Supplementary Online Content

van Sloten TT, Tafflet M, Périer M-C, et al. Association of change in cardiovascular risk factors with incident cardiovascular events. *JAMA*. doi:10.1001/jama.2018.16975

© 2018 American Medical Association. All rights reserved.

eTable 12. Time-varying Cox proportional hazard models for the association between individual cardiovascular health metrics and incident cardiovascular disease and all-cause mortality

eTable 13. Association of change in the individual cardiovascular health metrics between 1985/88 and 1997/99 with subsequent incident cardiovascular disease events and all-cause mortality

eFigure 1. Summary of the statistical analysis design

eFigure 2. Distribution of the number of ideal cardiovascular health metrics at each wave in the total study population (A), by age group (B), by sex (C) and in white versus non-white participants (D)

eFigure 3. Distribution of the change in cardiovascular health between 1985/88 and 1997/99 in the total study population (n=6326) (A), in individuals aged <45 (n=3591) and ≥45 years (n=2735) (B), in women (n=1874) and men (n=4452) (C) and in white (n=5854) versus non-white participants (n=472) (D)

eFigure 4. Distribution of the change in the number of ideal cardiovascular health metrics between 1985/88 and 1997/99 in the total study population (n=6326) (A), in individuals aged <45 (n=3591) and ≥45 years (n=2735) (B), in women (n=1874) and men (n=4452) (C) and in white (n=5854) versus non-white participants (n=472) (D)

eFigure 5. Hazards ratios of incident cardiovascular disease and all-cause mortality for change in the number of ideal cardiovascular health metrics between 1985/88 and 1997/99.

eFigure 6. Heatmap of unadjusted incidence rates of cardiovascular disease (A) and all-cause mortality (B) by change in the number of ideal health metrics between 1985/88 and 1997/99 in the total study population

This supplementary material has been provided by the authors to give readers additional information about their work.

© 2018 American Medical Association. All rights reserved.

Online-Only Supplements

Association of change in cardiovascular risk factors with incident cardiovascular events

Thomas T van Sloten[1.2.3], MD, PhD, Muriel Tafflet[1.2], MSc, Marie-Cécile Périer[1.2], MSc, Aline Dugravot[4.5], PhD, Rachel ED Climie[1.2.6.7], PhD, Archana Singh-Manoux, [4.5], PhD, Jean-Philippe Empana[1.2], MD, PhD

1. Université Paris Descartes, Sorbonne Paris Cité, Faculté de Médecine, Paris, France.
2. INSERM, UMR-S970, Paris Cardiovascular Research Center, Integrative Epidemiology of cardiovascular disease (Team 4), Paris, France.
3. Cardiovascular Research Institute Maastricht and Department of Internal Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands
4. INSERM, U1018, Centre for Research in Epidemiology and Population Health, France
5. Department of Epidemiology and Public Health, University College London, UK
6. Menzies Institute for Medical Research, University of Tasmania, Hobert, Australia
7. Baker Heart and Diabetes Institute, Melbourne, Australia

Contents

eTable 1. Definition of cardiovascular health metrics according to the American Heart Association for ascertainment of cardiovascular health status

Metric	Recommended ideal level	Intermediate level	Poor level
Smoking	Never or quit ≥12 months	Quit <12 months	Current smokers
Body mass index	BMI <25 kg/m^2	25-29.9 kg/m^2	≥30 kg/m^2
Physical activity[a]	≥75 min/week of vigorous activity, ≥150 min/week of moderate activity or a combination of the two	1–74 min/week vigorous activity, 1–149 min/week moderate activity or a combination of the two	None
Healthy diet[b]	At baseline (1985/88): ≥2 optimal out of the following 3 items: 2 servings of a fruit and vegetable portion/day and fish consumption ≥3 times/week. At last follow-up examination (2015/16): ≥2 optimal out of the following 3 items: ≥2 servings of a fruit and vegetable portion/day and consumption of fiber-rich aliments content ≥3 times/day For all other examination rounds: ≥4 optimal out of the following 5 items: ≥2 servings of a fruit and vegetable portion/day, fish consumption ≥3 times/week, consumption of fiber-rich aliments content ≥3 times/day, sodium consumption ≤1500 mg/day and ≤450 kcal of sugar-sweetened beverages/week	At baseline and last-follow-up examination: 1 optimal out of the 3 items For all other examination rounds: 2-3 optimal out of the 5 items	At baseline and last-follow-up examination: 0 optimal out of the 3 items For all other examination rounds: 0-1 optimal out of the 5 items
Blood pressure[c]	< 120/80 mmHg, untreated	< 120/80 mmHg on medications or 120-139/80-89 mmHg	≥ 140/90 mmHg
Fasting plasma glucose[d]	< 100 mg/dL, untreated	100 -126 mg/dL or < 100 mg/dL treated	> 126 mg/dL
Total cholesterol[d]	< 200 mg/dL, untreated	200 -240 mg/dL or < 200 mg/dL treated	> 240 mmol/L

[a] Physical activity was assessed using questions on frequency and duration of participation in mildly energetic (e.g., weeding, general housework, bicycle repair), moderately energetic (e.g., dancing, cycling, leisurely swimming), and vigorous physical activity (e.g., running, hard swimming, playing squash).[1,2]

[b] For the diet metric at baseline (1985/88), only the frequency consumption of fruits, vegetables and fish was reported, and at last follow-up (2015/16) only the frequency consumption of fruits, vegetables and fibers was reported. At subsequent examinations, the frequency consumption of the 5 AHA-recommended items was drawn from a validated 127-item food frequency questionnaire (FFQ).[3]

[c] Systolic blood pressure was measured twice with a sphygmomanometer in the sitting position after 5 min rest, and the average of the two readings was used in the present analyses. Participants reported their medications used in the previous 14 days; responses were coded using the British National Formulary.[4]

[d] Fasting blood glucose and total cholesterol were measured using standardized methods. Participants reported their medications used in the previous 14 days; responses were coded using the British National Formulary.[4] At baseline (1985/88), however, only prevalent diabetes and antidiabetic medications were available.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.

eTable 2. Characteristics of excluded and included study participants at baseline in 1985/88

	Included (N=9256)	Excluded (N=1052)	Difference (95% confidence interval)
Age, mean (SD), y	44.77 (6.02)	46.56 (6.11)	-1.79 (-2.18; -1.4)
Men, No. (%)	6315 (68.23)	580 (55.13)	13.1 (8.89; 17.31)
Depression[a], No. (%)	1272 (13.74)	159 (16.67)	-2.93 (-9.02; 3.16)
Education level, No. (%)			
High school	2368 (25.58)	295 (28.04)	-2.46 (-7.88; 2.96)
College	1744 (18.84)	138 (13.12)	5.72 (-0.2; 11.64)
Tertiary	2933 (31.69)	203 (19.30)	12.39 (6.71; 18.07)
Occupation grade, No. (%)			
Administrative	2791 (30.15)	237 (22.53)	7.62 (2.04; 13.2)
Professional/executive	4538 (49.03)	405 (38.50)	10.53 (5.57; 15.49)
Clerical/support	1927 (20.82)	410 (38.97)	-18.15 (-23.21; -13.09)
Marital status, No. (%)			
Married/cohabiting	6894 (74.48)	714 (70.41)	4.07 (0.57; 7.57)
Single	1509 (16.30)	181 (17.85)	-1.55 (-7.43; 4.33)
Divorced	742 (8.02)	91 (8.97)	-0.95 (-7.14; 5.24)
Widowed	111 (1.20)	28 (2.76)	-1.56 (-7.96; 4.84)
Race/ethnicity (white) , No. (%)	8389 (90.63)	792 (82.50)	8.13 (5.41; 10.85)
Family history, No. (%)			
Stroke	1609 (17.38)	173 (20.72)	-3.34 (-9.66; 2.98)
Myocardial infarction	2492 (26.92)	292 (33.41)	-6.49 (-12.17; -0.81)

[a] Depressive symptoms were ascertained using the 30-item General Health Questionnaire.[5]

eTable 3. Prevalence of individual cardiovascular health metrics at each wave of examination from 1985/88 up to 2015/2016

