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Original article

Animal-based food choice and associations with long-term weight maintenance and metabolic health after a large and rapid weight loss: The PREVIEW study

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SUMMARY

Background & aims: Low-energy diet replacement is an effective tool to induce large and rapid weight loss and improve metabolic health, but in the long-term individuals often experience significant weight regain. Little is known about the role of animal-based foods in weight maintenance and metabolic health. We aimed to examine longitudinal associations of animal-based foods with weight maintenance and glycaemic and cardiometabolic risk factors. We also modelled replacement of processed meat with other high-protein foods.

Methods: In this secondary analysis, longitudinal data were analysed from 688 adults (26–70 years) with overweight and prediabetes after 8-week low-energy diet-induced weight loss (≥8% of initial body weight) in a 3-year, multi-centre, diabetes prevention study (PREVIEW). Animal-based food consumption, including unprocessed red meat, processed red meat, poultry, dairy products, fish and seafood, and eggs, was repeatedly assessed using 4-day food records. Multi-adjusted linear mixed models and isoenergetic substitution models were used to examine the potential associations.

Results: The available-case analysis showed that each 10-g increment in processed meat, but not total meat, unprocessed red meat, poultry, dairy products, or eggs, was positively associated with weight regain (0.17 kg·year^{-1}, 95% CI 0.10, 0.25, $P < 0.001$) and increments in waist circumference, HbA_{1c}, and triacylglycerols. The associations of processed meat with HbA_{1c} or triacylglycerols disappeared when adjusted for weight change. Fish and seafood consumption was inversely associated with triacylglycerols

Abbreviations: AGEs, Advanced glycation end products; BMI, Body mass index; CVD, Cardiovascular disease; DEXA, Dual energy x-ray absorptiometry; FPG, Fasting plasma glucose; GI, Glycaemic index; HbA_{1c}, Haemoglobin A_{1c}; HDL-cholesterol, High-density lipoprotein cholesterol; HOMA-IR, Homeostatic model assessment of insulin resistance; LDL-cholesterol, Low-density lipoprotein cholesterol; RCT, Randomised controlled trial; TyG, Triacylglycerol-glucose index.

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and triacylglycerol-glucose index, independent of weight change. Modelled replacement of processed meat with isoenergetic (250–300 kJ·day^{-1} or 60–72 kcal·day^{-1}) dairy, poultry, fish and seafood, grains, or nuts was associated with −0.59 (95% CI -0.77, −0.41), −0.66 (95% CI -0.93, −0.40), −0.58 (95% CI -0.88, −0.27), and −0.69 (95% CI -0.96, −0.41) kg·year^{-1} of weight regain, respectively (all $P < 0.001$) and significant improvements in HbA_{1c}, and triacylglycerols.

Conclusions: Higher intake of processed meat, but not total or unprocessed red meat, poultry, dairy products, or eggs may be associated with greater weight regain and more adverse glycaemic and cardiometabolic risk factors. Replacing processed meat with a wide variety of high-protein foods, including unprocessed red meat, poultry, dairy products, fish, eggs, grains, and nuts, could improve weight maintenance and metabolic health after rapid weight loss. This study was registered as ClinicalTrials.gov, NCT01777893.

1. Introduction

Type 2 diabetes and cardiovascular disease (CVD) are major global health challenges. Obesity is a key driver and weight loss has been shown to be related to improvements in glycaemic and cardiometabolic risk factors [1,2]. Low-energy diet replacement, an effective tool to induce large and rapid weight loss, has been introduced in many weight management and type 2 diabetes prevention programmes [3], but individuals often experience significant weight regain and worsened metabolic outcomes in the long term [4,5].

Dietary intake may play a vital role in weight management and prevention of type 2 diabetes and CVD. Eating a diet with plant-based foods, such as vegetables, fruits, and nuts, has been shown to be inversely associated with weight gain and risk of type 2 diabetes and CVD [6,7]. Animal-based foods have recently been connected to worsened metabolic outcomes and emerging epidemiological evidence suggests that red and processed meat intake is associated with an increased risk of weight gain [8], type 2 diabetes [9], and CVD [10–12]. Prospective cohort studies show that replacing red meat with other foods such as nuts and grains is associated with a lower risk of type 2 diabetes and CVD [10,13,14]. Regarding other animal-based foods including dairy products, poultry, fish and seafood, and eggs, null or conflicting findings have been reported [8,15–18].

Very few previous studies focused on animal-based food choice and food substitutions for weight maintenance and metabolic health, especially after a low-energy diet-induced rapid weight loss. In a secondary analysis of the DIOGenes study, replacing meat protein with protein from other animal sources was associated with increased fasting insulin and homeostasis model assessment of insulin resistance (HOMA-IR), but not body weight or body fat during weight maintenance [19]. However, that analysis did not explore specific meats e.g. red meat, processed meat, and poultry and food substitutions for specific meats. Moreover, the DIOGenes study lasted for 6 months only [19].

The aim of the present secondary analysis was to examine the associations of animal-based foods (i.e. total meat, unprocessed red meat, processed red meat, poultry, dairy products, fish and seafood, and eggs) with 3-year weight maintenance and glycaemic and cardiometabolic risk factors in the participants from four intervention centres in the PREVIEW study. In addition, as many previous studies have shown detrimental effects of processed meat on human health [12,20], we also conducted a tertiary analysis and modelled associations between replacement of processed meat with other animal- and plant-origin high-protein foods and metabolic risk factors.

2. Methods

2.1. Study design

This secondary analysis was based on the PREVIEW study, a 3-year multi-centre diabetes intervention (ClinicalTrials.gov, NCT01777893). Detailed information regarding PREVIEW has already been described in a previous paper [21]. The main results have been published elsewhere [22,23]. The PREVIEW study was conducted at eight intervention centres in Denmark, Finland, the Netherlands, the UK, Spain, Bulgaria, New Zealand, and Australia. In the present analysis, we used data from four intervention centres (Finland, the UK, New Zealand, and Australia), because they provided food intake data in g·day^{-1} or serving·day^{-1} and complete food categories.

The main aim of PREVIEW was to assess the long-term effect of two diets combined with two physical activity programmes on risk of type 2 diabetes after an 8-week weight loss period. The primary outcome was the risk of type 2 diabetes between the two diet groups [23]. During the weight loss period, participants were provided with a low-energy diet (3400 kJ·day^{-1} or 810 kcal·day^{-1}). After this period, participants were assigned to one of the four diet–physical activity groups and commenced 148-week weight maintenance. During the weight maintenance intervention, participants were suggested to consume a high-protein/low-glycaemic index (GI) (25 E% protein, GI < 50) or moderate-protein/moderate-GI (15 E% protein, GI > 56 and < 70) diet combined with a high- or moderate-intensity physical activity programme. The diets were consumed ad libitum. The participants were provided with cooking books and examples of eating plans reflecting the macronutrient and GI requirements of the two diets. We also conducted a behavioural modification programme (PREMIT) and 17 group visits throughout the study to improve dietary and physical activity compliance. The PREVIEW protocol was approved by the Human Ethics Committees at all intervention centres. The PREVIEW study was conducted in accordance with the Declaration of Helsinki (59th WMA General Assembly, Seoul, Korea, October 2008).

