SUPPLEMENTARY DATA

Meat Cooking Methods and Risk of Type 2 Diabetes: Results from Three Prospective Cohort Studies

Appendix 1

Assessment of HAA intake

In the current study, the estimated dietary HAA intake (including PhIP, MeIQx, and DiMeIQx) was derived by multiplying the frequency of cooking meats with a prespecified portion size with HAA levels (ng/g meat) according to specific cooking methods and doneness level, and then summed. In this calculation, we used the Charred Database (created by Sinha et al. from the National Cancer Institute; https://dceg.cancer.gov/tools/design/charred) which was an online database containing data of HAA levels measured in meat samples cooked using different methods in different doneness levels (26, 27). Briefly, approximately 2500 individual pieces of meat were tested to provide data for 120 categories by cooking method and doneness levels. These data were ultimately used to create the HAA database (27). The levels of various HAAs (e.g., MeIQx, DiMeIQx, and PhIP) were measured in duplicate by solid-phase extraction and analyzed by high-performance liquid chromatography using a method previously reported by Gross and Gruter (27). Laboratory investigators were blinded to the cooking method and degree of doneness of each sample. More details were described elsewhere (27).

Ascertainment of T2D

A validated supplementary questionnaire regarding symptoms, diagnostic tests, and hypoglycemic therapy was mailed to participants who reported having diabetes in the biennial questionnaires. Before the release of the American Diabetes Association (ADA) criteria in 1997, The National Diabetes Data Group criteria were applied to diagnose self-reported T2D: (1) fasting glucose concentrations ≥7.8 mmol/l, blood glucose ≥11.1 mmol/l during an oral glucose tolerance test, or random blood glucose ≥11.1 mmol/l, together with one or more diabetes-related symptoms (weight loss, polyuria, excessive thirst, or hunger); (2) ≥2 elevated glucose concentrations in the absence of symptoms; or (3) treatment with hypoglycemic medication (insulin or an oral hypoglycemic agent). Since 1998, based on the ADA criteria, the diagnosis criterion of fasting glucose was lowered to 7.0 mmol/l. After 2010, HbA1c ≥6.5% was further included in the diagnosis criteria according to updated ADA diagnosis criteria.

The validity of self-reported T2D diagnosis has been documented previously (28,29). In a random sample of 62 cases from the NHS and 59 cases from the HPFS that were confirmed by the supplementary questionnaire, medical record review reconfirmed 61 cases (98%) and 57 cases (97%), respectively (28,29). In addition, the specificity of self-reported T2D status was assessed in a random sample of 200 participants who did not report a previous diagnosis of diabetes, with only one participant (0.5%) having an elevated fasting plasma glucose or plasma fructosamine concentrations barely above the diagnostic cut-offs .

Statistical analysis

Given BMI might be an intermediate outcome because red meat intake could promote weight gain, we further evaluated the extent to which the associations between frequency of open-flame and/or high-temperature cooking and T2D risk could be explained by BMI change and HAA intake, using a SAS macro %MEDIATE based on the work by Lin et al (30).

Results

Frequency of individual cooking methods for meats and T2D risk

During 1.74 million person-years of follow up, we documented 7,895 incident T2D cases. **Supplementary Table 2** shows the associations of frequency of individual cooking methods for chicken, fish, and red meat with risk of T2D. After multivariate adjustment including total intake of chicken, fish, and red meat, higher frequency of broiling and barbequing chicken, and higher frequency of roasting beef and grilling/barbequing steak were each associated with an increased T2D risk. In

contrast, the frequency of pan-frying chicken, pan-frying steak or hamburger, and broiling fish were not significantly associated with T2D risk (Model 2, Supplementary Table 2), which was mostly consistent with the results in our previous investigations that focused on red meat cooking methods (11). When comparing cooking frequency ≥4 times/month with <1 time/month, the pooled HR (95% CI) was 1.18 (1.12, 1.25; *P* trend=0.001) for broiling chicken, 1.09 (1.02, 1.17; *P* trend=0.01) for barbequing chicken, 1.04 (0.94, 1.16; *P* trend=0.27) for pan-frying chicken, 1.06 (0.99, 1.13; *P* trend=0.34) for broiling fish, 1.42 (1.33, 1.52; *P* trend<0.001) for roasting beef, 1.38 (1.27, 1.49; *P* trend<0.001) for grilling/barbequing steak, and 1.07 (0.84, 1.37; *P* trend=0.59) for pan-frying steak or hamburger. When baseline BMI was further adjusted or cooking methods were mutually adjusted, most of positive results were attenuated, but remained significant.

