Title:

Effect of major lifestyle risk factors, independent and jointly, on life expectancy with and without cardiovascular disease: results from the Consortium on Health and Ageing Network of Cohorts in Europe and the United States (CHANCES).

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Supplementary Material

Detailed statistical methods

The parameters of such a three state model were estimated through use of the R msm package[1]. In msm these transition rates q_{ij} (representing the instantaneous risk of moving from state *i* to state *j*) can be influenced by the characteristics of individuals (either time-dependent or constant covariates, **z**) in a proportional hazards fashion:

$$q_{ij}(\mathbf{z}) = q_{ij}^{(0)} \exp\left(\boldsymbol{\beta}_{ij}^{T} \mathbf{z}\right)$$

In msm we determine the unknown parameters $q_{ij}^{(0)}$ and $\boldsymbol{\beta}_{ij}$ through maximising the likelihood expression[2].

A multiple imputation (MI) procedure was implemented to account for missingness in the covariates[3]. Missing data (after exclusion criteria was applied) ranged from 0% to ~25% across the cohorts. In this case L =30 'complete' data sets were made for each cohort, imputing missing data from the distribution of the missing data given the observed. The msm package was then utilised on each of the 30 imputed data sets, giving 30 sets of parameter estimates for $q_{ij}^{(0)}$ and $\boldsymbol{\beta}_{ij}$ (estimates for $q_{ij}^{(0)}$ and $\boldsymbol{\beta}_{ij}$ are collectively labelled $\hat{\mathbf{B}}_l$ for the l^{th} imputed data set, with associated variance-covariance matrix $\hat{\boldsymbol{\sigma}}_l^2$). Rubin's rules for inference were deployed to determine the multiple imputation estimate of $\mathbf{B}$, $\hat{\mathbf{B}}_{\text{MI}}$:

$$\hat{\mathbf{B}}_{\text{MI}} = \frac{1}{L}\sum_{l=1}^{L} \hat{\mathbf{B}}_l,$$

with variance-covariance matrix given by:

$$\hat{\mathbf{V}}_{\text{MI}} = \frac{1}{L}\sum_{l=1}^{L} \hat{\boldsymbol{\sigma}}_l^2 + \left(1+\frac{1}{L}\right)\frac{1}{(L-1)}\sum_{l=1}^{L}\left(\hat{\mathbf{B}}_l - \hat{\mathbf{B}}_{\text{MI}}\right)^2.$$

Hazard ratios (HRs), $\exp\left(\left(\boldsymbol{\beta}_{ij}\right)_k\right)$, [indicating the effect of covariate *k* on the transition between state *i* and *j*] were thus determined, together with their corresponding confidence interval, based on their corresponding estimates within $\hat{\mathbf{B}}_{\text{MI}}$ and $\hat{\mathbf{V}}_{\text{MI}}$. [For those risk factors

having a significant independent effect on flow between states, the HR confidence interval will not span the value 1.]

Finally parameter estimates obtained were used to calculate LE with and without CVD at age 50 by risk factor level, both varying one risk factor at a time and varying many at a time. LE was calculated following the techniques of the R ELECT package[4].

The expected LE in state $s \in \{1,2\}$ given initial state $r \in \{1,2\}$ and covariates $\mathbf{z}$ (including one time dependent covariate of age - with $\text{age}(t=0)=a_0$) is given by:

$$e_{rs}\{\mathbf{z}, a_0\} = \int_0^\infty \Pr\left\{X_t = s \middle| X_0 = r, \mathbf{z},\ \text{age}(t=0) = a_0\right\} dt.$$

This integral is numerically approximated using:

$$e_{rs}\{\mathbf{z}, a_0\} \approx \frac{1}{2} + \sum_{g=1}^{G} \Pr\left\{X_{t=gh} = s \middle| X_0 = r, \mathbf{z},\ \text{age}(t=0) = a_0\right\} \times h,$$

where h denotes a small time interval and G is sufficiently large to ensure the integrand is negligible at $t = Gh$. In order to calculate the above integrand, the transition probability matrix $\mathbf{P}(t)$ (whose $(r,s)^{\text{th}}$ entry equals $\Pr\left\{X_t = s \middle| X_0 = r, \mathbf{z},\ \text{age}(t=0) = a_0\right\}$) is evaluated at each time point in the grid. Piecewise-constant transition rates $q_{ij}(\mathbf{z})$ are assumed within each time interval, so that:

$$\begin{aligned}
&\mathbf{P}(t = gh) \\
&\approx \mathbf{P}_h\left(t_1 = 0, t_2 = h \middle| \mathbf{z}, \text{age}{=}a_0\right) \times \mathbf{P}_h\left(t_1 = h, t_2 = 2h \middle| \mathbf{z}, \text{age}{=}a_0 + h\right) \\
&\quad \times \ldots \times \mathbf{P}_h\left(t_1 = (g-1)h, t_2 = gh \middle| \mathbf{z}, \text{age}{=}a_0 + (g-1)h\right)
\end{aligned}$$

where the $(r,s)^{\text{th}}$ entry of $\mathbf{P}_h\left(t_1, t_2 \middle| \mathbf{z}, \text{age}{=}a_g\right)$ equals $\Pr\left\{X_{t_2} = s \middle| X_{t_1} = r, \mathbf{z},\ \text{age} = a_g\right\}$. For the non-recoverable illness-death model $\mathbf{P}_h$ has the following analytic expression:

$$\mathbf{P}_h\left(t_1=\alpha, t_2=\alpha+h \middle| \mathbf{z}, \text{age}=a_g\right)=\exp\left(\mathbf{Q}\left(\mathbf{z}, a_g\right)h\right)$$

$$\begin{pmatrix} e^{-(q_{12}+q_{13})h} & \dfrac{q_{12}}{q_{12}+q_{13}-q_{23}}\left(e^{-q_{23}h}-e^{-(q_{12}+q_{13})h}\right) & 1-e^{-(q_{12}+q_{13})h}-\dfrac{q_{12}}{\left(q_{12}+q_{13}-q_{23}\right)}\left(e^{-q_{23}h}-e^{-(q_{12}+q_{13})h}\right) \\ 0 & e^{-q_{23}h} & 1-e^{-q_{23}h} \\ 0 & 0 & 1 \end{pmatrix}$$

where q_{12}, q_{13} and q_{23} are constant within each time interval - depending on $\mathbf{z}$ (in particular the given age) and the $q_{ij}^{(0)}$ and $\boldsymbol{\beta}_{ij}$ parameters as given within $\hat{\mathbf{B}}_{\text{MI}}$.

Uncertainty in the LE measures was assessed using simulation. That is, LE was calculated as described above, but samples from the multivariate normal $N\left(\hat{\mathbf{B}}_{\text{MI}}, \hat{\mathbf{V}}_{\text{MI}}\right)$ were drawn to estimate the $q_{ij}^{(0)}$ and $\boldsymbol{\beta}_{ij}$ parameters in the above scheme for each simulation.

Table S1. Hazard ratios for the different transitions, RCPH (Denmark)

	No CVD to CVD	No CVD to death	CVD to death
Number of events	403	691	253
Age	1.07 (1.05; 1.09)	1.07 (1.06; 1.09)	1.07 (1.05; 1.09)
Female	0.73 (0.59; 0.90)	0.67 (0.56; 0.79)	0.73 (0.55; 0.97)
Prevalent diabetes[a]	1.24 (0.80; 1.95)	1.47 (1.05; 2.07)	1.75 (0.98; 3.15)
Vigorous physical activity[a]	0.93 (0.71; 1.20)	0.70 (0.56; 0.87)	0.80 (0.55; 1.16)
Total/HDL cholesterol ratio	1.19 (1.13; 1.26)	0.98 (0.92; 1.03)	1.06 (0.99; 1.14)
Hypertension[a]	1.40 (1.13; 1.73)	1.26 (1.07; 1.48)	1.01 (0.78; 1.31)
Smoking			
Never	Ref	Ref	Ref
Former	-	1.01 (0.80; 1.27)	-
Current	1.50 (1.21; 1.86)	1.94 (1.59; 2.36)	1.35 (1.04; 1.75)
BMI[b]			
Underweight	1.79 (0.90; 3.58)	2.03 (1.28; 3.21)	1.17 (0.38; 3.60)
Normal	Ref	Ref	Ref
Overweight	0.82 (0.65; 1.03)	0.94 (0.79; 1.12)	0.87 (0.65; 1.17)
Obese	0.87 (0.65; 1.17)	1.04 (0.83; 1.31)	1.05 (0.71; 1.56)
Alcohol[c]			
Abstainer	0.87 (0.66; 1.14)	1.24 (1.02; 1.50)	1.11 (0.80; 1.56)
Light/moderate	Ref	Ref	Ref
Heavy	0.93 (0.53; 1.62)	1.34 (0.95; 1.89)	1.54 (0.77; 3.08)

[a]Dichotomous (Yes/No), Reference=No

[b]Underweight = <18.5 kg/m^2; normal = ≥18.5 & <25; overweight = ≥25 & <30; obese = ≥30