2.2. Study population

The recruitment took place from June 2013 to April 2015. The main inclusion criteria included: 1) age 25–70 years; 2) overweight (BMI 25–29.9 kg m^{-2}) or obesity (BMI≥30 kg m^{-2}); 3) prediabetes. Prediabetes was defined according to the American Diabetes Association criteria [24]: individuals with impaired fasting plasma glucose (FPG) (5.6–6.9 mmol L^{-1}) or with impaired glucose tolerance (2-h plasma glucose of 7.8–11.0 mmol L^{-1} and

FPG<7.0 mmol L^{-1}) after an oral ingestion of 75 g of glucose. HbA_{1c} was not used for defining prediabetes. The main exclusion was participants with type 1 diabetes or type 2 diabetes prior to the study. Eligible participants were assigned to one of the four diet–physical activity groups by gender and age (25–45, 46–54, or 55–70 years) and started 8-week weight loss. Those who successfully lost≥8% of initial body weight commenced 156-week weight maintenance. We excluded those with missing animal-based food data at 26 weeks and/or implausible low or high energy intake (<2520 kJ·day^{-1}/600 kcal·day^{-1} or >14,700 kJ·day^{-1}/3500 kcal·day^{-1} for women and <3360 kJ·day^{-1}/800 kcal·day^{-1} or >17,640 kJ·day^{-1}/4200 kcal·day^{-1} for men) [25,26].

2.3. Assessment of dietary intake

Dietary intake was assessed using self-reported 4-day food records including three working days and one weekend day. The food records were collected repeatedly at 26, 52, 104, and 156 weeks. Participants were instructed to report dietary intake by weighing foods or using household measurements e.g. cups, spoons, and glasses. In addition, participants were instructed to describe the food in detail e.g. type of foods and cooking methods. Collected dietary data were entered into nutrient analysis programmes with local food information i.e. AivoDiet (Finland), Nutritics (the UK), and Foodworks (Australia and New Zealand) for further calculation. All intervention centres followed the same standard operating procedure including necessary steps for recording of food intake, data entry, and analysis of the completed food records. Dietary intake was expressed in kg·day^{-1} or serving·day^{-1}. Serving sizes were converted to grams of food consumed according to the Australian Dietary Guidelines (2013) [27], and vice versa.

A cumulative average method was used to estimate long-term self-reported dietary intake during weight maintenance. Cumulative average dietary intake from 8 to 26, 52, 104, and 156 weeks was calculated. Dietary intake measured at 26 weeks was used to estimate the average dietary intake from 8 to 26 weeks. Detailed information is included in Supplementary Materials and Supplementary Table 1. Animal-based foods included total meat, unprocessed red meat, processed meat, poultry, fish and seafood, eggs, and dairy products. Total meat included unprocessed red meat, processed meat, and poultry. High-protein foods of plant-origin included grains, legumes, and nuts. The definition of individual food groups is included in Supplementary Table 2.

2.4. Assessment of outcomes

Body weight outcomes and glycaemic and cardiometabolic risk factors were measured repeatedly at 8, 26, 52, 104, and 156 weeks. Body weight was measured in fasting (>10 h) participants with light clothing or underwear. Fat mass was determined using dual energy x-ray absorptiometry (DEXA) in the UK (GE Lunar Prodigy, GE Healthcare, Madison, WI, USA), Australia (Hologic Discovery W, Hologic, Bedford, MA, USA), and New Zealand (GE Lunar, GE Healthcare, Madison, WI, USA) and bioelectrical impedance in Finland (InBody720 Body Composition Analyser, Biospace Co., Ltd, Korea). Blood samples were drawn from the antecubital vein after fasting (>10 h) and were initially stored locally at −80 °C. Then they were sent to the central laboratory in Finnish Institute for Health and Welfare, Helsinki, Finland for batch analysis of FPG, haemoglobin A_{1c} (HbA_{1c}), fasting insulin, fasting triacylglycerols, total cholesterol, and HDL-cholesterol. HOMA-IR was calculated as fasting insulin (mU·L^{-1}) × FPG (mmol·L^{-1})/22.5. The triacylglycerol-glucose (TyG) index, a measure reflecting insulin resistance and predicting the development of CVD, was calculated as Ln [triacylglycerols (mg·dL^{-1}) × FPG (mg·dL^{-1})/2] [28].

2.5. Assessment of covariates

Socio-demographic information including age, sex, ethnicity (Caucasian, Asian, Black, Arabic, Hispanic, or other), and smoking (daily, less than weekly, or no smoking) were self-reported by participants at baseline (0 weeks). Total physical activity was determined using a 7-day accelerometry (ActiSleep+; ActiGraph LLC, Pensacola, FL) at 26, 52, 104, and 156 weeks and was expressed by mean activity counts during valid wear time (counts·min^{-1}).

2.6. Statistical analysis

Baseline characteristics are presented as means ± standard deviation or median (25th and 75th percentiles) for continuous variables, or percentage of participants (n%) for categorical variables. Difference between completers and non-completers in baseline characteristics was examined by an independent-samples *t* test for approximately normally-distributed variables, a Mann–Whitney *U* non-parametric test for non-normally-distributed variable, and a χ^2 test for categorical variables.

We conducted both available-case and complete-case analyses to assess associations of animal-based foods with yearly changes in weight outcomes and glycaemic and cardiometabolic risk factors. Yearly changes in outcomes were calculated as changes in outcomes from 8 to 26, 52, 104, and 156 weeks divided by corresponding changes in years. We used multi-adjusted linear mixed models. Model 1 was adjusted for age, sex, ethnicity, intervention group, time (categorial), BMI at 8 weeks, and values of outcomes at 8 weeks as fixed effects and intervention centre and participant identifier as random effects. Model 2 included all animal-based foods simultaneously and was additionally adjusted for lifestyle factors as fixed effects, including smoking, physical activity, energy intake (kJ·day^{-1}), alcohol drinking (g·day^{-1}), sugars, grains, legumes, nuts, vegetables, and fruits (all in g·day^{-1}). Model 3 was additionally adjusted for yearly weight change as a fixed effect. The results were expressed as changes in study outcomes per year associated with 35-g increment in total meat, 25-g increment in red meat, 100-g increment in dairy products, 20-g increment in poultry, 20-g increment in fish and seafood, or 15-g increment in eggs—all based on the medians and 25th and 75th percentiles of animal-based food intakes over 3 years. If the associations showed significance in the model, but were lost in model 3 after adjustment for weight change, a mediation analysis based on Baron and Kenny's (1986) steps for mediation [29] was conducted to examine whether weight change was a mediator variable. We also examined potential effect modification by sex or age (25–45, 46–54, or 55–70 years) by adding interaction terms in the models.

For animal-based foods that showed significant associations with weight outcomes or glycaemic or cardiometabolic risk factors in model 2, we divided participants into tertiles at each time point separately according to the animal-based food intake at different time points. The median (25th, 75th percentiles) values of tertiles at different time points are presented in Supplementary Table 3. We conducted available-case analysis to examine the difference in weight outcomes or glycaemic and cardiometabolic risk factors among tertiles, using linear mixed models adjusted for the covariates in model 2. As the tertiles were defined afresh at each time point, we performed multiple comparisons with Bonferroni adjustment to compare outcomes of interest among the tertiles, regardless of the significance of time and group interaction.