Supplementary Figure 1 shows the associations between frequency of open-flame and/or high-temperature cooking and T2D risk according to baseline BMI categories. Compared with participants who were in the lowest tertiles of open-flame and/or high-temperature cooking frequency and baseline BMI, participants in the highest tertiles had a pooled HR (95% CI) of T2D of 8.07 (7.20, 9.06). No significant interaction was observed.

Supplementary Figure 2 shows the joint associations of open-flame and/or high-temperature cooking frequency and the meat doneness preference score in relation to T2D risk. Compared with participants who were in the lowest tertiles of open-flame and/or high-temperature cooking frequency and the meat doneness preference score, participants in the highest tertiles had a pooled HR (95% CI) of T2D of 1.28 (1.18, 1.40). No significant interaction was detected.

Dietary HAA intake and T2D risk

After multivariate adjustment, higher estimated intake of HAAs was significantly associated with an increased risk of T2D (**Supplementary Table 3**). Comparing extreme quintiles, the pooled HR (95% CI) was 1.47 (1.20, 1.81; *P* trend<0.001). The results remained significant when adjusting for baseline BMI (Model 4, Supplementary Table 3). Major HAAs, including PhIP, MeIQx, and DiMeIQx, were also consistently associated with a higher T2D risk.

Frequency of high-temperature cooking, weight gain, and obesity risk

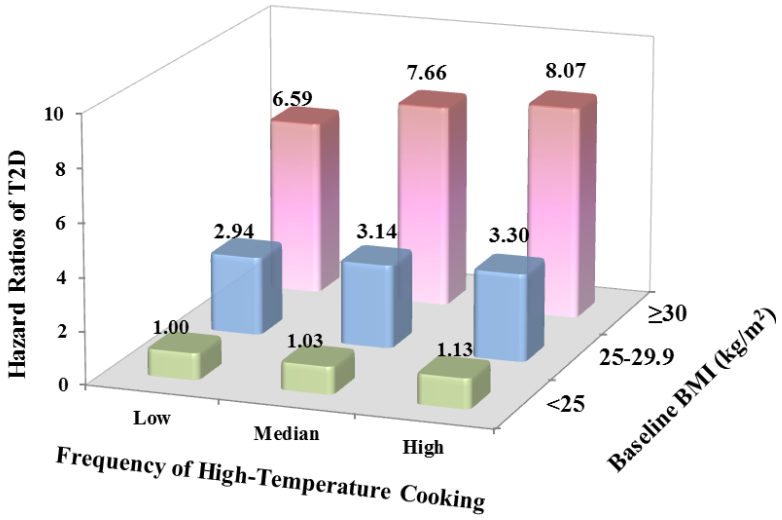
Higher frequency of open-flame and/or high-temperature cooking methods for meats was associated with a greater weight gain during the first 4-year follow-up (**Supplementary Table 4**). Positive associations were also observed for the risk of developing obesity. Comparing extreme cooking frequency, the pooled HR (95% CI) of obesity was 1.59 (1.50, 1.69; *P* trend<0.001).

Regarding high-temperature cooking and T2D risk, the associations were greatly attenuated but remained significant when further adjusting for HAA intake and BMI change during follow-up **(Supplementary Figure 3)**. Mediational analyses showed that the significant associations of open-flame and/or high-temperature cooking methods for animal flesh with T2D risk might be partially explained by HAA intake and BMI change.

