

## **Supplemental Materials**

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**Supplementary Table 1. Food group components and corresponding weights of the empirical dietary index for hyperinsulinemia (EDIH)**

<b>EDIH Food group</b>	<b>Weight per serving</b>
<b>Food components with higher insulinemic potential</b>	
Red meat	0.250
Low-energy beverages*	0.053
Cream soups	0.787
Processed meat	0.199
Margarine	0.054
Poultry	0.183
Butter	0.094
French fries	0.581
Other fish†	0.172
High-energy beverages‡	0.104
Tomatoes	0.095
Low-fat dairy products	0.025
Eggs	0.124
<b>Inverse components</b>	
Wine	-0.165
Coffee	-0.035
Whole fruit	-0.029
High-fat dairy products	-0.046
Green leafy vegetables	-0.055

\*Low-energy cola and other low-energy carbonated beverages

†Fish other than dark-meat (fatty) fish

‡Cola and other carbonated beverages with sugar

EDIH, empirical dietary index for hyperinsulinemia.

**Supplementary Table 2. Sensitivity analysis for the association of EDIH with all-cause and cause-specific mortality in NHS and HPFS pooled, adjusting for food groups highly contributing to EDIH\*†**

	Quintiles of EDIH					P-trend‡
	Q1	Q2	Q3	Q4	Q5	
All-cause mortality						
Full model	1.00	1.05 (1.02, 1.09)	1.09 (1.06, 1.13)	1.21 (1.17, 1.25)	1.35 (1.30, 1.39)	<0.001
Full model + alcohol	1.00	1.06 (1.03, 1.10)	1.10 (1.06, 1.13)	1.21 (1.17, 1.26)	1.34 (1.30, 1.39)	<0.001
Full model + coffee	1.00	1.05 (1.02, 1.09)	1.09 (1.05, 1.12)	1.21 (1.17, 1.25)	1.34 (1.29, 1.39)	<0.001
Full model + red and processed meat	1.00	1.04 (1.01, 1.07)	1.07 (1.03, 1.10)	1.17 (1.13, 1.21)	1.28 (1.23, 1.32)	<0.001
Full model + fruits and vegetables	1.00	1.06 (1.03, 1.10)	1.11 (1.07, 1.15)	1.23 (1.19, 1.28)	1.38 (1.33, 1.43)	<0.001
Cardiovascular mortality						
Full model	1.00	1.04 (0.97, 1.11)	1.07 (1.00, 1.15)	1.17 (1.09, 1.25)	1.30 (1.21, 1.39)	<0.001
Full model + alcohol	1.00	1.03 (0.96, 1.10)	1.06 (0.99, 1.13)	1.15 (1.07, 1.23)	1.27 (1.18, 1.36)	<0.001
Full model + coffee	1.00	1.03 (0.96, 1.10)	1.06 (0.99, 1.13)	1.15 (1.07, 1.23)	1.27 (1.18, 1.37)	<0.001
Full model + red and processed meat	1.00	1.03 (0.96, 1.10)	1.06 (0.99, 1.13)	1.14 (1.06, 1.23)	1.25 (1.16, 1.35)	<0.001
Full model + fruits and vegetables	1.00	1.05 (0.98, 1.13)	1.10 (1.03, 1.18)	1.22 (1.13, 1.30)	1.36 (1.27, 1.47)	<0.001
Cancer mortality						
Full model	1.00	1.02 (0.96, 1.08)	1.01 (0.95, 1.07)	1.11 (1.05, 1.18)	1.21 (1.13, 1.28)	<0.001
Full model + alcohol	1.00	1.04 (0.98, 1.10)	1.03 (0.97, 1.09)	1.14 (1.07, 1.21)	1.23 (1.16, 1.31)	<0.001
Full model + coffee	1.00	1.02 (0.97, 1.09)	1.02 (0.96, 1.08)	1.13 (1.07, 1.20)	1.23 (1.16, 1.31)	<0.001
Full model + red and processed meat	1.00	1.01 (0.95, 1.07)	0.99 (0.93, 1.05)	1.09 (1.02, 1.15)	1.16 (1.08, 1.24)	<0.001
Full model + fruits and vegetables	1.00	1.02 (0.96, 1.08)	1.00 (0.95, 1.07)	1.11 (1.04, 1.18)	1.19 (1.12, 1.27)	<0.001

\*EDIH scores were adjusted for energy intake using the residual method. All analyses were conducted using Cox models stratified by age and calendar years. Full multivariable adjusted models were further adjusted for race, smoking status, physical activity, current aspirin use, multivitamin use, family history of cancer, family history of diabetes, family history of myocardial infarction, baseline hypertension, baseline hypercholesterolemia, body mass index, and menopausal status and postmenopausal hormone use for women.