Examination round	1985/88	1991/93	1997/99	2002/04	2007/09	2012/13	2015/16
Prevalence of individual metrics, No. (%)	N=9256	N=8972	N=8539	N=8014	N=7363	N=6795	N=6334
Smoking							
Poor	1672 (18.06)	1537 (17.13)	1221 (14.30)	1014 (12.65)	848 (11.52)	563 (8.29)	473 (7.47)
Intermediate	387 (4.18)	197 (2.20)	227 (2.66)	144 (1.80)	148 (2.01)	654 (9.62)	722 (11.40)
Ideal	7197 (77.75)	7238 (80.67)	7091 (83.04)	6856 (85.55)	6367 (86.47)	5578 (82.09)	5139 (81.13)
Body mass index							
Poor	606 (6.55)	824 (9.18)	1025 (12.00)	1242 (15.50)	1212 (16.46)	1135 (16.70)	1086 (17.15)
Intermediate	2946 (31.83)	3289 (36.66)	3414 (39.98)	3407 (42.51)	3032 (41.18)	2787 (41.02)	2572 (40.61)
Ideal	5704 (61.62)	4859 (54.16)	4100 (48.01)	3365 (41.99)	3119 (42.36)	2873 (42.28)	2676 (42.25)
Diet							
Poor	8298 (89.65)	4404 (49.09)	3874 (45.37)	3390 (42.30)	3017 (40.98)	2429 (35.75)	2243 (35.41)
Intermediate	871 (9.41)	4291 (47.83)	4314 (50.52)	4234 (52.83)	3961 (53.80)	3923 (57.73)	2871 (45.33)
Ideal	87 (0.94)	277 (3.09)	351 (4.11)	390 (4.87)	385 (5.23)	443 (6.52)	1220 (19.26)
Physical activity							
Poor	1350 (14.59)	1522 (16.96)	1241 (14.53)	918 (11.45)	862 (11.71)	792 (11.66)	863 (13.62)
Intermediate	4989 (53.90)	4758 (53.03)	4873 (57.07)	4672 (58.30)	4249 (57.71)	3960 (58.28)	3744 (59.11)
Ideal	2917 (31.51)	2692 (30.00)	2425 (28.40)	2424 (30.25)	2252 (30.59)	2043 (30.07)	1727 (27.27)
Blood pressure							
Poor	1612 (17.42)	1575 (17.55)	1742 (20.40)	1794 (22.39)	1473 (20.01)	1534 (22.58)	1435 (22.66)
Intermediate	4107 (44.37)	4096 (45.65)	3671 (42.99)	3779 (47.15)	3711 (50.40)	3545 (52.17)	3356 (52.98)
Ideal	3537 (38.21)	3301 (36.79)	3126 (36.61)	2441 (30.46)	2179 (29.59)	1716 (25.25)	1543 (24.36)
Total cholesterol							
Poor	3326 (35.93)	4817 (53.69)	3398 (39.79)	2819 (35.18)	1999 (27.15)	1682 (24.75)	1352 (21.35)
Intermediate	3647 (39.40)	2881 (32.11)	3413 (39.97)	3507 (43.76)	3723 (50.56)	3683 (54.20)	3459 (54.61)
Ideal	2283 (24.67)	1274 (14.20)	1728 (20.24)	1688 (21.06)	1641 (22.29)	1430 (21.04)	1523 (24.04)
Fasting glucose							
Poor	80 (0.86)	168 (1.87)	252 (2.95)	376 (4.69)	406 (5.51)	414 (6.09)	453 (7.15)
Intermediate	0	2598 (28.96)	2652 (31.06)	3462 (43.20)	2819 (38.29)	2840 (41.80)	2618 (41.33)
Ideal	9176 (99.14)	6206 (69.17)	5635 (65.99)	4176 (52.11)	4138 (56.20)	3541 (52.11)	3263 (51.52)

eTable 4. Time-varying Cox proportional hazard model for incident coronary heart disease and stroke as separate outcomes

	Incident coronary heart disease			Incident stroke		
	n/N	Unadjusted HR (95%CI)	Adjusted HR (95%CI)	n/N	Unadjusted HR (95%CI)	Adjusted HR (95%CI)
Cardiovascular health status	1757/9256			295/9256		
Low (0-2 ideal metrics)		1 (Ref)	1 (Ref)		1 (Ref)	1 (Ref)
Moderate (3-4 ideal metrics)		0.69 (0.63; 0.76)	0.71 (0.65; 0.79)		0.74 (0.58; 0.93)	0.77 (0.60; 0.98)
High (5-7 ideal metrics)		0.44 (0.35; 0.55)	0.46 (0.36; 0.58)		0.54 (0.31; 0.94)	0.58 (0.33; 1.01)
Per additional ideal metric	1757/9256	0.81 (0.78; 0.85)	0.83 (0.79; 0.86)	295/9256	0.83 (0.75; 0.91)	0.85 (0.77; 0.93)
Per one-point increase in 14-point CVH score	1757/9256	0.86 (0.84; 0.88)	0.86 (0.84; 0.88)	295/9256	0.88 (0.84; 0.93)	0.89 (0.84; 0.95)

Hazard ratios and 95% confidence intervals were estimated by Cox proportional hazard model stratified by year of birth (5-year intervals) and using age as the time scale over a median follow-up of 29.5 (interquartile range 25.2 to 30.4) years for CVD starting from baseline. Cardiovascular health status, per additional ideal metric and per one-point increase in the 14-point CVH score were included as time-varying variables. The linearity assumption of the model per additional ideal metric and per one point increase in 14-point CVH score was evaluated by comparing the Akaike information criterion of a linear model with a quadratic and a cubic model. Multivariable hazards ratios were adjusted sex, race/ethnicity, depression, education, occupation and family history of cardiovascular disease at baseline. For the 141 participants who had both events, follow-up was censored at the date of first event.

HR stands for hazard ratio; CI for confidence interval; CVD for cardiovascular disease; and CVH for cardiovascular health.

eTable 5. Time-varying Cox proportional hazard model for cause-specific mortality (competing risk analysis)

	Cause of death	n/N	Unadjusted subHRs (95%CI)	Adjusted subHRs (95%CI)
Cardiovascular health status				
Low (0-2 ideal metrics)	CVD	408/9256	1 (Ref)	1 (Ref)
Moderate (3-4 ideal metrics)			0.59 (0.48; 0.73)	0.62 (0.50; 0.76)
High (5-7 ideal metrics)			0.28 (0.15; 0.52)	0.30 (0.16; 0.56)
Low (0-2 ideal metrics)	Cancer	748/9256	1 (Ref)	1 (Ref)
Moderate (3-4 ideal metrics)			0.79 (0.68; 0.91)	0.77 (0.66; 0.90)
High (5-7 ideal metrics)			0.99 (0.74; 1.30)	0.96 (0.72; 1.28)
Low (0-2 ideal metrics)	Other causes	501/9256	1 (Ref)	1 (Ref)
Moderate (3-4 ideal metrics)			0.66 (0.55; 0.80)	0.67 (0.56; 0.81)
High (5-7 ideal metrics)			0.56 (0.37; 0.86)	0.58 (0.38; 0.89)
Per additional ideal metric	CVD	408/9256	0.73 (0.67; 0.80)	0.75 (0.68; 0.82)
	Cancer	748/9256	0.91 (0.85; 0.97)	0.90 (0.85; 0.97)
	Other causes	501/9256	0.83 (0.77; 0.89)	0.84 (0.77; 0.90)
Per one-point increase in 14-point CVH score	CVD	408/9256	0.80 (0.76; 0.84)	0.80 (0.76; 0.84)
	Cancer	748/9256	0.92 (0.88; 0.95)	0.91 (0.88; 0.95)
	Other causes	501/9256	0.84 (0.81; 0.88)	0.85 (0.81; 0.88)

Subdistribution hazard ratios (subHRs) and 95% confidence intervals were estimated by Cox proportional hazard model stratified by year of birth (5-year intervals) using the Fine and Gray[6] method for competing risk over a median follow-up 30.2 (interquartile range 29.6 to 31.1) years for mortality starting from baseline. Cardiovascular health status, per additional ideal metric and per one-point increase in the 14-point CVH score were included as time-varying variables. The linearity assumption of the model per additional ideal metric and per one-point increase in 14-point CVH score was evaluated by comparing the Akaike information criterion of a linear model with a quadratic and a cubic model. Multivariable hazards ratios were adjusted sex, race/ethnicity, depression, education, occupation and family history of cardiovascular disease at baseline.

