

Ideal Cardiovascular Health and Incident Cardiovascular Disease: Heterogeneity Across Event Subtypes and Mediating Effect of Blood Biomarkers: The PRIME Study

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Background—The aim of this study was to investigate whether the association between baseline cardiovascular health (CVH) and incident cardiovascular disease differs according to coronary heart disease (CHD) and stroke subtypes, and to assess the mediating effect of inflammatory and hemostatic blood biomarkers.

Methods and Results—The association of ideal CVH with outcomes was derived in 93 12 middle-aged men from Northern Ireland and France (whole cohort) in multivariable Cox proportional hazards regression analysis. The mediating effect of baseline inflammatory and hemostatic blood biomarkers was evaluated in a case–control study nested within the cohort after 10 years of follow-up. After a median follow-up of 10 years, 6 14 first CHD events and 1 17 first stroke events were adjudicated. Compared with those with poor CVH, those with an ideal CVH profile at baseline had a 72% lower risk of CHD (hazard ratio=0.28; 95% confidence interval, 0.17; 0.46) and a 76% lower risk of stroke (hazard ratio =0.24; 95% confidence interval, 0.06; 0.98). The magnitude of the risk reductions was similar for incident angina and myocardial infarction, but was lower for ischemic stroke. In the controls, the mean concentrations of high-sensitivity C-reactive protein, IL-6, and fibrinogen decreased with higher CVH status. Furthermore, the association of behavioral CVH with incident CHD was partly mediated by high-sensitivity C-reactive protein (16.69%), IL-6 (8.52%), and fibrinogen (7.30%)

Conclusions—Our study shows no clear heterogeneity in the association of baseline CVH with the main subtypes of cardiovascular disease. This supports a universal promotion of ideal CVH for all cardiovascular disease subtypes. Furthermore, our mediation analysis suggests that the lower risk of CHD associated with ideal CVH is partly mediated by lower inflammatory and hemostatic blood biomarkers. (*J Am Heart Assoc.* 2017;6:e006389. DOI: 10.1161/JAHA.117.006389.)

Key Words: blood biomarkers • cardiovascular disease prevention • subtypes of cardiovascular diseases

Primordial prevention defined as the prevention of risk factor occurrence has been recently re-emphasized by the American Heart Association (AHA) to further strengthen the primary prevention of cardiovascular disease (CVD).¹ To this end, the AHA has developed a simplified 7-item tool including health behaviors (body mass index, smoking status, diet, and physical activity) and health factors (blood pressure,

blood cholesterol, and glycemia) to define an ideal cardiovascular health (CVH).¹ Accordingly, several cohort studies have reported substantial risk reductions in mortality and incident CVD in subjects with an ideal compared with subjects with poor CVH.^{2–6} Most of these studies, however, were conducted in the United States^{2,3} and in China,^{4,5} whereas only 1 study investigated a European population.⁶ Furthermore, although

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Accompanying Data S1, Tables S1 through S4, and Figure S1 are available at <http://jaha.ahajournals.org/content/6/10/006389/DC1/embed/inline-supplemental-ry-material-1.pdf>

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Clinical Perspective

What Is New?

- This is the first study addressing the possible heterogeneity in the association of cardiovascular health (CVH) status with incident coronary heart disease (CHD) and stroke subtypes.
- Risk reductions were of comparable magnitude between CHD and stroke, and across CHD subtypes and across stroke subtypes, indicating that there was no clear heterogeneity in the association of baseline CVH status with 10-year risk of cardiovascular disease, whatever types of cardiovascular disease.
- Our mediation analysis suggests that the lower risk of CHD associated with ideal CVH was partly mediated by lower inflammatory (high-sensitivity C-reactive protein and IL-6) and hemostatic (fibrinogen) blood biomarkers.

What Are the Clinical Implications?

- The results of this study support a universal promotion of ideal CVH for preventing all types of cardiovascular disease.
- Furthermore, our study results provide some insights regarding the possible pathways underlying the CHD risk reduction associated with CVH.

atherosclerosis is the process underlying most CVD events, some atherosclerotic risk factors included in CVH have been shown to be differentially associated with future CVD subtypes.^{7–12} For instance, smoking status has demonstrated highly heterogeneous association across 12 specific first manifestations of CVD.¹¹ It might therefore be hypothesized that the association between CVH and CVD differs according to subtypes. First, this question may raise the issue of whether or not the promotion of ideal CVH should be CVD disease specific or should concern all CVD subtypes. Second, any heterogeneity across CVD subtypes would imply the search for additional and more specific etiological metrics. Furthermore, studies on the possible pathways underlying the association between CVH and outcomes are scarce. Inflammatory and hemostatic blood biomarkers such as higher CRP (C-reactive protein), IL-6, and fibrinogen have been robustly associated with CHD or stroke and might represent relevant mediating factors to explore.^{13–16} So far, only the Framingham study has explored the possible role of blood biomarkers in the associations between ideal CVH and outcomes.¹⁷ This analysis did not include IL-6, which is a strong predictor of CVD. Therefore, how much the association of CVH with CHD and stroke is mediated by IL-6 is unknown.