†The main goal of adjusting for the major contributing components as a sensitivity analysis is to assess whether any of these components are mostly or entirely accounting for the observed association of EDIH with mortality. Our results in this table indicate that the EDIH-mortality association we observed are not entirely explained by these major contributing components. It's a combination of the effects from all

components. However, adjusting for the components might lead to “overcontrol”, because these components were already incorporated into EDIH. The interpretation of the EDIH and the adjusted component is altered somewhat due to the mutual adjustment. In the case of adjusting for fruit and vegetables, since EDIH is in the model, that part (or subgroup) of fruit and vegetables that influences the EDIH is already accounted for, so the remaining component of fruit and vegetables (i.e., the part that does not lower C-peptide) might have other effects, which can be beneficial or adverse (e.g., starch, simple sugars, pesticides). Controlling for these potential negative effects may enhance the association of the EDIH with mortality.

‡The P-trend was calculated by assigning the median to all the participants in the quintile and modeling as continuous variables.

Abbreviations: EDIH, empirical dietary index for hyperinsulinemia; NHS, Nurses’ Health Study; HPFS, Healthy Professionals Follow-up Study.

**Supplementary Table 3. Hazard ratios (95% CIs) of all-cause and cause-specific mortality according to EDIH in NHS and HPFS pooled (stop updating)\***

	Quintiles of EDIH					P-trend†
	Q1	Q2	Q3	Q4	Q5	
All-cause mortality						
Cases/person-years	7,751/558,549	7,677/558,944	7,668/558,960	7,613/558,608	7,620/557,488	
Age-adjusted	1.00	1.03 (0.99, 1.06)	1.09 (1.05, 1.12)	1.19 (1.16, 1.23)	1.46 (1.41, 1.50)	<0.001
MV-adjusted	1.00	1.00 (0.97, 1.03)	1.03 (1.00, 1.07)	1.10 (1.06, 1.14)	1.27 (1.23, 1.31)	<0.001
MV + BMI	1.00	1.01 (0.98, 1.04)	1.05 (1.01, 1.08)	1.11 (1.08, 1.15)	1.27 (1.23, 1.31)	<0.001
Cardiovascular mortality						
Cases/person-years	1,871/558,549	1,806/558,944	1,839/558,960	1,789/558,608	1,848/557,488	
Age-adjusted	1.00	1.01 (0.95, 1.08)	1.10 (1.03, 1.18)	1.21 (1.13, 1.29)	1.57 (1.47, 1.67)	<0.001
MV-adjusted	1.00	0.98 (0.92, 1.05)	1.03 (0.96, 1.10)	1.08 (1.01, 1.16)	1.32 (1.23, 1.41)	<0.001
MV + BMI	1.00	0.98 (0.92, 1.04)	1.01 (0.95, 1.08)	1.06 (0.99, 1.13)	1.25 (1.17, 1.34)	<0.001
Cancer mortality						
Cases/person-years	2,397/558,549	2,343/558,944	2,250/558,960	2,248/558,608	2,296/557,488	
Age-adjusted	1.00	1.01 (0.95, 1.07)	1.01 (0.95, 1.07)	1.08 (1.02, 1.15)	1.28 (1.20, 1.35)	<0.001
MV-adjusted	1.00	1.00 (0.94, 1.05)	0.98 (0.93, 1.04)	1.03 (0.97, 1.10)	1.17 (1.10, 1.24)	<0.001
MV + BMI	1.00	1.00 (0.94, 1.06)	0.99 (0.93, 1.05)	1.03 (0.98, 1.10)	1.16 (1.09, 1.23)	<0.001

\*EDIH scores were adjusted for energy intake using the residual method. All analyses were conducted using Cox models stratified by age and calendar years. Multivariable adjusted models were further adjusted for race, smoking status, physical activity, current aspirin use, multivitamin use, family history of cancer, family history of diabetes, family history of myocardial infarction, baseline hypertension, baseline hypercholesterolemia, and menopausal status and postmenopausal hormone use for women.

†The P-trend was calculated by assigning the median to all the participants in the quintile and modeling as continuous variables.

