Additional File 1 – BMC Medicine

Lifestyle Factors and Risk of Multimorbidity of Cancer and Cardiometabolic Diseases: A Multinational Cohort Study

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Table S1. Scoring of the healthy lifestyle index (HLI) and its simplified version

Modifiable lifestyle factor	Scoring HLI		Scoring sHLI	
Body mass index				
kg/m^2	≥22 to <24	4	≥18.5 to <25	1
	<22	3	≥25 to <30	0.5
	≥24 to <26	2	<18.5	0
	≥26 to <30	1	≥30	0
	≥30	0		
Smoking status				
Categories	Never	4	Never	1
	Former	2	Former	0.5
	Current	0	Current	0
Physical activity index[1]				
Categories	Active	4	Active	1
	Moderately active	3	Moderately active	1
	Moderately inactive	1	Moderately inactive	0
	Inactive	0	Inactive	0
Alcohol intake				
g/d	<6	4	<6 (W) or <12 (M)	1
	≥6 to <12	3	≥6 (W) or ≥12 (M)	0
	≥12 to <25	2		
	≥ to <60	1		
	>60	0		
Mediterranean diet score[2]				
Quintiles	Q5	4	≥ median	1
	Q4	3	< median	0
	Q3	2		
	Q2	1		
	Q1	0		
Range		0 to 20		0 to 5

HLI, healthy lifestyle index
sHLI, simplified healthy lifestyle index
W, women; M, men

[1] Wareham NJ, Jakes RW, Rennie KL, Schuit J, Mitchell J, Hennings S, Day NE. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Public Health Nutr. 2003 Jun;6(4):407-13.
[2] Buckland G, González CA, Agudo A, Vilardell M, Berenguer A, Amiano P, et al. Adherence to the mediterranean diet and risk of coronary heart disease in the spanish EPIC cohort study. Am J Epidemiol. 2009;170(12):1518–29.

Figure S1. Flowchart of exclusion steps in the EPIC (European Prospective Investigation into Cancer and Nutrition) multimorbidity data.

