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Types of diet, obesity, and incident type 2 diabetes: Findings from the UK Biobank prospective cohort study

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Abstract

Aim: To investigate the associations between types of diet and incident type 2 diabetes and whether adiposity mediated these associations.

Materials and Methods: In total, 203 790 participants from UK Biobank (mean age 55.2 years; 55.8% women) without diabetes at baseline were included in this prospective study. Using the dietary intake data self-reported at baseline, participants were categorized as vegetarians (n = 3237), fish eaters (n = 4405), fish and poultry eaters (n = 2217), meat eaters (n = 178 004) and varied diet (n = 15 927). The association between type of diet and incident type 2 diabetes was investigated using Cox-proportional hazards models with a 2-year landmark analysis. The mediation role of adiposity was tested under a counterfactual framework.

Results: After excluding the first 2 years of follow-up, the median follow-up was 5.4 (IQR: 4.8-6.3) years, during which 5067 (2.5%) participants were diagnosed with type 2 diabetes. After adjusting for lifestyle factors, fish eaters (HR 0.52 [95% CI: 0.39-0.69]) and fish and poultry eaters (HR 0.62 [95% CI: 0.45-0.88]) had a lower risk of incident type 2 diabetes compared with meat eaters. The association for vegetarians was not significant. Varied diet had a higher risk of type 2 diabetes. Obesity partially mediated the association of fish (30.6%), fish and poultry (49.8%) and varied (55.2%) diets.

Conclusions: Fish eaters, as well as fish and poultry eaters, were at a lower risk of incident type 2 diabetes than meat eaters, partially attributable to lower obesity risk.

KEYWORDS
fish, lacto-ovo diet, meat, poultry, type 2 diabetes, vegetarian

1 | INTRODUCTION

Around 9.3% of the world's adult population is estimated to have diabetes,[1] and this figure is predicted to rise to 10.9% by 2045.[2] Type 2 diabetes accounts for the majority of diabetes,[3] for example, in the

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UK, the number of people with diabetes will reach over 5 million by 2025, of whom 90% will have type 2 diabetes.[4] Lifestyle modifications play a key role in type 2 diabetes prevention and management. An unhealthy diet, including high consumption of red meat and processed meat, sugar-sweetened beverages and refined grains, has been suggested as a driving factor for the growing incidence of type 2 diabetes.[5] Conversely, diets rich in whole grains, dairy, vegetables, fruits, legumes, fish and poultry are suggested to be protective against the development of type 2 diabetes.[6,7]

However, the association between meat-based diets and type 2 diabetes is equivocal.[6-10] For instance, a recent meta-analysis of 28 prospective cohort studies indicated that red meat, processed meat, total meat, poultry and fish consumption was associated with a higher risk of type 2 diabetes.[9] Conversely, there are prospective cohort studies reported that poultry intake was not associated with type 2 diabetes risk,[8,10] particularly when adjusted for intake of other meats.[10] The association between fish intake and type 2 diabetes risk was also inconsistent,[11,12] possibly depending on geographical differences.[13,14] Furthermore, it has not been shown whether, and to what extent, diets containing no red meat (e.g. fish only and poultry and fish) are associated with type 2 diabetes risk.

Several studies have investigated the association between a vegetarian diet and risk of incident type 2 diabetes. Generally, vegetarians had lower type 2 diabetes risk, but the associations were attenuated following adjustment for body mass index (BMI).[15,16] Therefore it has been hypothesized that these alternative diets, which are often less caloric, could help with weight management and therefore reduce type 2 diabetes risk indirectly[17]; however, this hypothesis has not been empirically studied. To explore this further, we used data from UK Biobank to investigate the associations between vegetarian, fish, poultry, meat and varied diets and incident type 2 diabetes, as well as any mediation via adiposity, in a large prospective cohort study.

2 | MATERIALS AND METHODS

2.1 | Study population

The UK Biobank recruited approximately 502 000 men and women aged 37-73 years from the general population during 2006-2010 (5.5% response rate).[18] Participants attended one of 22 assessment centres across England, Wales, and Scotland.[19,20] At the assessment centres, participants completed an electronically signed consent form, a touchscreen questionnaire and physical measurements, as previously described.[19,20] Individuals with missing data for any dietary variables were excluded (n = 14 121; 2.8%). Vegans (no consumption of milk, cheese, fish, poultry or red meat) were excluded as the sample size was not sufficient for a separate category (n = 57; 0.01%)[21] (Figure S1). Among 488 309 participants with available dietary data, 264 611 (54.2%) were further excluded because there were no linked primary care data to ascertain type 2 diabetes. The lack of linkage is a result of the electronic record system used in their general practice and should be unrelated to the exposure or outcome. Of the remaining 223 698 participants, 12 206 (5.5%) were excluded, because they had prevalent type 1 or type 2 diabetes (either self-reported or in previous primary care record) and 1549 (0.7%) because they had undiagnosed diabetes (HbA1c ≥ 48 mmol/mol) at baseline, as well as 5037 (2.3%) relevant covariates and 1116 (0.5%) of any incident type 2 diabetes occurring in the first 2 years of the follow-up period (Figure S1). Therefore, the study population comprised 203 790 UK Biobank participants.

