

Supplementary Materials

Supplementary Methods

As an independent replication, we also analyzed the associations of dietary protein sources with T2D risk in 34,616 men and women who were free of diabetes at baseline with a median follow-up period of 11.4 years in the UKB prospective cohort. The detailed information of UKB has been introduced elsewhere.(1) In the UKB, food intake was assessed via internet-based administration of the Oxford WebQ, which is a 24-h recall of frequency from a set food list including >200 food items frequently consumed in the UK and took seasonal variations into consideration.(2; 3) Energy and nutrient values were calculated according to McCance and Widdowson's The Composition of Foods.(3) Compared with an interviewer-based 24h dietary recall, the Spearman's correlation for the majority of nutrients obtained from the WebQ ranged between 0.5 and 0.9, with 0.6 for protein.(2) A total of five rounds of assessment were completed on the recruitment assessment between April 2009 and September 2010 followed by four times of repeated measurements between February 2011 and June 2012.(4) To better reflect dietary habits, we included the participants with at least four rounds of dietary assessments in the current analysis. The average dietary intakes of the four repeated measurements were used in the analysis. The food items included in each of the 12 dietary protein sources were described in **Supplementary Table S2**.(5) In the UKB, incident T2D cases were ascertained using cumulative medical records of hospital diagnoses. T2D was defined by the International Classification of Diseases 10 code E11 (Non-insulin-dependent diabetes mellitus).(6)

We used Cox proportional hazard models to examine the associations of intake of one serving/day of dietary protein sources with risk of incident T2D, with adjustment for age, sex, residence area, Townsend deprivation index at recruitment, smoking status, drinking status, physical activity, family history of diabetes, multivitamin use, antihypertensive medication treatment, total energy intake, and other protein sources. Based on this model, we further calculated the HRs of T2D for protein sources substitution as the exponentiated difference between the coefficients of the two foods involved in substitution. The corresponding 95% confidence intervals (CIs) of HRs were calculated based on variance-covariance matrix.

Supplementary Table S1. Definition of dietary protein sources according to MyPyramid Equivalents Database in WHI¹⁻⁴

Protein sources	MPED Description
Red meat	M_Meat: Ounces of cooked lean meat from beef, pork, veal, lamb, and game, excludes lean meat organ meats and frankfurters, sausages, and luncheon meat
Processed meat	M_Frank: Ounces of cooked lean meat from frankfurters, sausages, and luncheon meats
Poultry	M_Poult: Ounces of cooked lean meat from chicken, turkey, and other poultry. Excludes poultry organ meats and poultry present in frankfurters, sausages, and luncheon meats
Eggs	M_Egg: Number of ounce equivalents, where one egg is one ounce equivalent of cooked lean meat. Includes eggs and egg substitutes
High omega-3 seafood	M_Fish_Hi: Ounces of cooked lean meat from fish, shellfish, and other seafood that are high in the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)
Low omega-3 seafood	M_Fish_Lo: Ounces of cooked lean meat from fish, shellfish, and other seafood that are low in the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)
Cheese	D_Cheese: Number of cup equivalents of cheese. Includes natural and processed cheese
Milk	D_Milk: Number of cup equivalents of milk
Yogurt	D_Yogurt: Number of cup equivalents of yogurt
Whole grains	G_Whl: Number of ounce equivalents of whole grains from the grains group
Legumes	Legumes: Number of cup equivalents of cooked dry beans and peas
Nuts	M_NutSd: Number of ounce equivalents of cooked lean meat from nuts and seeds, where ½ ounce of nuts and seeds is one ounce equivalent of cooked lean meat

¹ MyPyramid recommends making lean or low-fat food choices from the meat and beans group. Lean meat is defined as any meat, poultry, fish food item that contains 9.28 grams or less fat and at least 90.72 grams of nonfat meat component per 100 grams of cooked food item. Equivalents of cooked meat, poultry, fish were translated into the amount of meat contains 9.28 grams per 100 grams of food.

² High omega-3 is defined as a n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in amounts at or above 0.5 gram per 85 grams (3 ounces).

³ Low omega-3 is defined as a n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in amounts under 0.5 gram per 85 grams (3 ounces).