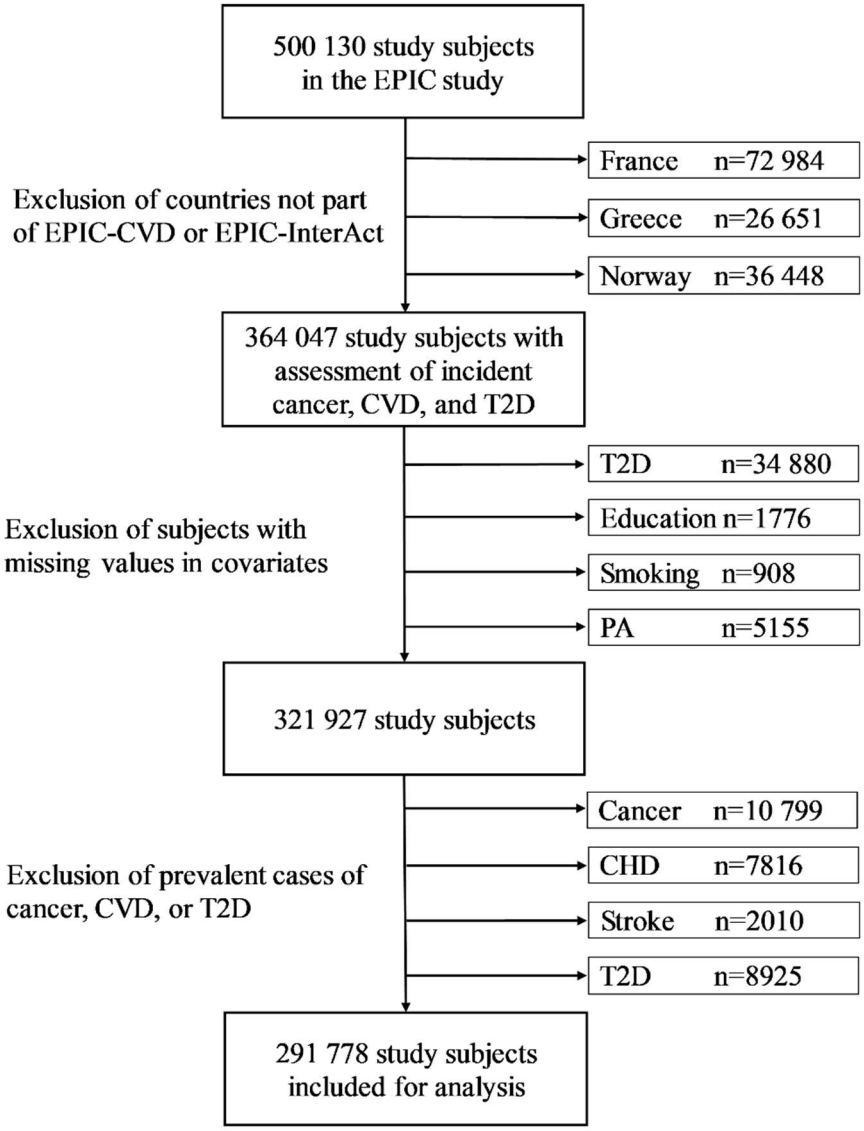

Figure S2. Transitions from baseline to cancer, cardiovascular disease (CVD), type-2 diabetes (T2D) and specific multimorbidity patterns within the EPIC study

State-specific number of events are in boxes, and transition-specific number of events and incidence rates per 1000 person-years are reported on arrows.

