

Online Appendix

Methods

Assessments of lifestyle factors

At baseline and every 2-4 years thereafter, a validated semi-quantitative FFQ with approximately 131 food items (1-3) was administered to collect and update dietary information. The FFQ was designed to measure the usual diet consumed over the past year. Nutrient intake was computed by multiplying the frequency of consumption of a food with a pre-specified portion size by its nutrient content and summing this value across all relevant food items (1). Information on smoking status and body weight was obtained from biennial follow-up questionnaire. The accuracy of self-reported body weight was validated in a random subset of participants in the NHS (N=140) and HPFS (n=123) (4). The Spearman correlation coefficient between self-reported and measured body weight was 0.97 for both cohorts (4). BMI was calculated as self-reported weight in kilograms divided by the square of height in meters (kg/m^2). Alcohol consumption was assessed using the FFQs, based on questions for daily consumption of beer, wine, and spirits during the past year (5). Information on the average time per week participants spent on leisure-time physical activities, including walking or hiking outdoors, running, jogging, bicycling, tennis/squash/racquetball, lap swimming, and calisthenics/aerobics/rowing machine exercise was updated every two years using a validated questionnaire (6). In addition, information on potential confounders, including age, ethnicity, menopausal status and use of postmenopausal hormones (women only), use of multivitamins, use of aspirin, family history of diabetes or myocardial infarction (MI), presence or absence of hypertension or hypercholesterolemia, and medication use (such as insulin, antihypertensive drug, or cholesterol-lowering medication) was obtained via biennial questionnaires. In addition, we also asked

diabetic patients to report recent hemoglobin A1c (HbA1c) levels in supplementary questionnaires administered in 2000 and 2005 in the NHS and 2000, 2004, and 2008 in the HPFS.