SUPPLEMENTARY DATA

Supplementary Figure 1. Joint analysis of open-flame and/or high-temperature cooking frequency and baseline BMI in relation to T2D risk among participants who consumed red meat, chicken, or fish regularly (≥2 servings/week).[a]

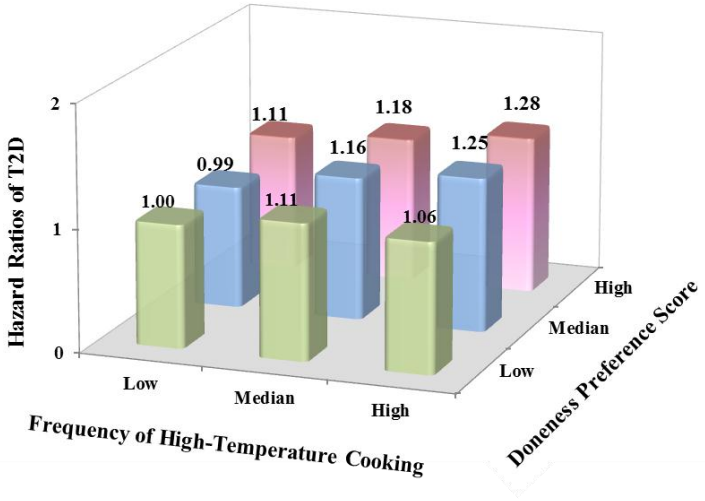
[a] Hazard ratios were adjusted for age, ethnicity, smoking status (never smoker, past smoker, or current smoker: 1-14, 15-24, or ≥25 cigarettes/day, or missing), alcohol intake (gram/day: 0, 0.1-4.9, 5.0-14.9, ≥15.0 in women; 0, 0.1–4.9, 5.0–29.9, or ≥30.0 in men; or missing), family history of diabetes (yes or no), marital status (married, not married, or missing), menopausal status and postmenopausal hormone use (pre-menopause, post-menopause (never, former, or current hormone use), or missing) (for women), physical activity (metabolic equivalent tasks/week: 0-2.9, 3-8.9, 9-17.9, 18-26.9, ≥27.0, or missing), total energy intake (kcal/day), the Alternative Healthy Eating Index without alcohol intake, and total intake of red meat, chicken, and fish.



SUPPLEMENTARY DATA

Supplementary Figure 2. Joint analysis of open-flame and/or high-temperature cooking frequency and meat doneness preference score in relation to T2D risk among participants who consumed red meat, chicken, or fish regularly (≥2 servings/week).[a]

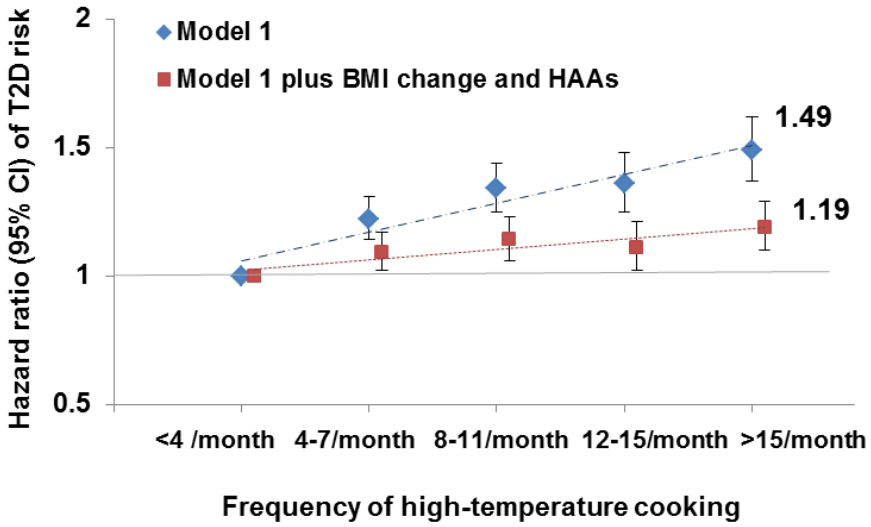
[a] Hazard ratios were adjusted for age, ethnicity, smoking status (never smoker, past smoker, or current smoker: 1-14, 15-24, or ≥25 cigarettes/day, or missing), alcohol intake (gram/day: 0, 0.1-4.9, 5.0-14.9, >15.0 in women; 0, 0.1–4.9, 5.0–29.9, or ≥30.0 in men; or missing), family history of diabetes (yes or no), marital status (married, not married, or missing), menopausal status and postmenopausal hormone use (pre-menopause, post-menopause (never, former, or current hormone use), or missing) (for women), physical activity (metabolic equivalent tasks/week: 0-2.9, 3-8.9, 9-17.9, 18-26.9, ≥27.0, or missing), total energy intake (kcal/day), the Alternative Healthy Eating Index without alcohol intake, total intake of red meat, chicken, and fish, and baseline BMI.