SubHRs stands for subdistribution hazard ratios; CI for confidence interval; CVD for cardiovascular disease; and CVH for cardiovascular health.

eTable 6. Baseline characteristics of included and excluded study participants for the analysis of change in cardiovascular health status between 1985/88 and 1997/99

	Included	Excluded[a]			P-value[b]
		All	Exclusion due to death or CVD event within interval	Exclusion due to drop-out or missing data	
Baseline characteristics	N=6326	N=2930	N=716	N=2214	
Age, mean (SD), y	44.47 (5.93)	45.41 (6.15)	47.79 (5.73)	44.64 (6.08)	<.0001
Men, No. (%)	4452 (70.38)	1863 (63.58)	504 (70.39)	1359 (61.38)	<.0001
Depression[c], No. (%)	838 (13.25)	434 (14.81)	102 (14.25)	332 (15.00)	.04
Education level, No. (%)					
High school	1465 (23.16)	903 (30.82)	213 (29.75)	690 (31.17)	<.0001
College	1185 (18.73)	559 (19.08)	141 (19.69)	418 (18.88)	
Tertiary	2110 (33.35)	823 (28.09)	189 (26.40)	634 (28.64)	
Occupation grade, No. (%)					
Administrative	2106 (33.29)	685 (23.38)	196 (27.37)	489 (22.09)	<.0001
Professional/executive	3189 (50.41)	1349 (46.04)	327 (45.67)	1022 (46.16)	
Clerical/support	1031 (16.30)	896 (30.58)	193 (26.96)	703 (31.75)	
Marital status, No. (%)					
Married/cohabiting	4797 (75.83)	2097 (71.57)	535 (74.72)	1562 (70.55)	<.0001
Single	997 (15.76)	512 (17.47)	116 (16.20)	396 (17.89)	
Divorced	464 (7.33)	278 (9.49)	59 (8.24)	219 (9.89)	
Widowed	68 (1.07)	43 (1.47)	6 (0.84)	37 (1.67)	
Race/ethnicity (white), No. (%)	5854 (92.54)	2535 (86.52)	617 (86.17)	1918 (86.63)	<.0001
Family history, No. (%)					
Stroke	1077 (17.02)	532 (18.16)	155 (21.65)	377 (17.03)	.18
Myocardial infarction	1688 (26.68)	804 (27.44)	245 (34.22)	559 (25.25)	.45
Baseline cardiovascular health					
Cardiovascular health status, No. (%)					
Low	1301 (20.57)	876 (29.90)	253 (35.34)	623 (28.14)	<.0001
Moderate	3974 (62.82)	1716 (58.57)	413 (57.68)	1303 (58.85)	
High	1051 (16.61)	338 (11.54)	50 (6.98)	288 (13.01)	

	Included	Excluded[a]			P-value[b]
		All	Exclusion due to event within interval	Exclusion due to drop-out or missing data	
	N=6326	N=2930	N=716	N=2214	
Number of ideal metrics, median (q1-q3)	3.00 (3.00; 4.00)	3.00 (2.00; 4.00)	3.00 (2.00; 4.00)	3,00 (2.00; 4.00)	<.0001
14-point CVH score, median (q1-q3)	9.00 (8.00; 10.00)	8.00 (7.00; 9.00)	8.00 (6.00; 9.00)	8.00 (7.00; 10.00)	<.0001

[a] Excluded participants are comprised of those who died in the interval (n=248), those who had a CVD event in the interval (n=468), those who dropped out (n=924) and those with incomplete CVH metrics (n=1290).

[b] P-value for contrast between included and excluded participants, derived from Pearson, chi-square and t-test where appropriate.

[c] Depressive symptoms were ascertained using the 30-item General Health Questionnaire.[5]

CVD stands for cardiovascular disease; q stands for quartile; and CVH for cardiovascular health.

106 **eTable 7. Baseline characteristics by pattern of change in cardiovascular health**

Pattern of change	Low-Low	Low-Mod	Low-High	Mod-Low	Mod-Mod	Mod-High	High-Low	High-Mod	High-High
	N=852	N=430	N=19	N=1141	N=2463	N=370	N=120	N=586	N=345
Age, mean (SD), y	45,45 (5,88)	45.41 (5.95)	45.28 (6.52)	44.73 (5.83)	44.66 (5.96)	44.08 (6.20)	43.00 (5.57)	43.03 (5.67)	41.95 (5.17)
Men, No. (%)	646 (75.82)	316 (73.49)	11 (57.89)	820 (71.87)	1717 (69.71)	252 (68.11)	85 (70.83)	377 (64.33)	228 (66.09)
Depression[a], No. (%)	111 (13.03)	50 (11.63)	0	165 (14.46)	324 (13.15)	49 (13.24)	18 (15.00)	71 (12.12)	50 (14.49)
Education level, No. (%)									
High school	226 (26.53)	103 (23.95)	3 (15.79)	292 (25.59)	567 (23.02)	56 (15.14)	28 (23.33)	133 (22.70)	57 (16.52)
College	182 (21.36)	81 (18.84)	5 (26.32)	206 (18.05)	451 (18.31)	64 (17.30)	26 (21.67)	105 (17.92)	65 (18.84)
Tertiary	227 (26.64)	137 (31.86)	6 (31.58)	381 (33.39)	792 (32.16)	149 (40.27)	39 (32.50)	231 (39.42)	148 (42.90)
Occupation, No. (%)									
Administrative	250 (29.34)	126 (29.30)	6 (31.58)	357 (31.29)	870 (35.32)	142 (38.38)	31 (25.83)	187 (31.91)	137 (39.71)
Professional-executive	436 (51.17)	221 (51.40)	10 (52.63)	574 (50.31)	1215 (49.33)	189 (51.08)	68 (56.67)	302 (51.54)	174 (50.43)
Clerical/support	166 (19.48)	83 (19.30)	3 (15.79)	210 (18.40)	378 (15.35)	39 (10.54)	21 (17.50)	97 (16.55)	34 (9.86)
Marital status, No. (%)									
Married/cohabiting	643 (75.47)	327 (76.05)	16 (84.21)	862 (75.55)	1868 (75.84)	280 (75.68)	95 (79.17)	455 (77.65)	251 (72.75)
Single	125 (14.67)	62 (14.42)	2 (10.53)	173 (15.16)	409 (16.61)	58 (15.68)	15 (12.50)	83 (14.16)	70 (20.29)
Divorced	68 (7.98)	38 (8.84)	1 (5.26)	86 (7.54)	165 (6.70)	29 (7.84)	10 (8.33)	45 (7.68)	22 (6.38)
Widowed	16 (1.88)	3 (0.70)	0	20 (1.75)	21 (0.85)	3 (0.81)	0	3 (0.51)	2 (0.58)
Race/ethnicity: white, No. (%)	766 (89.91)	393 (91.40)	17 (89.47)	1046 (91.67)	2300 (93.38)	351 (94.86)	110 (91.67)	544 (92.83)	327 (94.78)
Family history, No. (%)									
Stroke, No. (%)	161 (18.90)	69 (16.05)	3 (15.79)	221 (19.37)	408 (16.57)	58 (15.68)	23 (19.17)	85 (14.51)	49 (14.20)
MI, No. (%)	280 (32.86)	115 (26.74)	6 (31.58)	272 (23.84)	653 (26.51)	91 (24.59)	39 (32.50)	144 (24.57)	88 (25.51)

107 Low stands for low cardiovascular health; mod for moderate cardiovascular health; high for high cardiovascular health; MI for myocardial infarction; CVD for cardiovascular disease

108 [a] Depressive symptoms were ascertained using the 30-item General Health Questionnaire.[5]

eTable 8. Associations between 4 groups of change in cardiovascular health as defined in the Framingham study and incident cardiovascular disease and all-cause mortality

Change in CVH status[a]	n/N	Adjusted hazard ratio (95% confidence intervals)[b]
		High-High as reference
Incident cardiovascular disease		
	1114/6326	
Low-Low	238/874	1.94 (1.66; 2.26)
Low-high	136/609	1.38 (1.14; 1.67)
High-low	168/812	1.50 (1.26; 1.78)
High-high	572/4031	1 (Ref)
All-cause mortality		
	846/6326	
Low-Low	194/874	2.04 (1.71; 2.42)
Low-high	102/609	1.36 (1.09; 1.69)
High-low	130/812	1.57 (1.28; 1.91)
High-high	420/4031	1 (Ref)

Change in cardiovascular health status was computed over a median time interval of 10.4 (range 3.8 to 13.3) years in participants free of cardiovascular disease within this time interval.

[a] The 4 groups of change in CVH were defined as high-high (those with 14-point CVH score ≥8 at baseline and last score of ≥8; reference category), high-low (≥8 baseline and ≤7 last), low-high (≤7 baseline and ≥8 last) and low-low (≤7 baseline and ≤7 last) as used in the Framingham Offspring Study.[7]

[b] Hazard ratios and 95% confidence intervals were estimated by Cox proportional hazard model. All models are stratified by year of birth (5-year intervals) and using age as the time scale on a remaining median follow-up time of 18.9 (interquartile range 17.8 to 19.3) years for cardiovascular disease and 19.7 (interquartile range 18.9 to 19.8) years for mortality. Hazards ratios were adjusted for sex, race/ethnicity, depression, education, occupation and family history of cardiovascular disease at baseline.