⁴ Foods for which details on grain ingredients are not available to make a determination about the grain subgroups, Agricultural Research Service's Nutrient Data Laboratory food specialists provided guidance on determining the proportion of whole grain components present in a grain product.

Supplementary Table S2. Definition of dietary protein sources in the UKB

Protein sources	Food items
Red meat	Beef, lamb, pork
Processed meat	Sausage, bacon, ham
Poultry	Crumbed chicken, chicken, poultry
Eggs	Whole eggs, omelets, eggs disaggregated from mayonnaise in egg sandwiches
High omega-3 seafood	Oily fish
Low omega-3 seafood	White fish, breaded fish, battered fish, tinned tuna
Cheese	Low fat hard cheese, hard cheese, soft cheese, blue cheese, low fat cheese spread, cheese spread, cottage cheese, mozzarella cheese, goat cheese, other cheese
Milk	Whole milk, semi-skimmed milk, skimmed milk, powdered milk, goat/sheep milk
Yogurt	Yogurt
Whole grains	Muesli, oat crunch, bran cereal, whole wheat cereal, oatcake, couscous, whole meal pasta, brown rice
Legumes	Baked beans, pulses
Nuts	Salted peanuts, unsalted peanuts, salted other nuts, unsalted other nuts, seeds

Supplementary Table S3. Baseline characteristics of participants according to quintiles of energy-adjusted total protein intake in the UKB

	Total	Quintiles of energy-adjusted total protein intake				
		Q1	Q2	Q3	Q4	Q5
N	34,616	6924	6923	6923	6923	6923
Men, n (%)	14,902 (43.0)	3268 (47.2)	3022 (43.7)	2918 (42.1)	2779 (40.1)	2915 (42.1)
Follow-up duration (Person-years)	393,584	78,897	78,845	78,755	78,755	78,335
Incident diabetes, n (%)	663 (1.9)	107 (1.5)	131 (1.9)	118 (1.7)	127 (1.8)	180 (2.6)
Age at baseline, median (IQR), yr	58.0 (51.0, 62.0)	57.0 (50.0, 62.0)	58.0 (51.0, 63.0)	58.0 (51.0, 63.0)	58.0 (52.0, 63.0)	57.0 (50.0, 62.0)
White ethnicity, n (%)	33762 (97.5)	6733 (97.2)	6770 (97.8)	6773 (97.8)	6772 (97.8)	6714 (97.0)
College or University degree, n (%)	19068 (55.1)	4001 (57.8)	3946 (57.0)	3856 (55.7)	3688 (53.3)	3577 (51.7)
Physical activity (METs-h/wk), median (IQR)	28.3 (13.7, 53.0)	28.6 (13.8, 53.1)	28.2 (13.6, 51.2)	27.6 (13.8, 51.5)	28.3 (14.0, 55.0)	28.8 (13.6, 54.2)
Current drinker, n (%)	32566 (94.1)	6471 (93.5)	6517 (94.1)	6550 (94.6)	6527 (94.3)	6501 (93.9)
Current smoker, n (%)	2163 (6.2)	582 (8.4)	447 (6.5)	360 (5.2)	397 (5.7)	377 (5.4)
Townsend deprivation index, median (IQR)	-2.3 (-3.7, -0.0)	-2.0 (-3.6, 0.5)	-2.3 (-3.7, -0.0)	-2.4 (-3.7, -0.2)	-2.4 (-3.8, -0.3)	-2.4 (-3.8, -0.0)
Area, n (%)						
England	31914 (92.2)	6318 (91.2)	6346 (91.7)	6410 (92.6)	6413 (92.6)	6427 (92.8)
Scotland	1653 (4.8)	376 (5.4)	357 (5.2)	334 (4.8)	309 (4.5)	277 (4.0)
Wales	1049 (3.0)	230 (3.3)	220 (3.2)	179 (2.6)	201 (2.9)	219 (3.2)
Multivitamin use, n (%)	8097 (23.4)	1686 (24.4)	1540 (22.2)	1533 (22.1)	1623 (23.4)	1715 (24.8)
Antihypertension medication used, n (%)	5861 (16.9)	1068 (15.4)	1124 (16.2)	1161 (16.8)	1200 (17.3)	1308 (18.9)
Family history of diabetes, n (%)	7168 (20.7)	1367 (19.7)	1367 (19.7)	1358 (19.6)	1481 (21.4)	1595 (23.0)
Body mass index, median (IQR), kg/m ²	25.7 (23.3, 28.7)	25.1 (22.8, 27.9)	25.4 (23.0, 28.2)	25.7 (23.3, 28.7)	25.8 (23.5, 28.8)	26.5 (24.0, 29.7)
Total energy intake, median (IQR), kcal/day	2058 (1773, 2386)	2127 (1811, 2467)	2045 (1761, 2375)	2031 (1757, 2340)	2019 (1754, 2338)	2074 (1784, 2421)
Total carbohydrate, median (IQR), g/day	247.3 (208.2, 291.3)	264.9 (222.1, 311.6)	250.0 (211.3, 293.9)	244.8 (207.1, 285.7)	240.2 (204.1, 281.7)	238.7 (198.4, 281.8)
Total fat, median (IQR), g/day	75.8 (61.4, 92.2)	79.1 (63.4, 96.0)	76.0 (61.2, 91.8)	74.8 (61.0, 90.5)	73.9 (60.3, 89.2)	75.7 (61.4, 93.8)
Total protein, median (IQR), g/day	80.4 (69.2, 92.6)	65.9 (56.6, 76.1)	73.3 (64.9, 82.8)	79.2 (71.1, 88.0)	85.2 (77.3, 94.6)	98.2 (88.4, 110.4)
Dietary protein sources, median (IQR), g/day						