For animal-based foods that showed inverse associations with outcomes of interest, we also modelled associations of replacing them with other high-protein foods using isoenergetic (250–300 kJ·day^{-1} or 60–72 kcal·day^{-1}) substitution linear mixed

models adjusted for the covariates in models 2 and 3 [30]. We first converted grams of intakes of animal- and plant-based foods to serving sizes (0.5 serving·day^{-1} equals 250–300 kJ·day^{-1} or 60–72 kcal·day^{-1}). Then we obtained yearly mean changes in outcomes of interest (estimates or β) per 250–300 kJ·day^{-1} or 60–72 kcal·day^{-1} for processed meat and each of the other high-protein foods. Finally, we compared the two estimates and calculated the difference between the estimates, accounting for their variance and covariance. Data were analysed using IBM SPSS v28.0 software (Chicago, IL, USA). The statistical test was 2-sided with α set as 0.05.

3. Results

A total of 688 participants (2083–2273 observations of outcomes of interest) with complete animal-based food data at 26 weeks and plausible energy intake were included in the available-case analysis (Fig. 1). Of these, 479 participants (1734–1886 observations) were included in the complete-case analysis. The median age of the 688 participants (68.5% women) was 57 years (range: 26–70) at the start of weight maintenance. The median (25th, 75th percentiles) values were 29.5 kg m^{-2} (26.6, 33.4) for BMI, 34.2 g·day^{-1} (0, 66.3) for red meat intake, 12.0 g·day^{-1} (0, 29.7) for processed meat intake, and 30.9 g·day^{-1} (5.4, 63.7) for fish and seafood intake (Table 1).

Figure 2 shows associations of processed meat, fish and seafood intake with changes in weight outcomes and glycaemic and cardiometabolic risk factors during 3-year weight maintenance. In the available-case and complete-case analyses, processed meat intake was positively associated with weight and fat mass regains in models 1 and 2. In model 1, no associations were observed between processed meat intake and increases in waist circumference, whereas after adjustment for physical activity and dietary intake, processed meat intake was positively associated with increases in waist circumference. In models 1 and 2, processed meat intake was positively associated with HbA_{1c}, triacylglycerols, and TyG index, whereas the associations were not independent of weight change. The effect size of the association between processed meat intake and TyG index was small (Supplemental Table 4), According to Baron and Kenny's steps for mediation, weight change was a mediator variable. Processed meat intake influenced HbA_{1c} and triacylglycerols through weight change. In model 3, intake of fish and seafood was inversely associated with increments in triacylglycerols and TyG index (Supplementary Table 4), independent of weight change. The abovementioned associations were not modified by sex or age.

After adjustment for physical activity and dietary intake in model 2 and further adjustment for weight change in model 3, no associations were observed between total meat, unprocessed red meat, dairy products, poultry, or eggs and weight outcomes or glycaemic and cardiometabolic risk factors.

The reported significant associations in Fig. 2 remained robust in the tertile analysis (Fig. 3 and Supplementary Fig. 1), with an exception of the association between processed meat and TyG index (Supplementary Fig. 1). Compared with the lowest tertile, the highest tertile of processed meat intake (~49 g·day^{-1}) had greater weight regain and a greater increment in waist circumference at 52, 104, and 156 weeks, greater increments in FM and HbA_{1c} at 104 and 156 weeks, and a greater increment in TG at 104 weeks (Fig. 3). However, there were no differences in TyG index among tertiles of processed meat at each time point (Supplementary Fig. 1). Compared with the lowest tertile, the highest tertile of fish and seafood intake had greater decreases in TG at 104 and 156 weeks (Fig. 3) and greater decreases in TyG index at 156 weeks (Supplementary Fig. 1).

Figure 4 shows associations between isoenergetic substitution of processed meat with other high-protein foods and weight outcomes during 3-year weight maintenance. In model 2, replacing 250–300 kJ·day^{-1} or 60–72 kcal·day^{-1} of processed meat with isoenergetic dairy products, poultry, fish and seafood, egg, grains, legumes, or nuts was associated with smaller increments in body weight, fat mass, and waist circumference.

Figure 5 shows associations between isoenergetic substitution of processed meat with other high-protein foods and glycaemic and cardiometabolic risk factors during 3-year weight maintenance. Replacing of processed meat with isoenergetic other foods, but not legumes, was associated with a smaller increment in HbA_{1c} in model 2, whereas after adjustment for yearly weight change, all associations disappeared in model 3. In model 2, replacing of processed meat with other foods, but not eggs, was associated with smaller increments in triacylglycerols. Replacing of processed meat with other foods, but not eggs or grains, was associated with smaller increments in TyG index (Supplementary Table 5). After adjustment for yearly weight change, only the association with fish and seafood showed significance in model 3.

4. Discussion

In this secondary analysis, we found that higher consumption of processed meat was associated with greater body weight and fat mass regains and increases in waist circumference, HbA_{1c}, triacylglycerols, and TyG index. Processed meat influenced HbA_{1c}, triacylglycerols, and TyG index through weight change. Fish and seafood was associated with smaller increments in triacylglycerols and TyG index, independent of weight change. There were no associations of total meat, unprocessed red meat, poultry, dairy products, or eggs with any outcomes of interest. Replacing processed meat with isoenergetic amounts of other high-protein foods was associated with improvements in weight maintenance, fat mass, waist circumference, HbA_{1c}, triacylglycerols, and TyG index.

As emerging findings support that red meat is associated with an increased risk of multiple chronic diseases [8–11,31], some dietary recommendations e.g. US dietary guidance and Mediterranean-style and DASH (Dietary Approaches to Stop Hypertension)-style patterns advise individuals to reduce red meat intake [32,33]. Nonetheless, there is no specific recommendations for those who would like to maintain weight and metabolic health after large and rapid weight loss. In the present study, our findings do not support that adults after rapid weight loss should reduce or avoid unprocessed red meat intake. Similarly, in two meta-analyses of randomised controlled trials (RCTs), O'Connor et al. [33,34] found that intake of red meat did not result in deterioration of glycaemic and cardiometabolic risk factors, although the RCTs included did not have a large weight loss phase. In addition, although low red meat intake is recommended by DASH dietary patterns, some RCTs showed that DASH diets had equivalent efficacy in decreasing cardiometabolic risk factors when they contained higher amounts of red meat [35,36]. Furthermore, Iqbal et al. [20] did not find significant associations of red meat intake with risk of major CVD in the PURE (Prospective Urban Rural Epidemiology) study. In agreement with our findings, that study did not find associations between poultry intake and CVD risk [20].

In a recent review, Leroy and Cofnas [37] argued that dietary advice that identified meat as an intrinsic cause of chronic diseases seemed to be based on cherry-picking evidence and conflicting data being overlooked. In a recent meta-analysis, Zhang et al. [38] showed that the heterogeneity for the relationship between unprocessed red meat was high and the relative risks were consistently higher in US populations and consistently lower in Asian and European populations. In addition, cooking methods or preparation