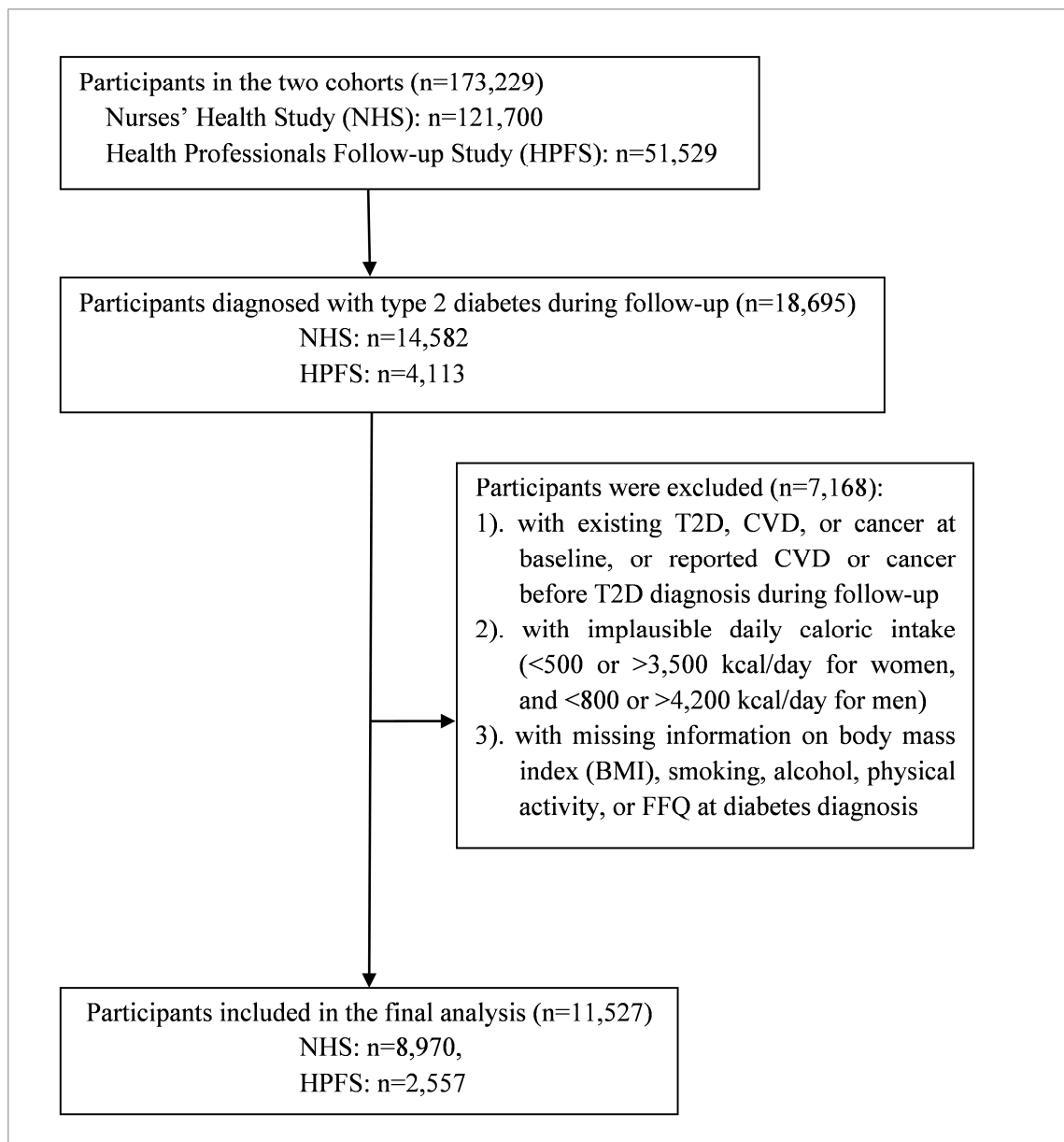
Ascertainment of T2D

The National Diabetes Data Group criteria were applied to ascertain T2D diagnosis before 1998:

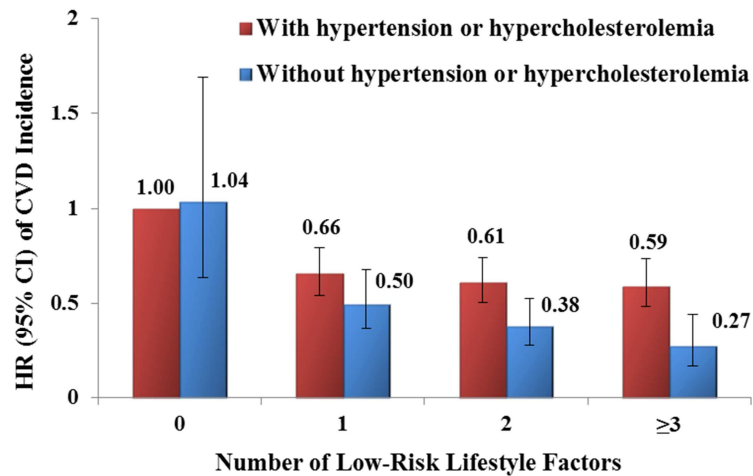
1) fasting glucose levels ≥ 126 mmol/l, blood glucose ≥ 200 mmol/l during an oral glucose tolerance test, or random blood glucose ≥ 200 mmol/l, together with one or more diabetes-related symptoms (weight loss, polyuria, excessive thirst, or hunger); 2) elevated glucose levels on more than one occasion in the absence of symptoms; or 3) treatment with hypoglycemic medication (insulin or an oral hypoglycemic agent) (7). Since 1998, the diagnosis criterion of fasting glucose was lowered to 7.0 mmol/l by ADA criteria. After 2010, HbA1c $\geq 6.5\%$ was further included in the diagnosis criteria (8).

Reference:

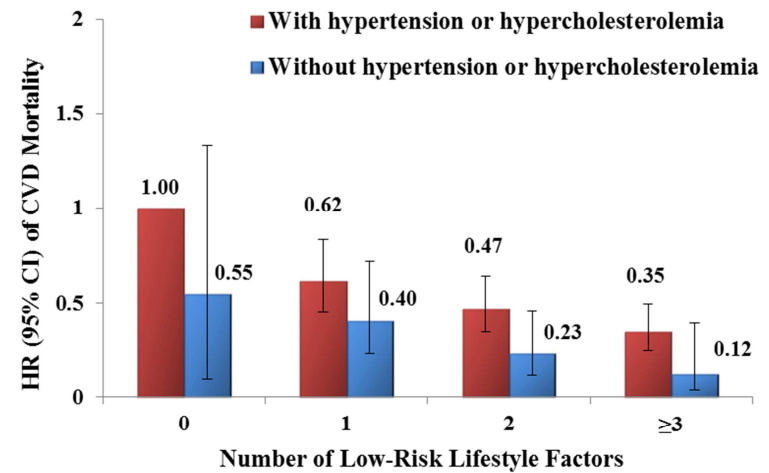
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2. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol* 1985;122:51-65
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4. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. *Epidemiology* 1990;1:466-473
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6. Wolf AM, Hunter DJ, Colditz GA, et al. Reproducibility and validity of a self-administered physical activity questionnaire. *Int J Epidemiol* 1994;23:991-999
7. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group. *Diabetes* 1979;28:1039-1057
8. Standards of medical care in diabetes--2010. *Diabetes Care* 2010;33 Suppl 1:S11-61