[c]Light/moderate = men (>0g & <60g daily), women (>0g & <40g daily); Heavy = men (≥60g daily), women (≥40g daily)

Table S2. Hazard ratios for the different transitions, ESTHER (Germany)

	No CVD to CVD	No CVD to death	CVD to death
Number of events	523	817	50
Age	1.06 (1.04; 1.07)	1.09 (1.07; 1.10)	1.08 (1.02; 1.14)
Female	0.59 (0.49; 0.70)	0.58 (0.49; 0.67)	0.55 (0.29; 1.02)
Prevalent diabetes[a]	1.35 (1.10; 1.65)	1.42 (1.21; 1.67)	3.15 (1.78; 5.58)
Vigorous physical activity[a]	0.93 (0.78; 1.12)	0.54 (0.46; 0.63)	0.61 (0.31; 1.18)
Total/HDL cholesterol ratio	1.08 (1.02; 1.15)	1.02 (0.96; 1.08)	1.11 (0.95; 1.31)
Hypertension[a]	1.59 (1.30; 1.96)	1.45 (1.23; 1.71)	1.32 (0.53; 3.27)
Smoking			
Never	Ref	Ref	Ref
Former	-	1.40 (1.17; 1.66)	-
Current	2.02 (1.63; 2.51)	2.61 (2.16; 3.15)	1.53 (0.70; 3.34)
BMI[b]			
Underweight	1.18 (0.32; 4.35)	2.39 (1.32; 4.33)	0.96 (0.02; 59.6)
Normal	Ref	Ref	Ref
Overweight	1.13 (0.90; 1.41)	0.73 (0.61; 0.86)	0.72 (0.34; 1.50)
Obese	1.17 (0.91; 1.50)	0.86 (0.71; 1.04)	1.15 (0.53; 2.49)
Alcohol[c]			
Abstainer	1.24 (1.02; 1.50)	1.33 (1.15; 1.55)	1.33 (0.73; 2.44)
Light/moderate	Ref	Ref	Ref
Heavy	0.97 (0.25; 3.76)	1.79 (0.81; 3.96)	0.98 (0.001; 816.24)

[a]Dichotomous (Yes/No), Reference=No

[b]Underweight = <18.5 kg/m^2; normal = ≥18.5 & <25; overweight = ≥25 & <30; obese = ≥30

[c]Light/moderate = men (>0g & <60g daily), women (>0g & <40g daily); Heavy = men (≥60g daily), women (≥40g daily)

Table S3. Hazard ratios for the different transitions, Tromsø (Norway)