Red meat	30.0 (0.0, 60.0)	0.0 (0.0, 30.0)	30.0 (0.0, 45.0)	30.0 (0.0, 60.0)	30.0 (24.0, 60.0)	60.0 (30.0, 90.0)
Processed meat	11.5 (0.0, 25.9)	5.8 (0.0, 20.8)	9.2 (0.0, 23.0)	11.5 (0.0, 25.9)	11.5 (0.0, 27.2)	14.4 (0.0, 34.5)
Eggs	12.5 (0.0, 30.0)	0.0 (0.0, 25.0)	6.2 (0.0, 25.0)	12.0 (0.0, 30.0)	12.5 (0.0, 30.0)	15.0 (0.0, 42.5)
Poultry	32.5 (0.0, 52.0)	0.0 (0.0, 32.5)	26.0 (0.0, 32.5)	32.5 (0.0, 48.8)	32.5 (13.0, 65.0)	48.8 (32.5, 81.2)
High omega-3 seafood	0.0 (0.0, 25.0)	0.0 (0.0, 12.5)	0.0 (0.0, 25.0)	0.0 (0.0, 25.0)	0.0 (0.0, 25.0)	0.0 (0.0, 25.0)
Low omega-3 seafood	0.0 (0.0, 30.0)	0.0 (0.0, 23.0)	0.0 (0.0, 25.0)	0.0 (0.0, 30.0)	0.0 (0.0, 30.0)	0.0 (0.0, 30.0)
Cheese	15.0 (5.0, 25.0)	15.0 (5.0, 26.2)	15.0 (5.0, 25.0)	15.0 (5.0, 25.0)	15.0 (5.0, 25.0)	15.0 (5.0, 28.8)
Milk	187.5 (105.0, 258.2)	156.2 (70.0, 228.8)	181.2 (100.0, 250.0)	190.0 (113.8, 257.5)	200.0 (122.5, 271.1)	207.0 (124.5, 283.8)
Yogurt	62.5 (0.0, 125.0)	50.0 (0.0, 125.0)	62.5 (0.0, 125.0)	62.5 (0.0, 125.0)	62.5 (0.0, 156.2)	62.5 (0.0, 187.5)
Whole grains	49.0 (20.0, 86.0)	46.5 (18.0, 84.5)	49.2 (20.0, 85.0)	50.0 (20.0, 85.2)	50.8 (20.0, 87.0)	48.5 (19.0, 86.9)
Legumes	0.0 (0.0, 17.5)	0.0 (0.0, 17.5)	0.0 (0.0, 17.5)	0.0 (0.0, 17.5)	0.0 (0.0, 17.5)	0.0 (0.0, 25.3)
Nuts	0.0 (0.0, 10.0)	0.0 (0.0, 10.0)	0.0 (0.0, 8.0)	0.0 (0.0, 8.0)	0.0 (0.0, 8.0)	0.0 (0.0, 10.0)

Data are presented as median (inter-quartile range, IQR) for non-normally distributed variables, and numbers (percentages) for categorical variables.