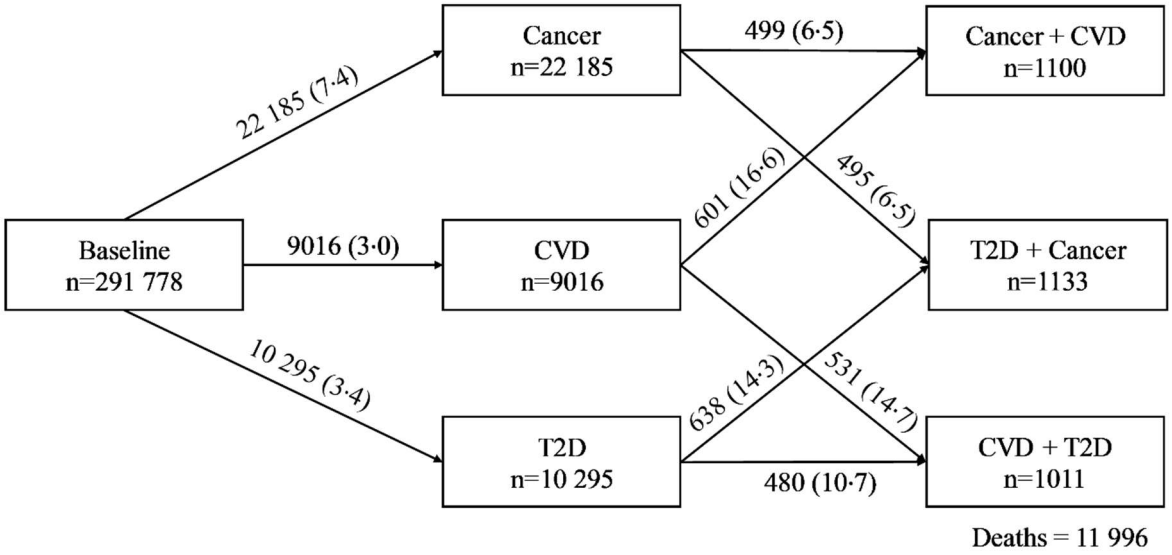

Figure S3. Subgroup analysis of associations of a 3-unit increment (~1 standard deviation) in the healthy lifestyle index (HLI) with first cancer at any site, cardiovascular disease (CVD), type-2 diabetes (T2D), and transitions to cancer-cardiometabolic multimorbidity.