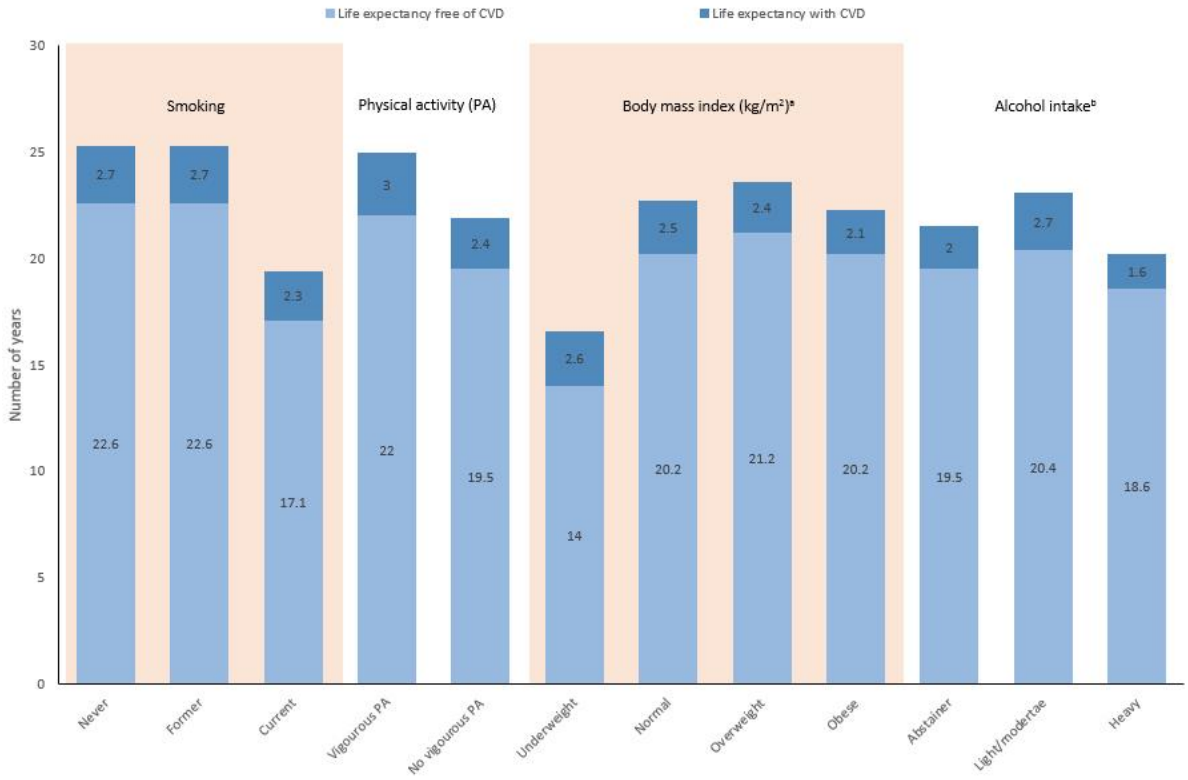
	No CVD to CVD	No CVD to death	CVD to death
Number of events	1713	2108	727
Age	1.06 (1.06; 1.07)	1.11 (1.10; 1.12)	1.11 (1.10; 1.12)
Female	0.57 (0.51; 0.63)	0.61 (0.55; 0.67)	0.74 (0.63; 0.87)
Prevalent diabetes[a]	2.10 (1.68; 2.63)	1.85 (1.50; 2.28)	1.88 (1.43; 2.48)
Vigorous physical activity[a]	0.94 (0.85; 1.05)	0.63 (0.56; 0.70)	0.80 (0.66; 0.96)
Total/HDL cholesterol ratio	1.15 (1.12; 1.19)	1.00 (0.97; 1.03)	1.03 (0.99; 1.08)
Hypertension[a]	1.75 (1.55; 1.97)	1.14 (1.03; 1.26)	1.27 (1.03; 1.58)
Smoking			
Never	Ref	Ref	Ref
Former	1.23 (1.23; 1.23)	1.07 (0.96; 1.20)	-
Current	1.85 (1.66; 2.06)	1.60 (1.42; 1.79)	1.52 (1.28; 1.81)
BMI[b]			
Underweight	0.88 (0.53; 1.46)	1.80 (1.41; 2.31)	1.30 (0.70; 2.43)
Normal	Ref	Ref	Ref
Overweight	1.23 (1.10; 1.38)	0.81 (0.73; 0.90)	0.85 (0.72; 1.01)
Obese	1.31 (1.14; 1.51)	0.91 (0.80; 1.03)	0.78 (0.63; 0.98)
Alcohol[c]			
Abstainer	1.06 (0.95; 1.20)	1.08 (0.98; 1.19)	0.94 (0.79; 1.11)
Light/moderate	Ref	Ref	Ref
Heavy	0.94 (0.11; 8.26)	1.10 (0.15; 7.88)	-

[a]Dichotomous (Yes/No), Reference=No

[b]Underweight = <18.5 kg/m^2; normal = ≥18.5 & <25; overweight = ≥25 & <30; obese = ≥30

[c]Light/moderate = men (>0g & <60g daily), women (>0g & <40g daily); Heavy = men (≥60g daily), women (≥40g daily)

Fig. S1a CVD-free life expectancy (LE free of CVD) and life expectancy with CVD (LE with CVD), in years at age 50 for men without CVD at baseline, RCPH (Denmark)