Online Figure 1. Flowchart of participants included in the analysis.



A



B

Online Figure 2. Hazard ratio (95% CI) of CVD incidence (A) and CVD mortality (B) according to number of low-risk lifestyle factors* among diabetic patients with and without hypertension and/or hypercholesterolemia†

* Low-risk lifestyle factors: non-smoking, moderate to vigorous physical activity (≥ 150 min/week), high quality diet (top two fifths of Alternative Healthy Eating Index), and moderate alcohol consumption (5-15 g/day for women and 5-30 g/day for men).

† Adjusted for age (years), sex (men or women), ethnicity (Caucasian, African American, Hispanic, or Asian), body mass index at diabetes diagnosis (<25.0 , $25.0-29.9$, $30.0-34.9$, ≥ 35.0 kg/m²), menopausal status (women only), family history of diabetes (yes/no), family history of myocardial infarction (yes/no), current aspirin use (yes/no), current multivitamin use (yes/no), and diabetes duration (years).

Online Table 1. Hazard ratio (95% CI) of CVD, CHD, and stroke incidence according to individual and combined lifestyle factors after diabetes diagnosis with further adjustment of presence of hypertension or hypercholesterolemia and medication use *

	Person Years	CVD Incidence		CHD Incidence		Stroke Incidence	
		Cases	HR† (95% CI)	Cases	HR† (95% CI)	Cases	HR† (95% CI)
Cigarette smoking							
Never	66079	902	1.00 (ref)	696	1.00 (ref)	217	1.00 (ref)
Past	72009	1108	1.07 (0.98-1.17)	917	1.12 (1.01-1.24)	207	0.91 (0.75-1.10)
Current 1-14 cigarettes/day	5669	124	1.79 (1.48-2.17)	94	1.75 (1.40-2.18)	31	1.94 (1.32-2.85)
Current ≥15 cigarettes/day	7209	177	2.10 (1.78-2.49)	137	2.10 (1.73-2.55)	43	2.12 (1.49-3.01)
Alcohol consumption (g/day)							
0	81615	1286	1.00 (ref)	1015	1.00 (ref)	288	1.00 (ref)
1.0-4.9	37982	533	0.89 (0.80-0.99)	423	0.86 (0.77-0.97)	116	0.99 (0.79-1.24)
5.0-14.9	18333	304	0.93 (0.81-1.06)	249	0.91 (0.78-1.06)	61	1.06 (0.79-1.42)
≥15.0	13035	188	0.72 (0.61-0.85)	157	0.70 (0.59-0.84)	33	0.77 (0.53-1.13)
Physical activity (hours/week)							
0	85436	1421	1.00 (ref)	1112	1.00 (ref)	326	1.00 (ref)
0.1-0.9	28895	396	0.96 (0.85-1.08)	323	0.99 (0.87-1.13)	78	0.84 (0.65-1.09)
1.0-3.4	14680	220	1.03 (0.89-1.20)	183	1.07 (0.91-1.25)	39	0.89 (0.63-1.25)
≥3.5	21955	274	0.88 (0.77-1.01)	226	0.89 (0.77-1.04)	55	0.88 (0.65-1.20)
Alternative healthy eating index (quintiles)							
Q 1	31223	517	1.00 (ref)	400	1.00 (ref)	121	1.00 (ref)
Q 2	30389	487	0.97 (0.86-1.10)	397	1.02 (0.89-1.17)	100	0.88 (0.67-1.15)
Q 3	30208	437	0.89 (0.78-1.01)	348	0.90 (0.78-1.05)	92	0.83 (0.63-1.10)
Q 4	30604	474	0.93 (0.82-1.05)	379	0.95 (0.82-1.09)	101	0.90 (0.68-1.18)
Q 5	28542	396	0.85 (0.74-0.97)	320	0.87 (0.75-1.02)	84	0.80 (0.60-1.08)
Number of low-risk factors ‡							
None	6443	148	1.00 (ref)	113	1.00 (ref)	38	1.00 (ref)
One	63036	987	0.61 (0.51-0.73)	782	0.64 (0.52-0.78)	212	0.51 (0.36-0.73)
Two	56610	840	0.55 (0.46-0.66)	658	0.56 (0.45-0.68)	199	0.54 (0.38-0.78)
Three or more	24877	336	0.48 (0.40-0.59)	291	0.53 (0.42-0.66)	49	0.33 (0.21-0.52)