CVH stands for cardiovascular health

eTable 9. Time-varying Cox proportional hazard model for incident cardiovascular disease and all-cause mortality – results using multiple imputations to account for missing values

	Cardiovascular disease		All-cause mortality	
	n/N	Adjusted HR (95%CI)	n/N	Adjusted HR (95%CI)
Cardiovascular health status[a]	2295/10186		1879/10186	
Low (0-2 ideal metrics)		1 (Ref)		1 (Ref)
Moderate (3-4 ideal metrics)		0.74 (0.66; 0.82)		0.67 (0.59; 0.76)
Ideal (5-7 ideal metrics)		0.48 (0.38; 0.60)		0.59 (0.46; 0.76)
Per additional ideal metric[a]	2295/10186	0.84 (0.80; 0.87)	1879/10186	0.81 (0.77; 0.85)
Per one-point increase in the 14-point CVH score[a]	2295/10186	0.87 (0.85; 0.90)	1879/10186	0.84 (0.82; 0.87)

Hazard ratios and 95% confidence intervals were estimated by Cox proportional hazard models stratified by year of birth (5-year intervals) and using age as the time scale over 29.5 (interquartile range 25.2 to 30.4) years for CVD and 30.2 (interquartile range 29.6 to 31.1) years for mortality starting from baseline.

[a] Cardiovascular health status, per additional ideal metric and per one point increase in the 14-point CVH score, were included as time-varying variables. Hazards ratios were adjusted for sex, race/ethnicity, depression, education, occupation and family history of cardiovascular disease at baseline. Missing CVH metrics and covariates were imputed by multiple imputation using fully conditional specification method under SAS MI procedure, n=10 imputations.

HR stands for hazard ratio; CI for confidence interval; and CVD for cardiovascular disease.

eTable 10. Change in cardiovascular health status between 1985/88 and 1997/99 and association with subsequent incident cardiovascular disease and all-cause mortality – results using multiple imputations to account for missing values

	Cardiovascular disease		All-cause mortality	
	n[a]/N[a]	Adjusted HR (95%CI)	n[a]/N[a]	Adjusted HR (95%CI)
Change in CVH status	1692/9368		1426/9368	
Low-Low	408.6/1586.3	1 (Ref)	384.2/1586.3	1 (Ref)
Low-Moderate	114.6/549.5	0.81 (0.63; 1.04)	115.5/549.5	0.86 (0.67; 1.09)
Low-High	0.9/23.3	-	3.4/23.3	0.57 (0.17; 1.90)
Moderate-Low	481.8/2273.6	0.87 (0.75; 1.00)	357.7/2273.6	0.68 (0.58; 0.79)
Moderate-Moderate	464.4/3059.9	0.59 (0.51; 0.69)	398/3059.9	0.55 (0.47; 0.64)
Moderate-High	40.7/438.6	0.36 (0.25; 0.52)	42.3/438.6	0.41 (0.29; 0.58)
High-Low	39.3/271.0	0.63 (0.44; 0.92)	22.3/271.0	0.43 (0.26; 0.71)
High-Moderate	100.7/793.9	0.54 (0.43; 0.68)	74.5/793.9	0.45 (0.34; 0.59)
High-High	41.0/371.9	0.52 (0.37; 0.74)	28.1/371.9	0.43 (0.29; 0.66)
Change in number of ideal metrics				
Per one additional ideal metric[b]	1692/9368	0.85 (0.81; 0.89)	1426/9368	0.90 (0.85; 0.95)
Change in 14-point CVH score				
Per one point increase in the 14-point CVH score[c]	1692/9368	0.88 (0.85; 0.91)	1426/9368	0.93 (0.88; 0.97)

Hazard ratios and 95% confidence intervals were estimated by Cox proportional hazard model stratified by year of birth (5-year intervals) and using age as the time scale on a remaining median follow-up time of 18.9 (interquartile range 17.8 to 19.3) years for CVD events and 19.7 (interquartile range 18.9 to 19.8) years for all-cause mortality. Multivariable hazards ratios were adjusted for sex, race/ethnicity, depression, education, occupation and family history of cardiovascular disease at baseline. Missing CVH metrics and covariates were imputed by multiple imputation using fully conditional specification method under SAS MI procedure, n=10 imputations.

[a] Average number of CVD events and death (n) and people (N) in each category of change across 10 series of imputations, explaining the presence of decimals.

[b] People with same number of ideal metrics between baseline and 1997/99 (no change, i.e. difference in the number of ideal metrics=0) are the reference group.

[c] People with same cardiovascular health score between baseline and 1997/99 (no change, i.e. difference in the score=0) are the reference group.

HR stands for hazard ratio; CI for confidence interval; CVH for cardiovascular health; and CVD for cardiovascular disease.

eTable 11. Change in the level of individual cardiovascular health metrics between 1985/88 and 1997/99

Pattern of change	Low-Low	Low-Mod	Low-High	Mod-Low	Mod-Mod	Mod-High	High-Low	High-Mod	High-High
Cardiovascular health metric, No. (%)									
Smoking	652 (10.31)	52 (0.82)	276 (4.36)	39 (0.62)	21 (0.33)	180 (2.85)	50 (0.79)	54 (0.85)	5002 (79.07)
Body mass index	278 (4.39)	34 (0.54)	2 (0.03)	470 (7.43)	1322 (20.90)	159 (2.51)	36 (0.57)	1259 (19.90)	2766 (43.72)
Diet	2184 (34.52)	3205 (50.66)	210 (3.32)	86 (1.36)	475 (7.51)	89 (1.41)	6 (0.09)	51 (0.81)	20 (0.32)
Physical activity	299 (4.73)	374 (5.91)	108 (1.71)	356 (5.63)	2315 (36.60)	911 (14.40)	142 (2.24)	1066 (16.85)	755 (11.93)
Blood pressure	471 (7.45)	397 (6.28)	65 (1.03)	648 (10.24)	1409 (22.27)	780 (12.33)	132 (2.09)	861 (13.61)	1563 (24.71)
Total cholesterol	1480 (23.40)	585 (9.25)	54 (0.85)	823 (13.01)	1372 (21.69)	363 (21.69)	113 (1.79)	635 (10.04)	901 (14.24)
Fasting glucose	17 (0.27)	8 (0.13)	11 (0.17)	-	-	-	140 (2,21)	1128 (17,83)	5022 (79,39)

Low stands for low cardiovascular health; mod for moderate cardiovascular health; high for high cardiovascular health.

eTable 12. Time-varying Cox proportional hazard models for the association between individual cardiovascular health metrics and incident cardiovascular disease and all-cause mortality

	Incident cardiovascular disease		All-cause mortality	
	n/N	Adjusted HR (95%CI)	n/N	Adjusted HR (95%CI)
Level of cardiovascular health metric				
Smoking				
Poor	2052/9256	1 (Ref)	1657/9256	1 (Ref)
Intermediate		0.78 (0.62; 0.98)		0.53 (0.42; 0.67)
Ideal		0.60 (0.53; 0.67)		0.39 (0.34; 0.44)
Body mass index				
Poor	2052/9256	1 (Ref)	1657/9256	1 (Ref)
Intermediate		0.78 (0.69; 0.88)		0.79 (0.69; 0.91)
Ideal		0.63 (0.55; 0.71)		0.92 (0.80; 1.05)
Diet				
Poor	2052/9256	1 (Ref)	1657/9256	1 (Ref)
Intermediate		0.90 (0.82; 0.99)		0.76 (0.69; 0.84)
Ideal		0.73 (0.57; 0.92)		0.53 (0.41; 0.69)
Physical activity				
Poor	2052/9256	1 (Ref)	1657/9256	1 (Ref)
Intermediate		0.83 (0.73; 0.95)		0.60 (0.53; 0.68)
Ideal		0.88 (0.77 ;1.01)		0.55 (0.48; 0.64)
Blood pressure				
Poor	2052/9256	1 (Ref)	1657/9256	1 (Ref)
Intermediate		0.74 (0.67; 0.82)		0.82 (0.73; 0.92)
Ideal		0.54 (0.47; 0.61)		0.82 (0.71; 0.94)
Total cholesterol				
Poor	2052/9256	1 (Ref)	1657/9256	1 (Ref)
Intermediate		0.77 (0.70; 0.85)		0.81 (0.72; 0.91)
Ideal		0.72 (0.64; 0.82)		1.00 (0.87; 1.14)
Fasting glucose				
Poor	2052/9256	1 (Ref)	1657/9256	1 (Ref)
Intermediate		0.63 (0.53; 0.76)		0.60 (0.51; 0.71)
Ideal		0.63 (0.53; 0.75)		0.46 (0.39; 0.54)

Hazard ratios and 95% confidence intervals were estimated by Cox proportional hazard models stratified by year of birth (5-year intervals) and using age as the time scale over a median follow-up of 29.5 (interquartile range 25.2 to 30.4) years for CVD and 30.2 (interquartile range 29.6 to 31.1) years for mortality starting from baseline.