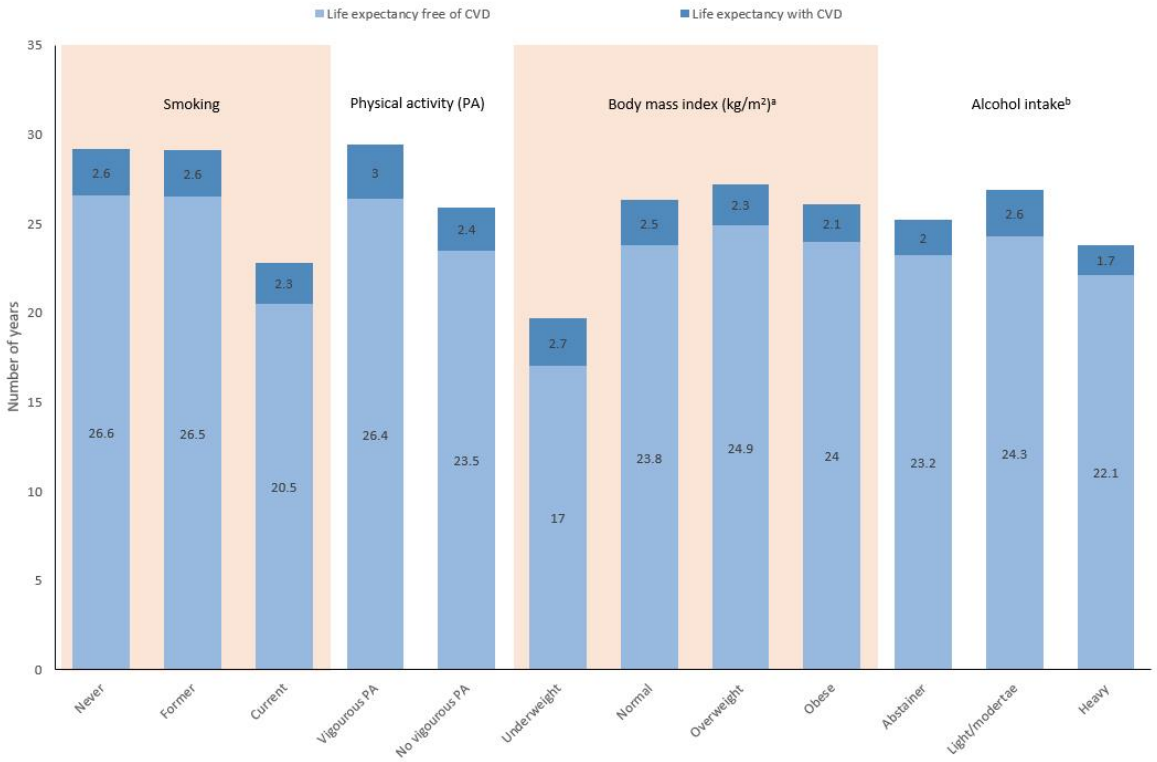
[a]Underweight = <18.5 kg/m^2; normal = ≥18.5 & <25; overweight = ≥25 & <30; obese = ≥30

[b]Light/moderate = >0g & <60g daily; Heavy = ≥60g daily

All corrected for age, history of diabetes, hypertension and total/HDL cholesterol ratio. Individually corrected for smoking status, physical activity, BMI and alcohol intake depending on model, i.e. Smoking corrected for physical activity, BMI and alcohol intake; BMI corrected for smoking status, physical activity, and alcohol intake

When using the repeated measures of covariates in the Markov model, the most recent available value for each measurement was used in the analysis

Fig. S1b CVD-free life expectancy (LE free of CVD) and life expectancy with CVD (LE with CVD), in years at age 50 for women without CVD at baseline, RCPH (Denmark)



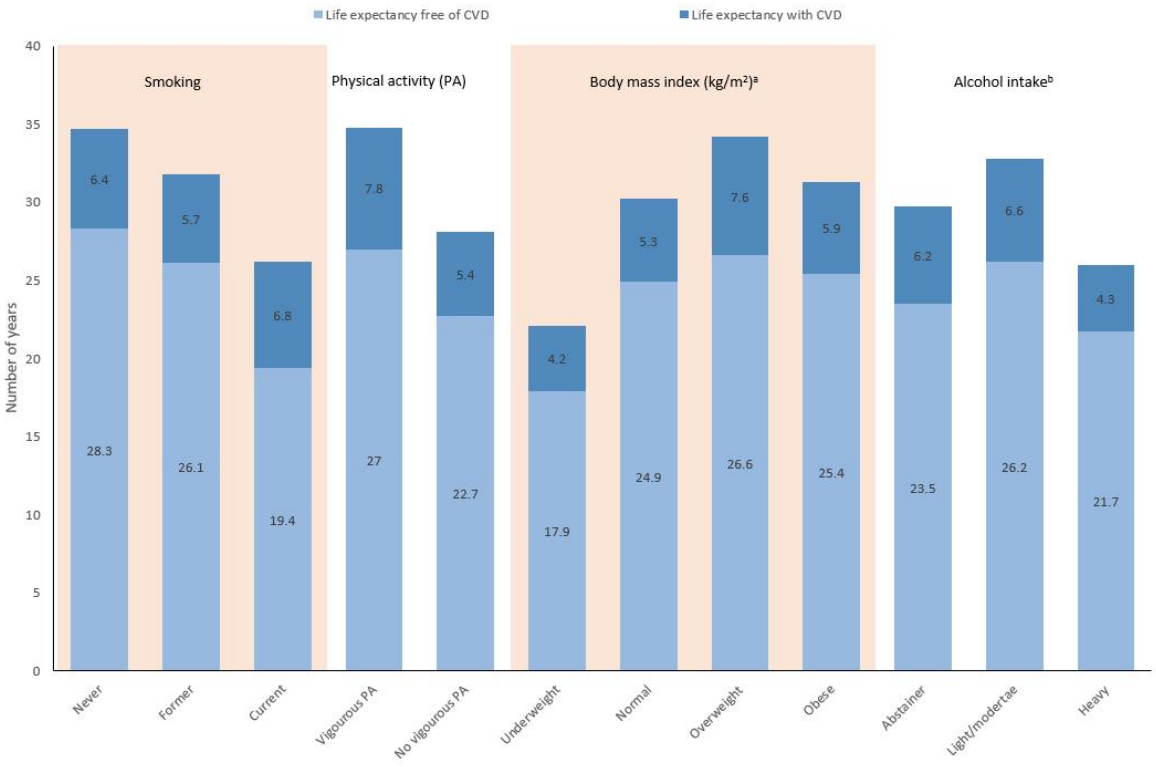
[a]Underweight = <18.5 kg/m2; normal = ≥18.5 & <25; overweight = ≥25 & <30; obese = ≥30