* Further adjustment of presence of hypertension or hypercholesterolemia and use of antihypertensive or cholesterol-lowering drugs, based on the model in Table 2.

† Adjusted for age (years), sex (men or women), ethnicity (Caucasian, African American, Hispanic, or Asian), body mass index at diabetes diagnosis (<25.0, 25.0-29.9, 30.0-34.9, ≥35.0 kg/m²), menopausal status (women only), family history

of diabetes (yes/no), family history of myocardial infarction (yes/no), current aspirin use (yes/no), current multivitamin use (yes/no), diabetes duration (years), presence of hypertension or hypercholesterolemia (yes/no), and use of antihypertensive or cholesterol-lowering drugs (yes/no). Individual lifestyle factors were mutually adjusted.

‡ Low-risk lifestyle factors: non-smoking, moderate to vigorous physical activity (≥ 150 min/week), high quality diet (top two fifths of Alternative Healthy Eating Index), and moderate alcohol consumption (5-15 g/day for women and 5-30 g/day for men).

Online Table 2. Hazard ratio (95% CI) of CVD incidence and mortality according to combined lifestyle factors after diabetes diagnosis with further adjustment of diabetes medication use and HbA1c levels in a subset of participants (n=4,650) *

	Person Years	CVD Incidence		CHD Incidence		Stroke Incidence		CVD Mortality	
		Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)
Number of low-risk factors †									
None	2582	57	1.00 (ref)	46	1.00 (ref)	13	1.00 (ref)	9	1.00 (ref)
One	26427	439	0.64 (0.48-0.86)	355	0.62 (0.45-0.85)	87	0.62 (0.33-1.15)	133	0.66 (0.33-1.34)
Two	23587	398	0.62 (0.46-0.83)	323	0.60 (0.44-0.83)	80	0.63 (0.34-1.17)	107	0.58 (0.29-1.17)
Three or more	10707	156	0.51 (0.37-0.70)	135	0.51 (0.36-0.72)	23	0.43 (0.21-0.89)	38	0.47 (0.22-0.99)

* Adjusted for age (years), sex (men or women), ethnicity (Caucasian, African American, Hispanic, or Asian), body mass index at diabetes diagnosis (<25.0, 25-29.9, 30.0-34.9, ≥ 35.0 kg/m²), menopausal status (women only), family history of diabetes (yes/no), family history of myocardial infarction (yes/no), current aspirin use (yes/no), current multivitamin use (yes/no), diabetes duration (years), presence of hypertension or hypercholesterolemia (yes/no), use of antihypertensive or cholesterol-lowering drugs (yes/no), diabetes medication use (oral medication only, insulin use, or others), and HbA1c levels (<7%, 7-7.9%, 8-9.9%, 10-11.9%, and $\geq 12\%$).

† Low-risk lifestyle factors: non-smoking, moderate to vigorous physical activity (≥ 150 min/week), high quality diet (top two fifths of Alternative Healthy Eating Index), and moderate alcohol consumption (5-15 g/day for women and 5-30 g/day for men).