Abbreviations: EDIH, empirical dietary index for hyperinsulinemia; NHS, Nurses' Health Study; HPFS, Healthy Professionals Follow-up Study; BMI, body mass index.

**Supplementary Table 4. Hazard ratios (95% CIs) of all-cause and cause-specific mortality according to EDIH in NHS and HPFS pooled (4-year lag)\***

	Quintiles of EDIH					P-trend†
	Q1	Q2	Q3	Q4	Q5	
All-cause mortality						
Cases/person-years	5,815/412,293	6,147/412,035	6,101/411,846	6,074/411,480	5,613/411,597	
Age-adjusted	1.00	1.06 (1.02, 1.09)	1.13 (1.09, 1.17)	1.26 (1.21, 1.30)	1.46 (1.40, 1.51)	<0.001
MV-adjusted	1.00	1.03 (1.00, 1.07)	1.08 (1.04, 1.12)	1.16 (1.12, 1.21)	1.28 (1.23, 1.33)	<0.001
MV + BMI	1.00	1.04 (1.00, 1.08)	1.09 (1.05, 1.13)	1.17 (1.13, 1.22)	1.29 (1.24, 1.34)	<0.001
Cardiovascular mortality						
Cases/person-years	1,335/412,293	1,355/412,035	1,419/411,846	1,371/411,480	1,236/411,597	
Age-adjusted	1.00	1.02 (0.94, 1.10)	1.16 (1.07, 1.25)	1.28 (1.18, 1.38)	1.50 (1.39, 1.63)	<0.001
MV-adjusted	1.00	0.97 (0.90, 1.05)	1.07 (0.99, 1.15)	1.14 (1.05, 1.23)	1.27 (1.17, 1.38)	<0.001
MV + BMI	1.00	0.97 (0.90, 1.05)	1.06 (0.98, 1.14)	1.12 (1.03, 1.21)	1.23 (1.13, 1.33)	<0.001
Cancer mortality						
Cases/person-years	1,772/412,293	1,769/412,035	1,704/411,846	1,780/411,480	1,659/411,597	
Age-adjusted	1.00	1.00 (0.94, 1.07)	1.02 (0.95, 1.09)	1.15 (1.07, 1.22)	1.25 (1.16, 1.33)	<0.001
MV-adjusted	1.00	1.00 (0.93, 1.06)	1.00 (0.94, 1.07)	1.10 (1.03, 1.18)	1.15 (1.07, 1.23)	<0.001
MV + BMI	1.00	0.99 (0.93, 1.06)	1.00 (0.93, 1.07)	1.09 (1.02, 1.17)	1.13 (1.05, 1.21)	<0.001

\*EDIH scores were adjusted for energy intake using the residual method. All analyses were conducted using Cox models stratified by age and calendar years. Multivariable adjusted models were further adjusted for race, smoking status, physical activity, current aspirin use, multivitamin use, family history of cancer, family history of diabetes, family history of myocardial infarction, baseline hypertension, baseline hypercholesterolemia, and menopausal status and postmenopausal hormone use for women.

†The P-trend was calculated by assigning the median to all the participants in the quintile and modeling as continuous variables.

Abbreviations: EDIH, empirical dietary index for hyperinsulinemia; NHS, Nurses' Health Study; HPFS, Healthy Professionals Follow-up Study; BMI, body mass index.

**Supplementary Table 5. Hazard ratios (95% CIs) of all-cause and cause-specific mortality in NHS and HPFS pooled, adjusting for other dietary quality scores\***