SUPPLEMENTARY DATA

Supplementary Figure 3. Hazard ratios (95% CI) of type 2 diabetes according to frequency of open-flame and/or high-temperature cooking of total meats with further adjustment of BMI change and HAAs [a]

[a] Hazard ratios were adjusted for age, ethnicity, smoking status (never smoker, past smoker, or current smoker: 1-14, 15-24, or ≥25 cigarettes/day, or missing), alcohol intake (gram/day: 0, 0.1-4.9, 5.0-14.9, ≥15.0 in women; 0, 0.1–4.9, 5.0–29.9, or ≥30.0 in men; or missing), family history of diabetes (yes or no), marital status (married, not married, or missing), menopausal status and postmenopausal hormone use (pre-menopause, post-menopause (never, former, or current hormone use), or missing) (for women), physical activity (metabolic equivalent tasks/week: 0-2.9, 3-8.9, 9-17.9, 18-26.9, ≥27.0, or missing), total energy intake (kcal/day), the Alternative Healthy Eating Index without alcohol intake, and total intake of chicken, fish, and red meat.



SUPPLEMENTARY DATA

Supplementary Table 1. Pearson correlation coefficients among frequency of each cooking method in participants who consumed red meat, chicken, or fish regularly (≥2 servings/week) [a]

	Pan-frying Chicken	Broiling Chicken	Barbequing Chicken	Broiling Fish	Roasting Beef	Barbequing Steak
NHS 1996						
Broiling Chicken	-0.08***	1.00				
Barbequing Chicken	-0.02***	**0.14***	1.00			
Broiling Fish	-0.04***	**0.36***	**0.17***	1.00		
Roasting Beef	0.09***	**0.10***	0.08***	0.01***	1.00	
Barbequing Steak	0.04***	0.07***	**0.33***	0.07***	**0.29***	1.00
Pan-frying steak	**0.22***	-0.03***	-0.03***	-0.05***	**0.18***	0.05***
NHS II 2001						
Broiling Chicken	-0.01***	1.00				
Barbequing Chicken	-0.04***	0.07***	1.00			
Broiling Fish	-0.03***	**0.26***	**0.12***	1.00		
Roasting Beef	0.09***	**0.12***	**0.10***	-0.003	1.00	
Barbequing Steak	0.07***	0.05***	**0.30***	0.03***	**0.33***	1.00
Pan-frying hamburger	**0.19***	0.06***	-0.02***	-0.08***	**0.27***	**0.15***
HPFS						
Broiling Chicken	-0.02***	1.00				
Barbequing Chicken	0.01	**0.16***	1.00			
Broiling Fish	-0.05***	**0.36***	**0.18***	1.00		
Roasting Beef	**0.21***	0.07***	0.06***	-0.04***	1.00	
Barbequing Steak	**0.14***	0.02***	**0.23***	0.01***	**0.39***	1.00
Pan-frying hamburger	**0.29***	-0.02***	-0.03***	**-0.11***	**0.37***	**0.23***

[a] Adjusted for age and ethnicity. *** $P<0.001$.