Our goals were 3-fold: (1) to quantify the association between CVH and incident CHD and stroke in a Northern Irish and French European population at contrasting risk of CHD and stroke; (2) to assess for potential heterogeneity of this association across CHD and stroke subtypes and between CHD and stroke events;

and (3) to explore the mediating effect of a panel of key inflammatory and hemostatic blood biomarkers.

Methods

The PRIME (Prospective Epidemiological Study of Myocardial Infarction) study is a prospective multicenter cohort of 10,602 middle-aged men (50–59 years) recruited in the framework of WHO MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) centers in Lille (North France), Strasbourg (North-East France), Toulouse (South France), and Belfast (Northern Ireland) between 1991 and 1993.¹⁸ The ethics committee of the Kremlin Bicêtre hospital approved the study and men signed a statement of informed consent.

As will be seen, heterogeneity across subtypes was assessed in the whole PRIME study while the mediating effect of inflammatory and hemostatic blood biomarkers was studied in a case-control study nested within the PRIME study. However, because fibrinogen was also available in the whole cohort, its influence was investigated in the whole PRIME study as well.

Baseline Examination

A full description of clinical and laboratory measurements has been already published¹⁸ and is summarized in Data S1.

Cardiovascular health

Each of the 7 metrics was categorized as poor, intermediate, or ideal using the AHA criteria.¹ Their definitions together with the food frequency and physical activity questionnaires^{19,20} are detailed in the supplemental material. According to the AHA, an ideal CVH is defined by the simultaneous presence of the 7 metrics at the ideal level and the absence of any previous CVD.¹ As only 1 participant met these requirements in the present study (see Results section), and consistently with previous studies, subjects having 0 to 2, 3 to 4, and 5 to 7 metrics at the ideal level were referred to as having poor, intermediate, and ideal *global CVH*, respectively.^{3,17,21} Those with 0 to 1, 2 or 3 to 4 ideal behavioral metrics were defined as having poor, intermediate, or ideal *behavioral CVH*. Those with 0 to 1, 2 or 3 ideal health factors were defined as having poor, intermediate, or ideal *health factor CVH*.²¹ By adding each individual metric level (scored 0, 1, and 2 for poor, intermediate, or ideal level), we also calculated a score for global CVH that ranged from 0 (all poor metrics) to 14 (all ideal metrics).

Follow-up and event definitions

The procedures of annual follow-up and adjudication of coronary heart disease and stroke events have been previously published.^{9,22} Briefly, participants were contacted annually by letter, over 10 years, and asked to complete a clinical event

questionnaire. For all men reporting a possible event, clinical information was sought directly from the hospital or general practitioner records. CHD and stroke were validated by 2 independent adjudication committees. CHD events (stable and unstable angina, myocardial infarction, and coronary death) were defined as previously described using clinical, biological, stress-test, scintigraphic, or angiographic criteria.²² Stroke (ischemic and hemorrhagic strokes) was defined according to WHO MONICA criteria, as a new focal or global neurological deficit with a rapid onset and of vascular origin, persisting for more than 24 hours. Transient ischemic attacks and strokes caused by a blood disease, a cerebral tumor or metastasis, or secondary to a trauma, were not considered by the stroke medical committee.

Nested case-control study and blood biomarkers measurements

The blood biomarkers analysis was conducted in the context of a case-control study nested within the PRIME cohort after 10 years of follow-up.²³ Given that there were only 2 incident

ischemic stroke events among men with intermediate or ideal CVH, we only considered CHD cases for analysis. Therefore, the present case-control study involves 617 CHD cases and 1234 matched controls (2 controls per case) with available baseline blood biomarkers. Matched controls were study participants recruited in the same center on the same day (± 3 days), of the same age (± 3 years) as the corresponding case, and who were free of CHD at the time of the index date. From the existing panel of inflammatory and hemostatic blood biomarkers measured at baseline in PRIME, we only selected those that have been previously shown to be significantly associated with future CHD over 10 years in PRIME, and for which robust evidence exists in the literature. These include inflammatory blood biomarkers (hs-CRP [high-sensitivity C-reactive protein]) and a hemostatic blood biomarker (fibrinogen).¹³⁻¹⁶ Blood biomarkers were assessed on frozen samples as previously indicated.²⁴ Multiplex bioassays were conducted using measurement kits from the following manufacturers: Indicia Biotechnology (Oullins,