Supplementary Table S4. Associations of dietary protein and food sources with risk of incident type 2 diabetes in the UKB

	HR (95% CI)	
	Full Model	Sensitivity Model
Total protein, 5% of energy	1.36 (1.17, 1.57)	1.14 (0.99, 1.32)
Red meat, serving/day	1.19 (1.07,1.31)	1.08 (0.97,1.19)
Processed meat, serving/day	1.35 (1.14,1.59)	1.11 (0.93,1.31)
Poultry, serving/day	1.13 (1.02,1.25)	1.06 (0.95,1.17)
Eggs, serving/day	1.12 (0.99,1.28)	1.03 (0.90,1.18)
Cheese, serving/day	0.92 (0.79,1.07)	0.89 (0.77,1.04)
Milk, serving/day	1.16 (1.02,1.31)	1.18 (1.04,1.34)
Yogurt, serving/day	0.94 (0.89,1.00)	0.93 (0.88,0.99)
High omega-3 seafood, serving/day	0.97 (0.79,1.19)	1.01 (0.83,1.24)
Low omega-3 seafood, serving/day	0.97 (0.82,1.15)	0.92 (0.78,1.09)
Whole grains, serving/day	0.94 (0.90,0.99)	0.98 (0.93,1.03)
Legumes, serving/day	1.08 (0.91,1.27)	1.05 (0.89,1.25)
Nuts, serving/day	0.96 (0.89,1.02)	0.98 (0.92,1.05)

In the full Model, HR of type 2 diabetes for dietary protein and food sources were calculated by using Cox proportional hazard models with adjustment for age, sex, residence area, Townsend deprivation index at recruitment, smoking status, drinking status, physical activity, family history of diabetes, multivitamin use, antihypertensive medication treatment, total energy intake, and other protein sources.

In the sensitivity Model, BMI and WHR were additionally adjusted.

Supplementary Table S5. Sensitivity analysis of the associations of substitution of different protein and food sources with risk of incident type 2 diabetes with additional adjustment for BMI and WHR in the WHI and the UKB¹⁻³

Substituted protein	Equivalent amount of substituted protein	WHI HR (95% CI)	UKB HR (95% CI)
5% of energy from animal protein	Plant protein	0.89 (0.84, 0.95)	NA
1 serving/day of red meat	Whole grains	0.92 (0.89, 0.94)	0.91 (0.82, 1.02)
	Nuts	0.97 (0.94, 0.99)	0.92 (0.81, 1.03)
	Legumes	1.00 (0.96, 1.04)	0.98 (0.80, 1.19)
	Yogurt	0.96 (0.93, 0.99)	0.87 (0.77, 0.97)
	Milk	0.96 (0.93, 0.98)	1.10 (0.93, 1.29)
	Cheese	0.96 (0.94, 0.98)	0.83 (0.70, 0.98)
	High-omega 3 seafood	1.00 (0.92, 1.07)	0.94 (0.76, 1.17)
	Low-omega 3 seafood	1.13 (1.03, 1.23)	0.85 (0.71, 1.02)
1 serving/day of processed meat	Whole grains	0.85 (0.80, 0.90)	0.89 (0.75, 1.05)
	Nuts	0.90 (0.85, 0.95)	0.89 (0.74, 1.06)
	Legumes	0.93 (0.87, 0.98)	0.95 (0.74, 1.22)
	Yogurt	0.89 (0.84, 0.94)	0.84 (0.70, 1.01)
	Milk	0.89 (0.84, 0.94)	1.07 (0.86, 1.32)
	Cheese	0.89 (0.84, 0.94)	0.81 (0.65, 1.00)
	High-omega 3 seafood	0.92 (0.84, 1.01)	0.92 (0.71, 1.18)
	Low-omega 3 seafood	1.04 (0.94, 1.16)	0.83 (0.66, 1.05)
1 serving/day of eggs	Whole grains	0.84 (0.80, 0.87)	0.95 (0.83, 1.09)
	Nuts	0.88 (0.85, 0.92)	0.95 (0.82, 1.11)
	Legumes	0.92 (0.87, 0.96)	1.02 (0.82, 1.27)
	Yogurt	0.88 (0.84, 0.92)	0.90 (0.78, 1.04)
	Milk	0.88 (0.84, 0.91)	1.15 (0.96, 1.37)
	Cheese	0.88 (0.84, 0.91)	0.87 (0.71, 1.06)
	High-omega 3 seafood	0.91 (0.84, 0.99)	0.98 (0.77, 1.26)
	Low-omega 3 seafood	1.03 (0.94, 1.14)	0.89 (0.72, 1.10)
1 serving/day of poultry	Whole grains	0.92 (0.88, 0.96)	0.93 (0.83, 1.04)
	Nuts	0.97 (0.94, 1.01)	0.93 (0.82, 1.05)
	Legumes	1.01 (0.96, 1.06)	1.00 (0.82, 1.21)
	Yogurt	0.97 (0.93, 1.01)	0.88 (0.78, 0.99)
	Milk	0.96 (0.93, 1.00)	1.12 (0.95, 1.31)
	Cheese	0.96 (0.93, 1.00)	0.84 (0.71, 1.00)
	High-omega 3 seafood	1.00 (0.92, 1.09)	0.96 (0.77, 1.20)
	Low-omega 3 seafood	1.13 (1.03, 1.25)	0.87 (0.72, 1.05)

