon” (2 slices, 13 g), “hot dogs” (one, 45 g), and “sausage, salami, bologna, and other processed red meats” (1 piece, 28 g). total red meat intake defined as unprocessed red meat and processed red meat combined. **serving-per-day calculated**. **1-serving-per-day increase or quintiles used.**

**Definition of mortality:** Briefly, deaths were identified by reports from next of kin, via postal authorities, or by searching the National Death Index, and at least 95% of deaths were identified.11 The cause of death was determined after review by physicians and were primarily based on medical records and death certificates. We used the International Classification of Diseases, Eighth Revision, which was widely used at the start of the cohorts, to distinguish deaths due to cancer (codes 140-207) and CVDs (codes 390-459 and 795).

**Variables considered:**

Age, total red meat intake, physical activity, BMI, race, current smoker, diabetes mellitus, hypertension, high cholesterol, family history of diabetes mellitus, family history of myocardial infarction, family history of cancer, current multivitamin use, current aspirin use, postmenopausal, current menopausal hormone use, total energy, alcohol, fruit, vegetables, whole grains, nuts, legumes, dairy products, fish, poultry

**Adjusting variables:**

**Model 1: age adjusted model**

**Model 2: Multivariate model**

intakes of total energy, whole grains, fruits, and vegetables (all in quintiles), age; body mass index (calculated as weight in kilograms divided by height in meters squared) (<23.0, 23.0-24.9, 25.0-29.9, 30.0-34.9, or ≥35.0); race (white or nonwhite); smoking status (never, past, or current [1-14, 15-24, or ≥25 cigarettes per day]); alcohol intake (0, 0.1-4.9, 5.0-14.9, or ≥15.0 g/d in women; 0, 0.1-4.9, 5.0-29.9, or ≥30.0 g/d in men); physical activity level (<3.0, 3.0-8.9, 9.0-17.9, 18.0-26.9, or ≥27.0 hours of metabolic equivalent tasks per week); multivitamin use (yes or no); aspirin use (yes or no); family history of diabetes mellitus, myocardial infarction, or cancer; and baseline history of diabetes mellitus, hypertension, or hypercholesterolemia. In women, we also adjusted for postmenopausal status and menopausal hormone use. We further adjusted for intakes of other major dietary variables (fish, poultry, nuts, legumes, and dairy products, all in quintiles) or several nutrients or dietary components (glycemic load, cereal fiber, magnesium, and polyunsaturated and trans fatty acids, all in quintiles) instead of foods;

**Analytical models:** **We used time-dependent Cox proportional hazards regression models to assess the association of red meat consumption with cause-specific and total mortality risks during follow-up**. We conducted analyses separately for each cohort. To better represent long-term diet and to minimize within-person variation, we created cumulative averages of food intake from baseline to death from the repeated FFQs.12 We replaced missing values in each follow-up FFQ with the cumulative averages before the missing values. We stopped updating the dietary variables when the participants reported a diagnosis of diabetes mellitus, stroke, coronary heart disease, angina, or cancer because these conditions might lead to changes in diet. **We conducted several sensitivity analyses to test the robustness of the results: (1) we further adjusted for intakes of other major dietary variables (fish, poultry, nuts, legumes, and dairy products, all in quintiles) or several nutrients or dietary components (glycemic load, cereal fiber, magnesium, and polyunsaturated and trans fatty acids, all in quintiles) instead of foods; (2) we corrected for measurement error13 in the assessment of red meat intake by using a regression calibration approach using data from validation studies conducted in the HPFS9 in 1986 and in the NHS10 in 1980 and 1986; (3) we repeated the analysis by using simply updated dietary methods (using the most recent dietary variables to predict mortality risk in the next 4 years)12 or continue to update a participant's diet even after he or she reported a diagnosis of major chronic disease or using only baseline dietary variables; and (4) we used the energy density of red meat intake (serving/1000 kcal × d−1) as the exposure instead of the crude intake.** **In addition, we used restricted cubic spline regressions with 4 knots to examine a dose-response relation between red meat intake and risk of total mortality.** **We estimated the associations of substituting 1 serving of an alternative food for red meat with mortality by including both as continuous variables in the same multivariate model, which also contained nondietary covariates and total energy intake.** The difference in their β coefficients and in their own variances and covariance were used to estimate the hazard ratios (HRs) and 95% CIs for the substitution associations.14 We calculated population-attributable risk (95% CI) to estimate the proportion of deaths in the 2 cohorts that would be prevented at the end of follow-up if all the participants were in the low-intake group.15 For these analyses, we compared participants in the low–red meat intake category (<0.5 servings daily, or 42 g/d) with the remaining participants in the cohorts.