2.2 | Outcome

Incident type 2 diabetes was ascertained from prospective linkage to primary care records data. Primary care, instead of hospitalization, data were used in this study, because in the UK most type 2 diabetes is diagnosed and managed in the primary care setting. Primary care records were available up to May 2017 for Scotland, September 2017 for Wales, and August 2017 for England. Detailed linkage procedures are available at http://biobank.ndph.ox.ac.uk/showcase/showcase/docs/primary_care_data.pdf. The READ codes used in primary care were converted into International Classification of Diseases (ICD-10) codes using UK Biobank's look-up table, and we defined incident type 2 diabetes as ICD-10 code E11.

2.3 | Exposure

At recruitment, participants were asked to complete a food frequency questionnaire using the touchscreen, to collect the frequency of consumption of cheese, milk, fish (oily and non-oily), poultry and red meat (beef, pork, lamb and processed red meat) over the previous year. In this study, all food items were dichotomized into consumed or not consumed as this study focuses on alternative diets such as vegetarian and pescatarian diets.

Participants were categorized into five types of diets: vegetarian, fish eaters, fish and poultry eaters, meat eaters and varied diet. Vegetarian participants were defined as those who reported consumption of cheese, milk, but not fish, poultry or red meat (i.e. lacto-ovo vegetarians). Fish eaters were those who reported consumption of cheese, milk and fish but not poultry or red meat. Fish and poultry eaters were those who reported consumption of cheese, milk, fish and poultry, but not red meat. Meat eaters were those that reported consumption of cheese, milk, fish, poultry and red meat. There were 15 927 (7.8%) participants who reported that their diets varied often and were categorized in a separate group.

Additionally, we included dietary information that was derived by using the Oxford WebQ (www.ceu.ox.ac.uk/research/oxford-webq), a web-based 24-hour recall questionnaire,[22] to supplement the dietary information of participants. The Oxford WebQ is only available in a small proportion of participants and therefore was not used to derive the primary diet variables in this study.

2.4 | Covariates

Sex was self-reported at baseline, and age was calculated from dates of birth and baseline assessment. Deprivation Index, an area-based

TABLE 2 Dietary intake by types of diet

Dietary intake	Data available[a]	Vegetarians	Fish eaters	Fish and poultry eaters	Meat eaters	Varied diet
Food frequency						
Red meat, portions per week	203 790	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	2.2 (1.4)	2.2 (1.5)
Poultry, times per week	203 751	0.0 (0.0)	0.0 (0.0)	2.1 (0.9)	2.4 (0.8)	2.3 (0.9)
Non-oily fish, times per week	203 089	0.0 (0.0)	2.0 (0.9)	2.0 (0.9)	1.8 (0.7)	1.8 (0.8)
Oily fish, times per week	202 873	0.0 (0.0)	2.0 (1.0)	2.0 (1.1)	1.6 (0.9)	1.7 (0.9)
Fruit and vegetables, portions per day	203 790	5.0 (2.8)	5.1 (2.7)	5.3 (3.1)	4.0 (2.3)	4.2 (2.6)
Cheese, times per week	201 363	3.1 (1.2)	3.0 (1.1)	2.4 (1.3)	2.5 (1.1)	2.5 (1.0)
Alcohol intake, times per week	203 790	3.5 (1.7)	3.0 (1.6)	3.5 (1.6)	2.9 (1.5)	2.9 (1.5)
Type of milk (n, %)	203 712					
Full cream	13 878	241 (7.5)	211 (4.8)	76 (3.4)	12 051 (6.8)	1299 (8.2)
Semi-skimmed	134 466	1719 (53.1)	2447 (55.6)	1174 (53.0)	118 936 (66.8)	10 190 (64.0)
Skimmed	40 885	637 (19.7)	957 (21.7)	598 (27.0)	35 689 (20.1)	3004 (18.9)
Soya	6673	450 (13.9)	482 (10.9)	214 (9.7)	4922 (2.8)	605 (3.8)
Other types of milk	2101	47 (1.5)	79 (1.8)	41 (1.9)	1699 (1.0)	235 (1.5)
Never/rarely	5709	142 (4.4)	229 (5.2)	114 (5.1)	4644 (2.6)	580 (3.6)
24-h dietary recall[b]						
TE, kcal/day	86 723	2080.8 (719.7)	2090.3 (649.3)	1970.1 (690.0)	2120.8 (636.6)	2128.4 (705.5)
Total CHO, % of TE	86 721	52.0 (7.9)	50.3 (8.0)	50.0 (8.8)	47.1 (8.0)	46.4 (8.6)
Sugar, % of TE	86 721	24.3 (7.5)	24.0 (7.0)	24.9 (7.9)	22.6 (6.9)	22.2 (7.4)
Starch, % of TE	86 721	25.2 (6.6)	23.8 (6.4)	22.7 (6.9)	22.7 (6.1)	22.2 (6.4)
Fibre, g/day	86 723	20.7 (8.1)	19.4 (7.1)	18.5 (7.7)	16.2 (6.4)	16.1 (7.1)
Total fat, % of TE	86 721	31.9 (7.0)	31.6 (6.8)	30.7 (7.4)	32.0 (6.6)	32.3 (6.9)
Saturated fat, % of TE	86 721	12.1 (3.6)	11.8 (3.4)	11.3 (3.6)	12.4 (3.3)	12.5 (3.5)
Polyunsaturated fat, % of TE	86 721	6.2 (2.4)	6.2 (2.3)	6.1 (2.3)	5.8 (2.2)	5.8 (2.2)
Total protein, % of TE	86 721	12.5 (2.3)	13.5 (2.8)	15.2 (3.5)	15.7 (3.6)	15.6 (3.8)
Alcohol, % of TE	86 721	3.6 (5.4)	4.6 (5.8)	4.1 (6.3)	5.2 (6.5)	5.7 (7.0)