Online Table 3. Hazard ratio (95% CI) of CVD incidence and mortality according to individual and combined lifestyle factors after diabetes diagnosis with further inclusion of BMI at diagnosis *

	Person Years	CVD Incidence		CHD Incidence		Stroke Incidence		CVD Mortality	
		Cases	HR [†] (95% CI)	Cases	HR [†] (95% CI)	Cases	HR [†] (95% CI)	Cases	HR [†] (95% CI)
BMI at diagnosis (kg/m²)									
<25.0	24395	364	1.00 (ref)	258	1.00 (ref)	109	1.00 (ref)	159	1.00 (ref)
25.0-29.9	52910	880	1.12 (0.99-1.27)	723	1.26 (1.09-1.45)	170	0.83 (0.65-1.06)	294	0.92 (0.76-1.12)
30.0-34.9	42094	647	1.14 (1.01-1.31)	527	1.27 (1.09-1.49)	132	0.87 (0.67-1.13)	232	1.10 (0.89-1.36)
≥35.0	31567	420	1.15 (1.00-1.34)	336	1.25 (1.05-1.49)	87	0.92 (0.68-1.25)	173	1.32 (1.05-1.66)
Cigarette smoking									
Never	66079	902	1.00 (ref)	696	1.00 (ref)	217	1.00 (ref)	320	1.00 (ref)
Past	72009	1108	1.09 (0.99-1.19)	917	1.14 (1.03-1.26)	207	0.91 (0.75-1.11)	457	1.27 (1.09-1.47)
Current 1-14 cigarettes/day	5669	124	1.78 (1.47-2.16)	94	1.74 (1.40-2.17)	31	1.88 (1.28-2.76)	35	1.57 (1.10-2.24)
Current ≥15 cigarettes/day	7209	177	2.09 (1.76-2.47)	137	2.09 (1.73-2.54)	43	2.08 (1.47-2.95)	46	2.21 (1.60-3.04)
Alcohol consumption (g/day)									
0	81615	1286	1.00 (ref)	1015	1.00 (ref)	288	1.00 (ref)	555	1.00 (ref)
1.0-4.9	37982	533	0.89 (0.80-0.99)	423	0.86 (0.77-0.97)	116	0.99 (0.79-1.24)	163	0.82 (0.69-0.99)
5.0-14.9	18333	304	0.93 (0.81-1.06)	249	0.90 (0.78-1.05)	61	1.06 (0.79-1.41)	73	0.62 (0.48-0.80)
≥15.0	13035	188	0.73 (0.62-0.86)	157	0.71 (0.59-0.85)	33	0.78 (0.53-1.14)	67	0.81 (0.62-1.07)
Physical activity (hours/week)									
0	85436	1421	1.00 (ref)	1112	1.00 (ref)	326	1.00 (ref)	629	1.00 (ref)

0.1-0.9	28895	396	0.94 (0.84-1.06)	323	0.98 (0.86-1.11)	78	0.82 (0.63-1.06)	121	0.79 (0.65-0.97)
1.0-3.4	14680	220	1.02 (0.88-1.18)	183	1.05 (0.90-1.24)	39	0.87 (0.62-1.23)	46	0.65 (0.48-0.88)
≥3.5	21955	274	0.87 (0.76-0.99)	226	0.88 (0.75-1.02)	55	0.86 (0.64-1.17)	62	0.62 (0.47-0.82)
Alternative healthy eating index (quintiles)									
Q 1	31223	517	1.00 (ref)	400	1.00 (ref)	121	1.00 (ref)	213	1.00 (ref)
Q 2	30389	487	0.97 (0.86-1.11)	397	1.02 (0.89-1.18)	100	0.87 (0.66-1.13)	188	0.97 (0.79-1.19)
Q 3	30208	437	0.89 (0.79-1.02)	348	0.91 (0.79-1.05)	92	0.83 (0.63-1.09)	168	0.90 (0.74-1.11)
Q 4	30604	474	0.93 (0.82-1.06)	379	0.96 (0.83-1.10)	101	0.88 (0.67-1.15)	158	0.84 (0.68-1.04)
Q 5	28542	396	0.84 (0.74-0.97)	320	0.87 (0.75-1.02)	84	0.78 (0.59-1.04)	131	0.77 (0.62-0.97)
Number of low-risk factors‡									
None	2867	61	1.00 (ref)	50	1.00 (ref)	13	1.00 (ref)	19	1.00 (ref)
One	38714	621	0.68 (0.52-0.89)	492	0.66 (0.49-0.88)	134	0.69 (0.38-1.24)	264	0.65 (0.40-1.04)
Two	55463	849	0.58 (0.44-0.75)	665	0.55 (0.41-0.74)	196	0.63 (0.35-1.13)	340	0.49 (0.30-0.78)
Three or more	53922	780	0.50 (0.38-0.65)	637	0.49 (0.36-0.66)	155	0.51 (0.28-0.92)	235	0.32 (0.20-0.52)

* Time-varying variables (except BMI) were used in the model. Few patients (n=24) had BMI<18.5 kg/m² at diagnosis in the study. BMI: body mass index.