The HRs from the final multivariate-adjusted models in each cohort were pooled to obtain a summary risk estimate with the use of an inverse variance–weighted meta-analysis by the random-effects model, which allowed for between-study heterogeneity.

**Article 16: The relationship between fermented food intake and mortality risk in the European Prospective Investigation into Cancer and Nutrition-Netherlands cohort**

**Author: Jaike Praagman**

**Study cohort: 40 011 initially, after exclusion, 34 409** European Prospective Investigation into Cancer and Nutrition-Netherlands cohort

**Exclusion criteria:** participants who gave no permission for linkage with both vital status and causes of death registries (n 2369) were excluded, as well as participants with missing questionnaires (n 177) or with an implausible energy intake as defined by the extreme percentiles of the ratio of reported energy intake:estimated BMR (n 347), and those with prevalent cancer or CVD at baseline (n 2709),

**Definition of meat:** Based on consumption frequencies and portion sizes, the mean daily intake **in g/d was calculated** for each subject individually. The total fermented food intake comprised fermented dairy foods (yogurt, buttermilk and quark, but no cheese), cheese, fermented meat (dried sausage), fermented vegetables (i.e. sauerkraut, pickles and olives), fermented soya (tempeh) and vinegar. **Quartiles used.**

**Definition of mortality:** Vital status was obtained through digital record linkage with the municipal administration registries, and causes of death were provided by Statistics Netherlands (Central Agency for Statistics). Causes of death were coded according to the Ninth Revision of the International Classification of Diseases (ICD-9) for deaths until 1996 and according to the Tenth Revision (ICD-10) for deaths thereafter. For cause-specific analysis, cause of death was further specified into death from cancer (ICD-9 140–239; ICD-10 C00–D48) and death from stroke (ICD-9 430–434, 436; ICD-10 I60–I66), CHD (ICD-9 410–414, 427.5, 798.1, 798.2, 798.9; ICD-10 I20–I25, I46, R96) and overall CVD (including ICD codes for stroke, CHD and ICD-9 428, 415.1, 443.9, 430–438, 440–442, 444; ICD-10 I26, G45, I60–I67, I69, I70–I74, I50).

**Variables considered:**

Sex, age, BMI, physical activity level, education, current smoker, hypertension, total energy intake, total fermented foods, fermented dairy foods, yogurt, cheese, fermented meat, fermented vegetables, fruit, vegetables, ethano

**Adjusting variables:**

In model 1, age, sex and total energy intake (model 1).

In model 2, additional adjustment was made for physical activity (inactive, moderately inactive, moderately active and active), education level (low, intermediate and high), hypertension at baseline (yes/no), smoking habit (non-smoker, former smoker and current smoker) and BMI.

In model 3, further adjustment was made for energy-adjusted intakes of fruit (continuous), vegetables (continuous) and alcohol (six categories).

Fully adjusted model: age, sex, total energy intake, smoking habit, BMI, physical activity, education level, hypertension at baseline, intakes of alcohol, energy-adjusted intakes of fruit and vegetables.

**Analytical models:** **Intakes of total and subtypes of fermented foods were adjusted for total energy intake according to the residual method. Based on the distribution of energy-adjusted intake, quartiles were constructed for each fermented food intake variable. Cox regression was used to estimate hazard ratios (HR) and 95 % CI for the relationship between total fermented food intake and all-cause mortality or cause-specific mortality, using the lowest quartile of intake as reference.** The analyses were repeated for the different subtypes of fermented foods, such as dairy products, cheese, vegetables and meat, and additionally yogurt. Vinegar and fermented soya foods were not analysed separately, because intakes were too low and the percentage of non-consumers was too high (47 and 75 % for vinegar and fermented soya, respectively). All analyses were stratified for cohort (Prospect or MORGEN**). To test for linear trends, fermented food intake values for each participant were replaced by the median values of the quartile to which they belonged and included in the model as a continuous covariate. To test for non-linear trends, quadratic terms of fermented food intake variables were added to the continuous models. When P values for these terms were < 0·05, we subsequently constructed restricted cubic splines with four knots. The proportional hazards assumption was checked by calculating Schoenfeld residuals and visual inspection of log–log plots, showing no significant deviations.** **In sensitivity analyses, we divided total fermented dairy food intake into low-fat food ( < 2 % fat) and high-fat food ( ≥ 2 % fat), and calculated HR for their associations with mortality. Also, we excluded BMI from the final model to examine whether this variable was an intermediate factor in our analyses.** Because of the high salt content of fermented food products, except for dairy products, we included Na intake as a potential confounder in the final model. **Since (fermented) food intake was only measured at baseline, misclassification of subjects may have occurred as a result of the changes in dietary behaviour during the follow-up. Therefore, we repeated the analyses for the first 5 years of follow-up by censoring all subjects alive after that time.** **Because the number of fatal stroke events during the first 5 years was too low (n 4), we also repeated the analysis for the first 8 years of follow-up.**