[b]Light/moderate = >0g & <40g daily; Heavy = ≥40g daily

All corrected for age, history of diabetes, hypertension and total/HDL cholesterol ratio. Individually corrected for smoking status, physical activity, BMI and alcohol intake depending on model, i.e. Smoking corrected for physical activity, BMI and alcohol intake; BMI corrected for smoking status, physical activity, and alcohol intake

When using the repeated measures of covariates in the Markov model, the most recent available value for each measurement was used in the analysis

Fig. S1c CVD-free life expectancy (LE free of CVD) and life expectancy with CVD (LE with CVD), in years at age 50 for men without CVD at baseline, ESTHER (Germany)



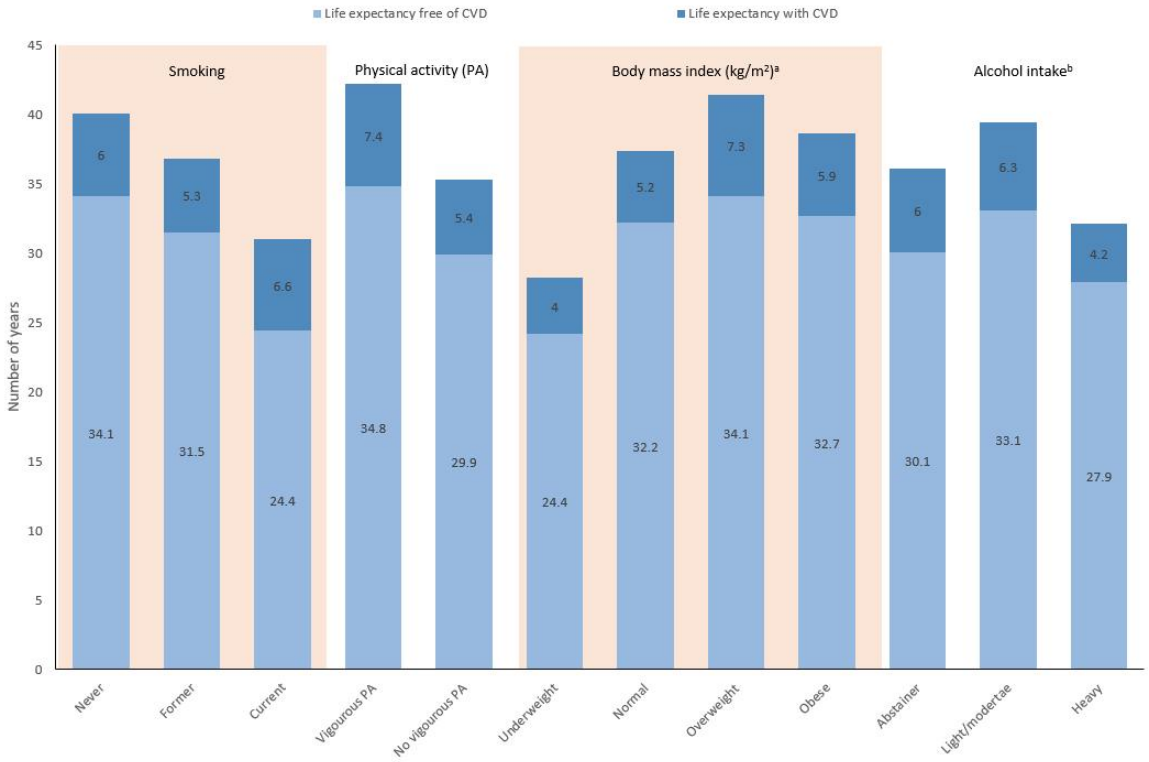
[a]Underweight = <18.5 kg/m2; normal = ≥18.5 & <25; overweight = ≥25 & <30; obese = ≥30