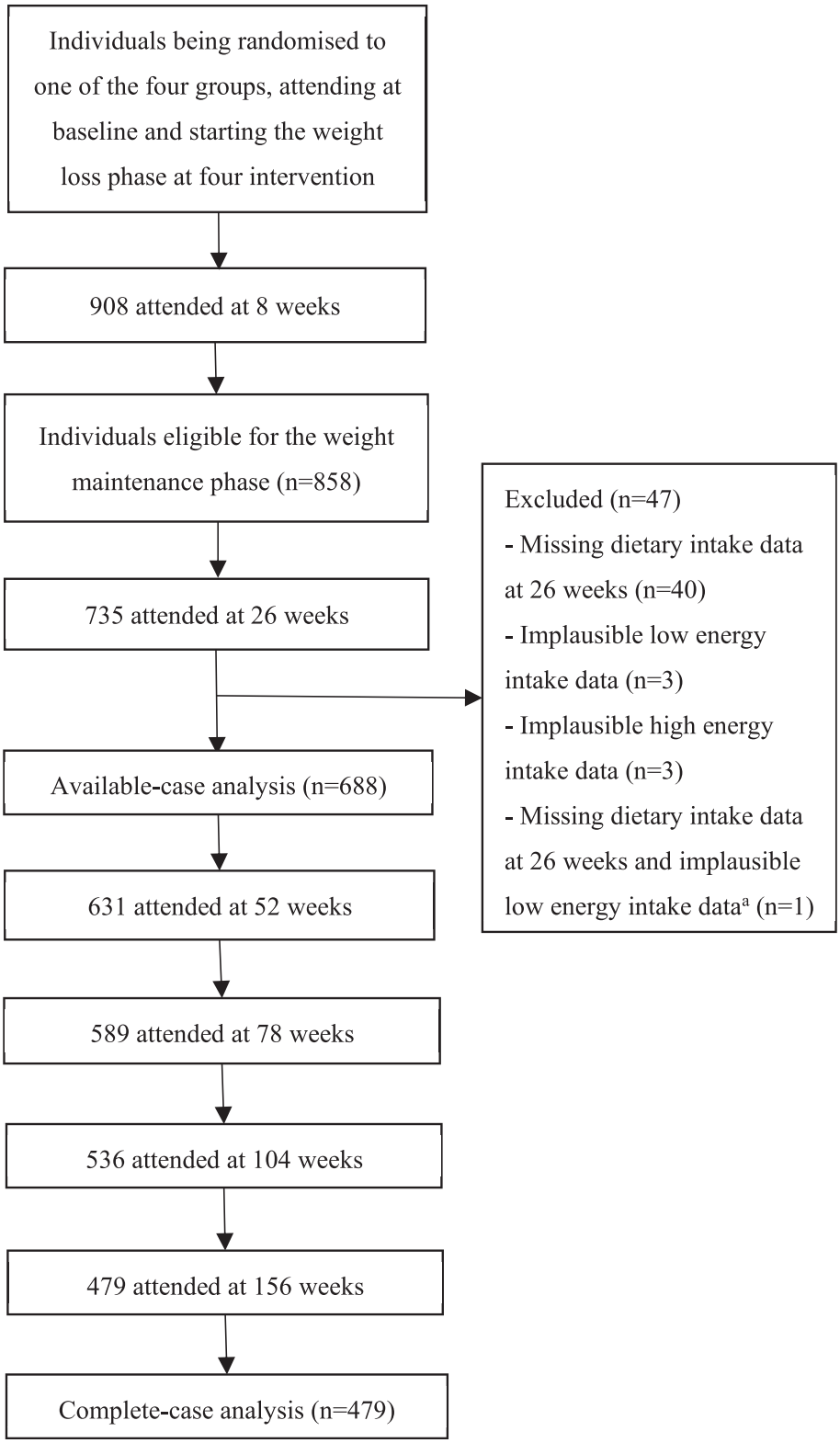

Fig. 1. Participant flow diagram. [a] Energy intake<2520 kJ·day^{-1}/600 kcal·day^{-1} or >14,700 kJ·day^{-1}/3500 kcal·day^{-1} for women and <3360 kJ·day^{-1}/800 kcal·day^{-1} or >17,640 kJ·day^{-1}/4200 kcal·day^{-1} for men was considered implausible.

of meats (e.g. broiling, barbecuing/grilling, roasting, frying, boiling, and steaming) of meats may be another potential explanation. Liu et al. [39] found that a higher frequency of open-flame and/or high-temperature cooking for both red meat and chicken was associated with greater weight gain and an increased risk of obesity and type 2 diabetes in three large US prospective cohorts, which may be attributed to hazardous substances including acrylamide, heterocyclic aromatic amines, and advanced glycation end products

Table 1
Characteristics of participants at the start of weight maintenance (8 weeks) or 26 weeks.

	All participants[c]	Completers	Non-completers	*P*-value
N	688	479	209	–
Socio-demographics				
Female, n (%)	471 (68.5)	316 (66.0)	155 (74.2)	0.033
Age (years)	57 (46, 63)	58 (49, 64)	53 (42, 61)	<0.001
Ethnicity, n (%)				0.003
Caucasian	595 (86.5)	427 (89.1)	168 (80.4)	–
Asian	24 (3.5)	16 (3.3)	8 (3.8)	–
Black	19 (2.8)	13 (2.7)	6 (2.9)	–
Arabic	4 (0.6)	3 (0.6)	1 (0.5)	–
Other	46 (6.7)	20 (4.2)	26 (12.4)	–
Smoking, n (%)				0.025
No	641 (93.2)	454 (94.8)	187 (89.5)	
Yes, but less than weekly	17 (2.5)	9 (1.9)	8 (3.8)	
Yes, at least daily	26 (3.8)	13 (2.7)	13 (6.2)	
Missing	4 (0.6)	3 (0.6)	1 (0.5)	
Anthropometrics and body composition[a]				
Body weight (kg)	86.0 ± 16.4	83.8 ± 15.4	90.8 ± 17.6	<0.001
Height (m)	1.7 (1.6, 1.7)	1.7 (1.6, 1.7)	1.7 (1.6, 1.7)	0.138
BMI ($kg \cdot m^{-2}$)	29.5 (26.6, 33.4)	28.7 (26.0, 32.5)	31.4 (28.7, 36.3)	<0.001
Fat mass (kg)	33.4 ± 12.2	31.3 ± 11.3	38.2 ± 12.8	<0.001
Waist circumference (cm)	100.1 ± 12.6	99.1 ± 12.0	102.5 ± 13.6	<0.001
Glycaemic and cardiometabolic risk factors[a]				
Fasting plasma glucose ($mmol \cdot L^{-1}$)	5.7 ± 0.5	5.7 ± 0.5	5.8 ± 0.6	0.042
HbA_{1c} ($mmol \cdot mol^{-1}$)	35.0 ± 3.1	34.9 ± 3.1	35.2 ± 3.1	0.324
HbA_{1c} (%)	5.4 ± 0.3	5.3 ± 0.3	5.4 ± 0.3	0.322
Fasting insulin ($mU \cdot L^{-1}$)	7.3 (5.3, 9.9)	6.9 (5.1, 9.4)	8.3 (5.8, 10.7)	<0.001
HOMA-IR	1.8 (1.3, 2.5)	1.7 (1.3, 2.4)	2.1 (1.4, 2.8)	<0.001
Triacylglycerols ($mmol \cdot L^{-1}$)	1.0 (0.8, 1.2)	0.9 (0.8, 1.2)	1.0 (0.8, 1.3)	<0.001
TyG index	8.4 ± 0.4	8.3 ± 0.3	8.5 ± 0.4	<0.001
Total cholesterol ($mmol \cdot L^{-1}$)	4.1 ± 0.9	4.0 ± 0.9	4.2 ± 0.9	<0.001
HDL-cholesterol ($mmol \cdot L^{-1}$)	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	0.301
LDL-cholesterol ($mmol \cdot L^{-1}$)	2.4 (1.9, 2.9)	2.4 (1.8, 2.9)	2.6 (2.1, 3.1)	<0.001
Energy and food intake[b]				
Energy ($kJ \cdot day^{-1}$)	7035.7 ± 1840.3	7107.3 ± 1794.5	6871.7 ± 1935.5	0.061
Energy ($kcal \cdot day^{-1}$)	1679.2 ± 439.2	1696.3 ± 428.3	1640.0 ± 461.9	0.061
Red meat ($g \cdot day^{-1}$)	34.2 (0, 66.3)	34.0 (0, 63.0)	36.3 (0, 73.5)	0.957
Processed meat ($g \cdot day^{-1}$)	12.0 (0, 29.7)	11.7 (0, 29.2)	12.5 (0, 30.3)	0.524
Dairy products ($g \cdot day^{-1}$)	317.3 (205.2, 449.8)	343.3 (218.3, 465.5)	260.5 (169.6, 389.2)	<0.001
Poultry ($g \cdot day^{-1}$)	37.2 (9.6, 70.4)	37.4 (4.9, 70.0)	37.2 (14.4, 71.2)	0.592
Fish and seafood ($g \cdot day^{-1}$)	30.9 (5.4, 63.7)	31.3 (7.5, 65.2)	30.5 (0, 60.3)	0.275
Eggs ($g \cdot day^{-1}$)	21.3 (5.2, 41.8)	21.3 (5.2, 42.4)	21.4 (5.2, 39.3)	0.848
Grains ($g \cdot day^{-1}$)	208.8 (146.9, 277.2)	204.8 (147.4, 277.0)	217.3 (145.7, 281.0)	0.607
Legumes ($g \cdot day^{-1}$)	0.3 (0, 27.2)	0.1 (0, 25.0)	2.8 (0, 30.4)	0.416
Nuts ($g \cdot day^{-1}$)	3.3 (0, 10.8)	3.7 (0, 12.3)	2.5 (0, 8.4)	0.019
Vegetables ($g \cdot day^{-1}$)	179.1 (93.8, 307.8)	187.5 (109.8, 308.1)	175.3 (82.2, 305.3)	0.091
Fruits ($g \cdot day^{-1}$)	169.5 (83.7, 260.1)	173.5 (98.6, 275.3)	153.2 (64.5, 236.7)	0.003