Cox proportional hazard models, stratified by age at inclusion (1-year categories), sex, centre and transition, in a clock-forward multi-state analysis with age as primary time variable, adjusted for education level (no schooling, primary, secondary and university or more), height (continuous), an indicator of alcohol use (no/yes), total energy intake (kcal/day), and use of hormones and menopausal status in women.

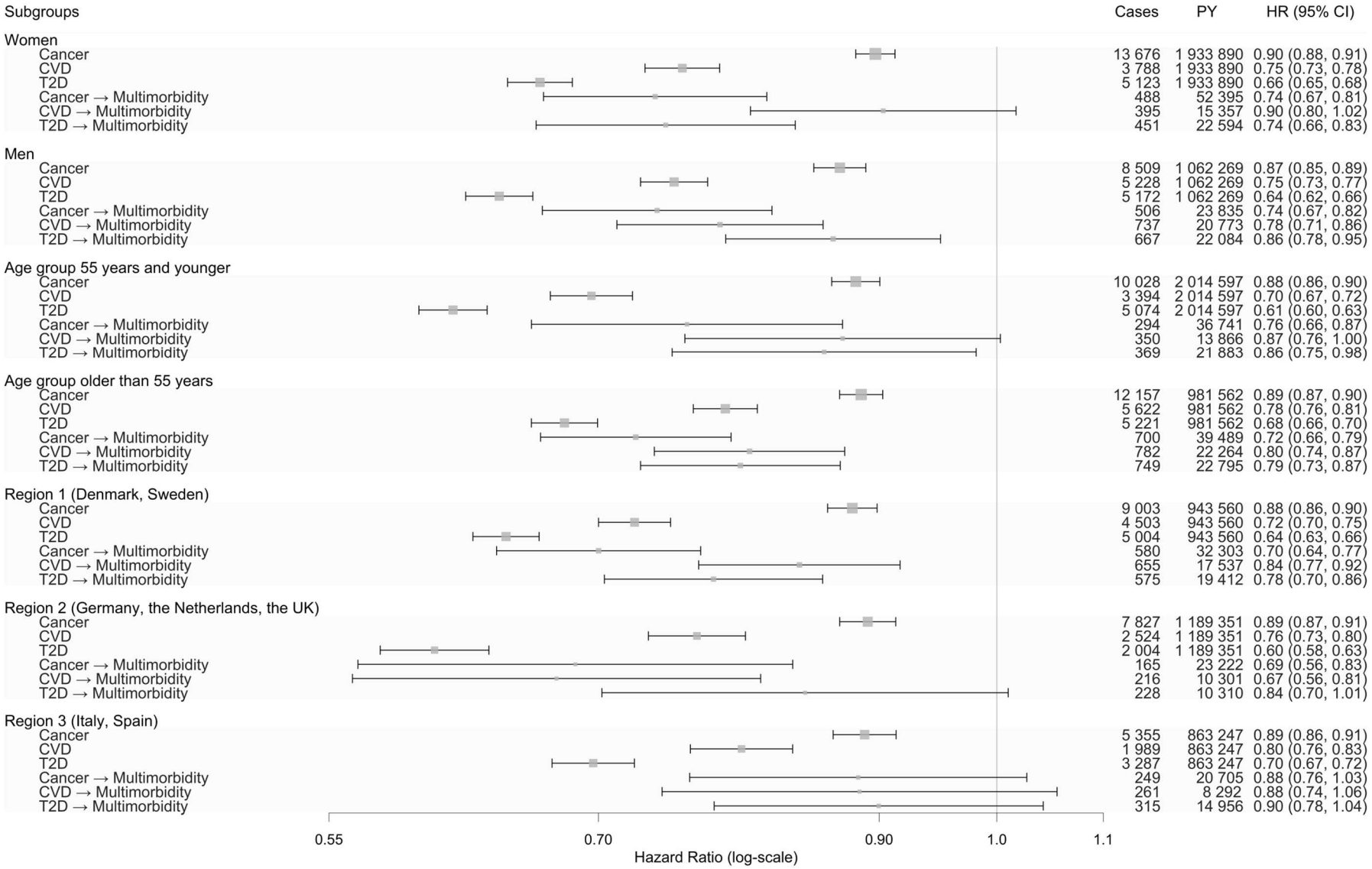

Figure S4. Cumulative incidence functions to develop first cancer at any site, cardiovascular disease (CVD), type-2 diabetes (T2D), and subsequent cancer-cardiometabolic multimorbodity (MM) for 55 years old men (dotted) and women (continuous) for values of the healthy lifestyle index (HLI) of 15 (healthy, 85th percentile in green) and 5 (unhealthy, 4th percentile in red); the HLI ranges from 0 to 20 units, with greater scores reflecting healthy lifesyles.

Cancer refers to first malignant tumors at any site excl. non-melanoma skin cancer. Deaths were censored and not modelled as a separate outcome.

The model was stratified for centre, sex, and adjusted for education level (no schooling, primary, secondary and university or more), height (continuous), binary indicator of alcohol use (no/yes), total energy intake (kcal/day), and use of hormones and menopausal status in women.