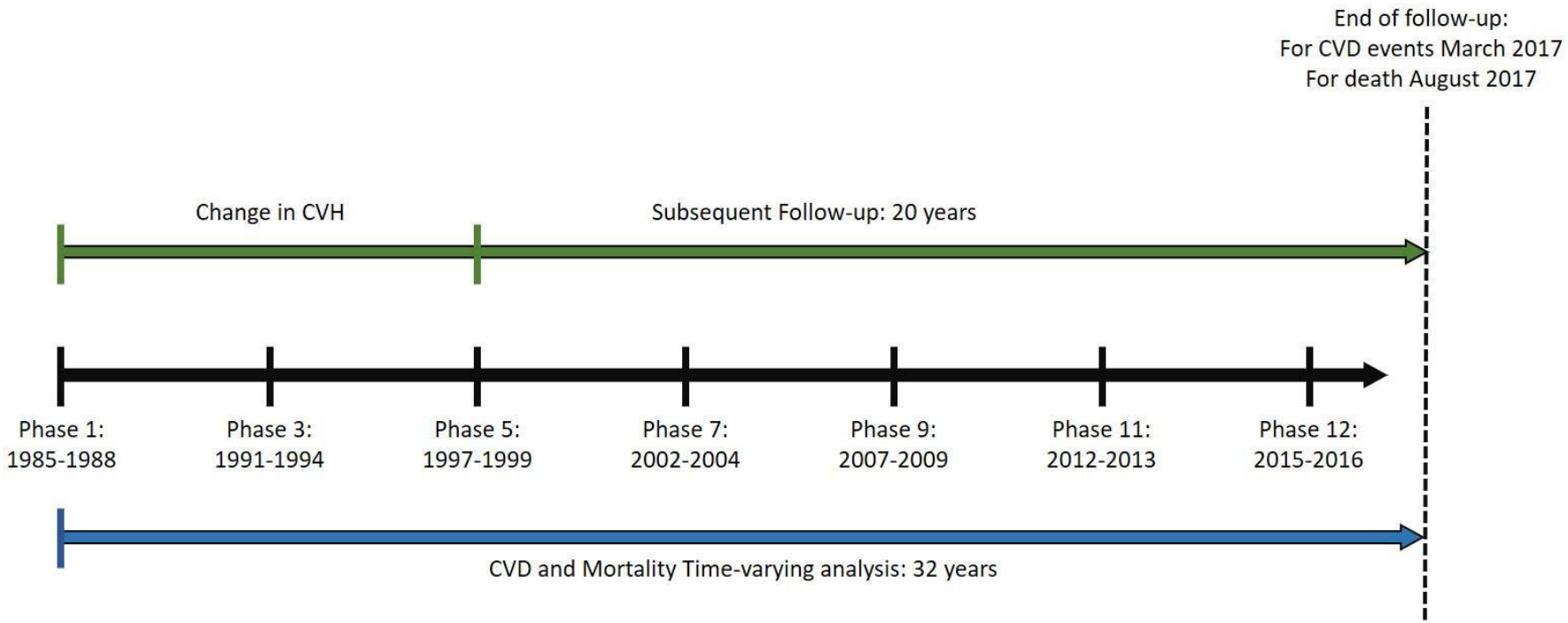
[a] Each individual cardiovascular health metric was included as a time-varying variable. Hazards ratios were adjusted for sex, race/ethnicity, depression, education, occupation and family history of cardiovascular disease at baseline.

HR stands for hazard ratio; CI for confidence interval..

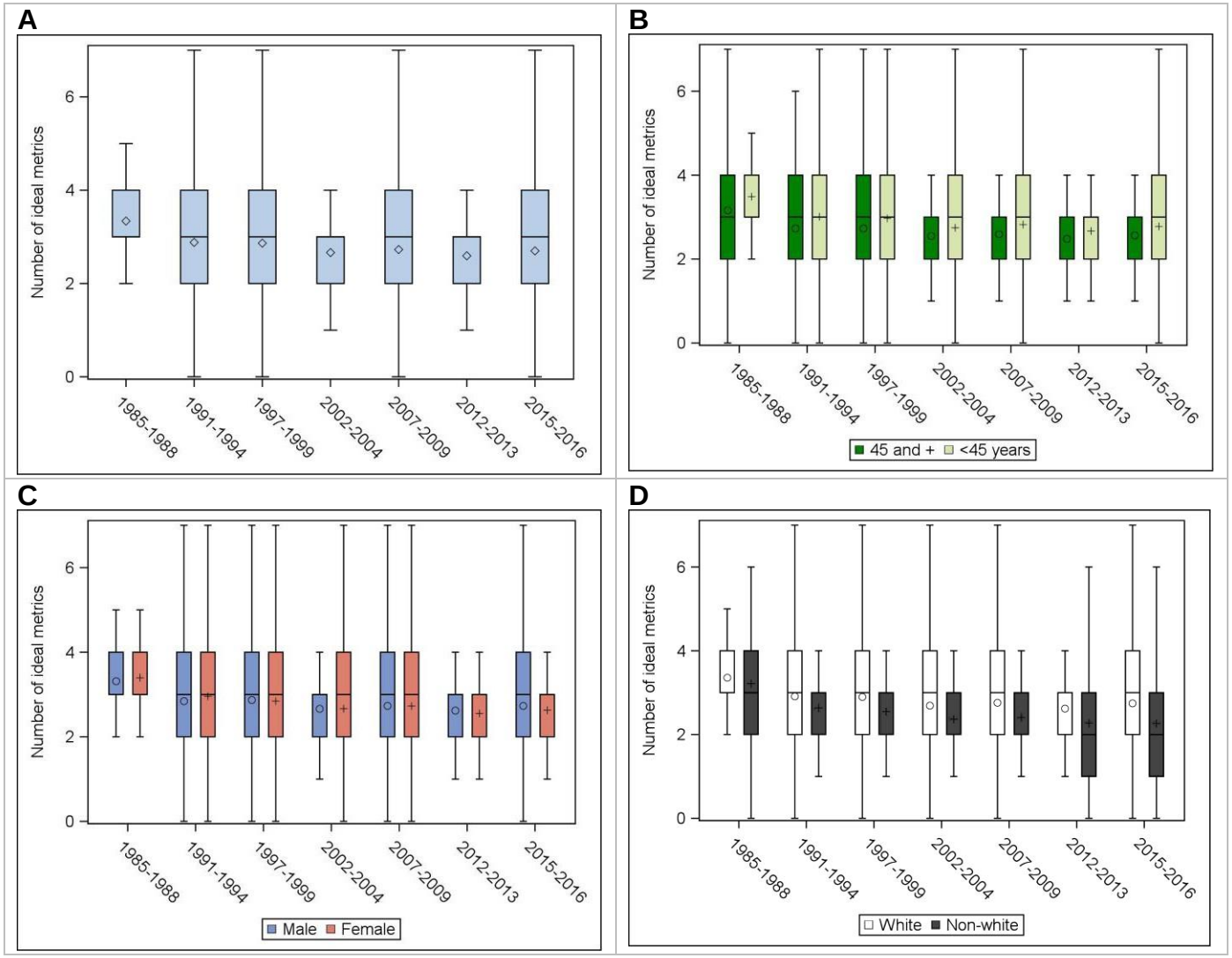
eTable 13. Association of change in the individual cardiovascular health metrics between 1985/88 and 1997/99 with subsequent incident cardiovascular disease events and all-cause mortality