**Article 17: Meat consumption and mortality - results from**

**the European Prospective Investigation into Cancer and Nutrition**

**Author: Sabine Rohrmann**

**Study cohort:** 511,781 initially, after exclusion, **448,568** European Prospective Investigation into Cancer and Nutrition (EPIC)

**Exclusion criteria:** we excluded individuals with a ratio for energy intake versus energy expenditure in the top or bottom 1% (n =10,197) and those with self-reported cancer, stroke or myocardial infarction at baseline (n = 29,300). We further excluded participants with unknown smoking status at baseline (n = 23,716).

**Definition of meat:** For this analysis, meats were grouped into red meat (beef, pork, mutton/lamb, horse, goat), processed meat (all meat products, including ham, bacon, sausages; small part of minced meat that has been bought as a ready-toeat product) and white meat (poultry, including chicken, hen, turkey, duck, goose, unclassified poultry, and rabbit (domestic)). Processed meat mainly refers to processed red meat but may contain small amounts of processed white meat as well, for example, in sausages. **g/day calculated. Treated both as continuous variable and categorical variables.**

**Definition of mortality:** Cause of death was coded according to the 10th Revision of the International Classification of Diseases (ICD-10). The underlying causes of death were used to estimate the cause-specific mortality: cancer (ICD-10: C00 to D48), cardiovascular diseases (I00 to I99), respiratory diseases (J30 to J98), digestive diseases (K20 to K92), and other diseases.

**Variables considered:**

Age, BMI, energy intake, alcohol intake, red meat, processed meat, poultry, vegetable intake, fruit intake, smoking, physical activity, education

**Adjusting variables:** stratified by age (one-year age groups), sex, study center, adjusted for education (five categories), body weight (continuous), body height (continuous), total energy intake (continuous), alcohol consumption (continuous), physical activity (four categories), smoking status (seven categories), smoking duration (six categories), meat intake mutually adjusted for each other. Additionally adjusting for fruit and vegetables. **Interaction examined sex and smoking status (never, former, current), alcohol consumption (dichotomized by sex-specific median), and fruit and vegetable consumption (dichotomized by sexspecific median).**

To adjust for lifelong tobacco smoking, we included baseline smoking status and intensity of smoking as one variable (never smokers (reference category); current cigarette smokers (three categories: 1 to 14, 15 to 24 and 25+ cigarettes/day); former smokers who stopped less than 10 years ago, 11 to 20 years ago, 20+ years ago; other smokers (one category including pipe or cigar smokers and occasional smokers)). In addition, duration of smoking in 10-year categories (≤10 (reference category), 11 to 20, 21 to 30, 31 to 40, 41 to 50, >50 years) is added as a second variable in the statistical models. Additionally, all analyses were adjusted for body weight and height, energy intake, intake of alcohol (all continuous), physical activity index (active, moderately active, moderately inactive, inactive, missing) [23], and education (none or primary school completed; technical/professional school; secondary school; university degree; missing). We additionally examined the effect of mutually adjusting intake of the three types of meat for each other. We also explored meat intake in models without adjusting for total energy intake. Additionally adjusting for fruit and vegetable consumption did not appreciably change the observed associations and was not included in the main models.