[b]Light/moderate = >0g & <60g daily; Heavy = ≥60g daily

All corrected for age, history of diabetes, hypertension and total/HDL cholesterol ratio. Individually corrected for smoking status, physical activity, BMI and alcohol intake depending on model, i.e. Smoking corrected for physical activity, BMI and alcohol intake; BMI corrected for smoking status, physical activity, and alcohol intake

When using the repeated measures of covariates in the Markov model, the most recent available value for each measurement was used in the analysis

Fig. S1d CVD-free life expectancy (LE free of CVD) and life expectancy with CVD (LE with CVD), in years at age 50 for women without CVD at baseline, ESTHER (Germany)



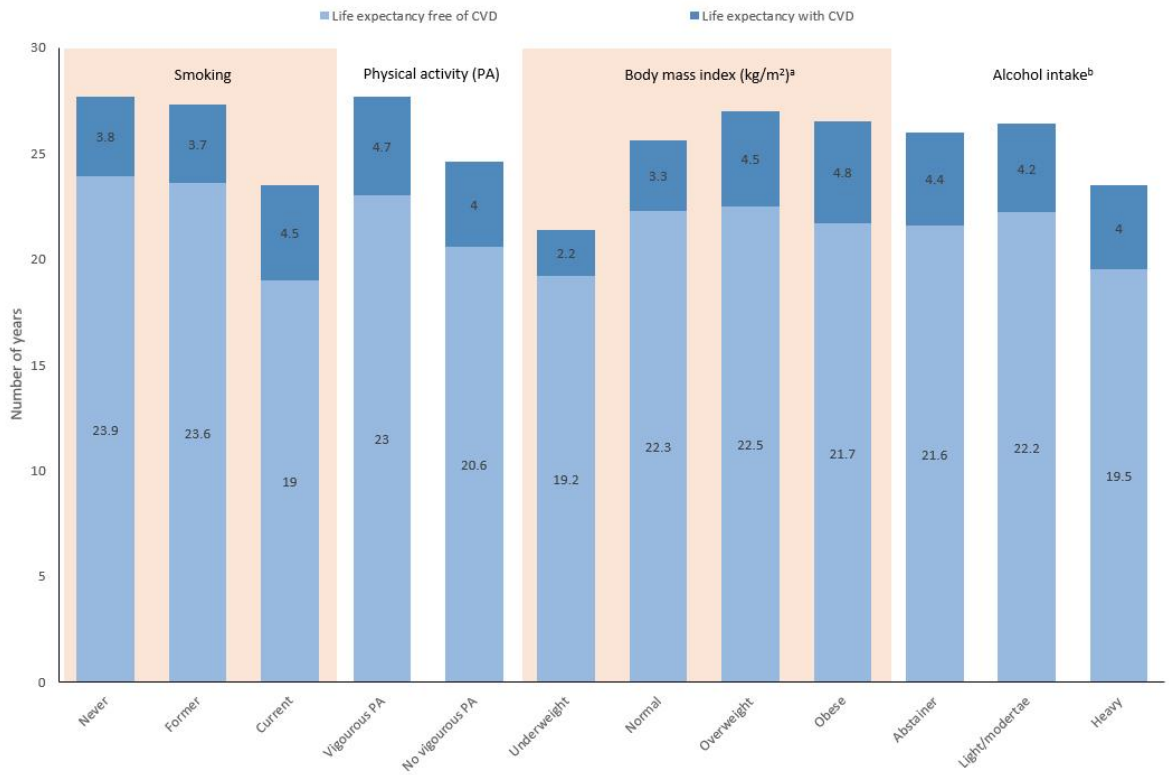
[a]Underweight = <18.5 kg/m2; normal = ≥18.5 & <25; overweight = ≥25 & <30; obese = ≥30

[b]Light/moderate = >0g & <40g daily; Heavy = ≥40g daily

All corrected for age, history of diabetes, hypertension and total/HDL cholesterol ratio. Individually corrected for smoking status, physical activity, BMI and alcohol intake depending on model, i.e. Smoking corrected for physical activity, BMI and alcohol intake; BMI corrected for smoking status, physical activity, and alcohol intake

When using the repeated measures of covariates in the Markov model, the most recent available value for each measurement was used in the analysis