Values represent mean ± standard deviation, median (25th, 75th percentiles), and the number of participants (%). Differences between completers and non-completers in baseline characteristics were examined by an independent-samples *t* test, a Mann–Whitney *U* non-parametric test, or a χ^2 test. BMI, body mass index; HbA_{1c}, haemoglobin A_{1c}; HDL-cholesterol, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL-cholesterol, low-density lipoprotein cholesterol; TyG, triacylglycerol-glucose index.

[a] Data were collected at 8 weeks.

[b] Data were collected at 26 weeks.

[c] Participants who entered the weight-maintenance phase.

(AGEs) produced during high temperature cooking. Advanced glycation end products were associated with weight gain, type 2 diabetes, and CVD [40,41]. In a recent randomised controlled-feeding trial, Gao et al. [42] suggested that fried meat intake impaired glucose homoeostasis by influencing the gut microbiota and microbial-host cometabolites.

Most observational studies have taken the amount of red meat or poultry intake into consideration only, but not the cooking methods. In the PREVIEW dietary dataset, we also did not include red meat subgroups with different cooking methods. In addition, most prospective cohort studies [8–11,43] used hard disease endpoints (i.e. risk of disease) over 5 years or longer, whereas the present study and RCTs [33,34] used intermediate disease markers (e.g. fasting insulin, HOMA-IR, triacylglycerols, and HDL-cholesterol) over a shorter period. Further, red meat consumption was found to be related to other unhealthy dietary habits, low physical activity and smoking [44]. These confounders may be impossible to measure accurately and to fully adjusted for in observational studies.

In the present study, we found that higher processed meat intake was associated with greater weight regain. Many previous studies also reported associations of processed meat intake with increased risk of weight gain and obesity [8,45]. During meat processing, food additives such as nitrites are added and acrylamide, heterocyclic aromatic amines, and AGEs might be created as a result of the Maillard reaction. For instance, bacon and sausages are commonly high in AGEs especially under frying [46] and AGE was found to be associated with weight change, which may be attributed to insulin resistance induced by higher AGE intake [40]. Furthermore, in the present study, we found that weight regain