SUPPLEMENTARY DATA

Supplementary Table 2. Pooled hazard ratios (95% confidence intervals) of type 2 diabetes according to frequencies of individual cooking method for red meat, chicken, or fish among participants who consumed regularly (≥2 servings/week)

	Frequency of Cooking				
	<1 time/month	1 time/month	2-3 times/month	≥4 times/month	*P* trend
Pan-frying Chicken					
Model 1	1.00	1.18 (1.10, 1.28)	1.13 (1.05, 1.22)	1.06 (0.96, 1.17)	0.16
P-heterogeneity		0.27	0.62	0.02	0.02
Model 2	1.00	1.18 (1.10, 1.27)	1.12 (1.04, 1.21)	1.04 (0.94, 1.16)	0.27
P-heterogeneity		0.25	0.64	0.02	0.03
Broiling Chicken					
Model 1	1.00	1.17 (1.09, 1.26)	1.18 (1.10, 1.25)	1.22 (1.15, 1.28)	0.001
P-heterogeneity		0.67	0.10	0.01	0.01
Model 2		1.17 (1.09, 1.26)	1.16 (1.09, 1.24)	1.18 (1.12, 1.25)	0.001
P-heterogeneity	1.00	0.66	0.06	0.01	0.01
Barbequing Chicken					
Model 1	1.00	1.06 (1.00, 1.13)	1.16 (1.09, 1.23)	1.13 (1.05, 1.20)	<0.001
P-heterogeneity		0.13	0.93	0.21	0.23
Model 2		1.06 (0.99, 1.13)	1.15 (1.08, 1.22)	1.09 (1.02, 1.17)	0.01
P-heterogeneity	1.00	0.12	0.91	0.17	0.17
Broiling Fish					
Model 1	1.00	1.09 (1.02, 1.16)	1.10 (1.04, 1.17)	1.11 (1.04, 1.19)	0.01
P-heterogeneity		0.57	0.55	0.28	0.15
Model 2		1.07 (1.01, 1.15)	1.08 (1.01, 1.15)	1.06 (0.98, 1.13)	0.34
P-heterogeneity	1.00	0.52	0.74	0.69	0.53
Pan-frying Steak [a]/Hamburger [b]					
Model 1	1.00	1.12 (1.04, 1.21)	1.21 (1.11, 1.32)	1.17 (0.94, 1.45)	0.13
P-heterogeneity		0.89	0.24	0.01	0.001
Model 2		1.09 (1.01, 1.18)	1.16 (1.06, 1.27)	1.07 (0.84, 1.37)	0.59
P-heterogeneity	1.00	0.84	0.23	0.01	0.001
Roasting Beef					
Model 1	1.00	1.16 (1.09, 1.24)	1.37 (1.29, 1.45)	1.52 (1.42, 1.63)	<0.001
P-heterogeneity		0.62	0.29	0.16	0.04
Model 2		1.13 (1.06, 1.20)	1.31 (1.23, 1.39)	1.42 (1.33, 1.52)	<0.001
P-heterogeneity	1.00	0.69	0.28	0.08	0.01
Grilling/Barbequing Steak					
Model 1	1.00	1.18 (1.11, 1.26)	1.32 (1.24, 1.40)	1.47 (1.36, 1.59)	<0.001
P-heterogeneity		0.91	0.84	0.10	0.18
Model 2		1.15 (1.08, 1.22)	1.26 (1.19, 1.34)	1.38 (1.27, 1.49)	<0.001
P-heterogeneity	1.00	0.85	0.67	0.04	0.06

[a] Only in NHS; [b] Only in NHS II and HPFS;

Model 1, adjusted for age, ethnicity, smoking status (never smoker, past smoker, or current smoker: 1-14, 15-24, or ≥25 cigarettes/day, or missing), alcohol intake (gram/day: 0, 0.1-4.9, 5.0-14.9, ≥15.0 in women; 0, 0.1–4.9, 5.0–29.9, or ≥30.0 in men; or missing), family history of diabetes (yes or no), marital status (married, not married, or missing), menopausal status and postmenopausal hormone use (pre-menopause, post-menopause (never, former, or current hormone use), or missing) (for women), physical activity (metabolic equivalent tasks/week: 0-2.9, 3-8.9, 9-17.9, 18-26.9, ≥27.0, or missing), total energy intake (kcal/day), and the Alternative Healthy Eating Index without alcohol intake; Model 2, further adjusted for total intake of red meat, chicken, and fish.