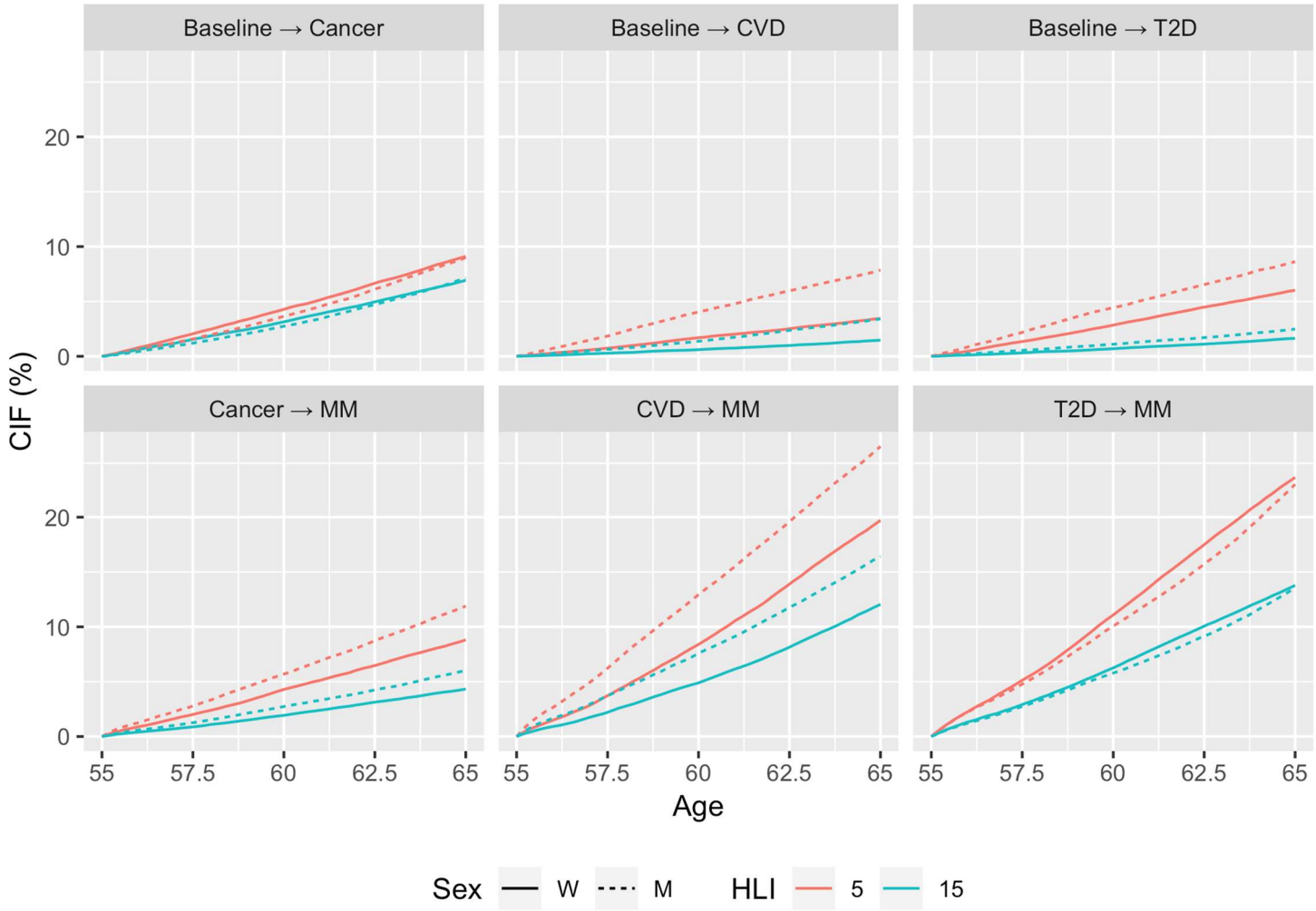

Figure S5. Sensitivity analysis excluding in turn one of the components of the healthy lifestyle index (HLI) of associations of a 3-unit increment (~1 standard deviation) in the HLI with first cancer at any site, cardiovascular disease (CVD), type-2 diabetes (T2D), and transitions to cancer-cardiometabolic multimorbidity.

Cox proportional hazard models, stratified by age at inclusion (1-year categories), sex, centre and transition, in a clock-forward multi-state analysis with age as primary time variable, adjusted for education level (no schooling, primary, secondary and university or more), height (continuous), an indicator of alcohol use (no/yes), total energy intake (kcal/day), and use of hormones and menopausal status in women.