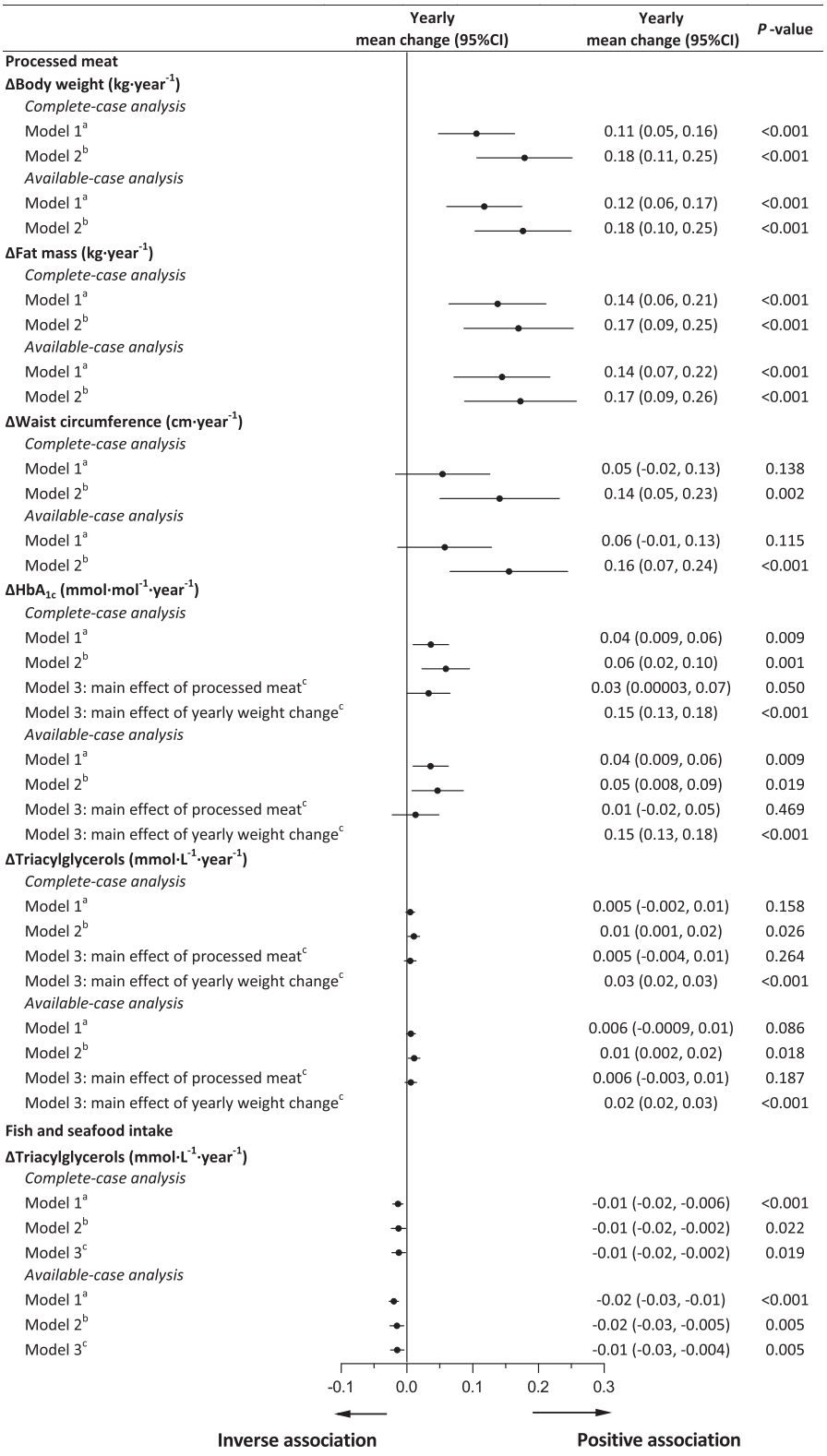

Fig. 2. Longitudinal associations of processed meat intake with yearly changes in weight outcomes and glycaemic and cardiometabolic risk factors during 3-year weight maintenance. Data are yearly mean change in outcomes and 95% CI, indicating changes in weight outcomes or glycaemic and cardiometabolic risk factors associated with 10-g increment in processed meat or 20-g increment in fish and seafood, unless otherwise stated. Analyses were performed using a linear mixed model. HbA_{1c}, haemoglobin A_{1c}. [a] Model 1 was adjusted for age, sex, ethnicity, BMI at 8 weeks, values of outcomes at 8 weeks, and time as fixed effects and intervention centre and participant identifier as random effects. [b] Model 2 included all animal-based foods simultaneously and was additionally adjusted for lifestyle factors as fixed effects, including smoking habits, physical activity, energy intake ($kJ \cdot day^{-1}$), alcohol intake ($g \cdot day^{-1}$), sugar intake, grain intake, legumes intake, nut intake, vegetable intake, and fruit intake (all in $g \cdot day^{-1}$). [c] Model 3 was additionally adjusted for yearly weight changes as a fixed effect.

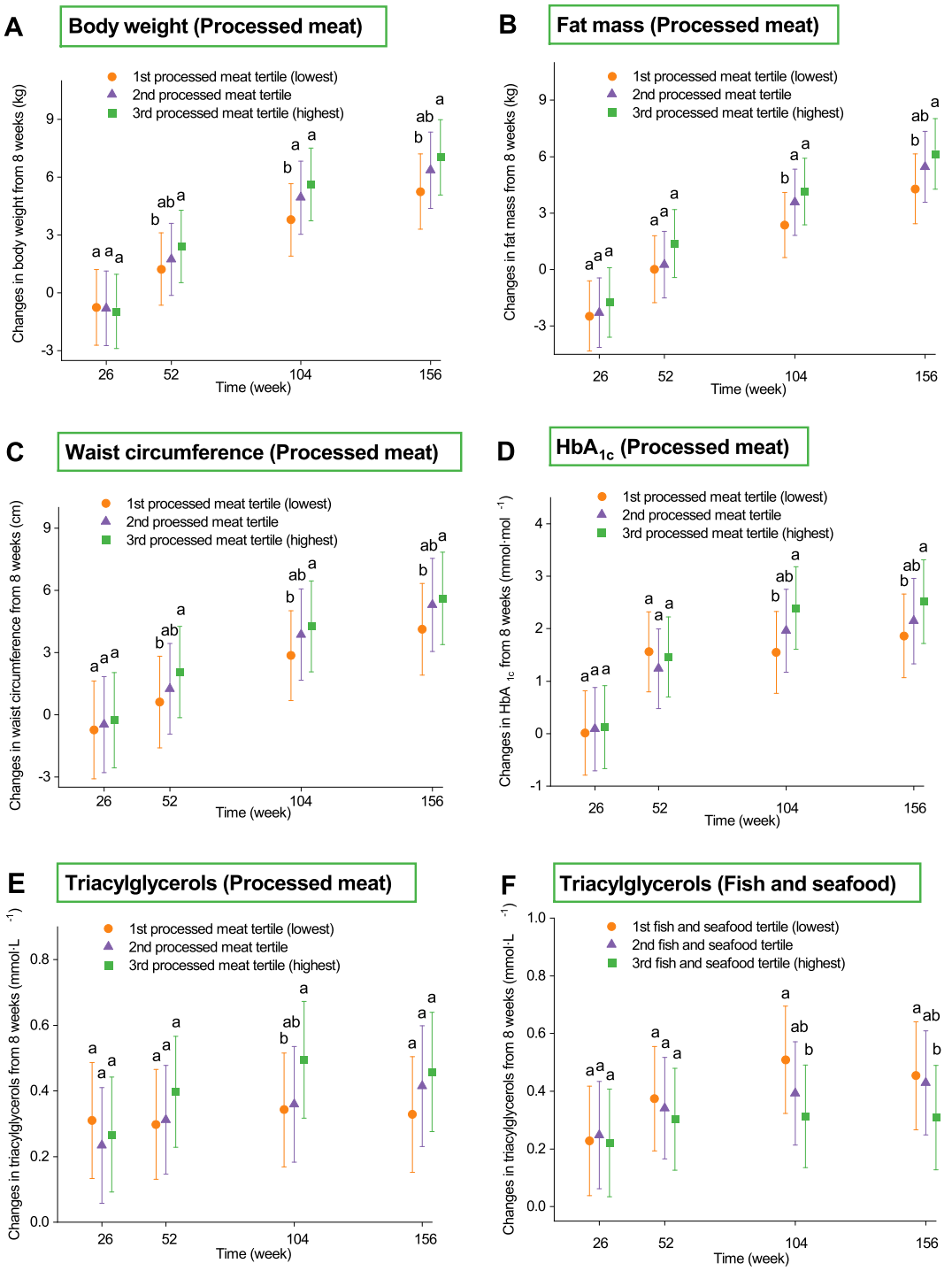

Fig. 3. Changes in weight outcomes and glycaemic and cardiometabolic risk factors during 3-year weight maintenance by tertiles of processed meat or fish and seafood intake. The tertiles were defined afresh according to the processed meat or fish and seafood intake at each time points. Values in the figure are estimated marginal mean and 95% CI in changes in body weight (A), fat mass (B), waist circumference (C), triacylglycerols (D), HbA_{1c} (E), and triacylglycerols (F). Analyses were performed using linear mixed models adjusted for age, sex, ethnicity, values of outcomes at 8 weeks, BMI at 8 weeks, time, physical activity, alcohol intake ($g \cdot day^{-1}$), energy intake ($kJ \cdot day^{-1}$), animal-based food intake, sugar intake, grain intake, legumes intake, nut intake, vegetable intake, and fruit intake (all in $g \cdot day^{-1}$) as fixed effects and participant identifier and intervention centre as random effects. As the tertiles were defined afresh at each time point, multiple comparisons with Bonferroni adjustment were performed to compare the tertiles at each time point, regardless of the significance of time and group interaction. Values with the different lowercase letters (a and b) are significantly different, $P < 0.05$. HbA_{1c}, haemoglobin A_{1c}.

which resulted from processes meat intake might, in turn, lead to deteriorating glycaemic and cardiometabolic risk factors. The association of obesity with type 2 diabetes and CVD has been reported by many studies [47]. Taken together, findings from our and other studies imply that compared with meat itself, meat processing, preparation, and cooking methods may play a more important role in health.