	Quintiles of EDIH					P-trend†
	Q1	Q2	Q3	Q4	Q5	
All-cause mortality						
Full model	1.00	1.05 (1.02, 1.09)	1.09 (1.06, 1.13)	1.21 (1.17, 1.25)	1.35 (1.30, 1.39)	<0.001
Full model + AHEI	1.00	1.02 (0.99, 1.05)	1.03 (1.00, 1.07)	1.11 (1.08, 1.15)	1.20 (1.15, 1.24)	<0.001
Full model + AMED	1.00	1.03 (1.00, 1.07)	1.06 (1.02, 1.09)	1.16 (1.12, 1.20)	1.29 (1.24, 1.33)	<0.001
Full model + DASH	1.00	1.04 (1.01, 1.08)	1.07 (1.04, 1.11)	1.18 (1.14, 1.22)	1.30 (1.25, 1.35)	<0.001
Cardiovascular mortality						
Full model	1.00	1.04 (0.97, 1.11)	1.07 (1.00, 1.15)	1.17 (1.09, 1.25)	1.30 (1.21, 1.39)	<0.001
Full model + AHEI	1.00	1.01 (0.94, 1.08)	1.03 (0.96, 1.10)	1.10 (1.02, 1.18)	1.20 (1.11, 1.29)	<0.001
Full model + AMED	1.00	1.02 (0.95, 1.09)	1.05 (0.98, 1.12)	1.13 (1.06, 1.22)	1.26 (1.17, 1.35)	<0.001
Full model + DASH	1.00	1.04 (0.97, 1.11)	1.08 (1.01, 1.16)	1.17 (1.09, 1.26)	1.30 (1.20, 1.40)	<0.001
Cancer mortality						
Full model	1.00	1.02 (0.96, 1.08)	1.01 (0.95, 1.07)	1.11 (1.05, 1.18)	1.21 (1.13, 1.28)	<0.001
Full model + AHEI	1.00	1.01 (0.95, 1.07)	0.98 (0.92, 1.04)	1.07 (1.01, 1.14)	1.13 (1.06, 1.21)	<0.001
Full model + AMED	1.00	1.00 (0.95, 1.06)	0.98 (0.92, 1.04)	1.08 (1.02, 1.15)	1.16 (1.09, 1.24)	<0.001
Full model + DASH	1.00	1.00 (0.95, 1.07)	0.98 (0.92, 1.04)	1.07 (1.01, 1.14)	1.13 (1.06, 1.21)	<0.001

\*EDIH scores were adjusted for energy intake using the residual method. All analyses were conducted using Cox models stratified by age and calendar years. Full multivariable adjusted models were further adjusted for race, smoking status, physical activity, current aspirin use, multivitamin use, family history of cancer, family history of diabetes, family history of myocardial infarction, baseline hypertension, baseline hypercholesterolemia, body mass index, and menopausal status and postmenopausal hormone use for women.

†The P-trend was calculated by assigning the median to all the participants in the quintile and modeling as continuous variables.

Abbreviations: EDIH, empirical dietary index for hyperinsulinemia; NHS, Nurses' Health Study; HPFS, Healthy Professionals Follow-up Study; AHEI, Alternative Healthy Eating Index; AMED, Alternative Mediterranean Diet Score; DASH, Dietary Approaches to Stop Hypertension.

**Supplementary Table 6. Hazard ratios (95% CIs) of all-cause and cause-specific mortality according to 8-year changes in EDIH in NHS and HPFS pooled\***

	Quintiles of 8-year changes in EDIH					P-trend†
	Q1	Q2	Q3	Q4	Q5	
Median change (NHS/HPFS)	-1.14/-1.09	-0.47/-0.42	-0.05/0	0.36/0.41	1.04/1.04	
All-cause mortality						
Cases/person-years	4,267/298,414	4,313/298,319	4,420/298,275	4,653/297,939	5,035/297,325	
Basic model	0.96 (0.92, 1.01)	0.96 (0.92, 1.01)	1.00	1.09 (1.05, 1.14)	1.21 (1.16, 1.27)	<0.001
MV-adjusted	0.99 (0.95, 1.03)	0.99 (0.95, 1.03)	1.00	1.06 (1.02, 1.10)	1.13 (1.09, 1.18)	<0.001
MV + weight change	0.98 (0.94, 1.03)	0.99 (0.95, 1.03)	1.00	1.06 (1.02, 1.11)	1.14 (1.09, 1.18)	<0.001
Cardiovascular mortality						
Cases/person-years	936/298,414	867/298,319	974/298,275	1087/297,939	1094/297,325	
Basic model	0.98 (0.89, 1.07)	0.88 (0.80, 0.97)	1.00	1.16 (1.06, 1.26)	1.20 (1.10, 1.32)	<0.001
MV-adjusted	1.02 (0.93, 1.12)	0.91 (0.83, 1.00)	1.00	1.11 (1.02, 1.21)	1.10 (1.01, 1.21)	0.006
MV + weight change	1.02 (0.93, 1.12)	0.91 (0.83, 1.00)	1.00	1.11 (1.02, 1.21)	1.10 (1.00, 1.20)	0.006
Cancer mortality						
Cases/person-years	1,214/298,414	1,251/298,319	1,291/298,275	1,275/297,939	1,366/297,325	
Basic model	0.94 (0.86, 1.02)	0.96 (0.89, 1.04)	1.00	1.00 (0.93, 1.08)	1.09 (1.01, 1.18)	<0.001
MV-adjusted	0.95 (0.87, 1.03)	0.98 (0.90, 1.06)	1.00	0.97 (0.90, 1.05)	1.01 (0.93, 1.10)	0.22
MV + weight change	0.95 (0.87, 1.03)	0.98 (0.91, 1.06)	1.00	0.97 (0.90, 1.05)	1.01 (0.93, 1.09)	0.24