**Analytical models: Cox proportional hazards regression** was used to examine the association of meat consumption with all-cause and cause-specific mortality. To explore the shape of the risk function, **we fitted a Cox proportional hazards model with restricted cubic splines for red and processed meat and poultry intake treated as continuous variables. We specified four knot positions at 10, 20, 40, and 80 g per day of red or processed meat intake.** Other knot positions were specified but did not appreciably change the curves. In a second step, **we modeled meat intake as categorical variables as follows: red and processed meat 0 to 9.9, 10 to 19.9, 20 to 39.9, 40 t0 79.9, 80 to 159.9, and ≥160 g/day;** **Age was used as the primary time variable in the Cox models.** Time at entry was age at recruitment, exit time was age when participants died, were lost to follow-up, or were censored at the end of the follow-up period, whichever came first. **The analyses were stratified by sex, center, and age at recruitment in one-year categories.**

In order to improve the comparability of dietary data across the participating centers, dietary intakes from the questionnaires were **calibrated using a standardized 24-hour dietary recall [24,25]**, thus, partly correcting for over- and underestimation of dietary intakes [26]. A 24-hour dietary recall was collected from an 8% random sample of each center’s participants. Dietary intakes were calibrated using a fixed effects linear model in which gender- and center-specific 24-hour dietary recall data were regressed on the questionnaire data controlling for weight, height, age, day of the week, and season of the year. The confidence intervals (CIs) of the risk estimates, obtained using calibrated data, were estimated using bootstrap sampling to take into account the uncertainty related to measurement error correction. **Calibrated and uncalibrated data were used to estimate the association of meat consumption with mortality on a continuous scale.** Results might differ between subgroups of the study population due to different health behaviors in, for example, men and women, or interactions between nutrients in different foods. Therefore, **sub-analyses were performed by sex and smoking status (never, former, current), alcohol consumption (dichotomized by sex-specific median), and fruit and vegetable consumption (dichotomized by sexspecific median).** **Including cross-product terms along with the main effect terms in the Cox regression model**

**tested for interaction on the multiplicative scale.** **We also examined whether the associations differed in the first two years and the succeeding years of follow-up.** **The population attributable risk (PAR),** which describes the proportion of cases that would be prevented if everyone in the study population had the reference level of the exposure, was estimated based on the formula [28].

**Article 18: Red Meat and Poultry Intakes and Risk of Total and Cause-Specific Mortality: Results from Cohort Studies of Chinese Adults in Shanghai**

**Author: Takata, Yumie**

**Study cohort:** 134,290 Chinese adult women and men in Shanghai, Shanghai Women’s Health Study (SWHS) and Shanghai Men’s Health Study (SMHS). The final analyses included **73,162 women and 61,128 men.**

**Exclusion criteria:** In the current analyses, we excluded participants with a prior history of cancer at baseline (1,579 women; no men were excluded, since this was an exclusion criterion for participation in the SMHS), those who reported a total caloric intake outside the range of 500 to 4,000 kcal per day (50 women and 91 men), and those with no follow up (5 women and 14 men). We further excluded participants who died during the first year of observation (145 deaths in women and 249 deaths in men) to minimize the possibility of reverse causality, and we excluded one male participant who did not answer all questions regarding smoking history.

**Definition of meat:** red meat intake was based on nine questions, which collected intake information on pork chops; pork ribs; pig’s feet; regular fresh pork; lean fresh pork; mixed fresh pork; pig, cow, and sheep liver; organ meat, including heart, brain, tongue, tripe, and intestine; and beef and lamb. Poultry intake was based on two questions on intakes of chicken, duck, and goose. Both FFQs assessed typical intake during the year before study enrollment by asking about the frequency (five categories ranging from never to every day) and the amount of consumption in liang (1 liang is equivalent to 50 grams). The Chinese Food Composition Tables were used to calculate intakes of total calories and nutrients [15]. **Quintiles used. g/day calculated; energy adjusted.**

**Definition of mortality:** The underlying cause of death reported on the death certificate was considered to be the cause of death in the analyses and was coded according to the International Classification of Diseases, Ninth Revision (ICD-9) [16]. Causes of death were first grouped into major diseases, including CVD (ICD-9 = 390–459) and cancer (ICD-9 = 140–208). Deaths due to CVD or cancer were further divided into the top three CVD-related causes and the top four cancer-related causes. For CVD, this included ischemic heart disease (ICD-9 = 410–414), hemorrhagic stroke (ICD-9 = 430–431), and ischemic stroke (ICD-9 = 433–435). For cancer, this included lung cancer (ICD = 162), stomach cancer (ICD = 151), colorectal cancer (ICD = 153–154), and liver cancer (ICD = 155). We also grouped cancers by smoking- and non-smoking-related cancers based on a report from the International Agency for Research on Cancer [17]. Since the number of deaths due to diabetes was relatively small (n = 93) in the SMHS due to the shorter follow-up time, diabetes mortality was not included in our analyses.