Pattern of change	Low-Low	Low-Mod	Low-High	Mod-Low	Mod-Mod	Mod-High	High-Low	High-Mod	High-High
CVH metric									
	Adjusted[a] hazard ratios (95% confidence interval) for incident cardiovascular disease: 1114/6326								
Smoking	1 (Ref)	0.67 (0.36; 1.24)	0.69 (0.50; 0.94)	0.87 (0.45; 1.71)	1.25 (0.58; 2.67)	0.50 (0.34; 0.74)	0.76 (0.39; 1.48)	0.71 (0.39; 1.31)	0.53 (0.44; 0.63
Body mass index	1 (Ref)	0.64 (0.28; 1.47)	NA	0.86 (0.62; 1.18)	0.85 (0.65; 1.12)	0.59 (0.38; 0.93)	0.49 (0.15; 1.56)	0.74 (0.56; 0.98)	0.62 (0.47; 0.80)
Diet	1 (Ref)	0.85 (0.75; 0.97)	0.98 (0.70; 1.36)	1.07 (0.65; 1.76)	0.93 (0.73; 1.18)	0.93 (0.55; 1.56)	1.19 (0.29; 4.78)	0.98 (0.51; 1.90)	0.77 (0.25; 2.40)
Physical activity	1 (Ref)	0.78 (0.56; 1.11)	0.94 (0.58; 1.52)	1.09 (0.77; 1.55)	0.76 (0.58; 1.01)	0.80 (0.59; 1.08)	1.07 (0.68; 1.69)	0.94 (0.70; 1.25)	0.91 (0.67; 1.25)
Blood pressure	1 (Ref)	0.95 (0.72; 1.24)	0.50 (0.25; 1.03)	0.96 (0.76; 1.21)	0.77 (0.62; 0.96)	0.57 (0.43; 0.74)	0.96 (0.64; 1.45)	0.75 (0.59; 0.95)	0.56 (0.44; 0.70)
Total cholesterol	1 (Ref)	0.76 (0.62; 0.94)	0.33 (0.12; 0.88)	0.88 (0.73; 1.06)	0.75 (0.63; 0.88)	0.55 (0.40; 0.75)	0.53 (0.30; 0.94)	0.71 (0.56; 0.90)	0.66 (0.54; 0.82)
Fasting glucose	1 (Ref)	0.53 (0.14; 2.10)	0.26 (0.06; 1.25)	-	-	-	0.60 (0.29; 1.28)	0.32 (0.16; 0.65)	0.31 (0.15; 0.62)
	Adjusted[a] hazard ratios (95% confidence interval) for all-cause mortality: 846/6326								
Smoking	1 (Ref)	0.64 (0.34; 1.22)	0.65 (0.47; 0.88)	0.76 (0.36; 1.63)	0.27 (0.07; 1.08)	0.34 (0.21; 0.55)	1.01 (0.53; 1.91)	0.43 (0.19; 0.98)	0.37 (0.61; 0.44)
Body mass index	1 (Ref)	0.89 (0.40; 1.95)	NA	0.73 (0.51; 1.04)	0.69 (0.52; 0.93)	0.94 (0.62; 1.43)	0.81 (0.33; 2.04)	0.56 (0.41; 0.76)	0.59 (0.44; 0.78)
Diet	1 (Ref)	0.91 (0.78; 1.05)	0.75 (0.50; 1.14)	1.45 (0.89; 2.37)	0.74 (0.55; 1.00)	0.67 (0.35; 1.31)	NA	0.75 (0.34; 1.69)	1.24 (0.46; 3.35)
Physical activity	1 (Ref)	0.75 (0.52; 1.07)	0.43 (0.22; 0.82)	1.18 (0.82; 1.70)	0.72 (0.53; 0.96)	0.64 (0.46; 0.90)	0.77 (0.46; 1.29)	0.61 (0.44; 0.84)	0.67 (0.48; 0.94)
Blood pressure	1 (Ref)	1.06 (0.77; 1.45)	1.02 (0.53; 1.97)	1.03 (0.78; 1.36)	0.92 (0.71; 1.18)	0.77 (0.57; 1.05)	1.05 (0.64; 1.71)	0.78 (0.58; 1.03)	0.79 (0.61; 1.04)
Total cholesterol	1 (Ref)	0.81 (0.63; 1.03)	1.61 (0.92; 2.82)	0.93 (0.74; 1.18)	0.87 (0.71; 1.06)	1.21 (0.92; 1.60)	0.20 (0.06; 0.62)	1.01 (0.77; 1.31)	1.01 (0.80; 1.29)
Fasting glucose	1 (Ref)	0.46 (0.05; 4.24)	0.51 (0.06; 4.62)	-	-	-	1.56 (0.56; 4.36)	0.76 (0.28; 2.06)	0,64 (0.24; 1.72)

Hazard ratios and 95% confidence intervals were estimated by Cox proportional hazard model stratified by year of birth (5-year intervals) and using age as the time scale. The follow-up of CVD events and mortality starts after 1997/99 and the median duration is 18.9 (interquartile range 17.8 to 19.3) years for CVD events and 19.7 (interquartile range 18.9 to 19.8) years for all-cause mortality. Participants with no change in the number of ideal metrics served as the reference category. [a] Adjusted for sex, race/ethnicity, depression, education, occupation and family history of cardiovascular disease at baseline. CVH stands for cardiovascular health; low stands for low cardiovascular health; mod for moderate cardiovascular health; high for high cardiovascular health; and CVD for cardiovascular disease.

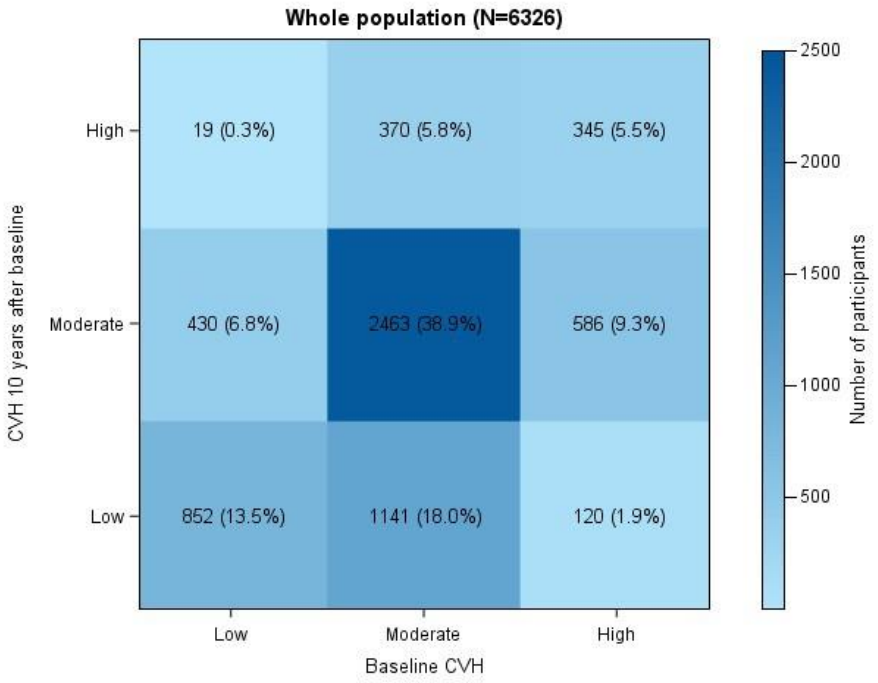


eFigure 1. Summary of the statistical analysis design

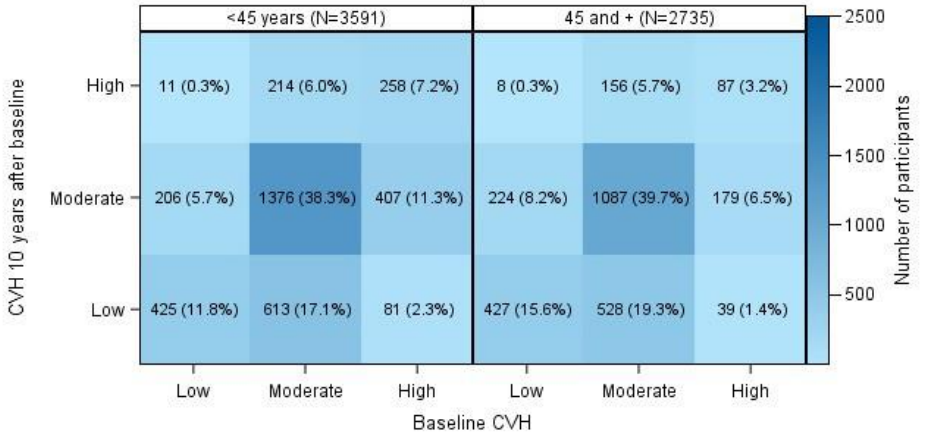


eFigure 2. Distribution of the number of ideal metrics at each phase in the whole population (A), by age group (B), by sex (C) and in white versus non-white participants (D)