SUPPLEMENTARY DATA

Supplementary Table 3. Hazard ratios (95% confidence intervals) of type 2 diabetes according to intake of heterocyclic aromatic amines (HAAs) among participants who consumed red meat, chicken, or fish regularly (≥2 servings/week)

	Quintile of HAAs					
	Q1	Q2	Q3	Q4	Q5	P_{trend}
NHS						
Cases/person-years	631/146434	708/146226	808/146147	919/146074	994/145870	
Model 1	1.00	1.12 (1.00, 1.24)	1.27 (1.15, 1.41)	1.45 (1.31, 1.60)	1.57 (1.42, 1.73)	<0.001
Model 2	1.00	1.10 (0.99, 1.22)	1.25 (1.13, 1.39)	1.40 (1.26, 1.55)	1.50 (1.35, 1.66)	<0.001
Model 3	1.00	1.06 (0.95, 1.19)	1.20 (1.08, 1.33)	1.31 (1.18, 1.46)	1.37 (1.23, 1.52)	<0.001
Model 4	1.00	0.99 (0.89, 1.10)	1.10 (0.99, 1.22)	1.19 (1.07, 1.32)	1.20 (1.08, 1.33)	<0.001
NHS II						
Cases/person-years	334/138086	374/138040	437/137920	496/137911	706/137727	
Model 1	1.00	1.17 (1.01, 1.36)	1.38 (1.20, 1.60)	1.59 (1.38, 1.82)	2.26 (1.98, 2.58)	<0.001
Model 2	1.00	1.14 (0.98, 1.32)	1.31 (1.14, 1.52)	1.48 (1.28, 1.70)	1.96 (1.71, 2.24)	<0.001
Model 3	1.00	1.12 (0.97, 1.30)	1.28 (1.11, 1.48)	1.42 (1.23, 1.63)	1.81 (1.58, 2.08)	<0.001
Model 4	1.00	1.02 (0.88, 1.18)	1.12 (0.97, 1.30)	1.16 (1.00, 1.33)	1.38 (1.20, 1.58)	<0.001
HPFS						
Cases/person-years	201/56868	260/56806	274/56802	291/56805	295/56829	
Model 1	1.00	1.31 (1.09, 1.57)	1.38 (1.15, 1.66)	1.48 (1.24, 1.77)	1.52 (1.27, 1.82)	<0.001
Model 2	1.00	1.29 (1.07, 1.55)	1.35 (1.12, 1.63)	1.45 (1.21, 1.75)	1.46 (1.21, 1.76)	<0.001
Model 3	1.00	1.24 (1.03, 1.49)	1.26 (1.05, 1.52)	1.31 (1.09, 1.59)	1.27 (1.05, 1.55)	0.07
Model 4	1.00	1.17 (0.97, 1.41)	1.20 (1.00, 1.45)	1.22 (1.01, 1.47)	1.23 (1.01, 1.48)	0.09
Pooled						
Model 3	1.00	1.11 (1.03, 1.20)	1.23 (1.14, 1.33)	1.34 (1.24, 1.45)	1.47 (1.20, 1.81)	<0.001
P-heterogeneity		0.39	0.76	0.69	0.01	0.04
Model 4	1.00	1.03 (0.94, 1.13)	1.12 (1.04, 1.21)	1.18 (1.10, 1.28)	1.26 (1.15, 1.38)	<0.001
P-heterogeneity		0.29	0.73	0.91	0.26	0.64

Model 1, adjusted for age;