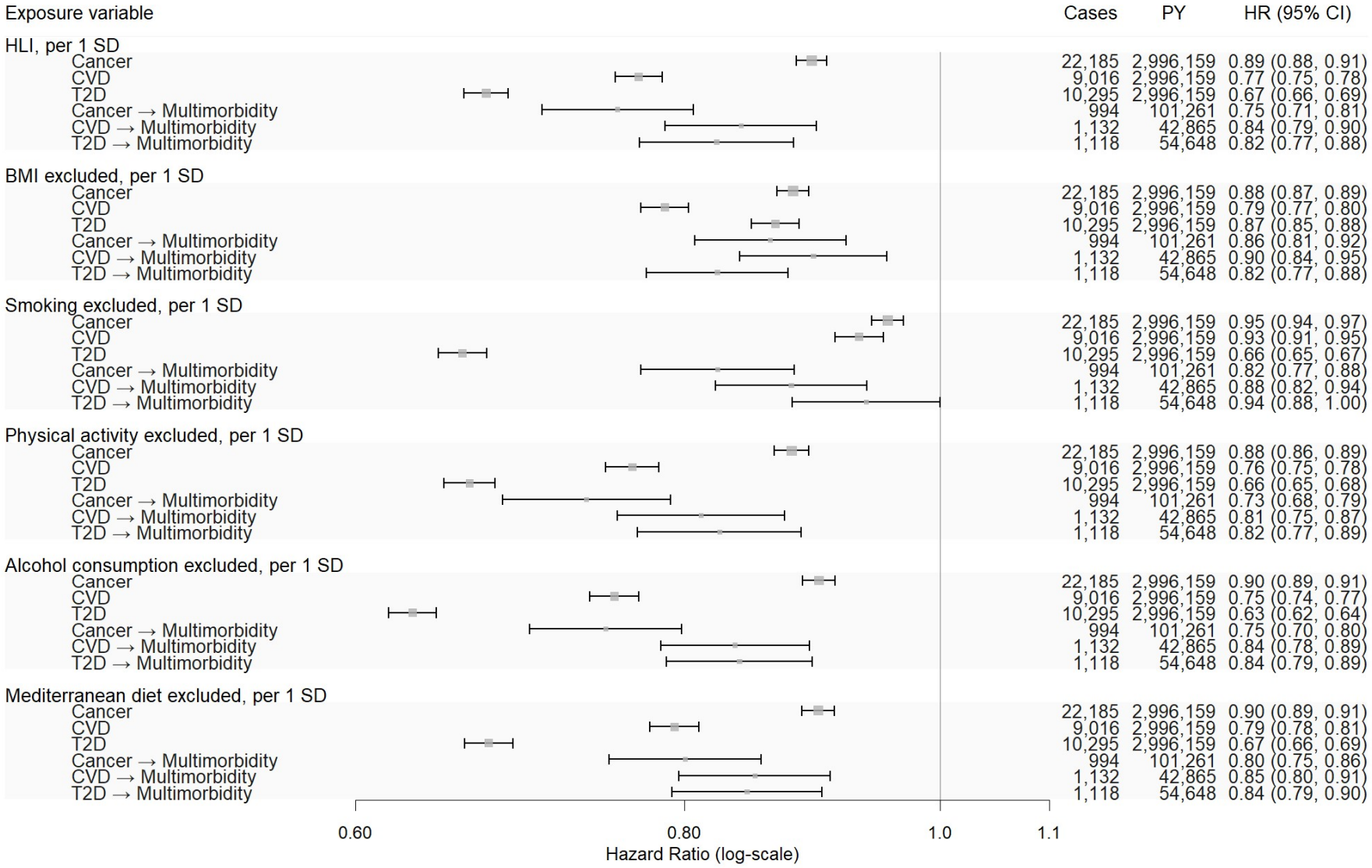

Figure S6. Sensitivity analysis comparing associations of 1 standard deviation (SD) increments in [A] the healthy lifestyle index (HLI), and [B] a simplified HLI, with first cancer at any site, cardiovascular disease (CVD), type-2 diabetes (T2D), and transitions to cancer-cardiometabolic multimorbidity.

Cox proportional hazard models, stratified by age at inclusion (1-year categories), sex, centre and transition, in a clock-forward multi-state analysis with age as primary time variable, adjusted for education level (no schooling, primary, secondary and university or more), height (continuous), an indicator of alcohol use (no/yes), total energy intake (kcal/day), and use of hormones and menopausal status in women.