Notably, according to the dietary data at the beginning of the weight maintenance phase, processed meat was not the main source of protein for most PREVIEW participants (median intake:

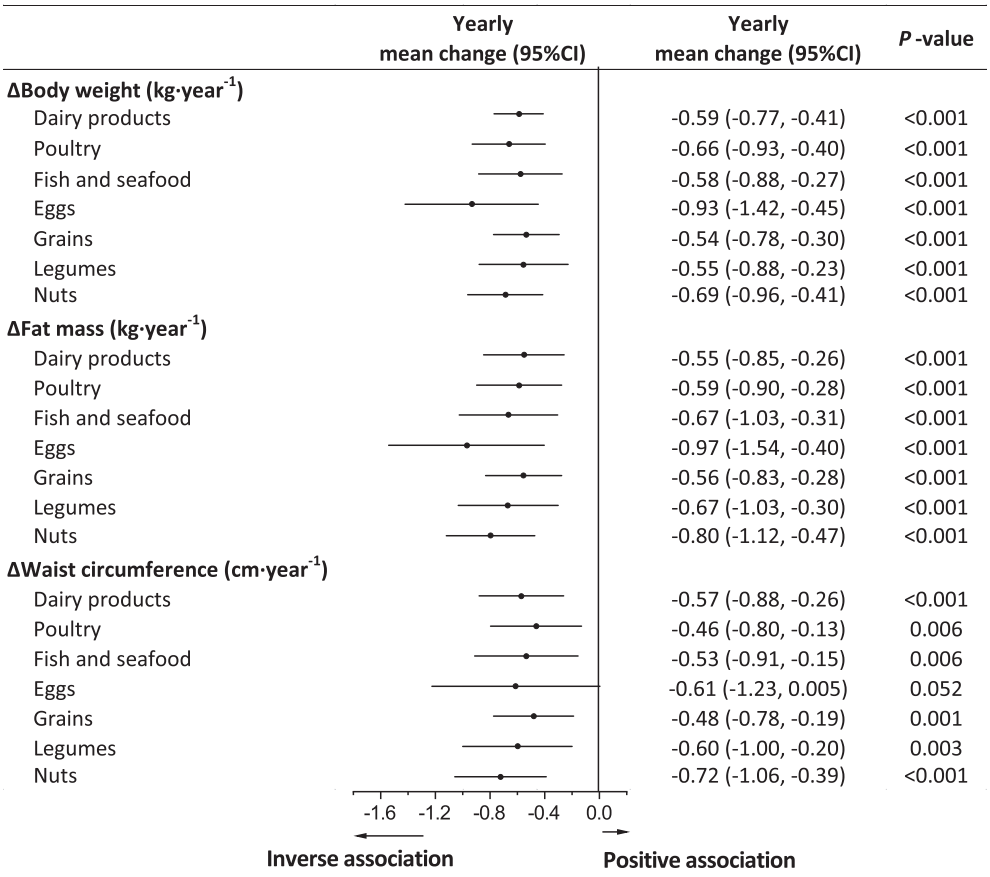

Fig. 4. Estimated yearly mean changes (95% CI) in weight outcomes after isoenergetic substitution of processed meat with other animal- and plant-origin high-protein foods during 3-year weight maintenance. Data are yearly mean change in outcomes and 95% CI, indicating changes in weight outcomes per year associated with replacing 250–300 kJ·day^{-1} or 60–72 kcal·day^{-1} of processed meat with other food sources of protein. Analyses were performed using a linear mixed model adjusted for age, sex, ethnicity, values of outcomes at 8 weeks, BMI at 8 weeks, time, physical activity, alcohol intake (g·day^{-1}), energy intake (kJ·day^{-1}), animal-based food intake, grain intake, legumes intake, nut intake (all in 0.5 serving·day^{-1}; 0.5 serving·day^{-1} equals 250–300 kJ·day^{-1} or 60–72 kcal·day^{-1}), vegetable intake, fruit intake, and sugar intake as fixed effects and participant identifier and intervention centre as random effects.

12 g·day^{-1}), whereas 25% participants had an intake>30 g·day^{-1} and in the highest tertile, 50% participants had an intake>40 g·day^{-1}. Assuming a 40-g·day^{-1} increment in processed meat intake in higher vs lower intake group, that would represent a weight gain of 2.04 kg (2.4% of initial body weight), an increment in waist circumference of 1.92 cm (1.9% of initial waist circumference), an increment in HbA_{1c} of 0.60 mmol mol^{-1} (1.7% of initial HbA_{1c}), and an increment in triacylglycerols of 0.12 mmol·L^{-1} (12% of initial triacylglycerols) at the end of the study (at 3 years). There may be clinical significance in changes in weight and triacylglycerols. For changes in waist circumference and HbA_{1c}, the effect sizes are small and whether it is the usual fluctuation of these two outcomes is needed to be examined by other longer-term studies.

Compared with red meat, other foods, especially plant-based foods, contain less saturated fat and more fibre, unsaturated fat, antioxidants, and polyphenols [48]. Some pervious RCTs examined the effect of replacement of red meat with plant-based foods (e.g. legumes and mushrooms) on weight change [49,50]. In the current study, fish and seafood intake was inversely associated with triacylglycerols and TyG index, independent of weight change. In a meta-analysis of RCTs, however, Guasch-Ferré et al. [48] argued that substituting red meat with plant-based foods, but not with fish, led to more favorable changes in blood lipids and lipoproteins. In that analysis, the authors did not investigate red meat and processed meat separately. In the current study, we found that poultry and eggs might also be a choice for weight maintenance. Although we did not observe any associations of these animal-based foods with metabolic outcomes, replacing processed meat with them was associated with improved weight outcomes, HbA_{1c}, or triacylglycerols. A recent meta-analysis of prospective cohort studies also suggested that replacing processed meat with poultry was inversely associated with the risk of CVD [18]. In terms of HbA_{1c}, we found that after adjustment for weight change, no associations of replacement of processed meat with other foods showed significance. However, Würtz et al. [14] reported that the association of replacement of red meat with both plant- and animal-based foods with risk of type 2 diabetes was independent of weight change in 3 US prospective cohorts.

The present study has some strengths. First, this is the first multi-centre, long-term study to investigated animal-based food choice and food substitutions for weight maintenance and metabolic health in individuals who experienced large weight loss. Second, the population in our study had a wide range of age, including young, middle-aged, and older adults. Furthermore, as outcomes were measured repeatedly at different time points, a large number of observations were obtained, which provided a sufficient statistical power to adjust for important confounders including plant-based foods and physical activity.

Nonetheless, this study also has limitations. First, the attrition rate was higher than expected. In order to reduce the attrition bias, we conducted both available-case and complete-case analyses. Second, fat mass was measured using different measurement tools