Model 2, further adjusted for ethnicity, smoking status (never smoker, past smoker, or current smoker: 1-14, 15-24, or ≥25 cigarettes/day, or missing), alcohol intake (gram/day: 0, 0.1-4.9, 5.0-14.9, or >15.0 in women; 0, 0.1–4.9, 5.0–29.9, or ≥30.0 in men; or missing), family history of diabetes (yes or no), marital status (married, not married, or missing), menopause status and postmenopausal hormones use (pre-menopause, post-menopause (never, former, or current hormone use), or missing) (for women), physical activity (metabolic equivalent tasks/week: 0-2.9, 3-8.9, 9-17.9, 18-26.9, ≥27.0, or missing), total energy intake (kcal/day), and the Alternative Healthy Eating Index without alcohol intake;

Model 3, model 2 plus further adjusted for total intake of chicken, fish, and red meat;

Model 4, model 2 plus further adjusted for baseline BMI.

SUPPLEMENTARY DATA

Supplementary Table 4. Weight changes (4 year) and risk of obesity according to the frequency of open-flame and/or high-temperature cooking among participants who consumed red meat, chicken, or fish regularly (≥2 servings/week)

		Frequency of open-flame and/or high-temperature cooking					
		<4 times/month	4-7 times/month	8-11 times/month	12-15 times/month	>15 times/month	P_{trend}
Weight change (kg) [a]							
NHS	Model 1	1.12±0.08	1.11±0.06	1.28±0.07	1.39±0.09	1.77±0.09	<0.001
	Model 2	1.16±0.08	1.11±0.06	1.28±0.07	1.37±0.09	1.74±0.09	<0.001
NHS II	Model 1	1.10±0.07	1.24±0.05	1.52±0.06	1.57±0.07	1.88±0.07	<0.001
	Model 2	1.14±0.07	1.24±0.05	1.51±0.06	1.56±0.07	1.85±0.07	<0.001
HPFS	Model 1	0.88±0.13	1.04±0.09	1.00±0.08	0.97±0.11	1.06±0.10	0.18
	Model 2	0.86±0.13	1.03±0.09	1.00±0.08	0.97±0.11	1.07±0.10	0.14
Hazard ratios of obesity							
NHS	Model 1	1.00	1.16 (1.08, 1.26)	1.27 (1.16, 1.38)	1.35 (1.23, 1.49)	1.64 (1.50, 1.80)	<0.001
	Model 2	1.00	1.13 (1.05, 1.23)	1.21 (1.11, 1.31)	1.27 (1.15, 1.40)	1.50 (1.37, 1.65)	<0.001
NHS II	Model 1	1.00	1.21 (1.11, 1.31)	1.38 (1.27, 1.50)	1.52 (1.39, 1.67)	1.74 (1.59, 1.89)	<0.001
	Model 2	1.00	1.19 (1.10, 1.29)	1.36 (1.25, 1.48)	1.50 (1.37, 1.64)	1.70 (1.56, 1.86)	<0.001
HPFS	Model 1	1.00	1.18 (1.00, 1.39)	1.29 (1.09, 1.52)	1.39 (1.16, 1.66)	1.54 (1.29, 1.82)	<0.001
	Model 2	1.00	1.15 (0.97, 1.36)	1.24 (1.05, 1.46)	1.34 (1.12, 1.61)	1.47 (1.24, 1.76)	<0.001
Pooled	Model 2	1.00	1.16 (1.10, 1.22)	1.28 (1.21, 1.35)	1.39 (1.30, 1.47)	1.59 (1.50, 1.69)	<0.001
	P-heterogeneity	1.00	0.69	0.14	0.04	0.12	0.06

[a] For weight change, analyses were restricted to the participants who were younger than 60 years at baseline. In addition, baseline body weight was included in the model. Data are least squared means ± standard error calculated from general linear model or hazard ratios calculated from Cox proportional hazards regression. Model 1, adjusted for age, ethnicity, smoking status (never smoker, past smoker, or current smoker: 1-14, 15-24, or ≥25 cigarettes/day, or missing), alcohol intake (gram/day: 0, 0.1-4.9, 5.0-14.9, ≥15.0 in women; 0, 0.1–4.9, 5.0–29.9, or ≥30.0 in men; or missing), family history of diabetes (yes or no), marital status (married, not married, or missing), menopausal status and postmenopausal hormone use (pre-menopause, post-menopause (never, former, or current hormone use), or missing) (for women), physical activity (metabolic equivalent tasks/week: 0-2.9, 3-8.9, 9-17.9, 18-26.9, ≥27.0, or missing), total energy intake (kcal/day), and the Alternative Healthy Eating Index without alcohol intake; Model 2, further adjusted for total intake of red meat, chicken, and fish.