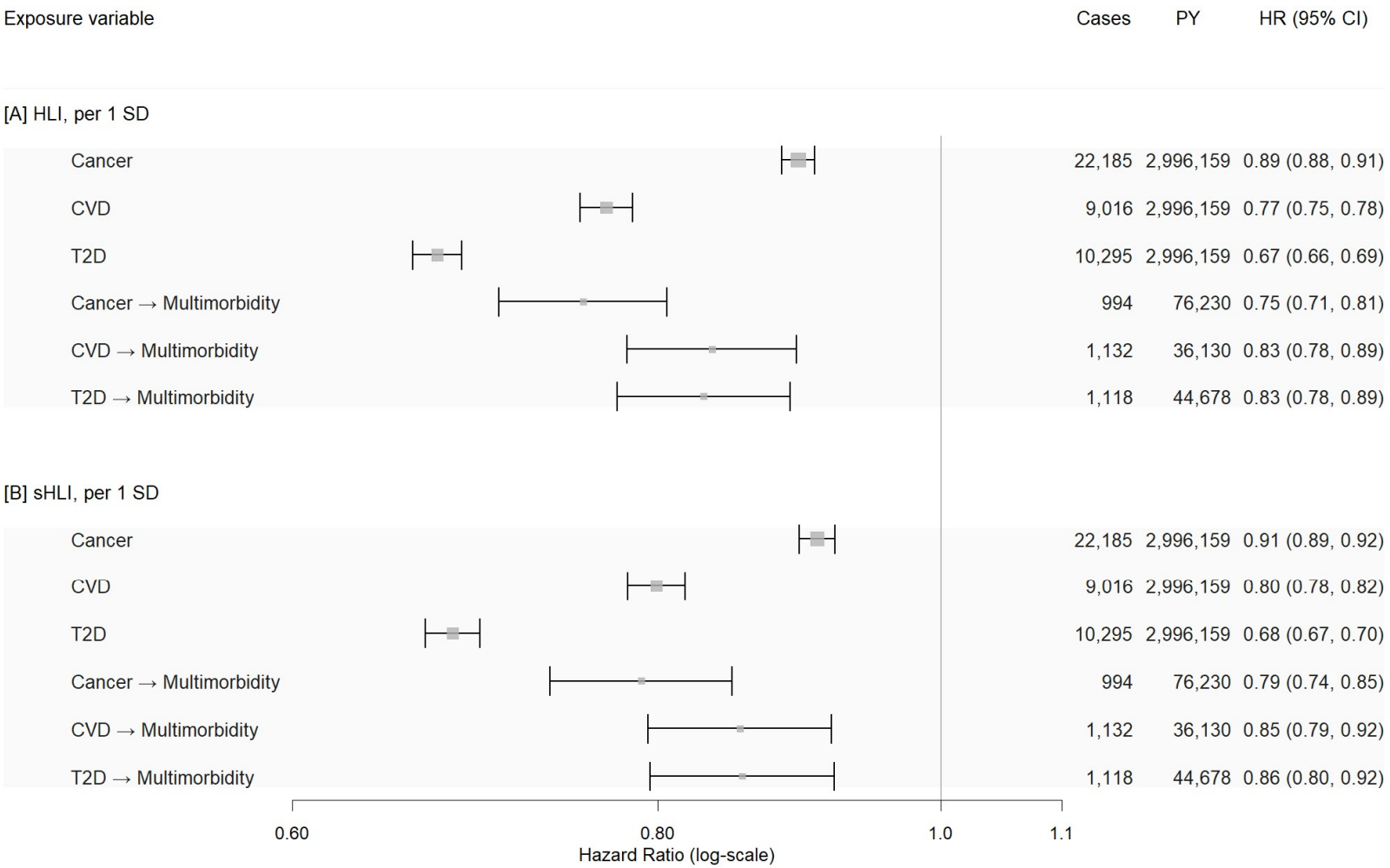

Figure S7. Cumulative incidence functions to develop first cancer at any site, cardiovascular disease (CVD), type-2 diabetes (T2D), and subsequent cancer-cardiometabolic multimorbodity (MM) for 65 years old men (dotted) and women (continuous) for values of the **simplified healthy lifestyle index (sHLI)** of 4 (four healthy lifestyle habits, 90th percentile in green) and 1 (unhealthy [one healthy lifestyle habit], 5th percentile in red); the sHLI ranges from 0 to 5 units.

Cancer refers to first malignant tumors at any site excl. non-melanoma skin cancer. Deaths were censored and not modelled as a separate outcome.

The model was stratified for centre, sex, and adjusted for education level (no schooling, primary, secondary and university or more), height (continuous), binary indicator of alcohol use (no/yes), total energy intake (kcal/day), and use of hormones and menopausal status in women