† Adjusted for age (years), sex (men or women), ethnicity (Caucasian, African American, Hispanic, or Asian), menopausal status (women only), family history of diabetes (yes/no), family history of myocardial infarction (yes/no), current aspirin use (yes/no), current multivitamin use (yes/no), and diabetes duration (years). Individual lifestyle factors were mutually adjusted.

‡ Low-risk lifestyle factors: 18.5≤BMI at diabetes diagnosis<25.0 kg/m², non-smoking, moderate to vigorous physical activity (≥150 min/week), high quality diet (top two fifths of Alternative Healthy Eating Index), and moderate alcohol consumption (5-15 g/day for women and 5-30 g/day for men).

Online Table 4. Hazard ratio (95% CI) of CVD incidence and mortality according to different combinations of low-risk lifestyle factors after diabetes diagnosis*

	Person Years	CVD Incidence		CVD Mortality	
		Cases	HR† (95% CI)	Cases	HR† (95% CI)
Two low-risk factors (high quality diet, moderate alcohol consumption) ‡					
None	74624	1198	1.00 (ref)	511	1.00 (ref)
One or more	76902	1113	0.91 (0.84-1.00)	347	0.81 (0.71-0.94)
Three low-risk factors (above two plus moderate to vigorous physical activity) ‡					
None	64810	1020	1.00 (ref)	442	1.00 (ref)
One	59962	918	0.94 (0.86-0.99)	328	0.78 (0.68-0.90)
Two or more	26654	373	0.85 (0.75-0.96)	88	0.53 (0.42-0.66)
Four low-risk factors (above three plus non-smoking) ‡					
None	6443	148	1.00 (ref)	47	1.00 (ref)
One	63036	987	0.62 (0.52-0.74)	442	0.63 (0.46-0.86)
Two	56610	840	0.55 (0.46-0.66)	294	0.46 (0.34-0.64)
Three or more	24877	336	0.48 (0.40-0.59)	75	0.32 (0.22-0.47)

* Low-risk lifestyle factors: $18.5 \leq \text{BMI}$ at diabetes diagnosis $< 25.0 \text{ kg/m}^2$, non-smoking, moderate to vigorous physical activity (≥ 150 min/week), high quality diet (top two fifths of Alternative Healthy Eating Index), and moderate alcohol consumption (5-15 g/day for women and 5-30 g/day for men).

† Adjusted for age (years), sex (men or women), ethnicity (Caucasian, African American, Hispanic, or Asian), menopausal status (women only), family history of diabetes (yes/no), family history of myocardial infarction (yes/no), current aspirin use (yes/no), current multivitamin use (yes/no), and diabetes duration (years).

‡ Each lifestyle factor was further adjusted when they were not included in the low-risk lifestyle score.

Online Table 5. Hazard ratio (95% CI) of CVD incidence and mortality according to individual and combined lifestyle factors shortly before diabetes diagnosis