Note: Data are presented as mean and standard variation (SD). For type of milk, data are presented as frequency and percentage (%).
Abbreviations: CHO, carbohydrate; TE, total energy intake.
[a]Data available for diet in the dataset. The analysis was conducted using 2-year landmark analyses and excluding participants with type 1 diabetes, type 2 diabetes or unknown diabetes at baseline.
[b]24-h recall data were collected according to the intake of the previous day using questions such as: 'Did you eat any fish yesterday?' The data were not included in this present study because of a small proportion of participants.

measure of socioeconomic status, was derived from the postcode of residence using the Townsend deprivation score.[23] Anthropometric measurements were obtained by trained personnel following standard operating procedures and using calibrated equipment. Weight was measured, without shoes and outdoor clothing, using the Tanita BC 418 body composition analyser. Height was measured, without shoes, using the wall-mounted SECA 240 height measure. Smoking status was self-reported as never, former, and current. Alcohol intake was self-reported as daily or almost daily, three to four times a week, once or twice a week, 1-3 times a month, special occasions only and never. Sedentary behaviour was self-reported and defined as discretionary screen-time, combining TV viewing and leisure PC screen time in hours per day.[24] It was classified by tertile into low, middle and high. Type of physical activity (PA) was self-reported in relation to five groups: walking for pleasure, other exercise (e.g. swimming, cycling), strenuous sports, light gardening duties (e.g. pruning, watering the lawn) and heavy gardening tasks and DIY (e.g. weeding, lawn mowing, carpentry and digging). Sleep duration was self-reported and categorized as short (<7 h/day), normal (7-9 h/day) and long (>9 h/day). BMI was calculated from weight (kg) divided by square of height (m). The World Health Organization's criteria were used to classify BMI into underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2) and obese (≥30 kg/m^2). Waist circumference (WC) was measured midway between lowest rib margin and iliac crest,

TABLE 1 Cohort characteristics of participants by type of diet (n = 203 790)