**Variables considered:** age, education, income, occupation, smoking, alcohol consumption, regular tea consumption, BMI, vitamin supplement use, physical activity, total caloric intake, red meat intake (g/day energy adjusted), poultry intake, fish intake, vegetable intake, fruit intake

**Adjusting variables:** These included age at baseline (continuous), total caloric intake (continuous), smoking history (pack-years of smoking for men and ever/never smoking for women), income (four categories), occupation (three categories), education (four categories), comorbidity index (three categories based on the number of existing chronic diseases [18]), physical activity (categories based on MET-hours per day), total vegetable intake (quintiles), total fruit intake (quintiles), and regular alcohol consumption for men (three categories), fish intake, red meat or poultry intake where appropriate.

**Analytical models:** Very few participants had missing data for covariates; **we replaced missing covariate data with the most common category** [e.g., education (0.65%), occupation (0.05%), income (0.11%), BMI (0.03%), and pack-years of smoking among men (0.002%)] in each of the cohorts. **Characteristics of the study population were described according to quintiles of red meat intake after adjusting for age at baseline, separately for women and men. Likewise, intakes of meats, fish, fruits, and vegetables were described after further adjusting for total caloric intake.** **Sex-specific quintiles of intakes of red meat (sum of pork and beef/lamb intakes), poultry, and pork were created based on the distribution among all cohort members at baseline.** **Cox proportional hazards regression with age as the time scale was performed to calculate hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) for each quintile of intake by using the lowest quintile as the reference.** HRs and 95% CIs were derived separately for women and men. **We also tested non-linear associations of red meat intake with total and cause-specific mortality by using restricted cubic spline Cox regression models placing knots at the 5th, 35th, 65th, and 95th percentiles of intake.** **Results for women and men were combined to obtain summary risk estimates using the meta-analysis approach.** **Stratified analyses were conducted by income (lower than 1,000 yuan per capita or higher for men and lower than 20,000 yuan per household or higher for women), education [low (up to and including middle school) or high (high school and higher)], the existence of comorbidity (none or any), history of hypertension at baseline (yes or no), history of diabetes at baseline (yes or no), regular exercise (yes or no), and BMI (<25 kg/m2 or ≥25 kg/m2). Among men, stratified analyses by smoking status (never, past, or current smokers) and by regular alcohol consumption (none, <2 drinks/day, or ≥2 drinks/day) were also conducted. Interaction effects between meat intake and selected characteristics were tested by including the main effects and the product terms in a model and assessing the P-value of the product term. Sensitivity analyses were conducted by excluding the first two years of observation and related deaths (216 deaths in women and 397 deaths in men during the second year of observation).**

**Article 19: Dietary questions as determinants of mortality: the OXCHECK experience**

**Author: David Whiteman**

**Study cohort: 11 090 OXCHECK study**

**Definition of meat:** Dietary details were elicited by a series of simple food frequency questions modified from a ‘health and lifestyle survey’ 4. Participants were given a list of foods (Appendix 1) and asked ‘About how often do you eat the following foods’; **permissible responses were ‘never’, ‘less than once a week’, ‘1–3days a week’ or ‘4–7 days a week’. Dietary exposures were analysed as categorical variables, with data for intake frequency groups ‘never’ and ‘less than once a week’ collapsed to form the reference category.**

**Definition of mortality:** Death certificates were obtained and cause of death determined according to ONS ICD-9 coding practice. For the analyses in this paper, deaths were assigned to three mutually exclusive categories, namely IHD (ICD-9 codes 410.0–414.9), all cancers (ICD-9 codes 140.0–239.9) and other causes of death (all other ICD-9 categories).

**Variables considered:** sex, age, smoking, long-standing disease, participation in OXCHECK, social class, BMI, vigorous exercise

**Adjusting variables:** gender, smoking, age group, alcohol, social class, fruit, vegetables, puddings, meat, fresh or frozen green vegetables or salad, fresh or frozen red meat, fresh fruit or fruit juice, puddings, cakes, biscuits, sweets.