	Person Years	CVD Incidence		CHD Incidence		Stroke Incidence		CVD Mortality	
		Cases	HR* (95% CI)	Cases	HR* (95% CI)	Cases	HR* (95% CI)	Cases	HR* (95% CI)
BMI (kg/m²)									
<25.0	23982	359	1.00 (ref)	256	1.00 (ref)	106	1.00 (ref)	146	1.00 (ref)
25.0-29.9	52391	844	1.08 (0.95-1.23)	702	1.22 (1.05-1.41)	155	0.79 (0.61-1.02)	287	0.94 (0.76-1.15)
30.0-34.9	40204	633	1.19 (1.04-1.37)	520	1.33 (1.14-1.56)	122	0.90 (0.69-1.18)	214	1.22 (0.98-1.52)
≥35.0	28705	392	1.21 (1.04-1.41)	306	1.25 (1.04-1.49)	89	1.19 (0.88-1.61)	154	1.72 (1.35-2.19)
Cigarette smoking									
Never	65362	896	1.00 (ref)	695	1.00 (ref)	211	1.00 (ref)	315	1.00 (ref)
Past	61204	898	1.05 (0.95-1.16)	750	1.13 (1.01-1.26)	160	0.81 (0.66-1.01)	319	1.06 (0.90-1.26)
Current 1-14 cigarettes/day	6664	145	1.79 (1.49-2.14)	120	1.93 (1.58-2.35)	25	1.29 (0.84-1.97)	41	1.70 (1.23-2.31)
Current ≥15 cigarettes/day	12053	289	1.91 (1.66-2.20)	219	1.88 (1.60-2.21)	76	2.08 (1.57-2.75)	116	2.58 (2.07-3.22)
Alcohol consumption (g/day)									
0	65999	996	1.00 (ref)	796	1.00 (ref)	210	1.00 (ref)	360	1.00 (ref)
1.0-4.9	43891	675	0.96 (0.87-1.06)	532	0.93 (0.83-1.04)	153	1.14 (0.92-1.42)	226	0.84 (0.71-1.00)
5.0-14.9	21614	336	0.83 (0.73-0.95)	276	0.81 (0.70-0.93)	66	0.98 (0.73-1.30)	122	0.82 (0.66-1.03)
≥15.0	13779	221	0.80 (0.68-0.94)	180	0.77 (0.64-0.91)	43	0.99 (0.70-1.41)	83	0.85 (0.66-1.10)
Physical activity (hours/week)									

0	68326	971	1.00 (ref)	765	1.00 (ref)	212	1.00 (ref)	332	1.00 (ref)
0.1-0.9	35689	549	1.02 (0.91-1.14)	442	1.06 (0.94-1.21)	117	0.91 (0.71-1.16)	217	1.23 (1.02-1.47)
1.0-3.4	17153	301	1.23 (1.07-1.40)	246	1.27 (1.09-1.47)	60	1.12 (0.83-1.51)	106	1.47 (1.17-1.83)
≥3.5	24114	407	1.14 (0.99-1.29)	331	1.17 (0.99-1.34)	83	1.07 (0.82-1.40)	146	1.18 (0.96-1.47)
Alternative healthy eating index (quintiles)									
Q 1	36232	533	1.00 (ref)	432	1.00 (ref)	106	1.00 (ref)	189	1.00 (ref)
Q 2	31295	482	1.01 (0.89-1.15)	390	1.03 (0.89-1.18)	97	0.97 (0.73-1.28)	178	1.07 (0.86-1.31)
Q 3	28442	458	1.05 (0.92-1.19)	374	1.06 (0.92-1.22)	88	1.01 (0.76-1.35)	155	0.95 (0.76-1.18)
Q 4	26501	439	1.09 (0.95-1.24)	345	1.05 (0.91-1.22)	100	1.24 (0.94-1.65)	157	1.02 (0.82-1.27)
Q 5	22815	316	0.88 (0.76-1.02)	243	0.84 (0.71-0.99)	81	1.12 (0.83-1.51)	122	0.96 (0.76-1.22)
Number of low-risk factors†									
None	3375	77	1.00 (ref)	60	1.00 (ref)	18	1.00 (ref)	32	1.00 (ref)
One	38054	588	0.75 (0.58-0.96)	467	0.76 (0.57-1.02)	127	0.68 (0.41-1.13)	203	0.58 (0.40-0.85)
Two	52169	758	0.61 (0.47-0.78)	618	0.64 (0.48-0.85)	147	0.50 (0.30-0.82)	285	0.45 (0.31-0.65)
Three or more	51687	805	0.59 (0.46-0.76)	639	0.58 (0.44-0.79)	180	0.60 (0.36-0.98)	281	0.39 (0.27-0.56)

* Adjusted for age (years), sex (men or women), ethnicity (Caucasian, African American, Hispanic, or Asian), menopausal status (women only), family history of diabetes (yes/no), family history of myocardial infarction (yes/no), current aspirin use (yes/no), current multivitamin use (yes/no), and diabetes duration (years). Individual lifestyle factors were mutually adjusted. BMI: body mass index.

† Low-risk lifestyle factors before diabetes diagnosis: $18.5 \leq \text{BMI} < 25.0 \text{ kg/m}^2$, non-smoking, moderate to vigorous physical activity (≥ 150 min/week), high quality diet (top two fifths of Alternative Healthy Eating Index), and moderate alcohol consumption (5-15 g/day for women and 5-30 g/day for men).