Characteristics	Vegetarians	Fish eaters	Fish and poultry eaters	Meat eaters	Varied diet
Participants, n (%)	3237 (1.6)	4405 (2.2)	2217 (1.1)	178 004 (87.3)	15 927 (7.8)
Sociodemographic					
Age (y), mean (SD)	52.8 (7.9)	54.1 (8.0)	56.4 (8.2)	56.5 (8.1)	56.0 (8.1)
Townsend deprivation index, n (%)					
Lower deprivation	867 (26.8)	1295 (29.4)	634 (28.6)	62 039 (34.9)	4907 (30.8)
Middle deprivation	1059 (32.7)	1551 (35.2)	781 (35.2)	61 297 (34.4)	5224 (32.8)
Higher deprivation	1311 (40.5)	1559 (35.4)	802 (36.2)	54 668 (30.7)	5796 (36.4)
Ethnicity, n (%)					
White	2685 (83.3)	4155 (94.8)	2052 (92.7)	171 599 (96.6)	14 945 (94.3)
South Asian	487 (15.1)	126 (2.9)	88 (4.0)	2142 (1.2)	373 (2.4)
Black	9 (0.3)	40 (0.9)	31 (1.4)	1544 (0.9)	226 (1.4)
Chinese	4 (0.1)	6 (0.1)	1 (0.1)	430 (0.2)	45 (0.3)
Mixed	37 (1.2)	54 (1.2)	42 (1.9)	1856 (1.1)	267 (1.7)
Education, n (%)					
College or university degree	1804 (61.1)	2608 (63.8)	949 (51.1)	66 623 (45.6)	5750 (44.6)
A/AS levels or equivalent	394 (13.3)	535 (13.1)	257 (13.8)	19 678 (13.5)	1655 (12.8)
O levels/GCSEs or equivalent	524 (17.7)	686 (16.8)	417 (22.5)	38 522 (26.4)	3345 (25.9)
SEs or equivalent/NVQ or HND or HNC	233 (7.9)	256 (6.3)	234 (12.6)	21 333 (14.6)	2158 (16.7)
Lifestyle					
Smoking status, n (%)					
Never	2085 (64.4)	2563 (58.2)	1325 (59.8)	99 378 (55.8)	8142 (51.1)
Previous	940 (29.0)	1548 (35.1)	732 (33.0)	60 705 (34.1)	5457 (34.3)
Current	212 (6.6)	294 (6.7)	160 (7.2)	17 921 (10.1)	2328 (14.6)
Sleep categories, n (%)					
Short sleep (<7 h per day)	895 (27.7)	1055 (24.0)	594 (26.8)	42 214 (23.7)	11 189 (70.3)
Normal (7-9 h per day)	2296 (70.9)	3292 (74.7)	1573 (71.0)	132 960 (74.7)	4411 (27.7)
Long sleep (>9 h per day)	46 (1.4)	58 (1.3)	50 (2.3)	2830 (1.6)	327 (2.1)
Types of PA, n (%)					
Walking for pleasure	2382 (78.4)	3506 (82.4)	1657 (79.2)	128 568 (76.8)	11 218 (76.1)
Other exercise: Swimming, cycling	383 (12.6)	502 (11.8)	280 (13.4)	21 487 (12.8)	1870 (12.7)
Strenuous sports	29 (1.0)	38 (0.9)	15 (0.7)	1406 (0.8)	86 (0.6)
Light gardening duties: Pruning, watering the lawn	203 (6.7)	163 (3.8)	108 (5.2)	11 526 (6.9)	1135 (7.7)
Heavy gardening tasks and DIY: Weeding, lawn mowing, carpentry	41 (1.4)	45 (1.1)	33 (1.6)	4404 (2.6)	438 (3.0)
Sedentary time, n (%)					
Low	1962 (60.6)	2673 (60.7)	1260 (56.8)	80 192 (45.1)	7038 (44.2)
Middle	817 (25.2)	1159 (26.3)	616 (27.8)	62 176 (34.9)	5230 (32.8)
High	458 (14.2)	573 (13.0)	341 (15.4)	35 636 (20.0)	3659 (23.0)
Adiposity					
WC, cm (mean, SD)	84.6 (12.5)	82.7 (11.8)	82.46 (12.2)	89.5 (12.8)	91.7 (13.3)
BMI, kg/m^2 (mean, SD)	25.6 (4.5)	25.1 (4.1)	25.39 (4.4)	27.2 (4.5)	28.3 (5.0)
BMI category, n (%)					
Underweight (<18.5 kg/m^2)	50 (1.5)	76 (1.7)	39 (1.8)	802 (0.5)	59 (0.4)
Normal (18.5-24.9 kg/m^2)	1579 (48.8)	2360 (53.6)	1130 (51.0)	58 542 (32.9)	4117 (25.9)
Overweight (25-29.9 kg/m^2)	1164 (36.0)	1482 (33.6)	741 (33.4)	78 244 (44.0)	6809 (42.8)
Obese (≥30.0 kg/m^2)	444 (13.7)	487 (11.1)	307 (13.9)	40 416 (22.7)	4942 (31.0)

Note: Data are presented as mean and standard variation (SD) for continuous variables, and as frequency and percentage (%) for categorical variables. Sedentary time was classified by tertile into low, middle and high.

Abbreviations: A/AS level, Advanced/Advanced Subsidiary level; BMI, body mass index; GCSE, General Certificate of Secondary Education; HNC, Higher National Certificate; HND, Higher National Diploma; NVQ, National Vocational Qualification; O level, Ordinary level; SE, Secondary Education; PA, physical activity; WC, waist circumference.