Fig. S1e CVD-free life expectancy (LE free of CVD) and life expectancy with CVD (LE with CVD), in years at age 50 for men without CVD at baseline, Tromsø (Norway)



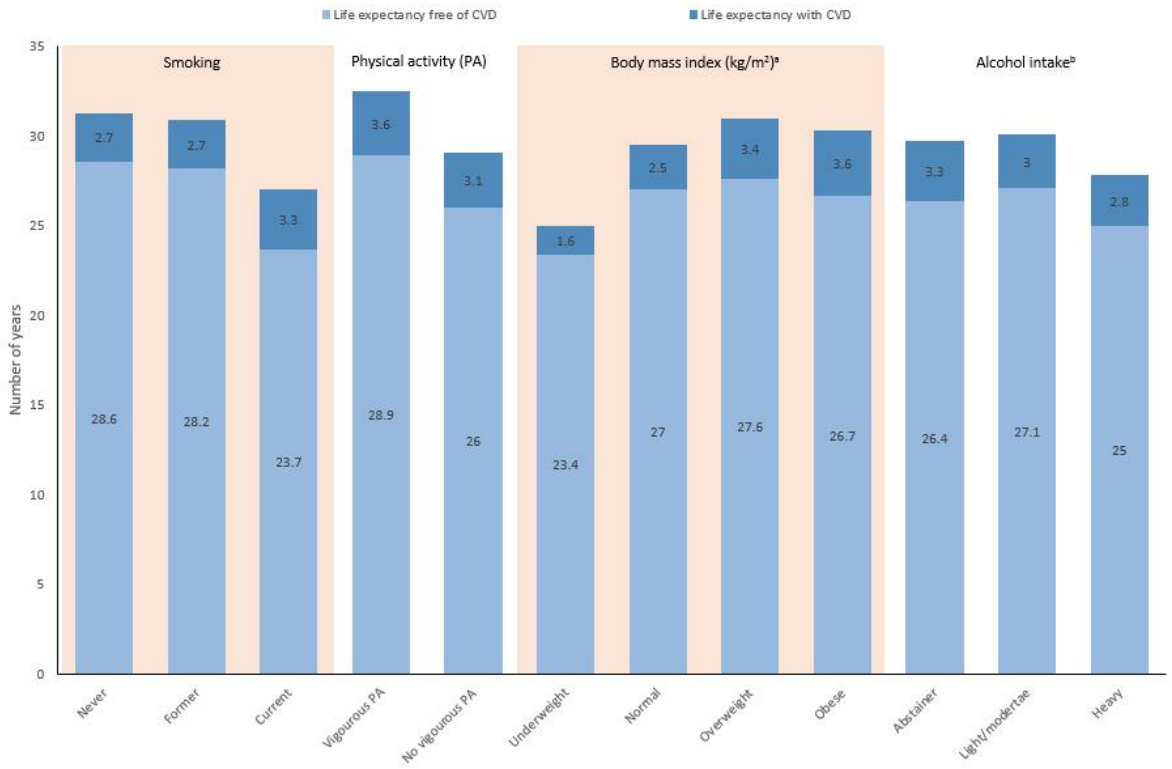
[a]Underweight = <18.5 kg/m2; normal = ≥18.5 & <25; overweight = ≥25 & <30; obese = ≥30

[b]Light/moderate = >0g & <60g daily; Heavy = ≥60g daily

All corrected for age, history of diabetes, hypertension and total/HDL cholesterol ratio. Individually corrected for smoking status, physical activity, BMI and alcohol intake depending on model, i.e. Smoking corrected for physical activity, BMI and alcohol intake; BMI corrected for smoking status, physical activity, and alcohol intake

When using the repeated measures of covariates in the Markov model, the most recent available value for each measurement was used in the analysis

Fig. S1f CVD-free life expectancy (LE free of CVD) and life expectancy with CVD (LE with CVD), in years at age 50 for women without CVD at baseline, Tromsø (Norway)



[a]Underweight = <18.5 kg/m2; normal = ≥18.5 & <25; overweight = ≥25 & <30; obese = ≥30

[b]Light/moderate = >0g & <40g daily; Heavy = ≥40g daily

All corrected for age, history of diabetes, hypertension and total/HDL cholesterol ratio. Individually corrected for smoking status, physical activity, BMI and alcohol intake depending on model, i.e. Smoking corrected for physical activity, BMI and alcohol intake; BMI corrected for smoking status, physical activity, and alcohol intake

When using the repeated measures of covariates in the Markov model, the most recent available value for each measurement was used in the analysis

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