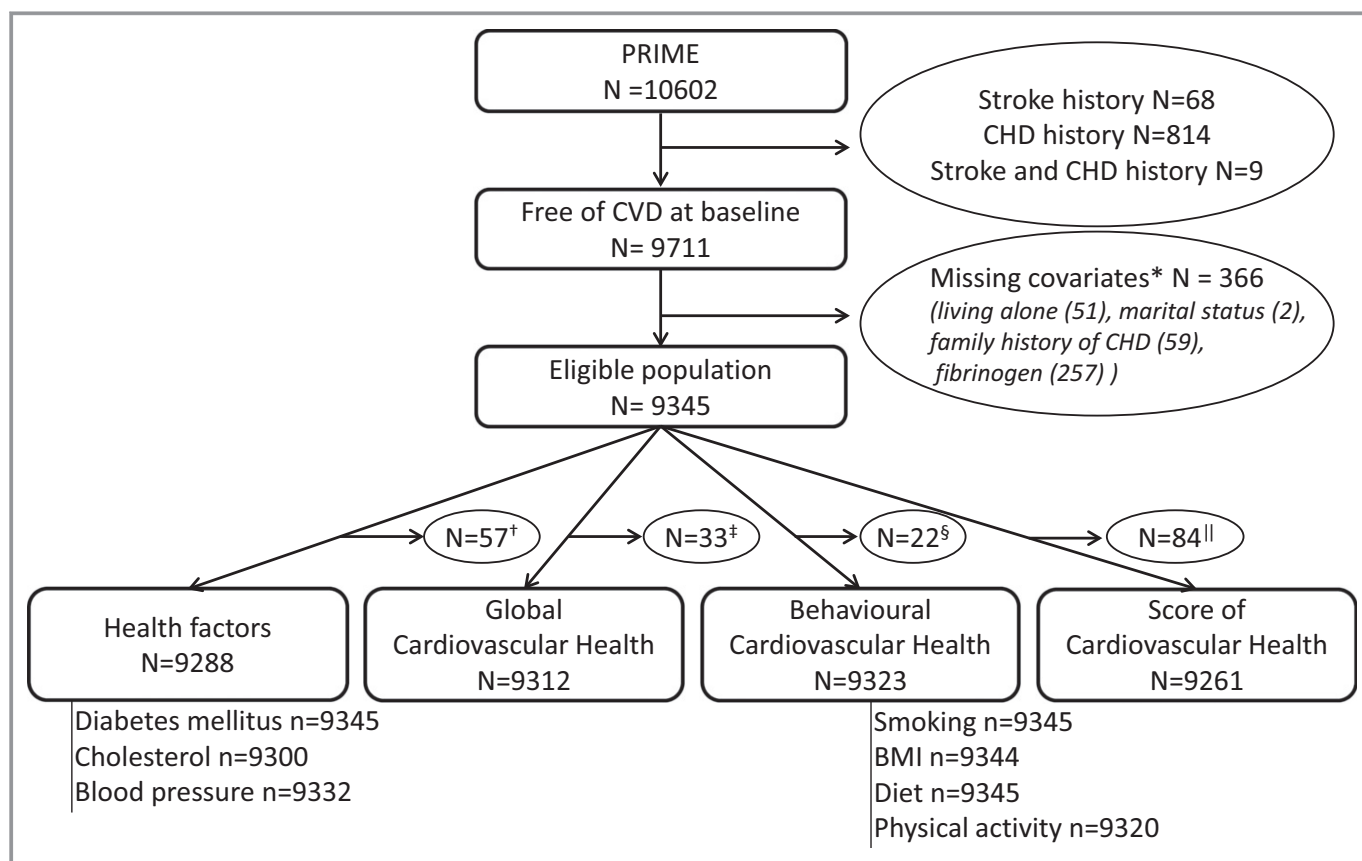


Figure 1. Study flowchart of the whole PRIME cohort. *Missing covariates do not add up to 369 because 1 subject had missing data for marital status and living alone, simultaneously and 2 subjects had missing data for fibrinogen and family history of CHD, simultaneously. †Subjects with missing data for diabetes mellitus, cholesterol, or blood pressure. ‡Subjects with missing data for at least 1 CVH metric and the information on the other metrics was not sufficient to assign a CVH status. §Subjects with missing data for smoking, BMI, diet, or physical activity. ||Subjects with missing data for at least 1 CVH metric. BMI indicates body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; CVH, cardiovascular health; PRIME, Prospective Epidemiological Study of Myocardial Infarction.