\*Changes in EDIH scores were calculated as the difference between energy-adjusted EDIH from 1986 to 1994. All analyses were conducted using Cox models stratified by age and calendar years. The basic model was adjusted for initial EDIH. Multivariable adjusted models were further adjusted for race, smoking status, initial physical activity, changes in physical activity, current aspirin use, multivitamin use, family history of cancer, family history of diabetes, family history of myocardial infarction, baseline hypertension, baseline hypercholesterolemia, body mass index, and menopausal status and postmenopausal hormone use for women.

†The P-trend was calculated by assigning the median to all the participants in the quintile and modeling as continuous variables.

Abbreviations: EDIH, empirical dietary index for hyperinsulinemia; NHS, Nurses' Health Study; HPFS, Healthy Professionals Follow-up Study.



**Supplementary Table 7. Hazard ratios (95% CIs) of all-cause and cause-specific mortality according to 8-year changes in EDIH in NHS and HPFS pooled (4-year lag)\***

	Quintiles of 8-year changes in EDIH					P-trend†
	Q1	Q2	Q3	Q4	Q5	
Median change (NHS/HPFS)	-1.14/-1.09	-0.47/-0.42	-0.05/0	0.37/0.41	1.04/1.04	
All-cause mortality						
Cases/person-years	3405/218,361	3426/218,341	3513/218,233	3720/217,919	4022/217,377	
Basic model	0.98 (0.94, 1.03)	0.97 (0.92, 1.01)	1.00	1.09 (1.04, 1.14)	1.21 (1.16, 1.27)	<0.001
MV-adjusted	1.01 (0.96, 1.06)	0.99 (0.94, 1.03)	1.00	1.06 (1.01, 1.11)	1.13 (1.08, 1.19)	<0.001
MV + weight change	1.00 (0.96, 1.05)	0.99 (0.94, 1.03)	1.00	1.06 (1.01, 1.11)	1.14 (1.08, 1.19)	<0.001
Cardiovascular mortality						
Cases/person-years	722/218,361	669/218,341	727/218,233	819/217,919	860/217,377	
Basic model	1.04 (0.93, 1.16)	0.92 (0.82, 1.02)	1.00	1.16 (1.05, 1.28)	1.26 (1.13, 1.40)	<0.001
MV-adjusted	1.09 (0.98, 1.21)	0.94 (0.84, 1.04)	1.00	1.12 (1.01, 1.23)	1.16 (1.04, 1.28)	0.04
MV + weight change	1.09 (0.98, 1.21)	0.94 (0.84, 1.04)	1.00	1.12 (1.01, 1.23)	1.15 (1.04, 1.28)	0.04
Cancer mortality						
Cases/person-years	920/218,361	917/218,341	942/218,233	954/217,919	1012/217,377	
Basic model	0.99 (0.90, 1.09)	0.97 (0.88, 1.06)	1.00	1.02 (0.93, 1.11)	1.09 (0.99, 1.19)	0.05
MV-adjusted	1.01 (0.91, 1.11)	0.99 (0.90, 1.08)	1.00	0.99 (0.90, 1.08)	1.01 (0.92, 1.11)	0.93
MV + weight change	1.01 (0.92, 1.11)	0.99 (0.90, 1.08)	1.00	0.99 (0.90, 1.08)	1.01 (0.92, 1.11)	0.98

\*Changes in EDIH scores were calculated as the difference between energy-adjusted EDIH from 1986 to 1994. All analyses were conducted using Cox models stratified by age and calendar years. The basic model was adjusted for initial EDIH. Multivariable adjusted models were further adjusted for race, smoking status, initial physical activity, changes in physical activity, current aspirin use, multivitamin use, family history of cancer, family history of diabetes, family history of myocardial infarction, baseline hypertension, baseline hypercholesterolemia, body mass index, and menopausal status and postmenopausal hormone use for women.

†The P-trend was calculated by assigning the median to all the participants in the quintile and modeling as continuous variable.

Abbreviations: EDIH, empirical dietary index for hyperinsulinemia; NHS, Nurses' Health Study; HPFS, Healthy Professionals Follow-up Study.