¹ One serving size was defined as 50g/day for red meat, processed meat, eggs, high omega-3 seafood, low omega-3 seafood, and legumes; 30g/day for cheese and whole grains; 200g/day for milk; 70g/day for yogurt; and 10g/day for nuts.

²In the WHI, the substitution analysis models were adjusted for age, study group indicator, self-identified race/ethnicity, region of residence, family income, education, and family history of diabetes, smoking status, alcohol intake, physical activity, hormone replacement therapy, multivitamin use, antihypertensive medication use, total energy intake, modified Alternate Healthy Eating Index (AHEI) 2010, other protein sources, BMI, and WHR.

³In the UKB, the substitution analyses were adjusted for age, sex, residence area, Townsend deprivation index at recruitment, smoking status, drinking status, physical activity, family history of diabetes, multivitamin use, antihypertensive medication treatment, total energy intake, other protein sources, BMI, and WHR.

NA: In the UKB, only total protein was calculated and released. The variables of animal protein and plant protein intake were not available in the UKB database; therefore, the according substitution analysis cannot be conducted.

Abbreviations: WHI, Women's Health Initiative; UKB, United Kingdom Biobank.

Supplementary Table S6. Baseline characteristics of 3464 postmenopausal women enrolled in the case-control studies nested in the WHI

	Control	Case	<i>P</i> value
N	2019	1445	
Age at baseline (yr)	62 ± 7	63 ± 7	0.18
Race, n (%)			<0.001
White	150 (7.4 %)	77 (5.3 %)	
Black	256 (12.7 %)	119 (8.2 %)	
Others/unknown	1613 (79.9 %)	1249 (86.4 %)	
Region of residence, n (%)			0.39
Northeast	364 (18.0 %)	282 (19.5 %)	
South	686 (34.0 %)	472 (32.7 %)	
Midwest	430 (21.3 %)	328 (22.7 %)	
West	539 (26.7 %)	363 (25.1 %)	
Education, n (%)			<0.001
<High school	1169 (57.9 %)	986 (68.2 %)	
High school	830 (41.1 %)	445 (30.8 %)	
≥College	20 (1 %)	14 (1 %)	
Physical activity (METs-h/wk)	13.3 ± 14.3	9.7 ± 12.4	<0.001
Alcohol intake (g/day)	4.2 ± 10.6	2.5 ± 6.9	<0.001
Smoking status, n (%)			0.05
Never smoked	1114 (55.2 %)	738 (51.1 %)	
Past smoker	775 (38.4 %)	599 (41.5 %)	
Current smoker	130 (6.4 %)	108 (7.5 %)	
Income (U.S. dollars)			<0.001
<20,000	314 (15.6 %)	317 (21.9 %)	
20,000-49,999	989 (49.0 %)	735 (50.9 %)	
>50,000	716 (35.5 %)	393 (27.2 %)	
Family history of diabetes, n (%)	691 (34.2 %)	776 (53.7 %)	<0.001
Multivitamin use, n (%)	66 (3.3 %)	43 (3.0 %)	0.70
Hormone replacement therapy, n (%)			<0.001
Never	704 (34.9 %)	591 (40.9 %)	
Past	399 (19.8 %)	327 (22.6 %)	
Current	916 (45.4 %)	527 (36.5 %)	
Antihypertension medicine, n (%)			<0.001
Never treated	1358 (67.3 %)	675 (46.7 %)	
Previously treated	150 (7.4 %)	154 (10.7 %)	
Currently treated	511 (25.3 %)	616 (42.6 %)	
Total energy intake (kcal/day)	1555 ± 651	1688 ± 712	<0.001
Total carbohydrate (g/day)	203.5 ± 82.3	208.9 ± 78.7	0.05
Total fat (g/day)	54.2 ± 31.7	62.5 ± 33.6	<0.001