SUPPLEMENTARY DATA

Supplementary Table 5. Stratified analysis of the associations [hazard ratio (95% CI)] between open-flame and/or high-temperature cooking and risk of type 2 diabetes among participants who consumed red meat, chicken, or fish regularly (≥2 servings/week) [a]

	Frequency of open-flame and/or high-temperature cooking					
	<4 times/month	4-6 times/month	7-9 times/month	10-12 times/month	>12 times/month	P_{trend}
Age						
Age<60	1.00	1.29 (1.17, 1.42)	1.40 (1.27, 1.56)	1.46 (1.31, 1.64)	1.76 (1.58, 1.96)	<0.001
P-heterogeneity		0.19	0.43	0.12	0.01	0.01
Age≥60	1.00	1.22 (1.13, 1.33)	1.34 (1.22, 1.46)	1.34 (1.22, 1.48)	1.45 (1.32, 1.60)	<0.001
P-heterogeneity		0.13	0.29	0.14	0.01	0.01
Body mass index (BMI)						
BMI<30	1.00	1.14 (1.04, 1.26)	1.17 (1.05, 1.29)	1.24 (1.10, 1.39)	1.27 (1.13, 1.42)	<0.001
P-heterogeneity		0.91	0.97	0.34	0.15	0.04
BMI≥30	1.00	1.19 (1.08, 1.32)	1.31 (1.18, 1.46)	1.22 (1.08, 1.37)	1.34 (1.19, 1.50)	<0.001
P-heterogeneity		0.42	0.98	0.94	0.41	0.30
Physical activity						
< median level	1.00	1.22 (1.13, 1.33)	1.35 (1.24, 1.48)	1.40 (1.26, 1.54)	1.45 (1.31, 1.60)	<0.001
P-heterogeneity		0.51	0.37	0.79	0.27	0.10
≥ median level	1.00	1.18 (1.03, 1.36)	1.27 (1.11, 1.46)	1.24 (1.06, 1.44)	1.46 (1.26, 1.69)	<0.001
P-heterogeneity		0.11	0.04	0.03	0.01	0.01
Current smoking status						
Smoker	1.00	1.20 (1.12, 1.30)	1.34 (1.24, 1.45)	1.34 (1.23, 1.47)	1.47 (1.34, 1.60)	<0.001
P-heterogeneity		0.10	0.23	0.14	0.01	0.01
Non-smoker	1.00	1.27 (1.03, 1.56)	1.29 (1.04, 1.61)	1.44 (1.12, 1.85)	1.61 (1.25, 2.06)	<0.001
P-heterogeneity		0.41	0.13	0.34	0.83	0.97

[a] Hazard ratios were adjusted for age, ethnicity, smoking status (never smoker, past smoker, or current smoker: 1-14, 15-24, ≥25 cigarettes/day, or missing), alcohol intake (gram/day: 0, 0.1-4.9, 5.0-14.9, ≥15.0 in women; 0, 0.1–4.9, 5.0–29.9, or ≥30.0 in men; or missing), family history of diabetes (yes or no), marital status (married, not married, or missing), menopausal status and postmenopausal hormone use (pre-menopause, post-menopause (never, former, or current hormone use), or missing) (for women), physical activity (metabolic equivalent tasks/week: 0-2.9, 3-8.9, 9-17.9, 18-26.9, ≥27.0, or missing), total energy intake (kcal/day), the Alternative Healthy Eating Index without alcohol intake, and total intake of red meat, chicken, and fish. Stratifying variables were not included in the model when analyses were stratified by these variables individually.