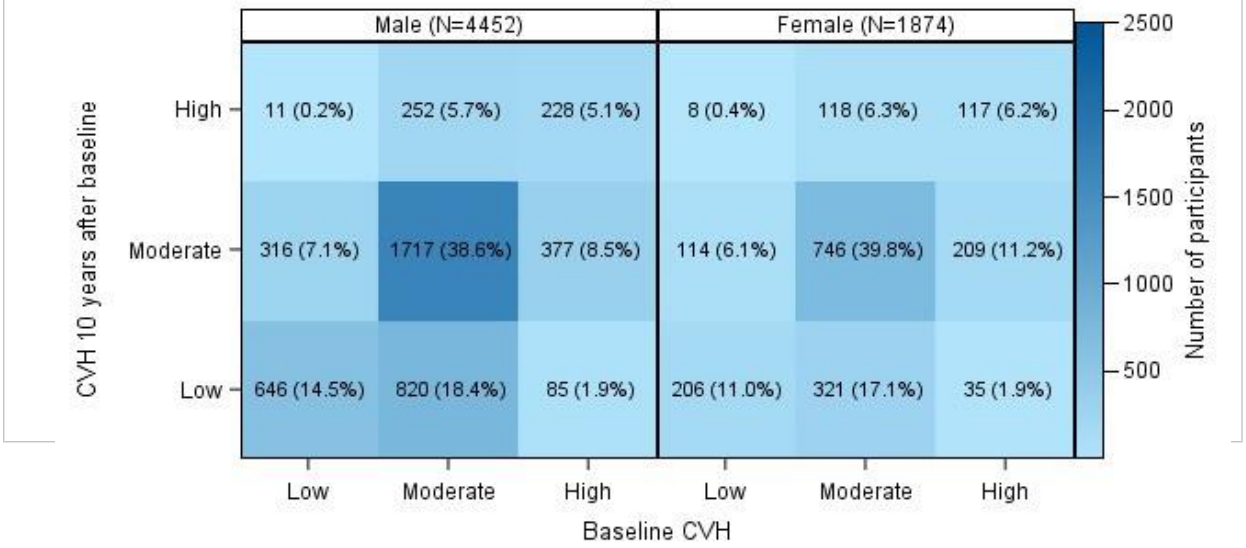
A



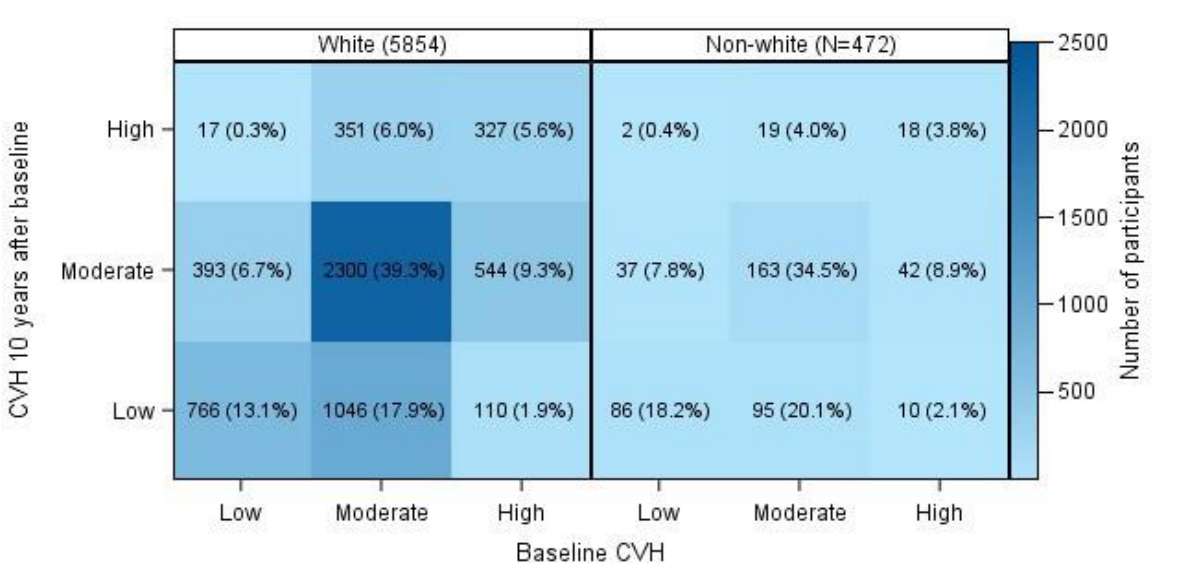
B



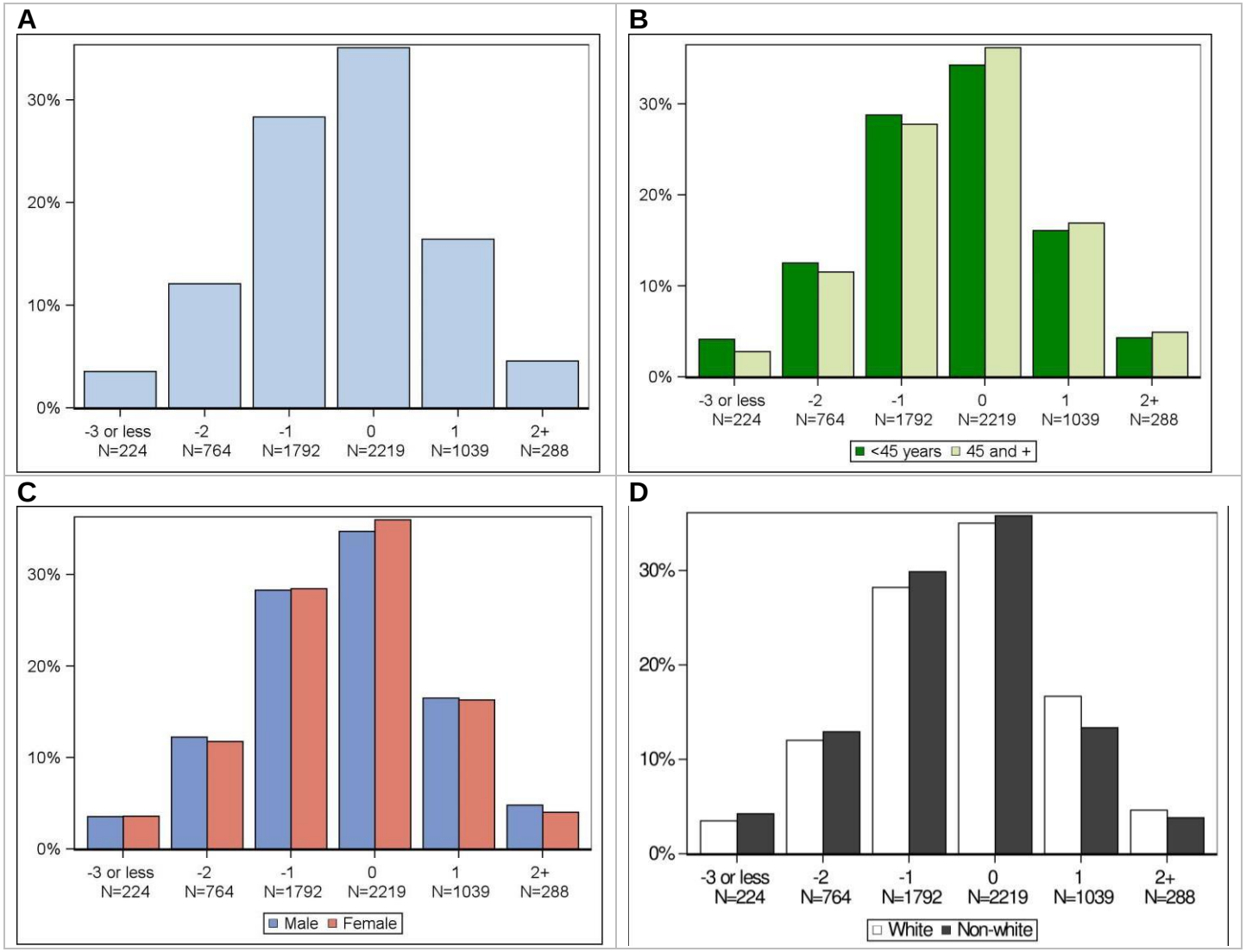
C



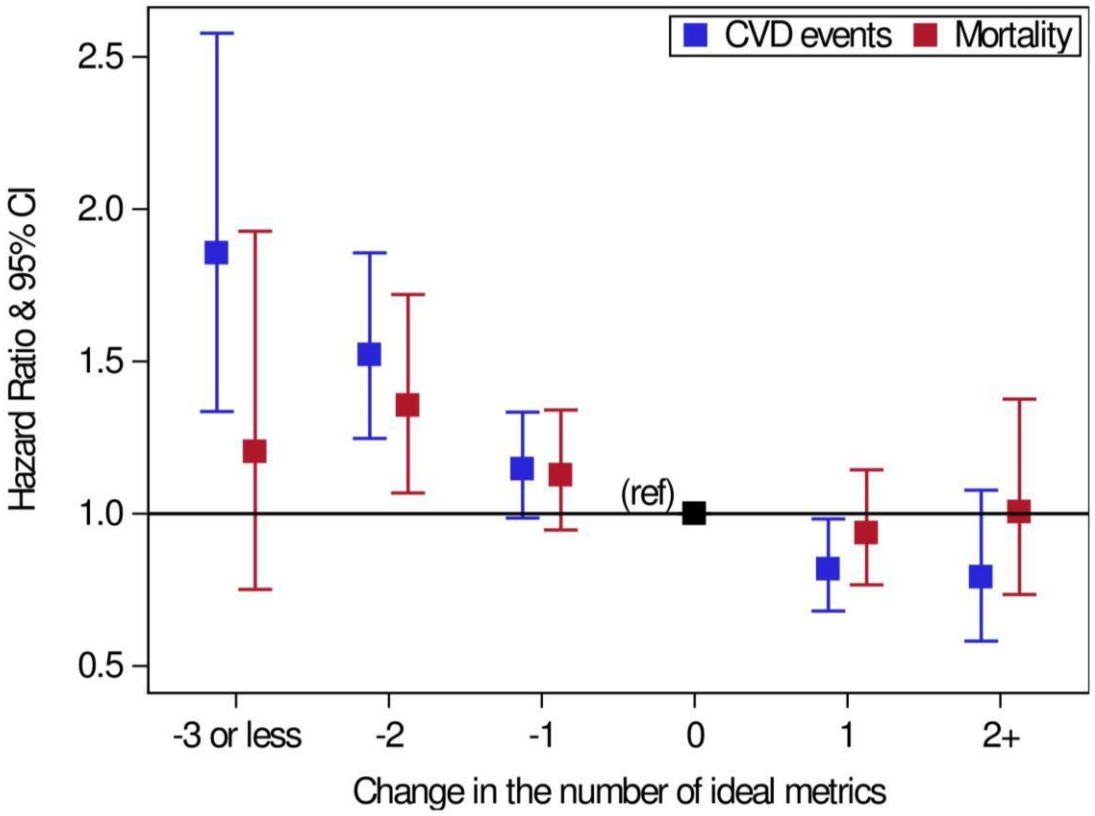
D



eFigure 3. Distribution of the change in cardiovascular health between 1985/88 and 1997/99 in the total study population (n=6326) (A), in individuals aged <45 (n=3591) and ≥45 years (n=2735) (B), in women (n=1874) and men (n=4452) (C) and in white (n=5854) versus non-white participants (n=472) (D)



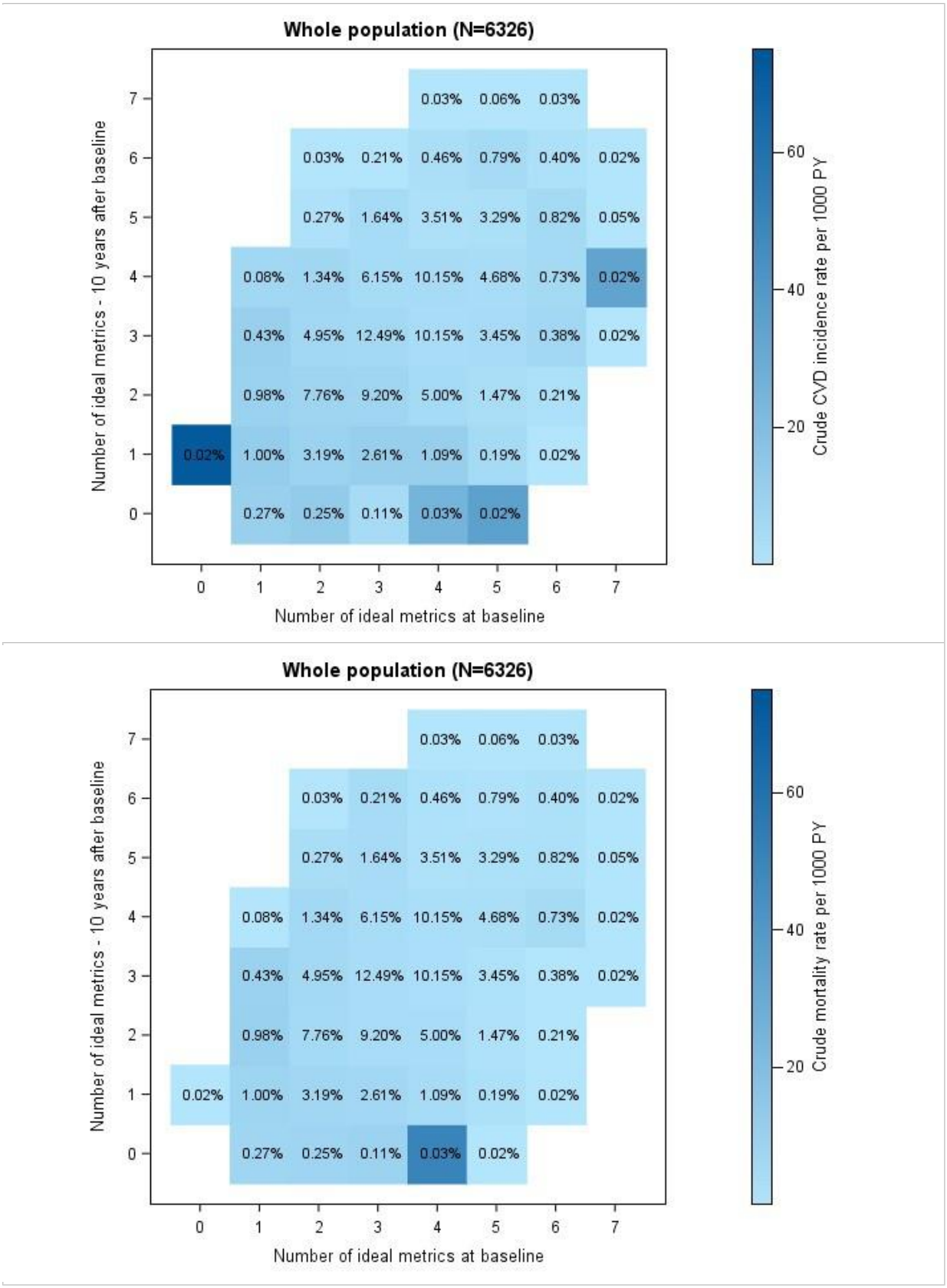
eFigure 4. Distribution of the change in the number of ideal cardiovascular health metrics between 1985/88 and 1997/99 in the total study population (n=6326) (A), in individuals aged <45 (n=3591) and ≥45 years (n=2735) (B), in women (n=1874) and men (n=4452) (C) and in white (n=5854) versus non-white participants (n=472) (D)



eFigure 5. Hazards ratios of incident cardiovascular disease and for all-cause mortality for change in the number of ideal metrics between 1985/88 and 1997/99.

Hazard ratios and 95% confidence intervals were estimated by Cox proportional hazard model stratified by year of birth (5-year intervals) and using age as the time scale. The remaining median follow-up time after 1997/99 was 18.9 (interquartile range 17.8 to 19.3) years for CVD events and 19.7 (interquartile range 18.9 to 19.8) years for all-cause mortality. Subjects with no change in the number of ideal metrics served as the reference category. Multivariable hazards ratios were adjusted for sex, race/ethnicity, depression, education, occupation, family history of cardiovascular disease at baseline and number of ideal metrics at baseline.

CVD stands for cardiovascular disease; CI for confidence intervals