Saturated fat	17.7 ± 11.1	20.7 ± 11.8	<0.001
Monounsaturated fat	20.6 ± 12.4	23.7 ± 13.0	<0.001
Polyunsaturated fat	11.5 ± 7.0	13.0 ± 7.3	<0.001
Total protein (g/day)	63.7 ± 29.2	69.4 ± 27.6	<0.001
Animal protein	43.8 ± 24.1	48.9 ± 22.4	<0.001
Plant protein	19.8 ± 8.9	20.4 ± 8.4	0.06
Dietary protein food source (g/day) ¹			
Red meat	36.4 ± 34.8	47.7 ± 42.1	<0.001
Processed meat	10.2 ± 13.7	15.0 ± 18.8	<0.001
Eggs	14.6 ± 18.3	19.0 ± 23.6	<0.001
Poultry	27.5 ± 25.2	29.1 ± 25.9	0.07
High omega-3 seafood	8.9 ± 11.3	7.9 ± 10.2	0.01
Low omega-3 seafood	8.6 ± 10.2	9.3 ± 10.1	0.07
Cheese	91.2 ± 110	106.2 ± 104.9	<0.001
Milk	221.4 ± 262.1	235.3 ± 245	0.11
Yogurt	36.8 ± 68.4	36.9 ± 68.2	0.98
Whole grains	32.7 ± 29.0	32.5 ± 28.5	0.84
Legumes	21.1 ± 28.6	21.2 ± 32.7	0.87
Nuts	8.7 ± 14.8	10 ± 17.7	0.03
Modified AHEI 2010	34.7 ± 8.1	33.3 ± 8.2	<0.001

¹Units of protein source, which vary by MPED group, were transformed to g/day in analysis.

Continuous variables are presented as mean ± SD. Categorical variables are presented as n (%).

P values were calculated with Chi-square test for categorical variables and t test for continuous variables.

Abbreviations: BMI, body mass index; METs, metabolic equivalent of task; AHEI, alternative healthy eating index.

Supplementary Table S7. Circulating levels of biomarkers among postmenopausal women enrolled in the case-control studies nested in the WHI

	N	Control	Case	P value
Obesity-related measurements				
BMI, kg/m ²	3420	27.5 ± 5.86	32.3 ± 7.05	<0.001
Waist circumference, cm	3451	83.9 ± 12.8	97.9 ± 15.5	<0.001
Inflammation factors				
TNFα-R2, pg/mL	3004	2479 ± 795	2809 ± 881	<0.001
IL-6, pg/mL	3015	2.77 ± 4.45	4.17 ± 5.36	<0.001
hs-CRP, mg/L	3024	0.38 ± 0.55	0.68 ± 1.45	<0.001
Endothelial dysfunction				
VCAM-1, ng/ml	3012	714 ± 243	804 ± 308	<0.001
E-selectin, ng/ml	3005	39.6 ± 20.1	55.5 ± 31.7	<0.001
SICAM-1, ng/ml	2984	284 ± 89.2	334 ± 109	<0.001
Sex steroids and SHBG				
Estradiol, pg/mL	1471	31.9 ± 44.2	29.6 ± 38.9	0.42
Testosterone, mg/mL	1471	0.15 ± 0.18	0.18 ± 0.22	0.002
SHBG, nmol/L	1471	89.7 ± 56.1	58.3 ± 46.6	<0.001
Leptin and leptin receptor				
Leptin, ng/ml	1472	30.0 ± 21.2	36.9 ± 24.3	<0.001
Soluble leptin receptor, ng/ml	1472	35.5 ± 11.4	33.7 ± 10.4	0.006
Cellular aging				
Leucocyte telomere length, kb	3368	4.09 ± 1.44	3.95 ± 1.44	0.06