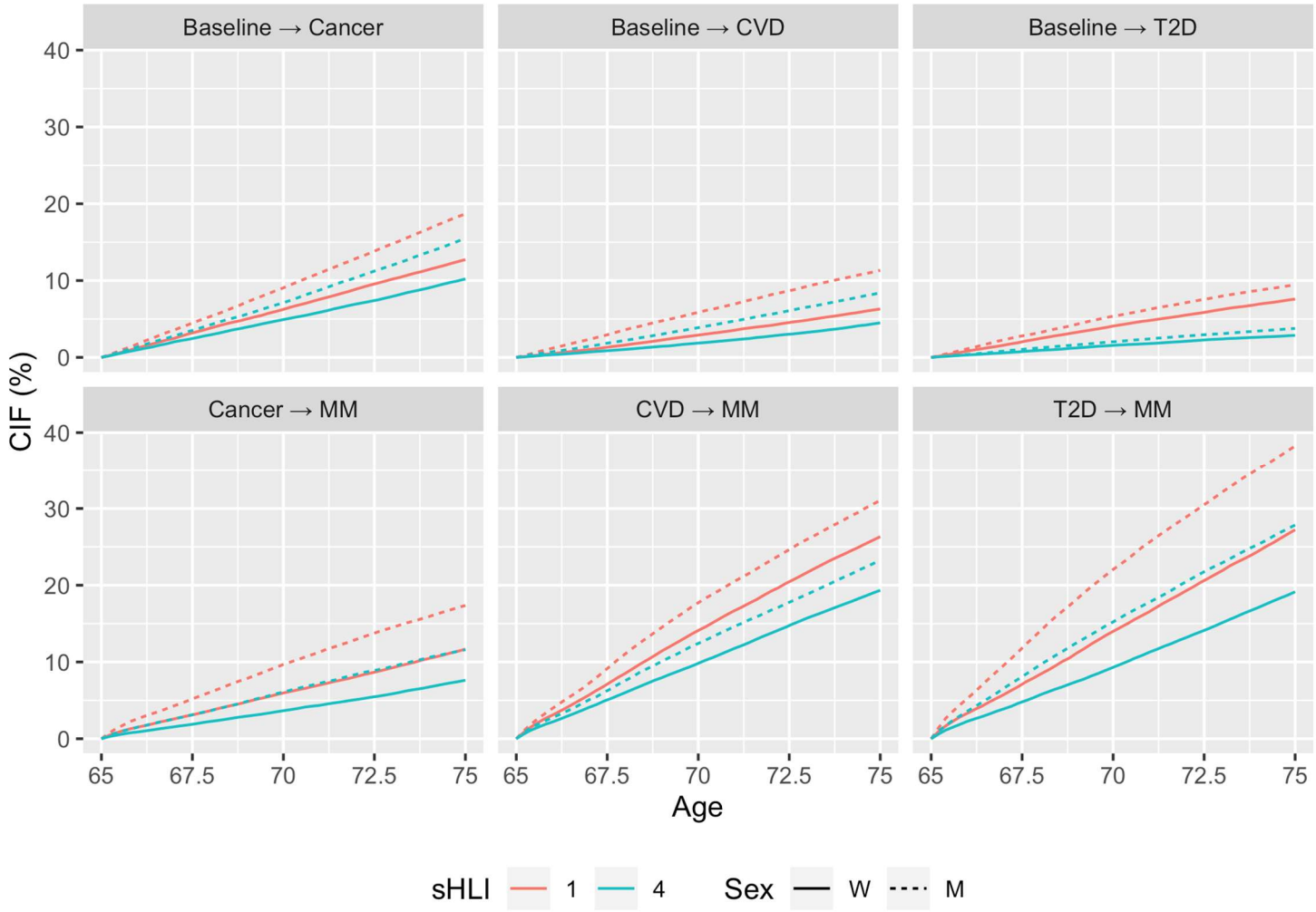

Figure S8. Cumulative incidence functions to develop cancer-cardiometabolic multimorbodity (MM) for 65 years old men (dotted) and women (continuous) after a less and more survivable cancer*, and after cardiovascular disease (CVD), and type-2 diabetes (T2D) for values of the healthy lifestyle index (HLI) of 15 (healthy, 85th percentile in green) and 5 (unhealthy, 4th percentile in red); the HLI ranges from 0 to 20 units, with greater scores reflecting healthy lifesyles.

*Cancer refers to first malignant tumors at any site excl. non-melanoma skin cancer, which were grouped according to 5-year relative survival rates into two distinct groups: (1) "less survivable cancer" with 5-year relative survival rates of less than 40% included pancreas, gallbladder, liver, lung, oesophagus, glioma, and stomach; (2) "more survivable cancer" with 5-year relative survival rates of equal or higher than 40% included ovarian, multiple myeloma, leukemia, colorectum, head and neck, non-Hodgkin's lymphoma, kidney, meningioma, bladder, endometrium, breast, thyroid, and prostate.

Deaths were censored and not modelled as a separate outcome.

The model was stratified for centre, sex, and adjusted for education level (no schooling, primary, secondary and university or more), height (continuous), binary indicator of alcohol use (no/yes), total energy intake (kcal/day), and use of hormones and menopausal status in women