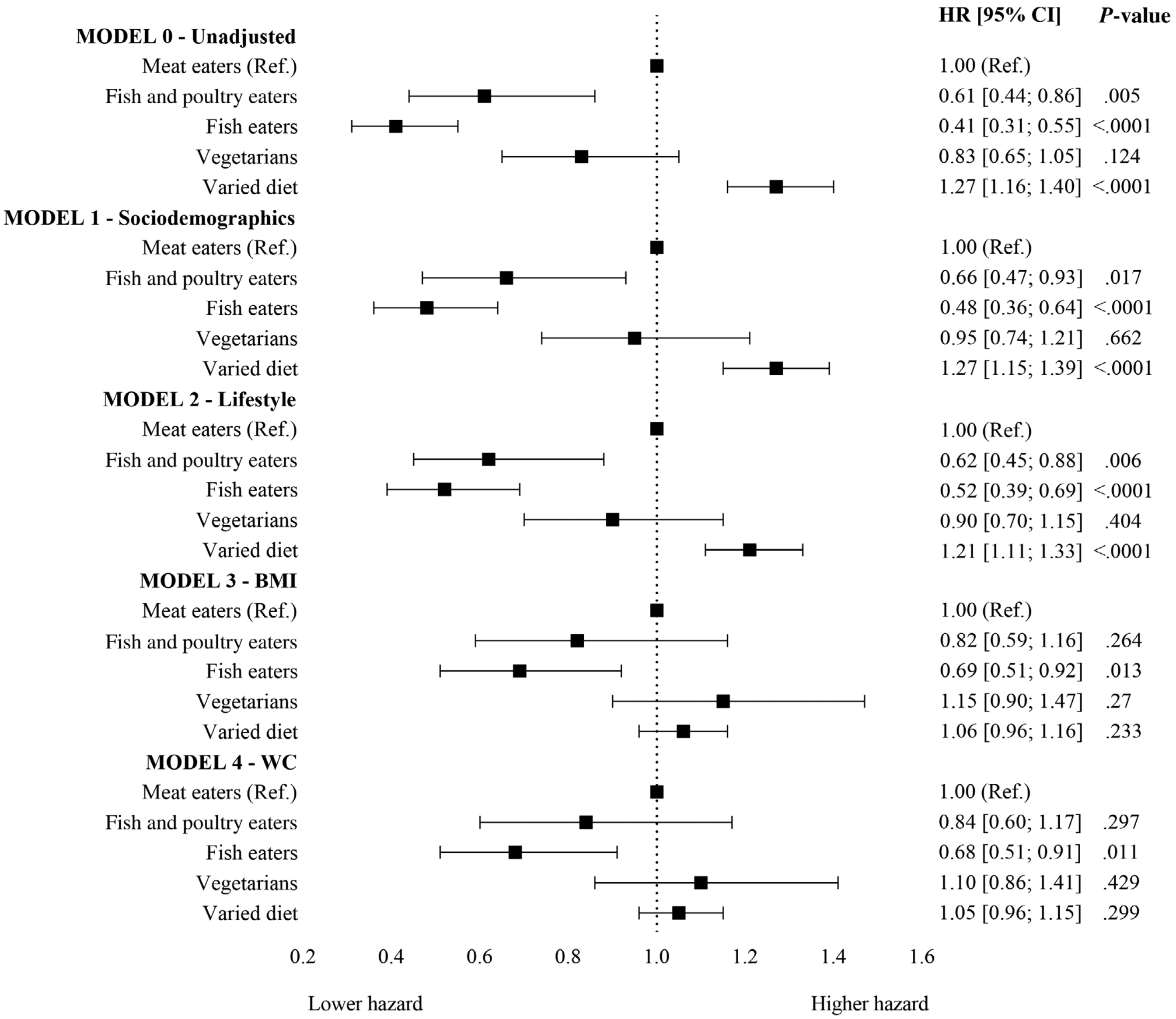

FIGURE 1 Association between types of diet and incidence of type 2 diabetes. Data are presented as hazard ratio (HR) and 95% CI. Meat eaters was a reference group (Ref.). Model 1 (sociodemographics) was adjusted for age, sex and deprivation; model 2 (lifestyle) was adjusted for all covariates included in model 1 plus lifestyle variables (alcohol, smoking, sedentary time, sleep time and type of physical activity); model 3 (body mass index [BMI]) was adjusted for all covariates included in model 2 plus BMI; and model 4 (waist circumference [WC]) was adjusted for all covariates included in model 2 plus WC. All analyses were conducted using 2-year landmark analyses and excluding participants with type 1 diabetes, type 2 diabetes or unknown diabetes at baseline

in a horizontal plane, using a non-elastic SECA 200 tape measure. Central obesity was defined as WC more than 88 cm for women and more than 102 cm for men. Additional details about these measurements can be found in the UK Biobank online protocol.[25]

2.5 | Statistical analyses

Categorical variables are summarized as frequencies and percentages, and continuous variables as means and standard deviations (SDs). Cox-proportional hazard models were used to investigate the associations between types of diet (vegetarians, fish eaters, fish and poultry eaters, meat eaters and varied diet) and incident type 2 diabetes. Meat eaters were treated as the referent group. The results were reported as hazard ratios (HRs) together with 95% confidence intervals (95% CIs). The analyses excluded all participants with prevalent diabetes (type 1 or type 2 diabetes) or undiagnosed diabetes at baseline. To minimize reverse causation, all participants who developed incident type 2 diabetes in the first 2 years of follow-up (2-year landmark) were also excluded.