eFigure 6. Heatmap of unadjusted incidence rates of cardiovascular disease (A) and all-cause mortality (B) by change in the number of ideal health metrics between 1985/88 and 1997/99 in the total study population (n=6236).

The median follow-up time for cardiovascular disease after 1997/99 was 18.9 (interquartile range 17.8 to 19.3) years and 19.7 (interquartile range 18.9 to 19.8) years for mortality. CVH stands for cardiovascular health; CVD for cardiovascular disease; PY for person-years

References

1. Richardson MT, Leon AS, Jacobs DR, Jr., Ainsworth BE, Serfass R. Comprehensive evaluation of the Minnesota Leisure Time Physical Activity Questionnaire. *J Clin Epidemiol.* 1994;47(3):271-281.
2. Sabia S, Dugravot A, Dartigues JF, et al. Physical activity, cognitive decline, and risk of dementia: 28 year follow-up of Whitehall II cohort study. *BMJ.* 2017;357:j2709.
3. Brunner E, Stallone D, Juneja M, Bingham S, Marmot M. Dietary assessment in Whitehall II: comparison of 7 d diet diary and food-frequency questionnaire and validity against biomarkers. *Br J Nutr.* 2001;86(3):405-414.
4. Joint Formulary Committee British national formulary, 32th edition. London, United Kingdom: BMJ Group and Pharmaceutical Press; 1996.
5. Stansfeld SA, Marmot MG. Social class and minor psychiatric disorder in British Civil Servants: a validated screening survey using the General Health Questionnaire. *Psychol Med*. 1992;22:739-49.
6. Fine JP. Gray RJ. A proportional hazards model for the subdistribution of competing risks in survival analysis. J Am Stat Assoc. 1999;94:496–509.
7. Enserro DM, Vasan RS, Xanthakis V. Twenty-Year Trends in the American Heart Association Cardiovascular Health Score and Impact on Subclinical and Clinical Cardiovascular Disease: The Framingham Offspring Study. *J Am Heart Assoc.* 2018;7(11).