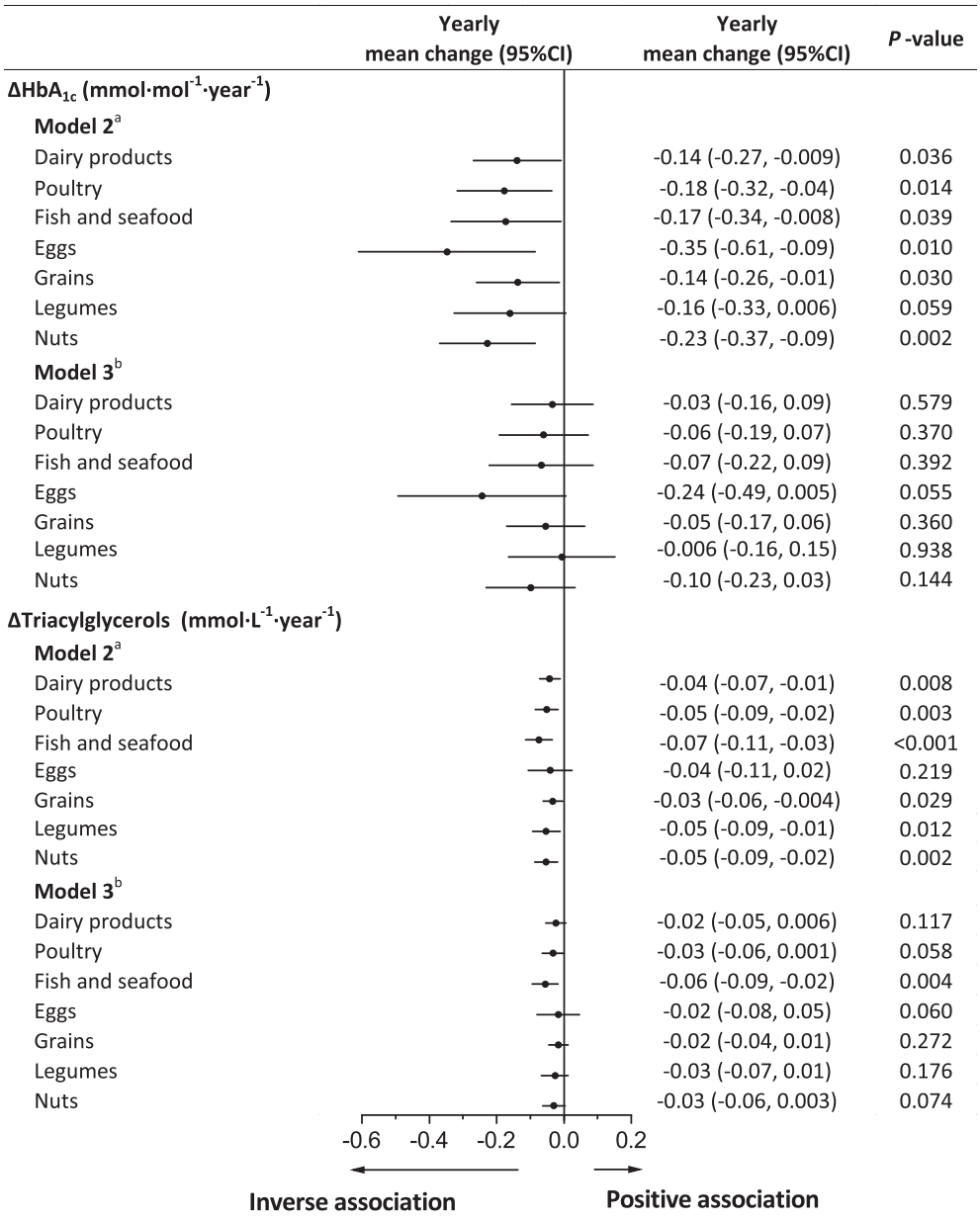

Fig. 5. Estimated yearly mean changes (95% CI) in weight outcomes and glycaemic and cardiometabolic risk factors after isoenergetic substitution of processed meat with other animal- and plant-origin high-protein foods during 3-year weight maintenance. Data are yearly mean change in outcomes and 95% CI, indicating changes in glycaemic and cardiometabolic risk factors per year associated with replacing 250–300 kJ·day^{-1} of processed meat with other food sources of protein. Analyses were performed using a linear mixed model. HbA_{1c}, haemoglobin A_{1c}. [a] Model 2 was adjusted for age, sex, ethnicity, values of outcomes at 8 weeks, BMI at 8 weeks, time, physical activity, alcohol intake (g·day^{-1}), energy intake (kJ·day^{-1}), animal-based food intake, grain intake, legumes intake, nut intake (all in 0.5 serving·day^{-1}; 0.5 serving·day^{-1} equals 250–300 kJ·day^{-1} or 60–72 kcal·day^{-1}), vegetable intake, fruit intake, and sugar intake as fixed effects and participant identifier and intervention centre as random effects. [b] Model 3 was additionally adjusted for yearly weight change as a fixed effect.

(i.e. DEXA in the UK, Australia, and New Zealand and bioelectrical impedance in Finland) and some previous studies demonstrated that compared with DEXA, the bioelectrical impedance analysis may underestimate fat mass in obese individuals [51,52]. Third, in the tertile analysis, participants were divided according to intake of animal-based foods at each time point instead of being randomly allocated. Accordingly, participants' baseline characteristics among the tertiles may be unbalanced and the statistical phenomenon "regression to the mean", which makes natural variation in outcomes look like real change [53], may differently affect the tertiles and cannot be counteracted or adjusted for. Moreover, our findings cannot provide a deep insight into consumption of dairy products and red meat, because we did not include specific dairy product subgroups (e.g. whole-fat and reduced-fat dairy products) and red meat with different cooking methods or preparation. Finally, as the present secondary analysis is observational and exploratory, residuals and unmeasured confounders are possible. Smoking status, an important confounder, was collected at baseline only in this study. Adjustment for baseline values instead of a time-varying variable may cause bias, because smokers may quit smoking during a 3-year healthy lifestyle modification. With regard to the tertiary analysis, the food replacement was inferred according to a statistical model and no actual replacement ever occurred in the study. Taken together,

given the secondary and tertiary nature of the present study, our findings should be interpreted with caution.

5. Conclusion

Higher consumption of processed meat, but not total meat or red meat or poultry, may be associated with long-term weight regain and deteriorating glycaemic and cardiometabolic risk factors after low-energy diet-induced large and rapid weight loss. Replacing processed meat with both animal- and plant-based foods could improve weight maintenance and glycaemic and cardiometabolic risk factors. Our findings should be confirmed by solid conclusions based on RCTs. In addition, as cooking methods may be a key confounder, future studies should pay more attention to cooking methods of red meat and other animal-based foods.

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Authors' contributions

AR and RZ conceived the idea and initiated the analysis plan for the current secondary analysis. RZ conducted data analysis and take responsibility for the accuracy of the data analysis. RZ drafted the manuscript with supervision form AR. All authors contributed to critical revision of the manuscript for important intellectual content. All authors agreed that the accuracy and integrity of the work has been appropriately investigated and resolved, and all approved the final version of the manuscript. AR attests that all listed authors meet authorship criteria, and that no others meeting the criteria have been omitted. AR and RZ are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data.

Data availability statement

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest

AR has received honorariums from the International Sweeteners Association and Unilever. JB-M is President and Director of the Glycemic Index Foundation, oversees of a glycemic index testing service at the University of Sydney and is a co-author of books about diet and diabetes. She is also a member of the Scientific Advisory Board of the Novo Foundation and of ZOE Global. IAM was a member of the UK Government Scientific Advisory Committee on Nutrition, Treasurer of the Federation of European Nutrition Societies, Treasurer of the World Obesity Federation, member of the Mars Scientific Advisory Council, member of the Mars Europe Nutrition Advisory Board, and Scientific Adviser to the Waltham Centre for Pet Nutrition. He was also a member of the Nestle Research Scientific Advisory Board, and of the Novozymes Scientific Advisory Board. He withdrew from all of these roles in 2020 and on August 1 2020 became Professor Emeritus at the University of Nottingham and took up the post of Scientific Director of the Nestle Institute of Health Sciences in Lausanne, Switzerland. SDP was the Fonterra Chair in Human Nutrition during the PREVIEW intervention. The rest of the authors declare that they have no potential conflicts of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2022.02.002.

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