**Analytical models: The relative risk (and 95% confidence intervals) of dying associated with each level of exposure to dietary factors was estimated by the hazard ratio in a series of Cox regression models.** Of the food groups assessed in the dietary questionnaire, the following were hypothesized a priori to be associated with a higher risk of mortality at higher levels of consumption: processed meats; fresh or frozen red meat; chips; and biscuits, cakes, puddings or sweets (collectively). Conversely, frequent consumption of fresh or frozen green vegetables, fresh fruit or fruit juice, skimmed milk, polyunsaturated margarine and fresh or frozen fish were each hypothesized to be associated with reduced mortality risks. Relative risks were separately estimated for all-cause mortality and for the three specific categories of death (cause-specific mortality). For alcohol consumption, abstainers formed the reference category, light drinkers were defined as males who drank no more than 20 units per week or females who drank no more than 15 units per week; participants with higher levels of consumption were classified as moderate to heavy drinkers. **Because patients with a prior history of angina or myocardial infarction may have modified their diet just prior to baseline dietary collection, dietary analyses were restricted to the 10 522 patients who reported no previous episodes of chest pain.** Confounding and effect modification were investigated by conducting analyses stratified by the exposure levels of other risk factors. Where no effect modification was observed across strata, possible confounding was controlled through the inclusion of design variables in multivariable Cox regression analyses.

**Article 20: Mortality in vegetarians and nonvegetarians: detailed findings from a collaborative analysis of 5 prospective studies**

**Author: Timothy J Key**

**Study cohort: 76172** from 5 studies Adventist Mortality, Health Food Shoppers, Adventist Health, Heidelberg, Oxford Vegetarian study

**Exclusion criteria:** Subjects were eligible for analysis if they were aged 16–89 y at recruitment, if they had not been diagnosed with cancer before recruitment [except for International Classification of Diseases, ninth revision (ICD-9) 173, nonmelanoma skin cancer ([7](javascript:;))], and if they provided sufficient information for classifying diet group and smoking category.

**Definition of meat: The main analysis compared mortality in vegetarians with that in nonvegetarians.** In the Health Food Shoppers Study, vegetarians were people who replied “yes” to the question “Are you a vegetarian?,” whereas in the 4 other studies vegetarians were defined as people who reported that they did not eat any meat or fish; all others were defined as nonvegetarians.

**Definition of mortality:** The endpoints examined were stomach cancer (ICD-9 151), colorectal cancer (ICD-9 153 and 154), lung cancer (ICD-9 162), female breast cancer (ICD-9 174), prostate cancer (ICD-9 185), ischemic heart disease (ICD-9 410–414), cerebrovascular disease (ICD-9 430–438), all other causes, and all causes combined (7).

**Variables considered: age, smokers, BMI, alcohol users, education level, exercise level**

**Adjusting variables: sex, smoking status, age, body mass index, alcohol use, education level, and exercise level.** Men and women were categorized into thirds of the distribution of body mass index of all men and all women, respectively. Alcohol users were categorized as regular drinkers or nonregular drinkers, definitions varied between studies, but the guideline was that regular drinkers consumed ≥1 alcoholic drink/wk. Education was classified as high—equivalent to the completion of American high school or above—or low; in the Oxford Vegetarian Study only data on social class were available and social classes I and II (8) were considered to be equivalent to high education. Exercise was classified as high or low on the basis of criteria used to define the level of activity in each study, with the guideline of producing 2 approximately equal-sized groups in each study.

**Analytical models:** **Smokers were categorized as never smokers, former smokers, current light smokers (1–14 cigarettes/d, user of other tobacco, or both), and current heavy smokers (≥15 cigarettes/d).** Subjects were censored on reaching age 90 y. Person-years at risk were calculated using the PERSON-YEARS computer program (9), and **death rate ratios** in each study were calculated by **Poisson regression** using GLIM-4 (10). **All death rate ratios were adjusted for age in 5-y increments, sex, and smoking (never, former, current light, and current heavy)**. Mortality ratios for the separate studies were then combined to give a pooled estimate of effect using the **random-effects model** of DerSimonian and Laird (11), which both tests and allows for heterogeneity between studies. The test for heterogeneity was also applied to the pooled all-studies results to test for heterogeneity of effect between sexes and age groups.