The main analyses were adjusted for potential confounding factors: age, sex, deprivation, alcohol intake, smoking status, total sedentary time, sleep time, type of PA and adiposity (BMI and WC). These covariates were included incrementally: model 1 (sociodemographics) was unadjusted for age, sex and deprivation. Model 2 (lifestyle) was adjusted for all covariates included in model 1 plus alcohol intake, smoking status, total sedentary time, sleep time and type of PA. Model 3 (BMI) was adjusted for all covariates included in model 2 plus BMI. Model 4 (WC) was the same as model 3, except BMI was replaced by WC.

The mediation role of BMI was formally tested under a causal counterfactual framework.[26] The g-formula[27] approach was used to study the mediation role of obesity in the association between diet and type 2 diabetes, adjusting for all the confounders included in model 2. Assuming causality after adjusted for the confounders, the total effect of diet on type 2 diabetes was decomposed as natural direct effect and natural indirect effect, where the latter indicates the effect that was mediated through obesity. Proportion of mediation was calculated to quantify how much of the association between types of diet and type 2 diabetes could be attributed to obesity. Non-parametric bootstrapping (500 times) was used to estimate 95% CI and *P* values. Analysis was repeated, replacing obesity by central obesity.

The proportional hazard assumption was tested by Schoenfeld residuals. Statistical analyses were performed using the statistical software packages STATA 16 (StataCorp LP) and R v. 4.0.2 with the CMAverse package.[28] *P* values of less than .05 were regarded as statistically significant.

2.6 | Ethics statement

The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee (Ref. 11/NW/0382) on 17 June 2011 and all participants provided their written informed consent to participation. The study protocol is available at http://www.ukbiobank.ac.uk/. This research has been conducted using the UK Biobank resource under application number 7155.

3 | RESULTS

Among the 203 790 (55.8% women) participants, meat eaters were the largest group (87.3%), while fish and poultry eaters were the smallest (1.1%). After excluding the first 2 years, the median follow-up period was 5.4 (interquartile range [IQR]: 4.8-6.3) years. Over the follow-up period, 5067 (2.5%) participants were diagnosed with incident type 2 diabetes (2147 women and 2920 men).

The primary cohort characteristics of participants by type of diet are presented in Table 1. Vegetarians were younger, more deprived, and less probable to smoke. Fish and poultry eaters were more physically active. Participants with varied diet were the most probable to be obese, followed by meat eaters, fish and poultry eaters, vegetarians, then fish eaters. The cohort characteristics by sex are presented in Tables S1 and S2. In terms of energy and nutrient intake, as shown in Table 2, fish and poultry eaters had a lower total energy (TE) intake (1970 kcal/day). Participants with a varied diet and meat eaters had a lower total carbohydrate (46% and 47% of TE), but a higher total fat (32% of TE) intake. Sugar intake was higher in fish and poultry eaters and lower in meat eaters.

Figure 1 shows the associations between type of diet and incident type 2 diabetes. In the sociodemographic model (model 1), fish eaters (HR 0.48 [95% CI: 0.36-0.64]) and fish and poultry eaters (HR 0.66 [95% CI: 0.47-0.93]) had a lower risk of type 2 diabetes compared with meat eaters. Those with a varied diet had a higher risk of type 2 diabetes (HR 1.27 [95% CI: 1.15-1.39]) than meat eaters. However, there was no association with vegetarian diets (HR 0.95 [95% CI: 0.74-1.21]). The magnitude of the associations with fish eaters (HR 0.52 [95% CI: 0.39-0.69]), fish and poultry eaters (HR 0.62 [95% CI: 0.45-0.88]), and participants with varied diets (HR 1.21 [95% CI: 1.11-1.33]) remained similar when the models were additionally adjusted for lifestyle factors (model 2). Further adjustment for BMI (model 3) or WC (model 4) attenuated the associations, and only fish eaters remained associated with incident type 2 diabetes (HR 0.69 [95% CI: 0.51-0.92] and HR 0.68 [95% CI: 0.51-0.91], respectively).

Formal mediation analysis was conducted on adiposity. As shown in Table 3, general obesity was a partial mediator for both fish diets and fish and poultry diets, accounting for 30.6% and 49.8% of their

TABLE 3 Mediation analysis between types of diet and type 2 diabetes via adiposity

	Mediation via obesity	Mediation via central obesity
Fish and poultry diet		
Total Effect	0.71 (0.52-0.92)	0.72 (0.52-0.91)
NDE	0.85 (0.62-1.11)	0.89 (0.66-1.13)
NIE	0.83 (0.80-0.86)	0.81 (0.78-0.83)
Proportion mediated (%)	49.8 (20.0-100.0)	61.4 (25.4-100.0)
Fish diet		
Total Effect	0.56 (0.43-0.67)	0.58 (0.45-0.72)
NDE	0.70 (0.53-0.87)	0.69 (0.54-0.86)
NIE	0.81 (0.79-0.83)	0.83 (0.81-0.85)
Proportion mediated (%)	30.6 (16.9-56.0)	28.2 (16.3-51.1)
Varied diet		
Total Effect	1.27 (1.18-1.39)	1.28 (1.17-1.38)
NDE	1.12 (1.03-1.22)	1.13 (1.04-1.22)
NIE	1.13 (1.12-1.15)	1.13 (1.11-1.14)
Proportion mediated (%)	55.2 (42.4-78.6)	52.9 (41.5-77.9)