variables are presented as mean ± SD. *P* values were calculated using logistic regression model with adjustment for age, self-identified race/ethnicity, region of residence at baseline, family income, and education.

Abbreviation: hs-CRP, high-sensitivity C-reactive protein; SICAM-1, soluble intercellular adhesion molecule 1; SHBG, sex hormone-binding globulin; TNFα-R2, tumor necrosis factor α receptor 2; VCAM-1, vascular cell adhesion molecule 1.

Supplementary Table S8. Mediating effects of biomarkers on the association of iso-caloric substitution of plant protein for animal protein with risk of type 2 diabetes with adjustment for BMI among postmenopausal women enrolled in the nested case-control studies in the WHI¹⁻²

Substituting 5% energy from plant protein for 5% energy from animal protein → T2D					
Mediators	N	Total effect, OR (95% CI)	Indirect effect, OR (95% CI)	Direct effect, OR (95% CI)	Proportion mediated, %
Inflammation factors					
TNFR2	2771	1.04 (0.71, 1.53)	1.00 (0.96, 1.03)	1.04 (0.71, 1.54)	NA
IL-6	2780	1.02 (0.71, 1.54)	0.95 (0.90, 1.01)	1.08 (0.74, 1.64)	NA
hs-CRP	2786	1.02 (0.68, 1.48)	0.91 (0.84, 0.98)	1.13 (0.74, 1.63)	NA
Inflammation score	2769	1.03 (0.71, 1.49)	0.96 (0.89, 1.02)	1.08 (0.75, 1.59)	NA
Endothelial dysfunction					
VCAM-1	2778	1.04 (0.69, 1.54)	1.01 (0.98, 1.05)	1.03 (0.68, 1.52)	2
E-selectin	2772	1.12 (0.76, 1.69)	0.98 (0.90, 1.08)	1.14 (0.78, 1.71)	NA
SICAM-1	2752	1.10 (0.76, 1.63)	1.05 (0.98, 1.12)	1.05 (0.73, 1.57)	18
Sex steroids and SHBG					
Estradiol	1402	0.98 (0.62, 1.52)	1.00 (0.96, 1.01)	0.99 (0.62, 1.54)	NA
Testosterone	1402	0.98 (0.61, 1.52)	1.00 (0.95, 1.05)	0.98 (0.62, 1.52)	NA
SHBG	1402	1.02 (0.63, 1.62)	0.97 (0.86, 1.10)	1.05 (0.65, 1.65)	2
Leptin and leptin receptor					
Leptin	1403	1.00 (0.63, 1.56)	0.99 (0.94, 1.04)	1.00 (0.64, 1.57)	1
Soluble leptin receptor	1403	0.99 (0.62, 1.57)	1.01 (0.99, 1.06)	0.97 (0.61, 1.54)	NA
Cellular aging					
Leucocyte telomere length	3101	0.99 (0.68, 1.42)	1.00 (0.98, 1.01)	0.99 (0.68, 1.43)	NA

¹ The covariates adjusted in the mediation analyses included age, ethnicity, education, smoking, drinking, physical activity, and BMI.

² Proportion mediated was not calculated when the point estimate of the direct effect was in an opposite direction as the indirect effect.

Inflammation score was calculated by summing up inflammation markers above the median value.

Abbreviations: WHI, Women's Health Initiative; T2D, type 2 diabetes mellitus; BMI, body mass index; TNF α -R2, tumor necrosis factor receptor 2; IL-6, interleukin 6; hs-CRP, high-sensitivity C-reactive protein; VCAM-1, vascular cell adhesion protein 1; SICAM-1, soluble intercellular adhesion molecule-1; SHBG, sex hormone-binding globulin.

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