Note: The analyses were adjusted for age, sex, deprivation, alcohol intake, smoking status, total sedentary time, sleep time and type of physical activity (model 2). All analyses were conducted using 2-year landmark analyses and excluding participants with type 1 diabetes, type 2 diabetes or unknown diabetes at baseline. Data presented as HR (95% CI) except for proportion mediated. Obesity defined as BMI ≥ 30 kg/m^2; central obesity defined as WC > 88 cm for women and >102 cm for men.
Abbreviations: BMI, body mass index; NDE, natural direct effect; NIE, natural indirect effect; WC, waist circumference.

lower risk of type 2 diabetes, respectively. Similarly, central obesity partially mediated the associations between fish diets, as well as fish and poultry diets, and incident type 2 diabetes (Table 3). Similarly, general and central obesity mediated 55.2% and 52.9% of the elevated risk of participants with a varied diet. Mediation analysis for vegetarians was not conducted as there was no association with type 2 diabetes risk.

4 | DISCUSSION

In this large prospective cohort study, we showed that fish diets, as well as fish and poultry diets, were associated with a lower risk of type 2 diabetes compared with meat eaters, independent of sociodemographic and lifestyle factors. Obesity accounted for half of the association of fish and poultry diets, and a third of that of fish diets. Vegetarian diets were not associated with a lower risk of type 2 diabetes. These findings provide important information for dietary guidelines for type 2 diabetes, reinforcing regular fish consumption, while limiting red and processed meat intake, as well as details regarding the potential mechanism of these diets.

There are several strengths in this study. First, we were able to quantify the mediation role of obesity using a counterfactual causal framework. This study also used a comprehensive adjustment scheme in a large cohort. To minimize reverse causation, we have excluded prevalent and undiagnosed diabetes at baseline, as well as incident diabetes cases diagnosed over the first 2 years of follow-up. However, there are still several limitations to the present study. UK Biobank is not representative of the UK general population in terms of sociodemographic, physical, lifestyle and health-related characteristics. However, a previous study has confirmed that the effect size estimates derived from UK Biobank are consistent with those from more representative general population cohorts.[29] Because of the smaller sample size for participants who completed the 24-hour dietary recall, there is not sufficient power to study variables derived from that questionnaire. This study focuses on alternative diets rather than the dosage of individual food items. Future studies should consider the total consumption of these food items to identify whether there is a dose–response relationship. The meat eater group is heterogenous, but there were very few people who only had red meat but not fish or poultry (0.04%), limiting us from further categorization. Similarly, for participants who reported having a varied diet, there was insufficient information to identify the dietary components that can be attributed to their higher risk. Future studies could consider other tools (e.g. diet quality) to further risk stratify the meat eater group. Lastly, despite our best efforts, we cannot rule out residual confounding and reverse causation, as in all observational studies.

The previous existing evidence on this topic was inconsistent. The European Prospective Investigation into Cancer and Nutrition Oxford (EPIC-Oxford) study of 45 314 participants with a mean follow-up of 17.6 years showed an association of fish eaters, low meat eaters and vegetarians with a lower risk of type 2 diabetes compared with regular meat eaters.[30] They reported that, after adjusting for sociodemographic and lifestyle factors, fish eaters (HR 0.47 [95% CI: 0.38-0.59]), low meat eaters (HR 0.63 [95% CI: 0.54-0.75]) and vegetarians (HR 0.63 [95% CI: 0.54-0.74]) were at a lower risk of type 2 diabetes.[30] Similarly, our findings found that fish eaters were at an approximately 50% lower risk of type 2 diabetes (HR 0.52 [95% CI: 0.39-0.69]). All these HR estimates for all types of diet were attenuated, but remained significant after adjusting for BMI in the EPIC-Oxford study.[30] By contrast, we only observed an independent association for fish eaters.

A prospective cohort study conducted in Japan investigated the associations between consumption of total meat, total red meat, unprocessed red meat, processed red meat and poultry and type 2 diabetes risk among women and men. They found that the highest quartile of total meat, total red meat and unprocessed red meat intake had 36% (HR 1.36 [95% CI: 1.07-1.73], 48% (HR 1.48 [95% CI: 1.15-1.90]) and 42% (HR 1.42 [95% CI: 1.12-1.81]) higher risk of type 2 diabetes, respectively, among men compared with the lowest quartile, after adjusting for lifestyle factors and BMI.[8] However, they did not find a significant association with poultry intake among men, nor between any diet type and type 2 diabetes risk among women.[8] More recently, a study in China concluded that increased consumption of fish and red meat of 50 g/day was associated with a 6% (HR 1.06 [95% CI 1.00-1.13]) and 11% (HR 1.11 [95% CI 1.04-1.20]) higher risk of type 2 diabetes, respectively, after adjusting for sociodemographic and lifestyle factors and adiposity, although no significant association was found for poultry eaters.[10] It is interesting to note that a recent study conducted on UK Biobank found that individuals who reported less than one serving per week, weekly, and at least two servings per week of oily fish had a 16% (HR 0.84 [95% CI: 0.78-0.91]), 22% (HR 0.78 [95% CI: 0.72-0.85]) and 22% (HR 0.78 [95% CI: 0.71-0.86]) lower risk of type 2 diabetes, respectively, compared with no consumption, but found no association between non-oily fish intake and incident type 2 diabetes.[31]

Evidence on the substitution of meat with fish or poultry supports our findings. A Danish study reported that substitution of total red meat with fish was associated with a 4% lower risk of type 2 diabetes (HR 0.96 [95% CI: 0.94-0.99]), replacing processed red meat with fish produced a 6% lower risk (HR 0.94 [95% CI: 0.91-0.97]), and replacing processed red meat with poultry produced a 4% lower risk (HR 0.96 [95% CI: 0.93-0.99)], after adjusting for overall food pattern.[32]

This study showed that fish diets were associated with a lower type 2 diabetes risk, partly because these diets were associated with lower BMI and WC. However, there was still a substantial proportion of the association that was unexplained. Because fish is a major dietary source of polyunsaturated fatty acid (PUFA), it is possible that PUFA intake is a mechanism between fish-based diet and type 2 diabetes. A systematic review on interventional studies showed that long-term consumption (at least 8 weeks) of 5.0 g/day of PUFA improved glycaemic control in patients with type 2 diabetes, although the evidence is heterogeneous.[33] It was hypothesized that the PUFA anti-inflammatory pathway and signalling molecules in the cell processes and immunological processes (e.g. PGR40, PGR120 or GLUT4) could improve insulin sensitivity and secretion.[33]

Randomized controlled trials might be warranted to investigate the causality between fish, PUFA and type 2 diabetes risk, as well as glycaemic control.

Our study found no association between vegetarian diets and type 2 diabetes, in contrast to previous studies. The Adventist Health Study-2 found that lacto-ovo vegetarians (odds ratio [OR] 0.618 [95% CI: 0.503-0.760]), vegans (OR 0.381 [95% CI: 0.236-0.617]) and semi-vegetarians (OR 0.486 [95% CI: 0.312-0.755]) were at a lower risk of type 2 diabetes compared with all other non-vegetarian diets, after adjusting for a similar set of confounders to those included in this study.[34] In addition, a study that excluded participants who had type 2 diabetes, fasting blood glucose of 7.0 mmol/L or higher, cancer, coronary heart disease and stroke at baseline, reported that vegetarians and converted vegetarians (individuals who became vegetarians within 5 years) had a 35% and 53% lower risk of type 2 diabetes, respectively, compared with non-vegetarians, after adjusting for gender, age, education, family history of diabetes, PA, use of lipid-lowering medications, follow-up methods and baseline BMI.[35] The inconsistent results pertaining to vegetarian diets could be related to the TE intake, and macronutrient and micronutrient patterns of the participants, which warrants further study. It should also be noted that HRs across different Cox models might not be meaningfully compared as HRs are dependent on the adjustment variables due to non-collapsibility.[36]

Qian et al. found that the association between plant-based diets and the risk of type 2 diabetes was considerably attenuated when adjusting for BMI.[17] The current study meaningfully extends the literature by showing that adiposity, as indicated by BMI and WC, is indeed a mediator for fish diets. This finding mirrors a study conducted on healthy diet patterns and the risk of type 2 diabetes that concluded adiposity was a sizeable mediator.[37] Further studies should explore other potential mediators, such as blood pressure and lipid profile.

In conclusion, this study showed that fish diets were associated with a lower risk of incident type 2 diabetes compared with diets including red meat. The associations were partially mediated by adiposity.

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CONFLICT OF INTEREST

The authors declare that there are no potential conflicts of interests. The funders have no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

AUTHOR CONTRIBUTIONS

J.B., S.R.G., C.C.-M., and F.K.H. contributed to the study conception and design, advised on all statistical aspects, and interpreted the data. J.B., S.R.G., C.C.-M., and F.K.H. performed the statistical analyses. J.B., S.R.G., C.C.-M., and F.K.H. drafted the manuscript. J.B., S.P., F.P.-R., J.P.P., S.R.G., C.C.-M., and F.K.H. critically reviewed and revised the manuscript and approved the final version to be published. J.B., S.R.G., C.C.-M., and F.K.H. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data can be requested from the UK Biobank (http://www.ukbiobank.ac.uk/).

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SUPPORTING INFORMATION

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