Table 1. Baseline Characteristics According to Global CVH Status in the Whole PRIME Study

	Global CVH			P Value
	Poor (N=3699)	Intermediate (N=4957)	Ideal (N=656)	
Study center*				
Belfast	946 (25.6)	1190 (24.0)	156 (23.8)	<0.0001
Strasbourg	925 (25.0)	1296 (26.1)	117 (17.8)	
Toulouse	754 (20.4)	1350 (27.2)	267 (40.7)	
Lille	1074 (29.0)	1121 (22.6)	116 (17.7)	
Age [†]	55.0 (2.9)	54.8 (2.9)	54.4 (2.8)	<0.0001
Family history of CHD*	424 (11.5)	478 (9.6)	61 (9.3)	0.0151
Social status*				
High	1074 (29.0)	1405 (28.3)	221 (33.7)	0.0006
Middle	1884 (50.9)	2639 (53.2)	344 (52.4)	
Low	741 (20.0)	913 (18.4)	91 (13.9)	
Secondary level diploma or more*	2297 (62.1)	3214 (64.8)	437 (66.6)	0.0101
Living alone*	322 (8.7)	329 (6.6)	56 (8.5)	0.001
Marital status*				
Single	198 (5.4)	232 (4.7)	29 (4.4)	0.0165
Cohabiting	3186 (86.1)	4383 (88.4)	564 (86.0)	
Widowed	85 (2.3)	92 (1.9)	13 (2.0)	
Separated	230 (6.2)	250 (5.0)	50 (7.6)	
Number of min per wk of moderate activity [‡]	0.0 (0.0–60.0)	40.0 (0.0–270)	138 (0.0–330)	<0.0001
Number of min per wk of vigorous activity [‡]	0.0 (0.0–0.0)	0.0 (0.0–175)	71.0 (0.0–240)	<0.0001
Number of kilocalories per wk of alcohol [‡]	1515 (472–2852)	1191 (298–2312)	741 (140–1612)	<0.0001
Number of fruits and vegetables per d [‡]	2.3 (1.5–3.3)	2.6 (1.7–3.6)	3.0 (2.0–4.1)	<0.0001
BMI, kg/m ^{2†}	28.0 (3.3)	25.9 (3.2)	23.5 (2.2)	<0.0001
Systolic blood pressure, mm Hg [†]	139 (18.4)	131 (18.0)	117 (14.3)	<0.0001
Treatment for diabetes mellitus*	559 (15.1)	186 (3.8)	7 (1.1)	<0.0001
Blood pressure-lowering drugs*	660 (17.9)	559 (11.3)	24 (3.7)	<0.0001
Glucose-lowering drugs*	164 (4.4)	49 (1.0)	0 (0.0)	<0.0001
Lipid-lowering drugs*	488 (13.2)	360 (7.3)	15 (2.3)	<0.0001
Fibrinogen, g/L [‡]	3.17 (2.74–3.76)	3.04 (2.66–3.57)	2.98 (2.60–3.50)	<0.0001

Results are n (%)* or mean (SD)[†], or median (interquartile range)[‡] where appropriate. P values are from Pearson χ^2 test, or Student analysis of variance, or Kruskal–Wallis test where appropriate. BMI indicates body mass index; CHD, coronary heart disease; CVH, cardiovascular health status; PRIME, Prospective Epidemiological Study of Myocardial Infarction.

France) for hs-CRP (LOB1707). IL-6 was measured by high-sensitivity ELISA (BMS213HS; Bender MedSystems, Vienna, Austria).

Statistical Analysis

Heterogeneity across event subtypes: whole cohort

The baseline characteristics by global CVH status were compared using analysis of variance or Kruskal–Wallis test or Pearson χ^2 tests where appropriate. Unadjusted survival free of

all-cause mortality and of CHD and stroke events by global CVH status were plotted on Kaplan–Meier curves and compared using the log-rank test. Hazard ratios (HR) and 95% confidence intervals (CI) of baseline intermediate and ideal CVH status (according to global, behavioral, and health factor) for all-cause mortality, and for CHD, stroke, and their respective subtypes were estimated in a separate Cox proportional hazards regression model, using baseline poor CVH as the reference exposure category. Follow-up was censored at the date of first event, at the date of death, or at the end of follow-up, whichever came first. HRs were adjusted for age, study center, education,

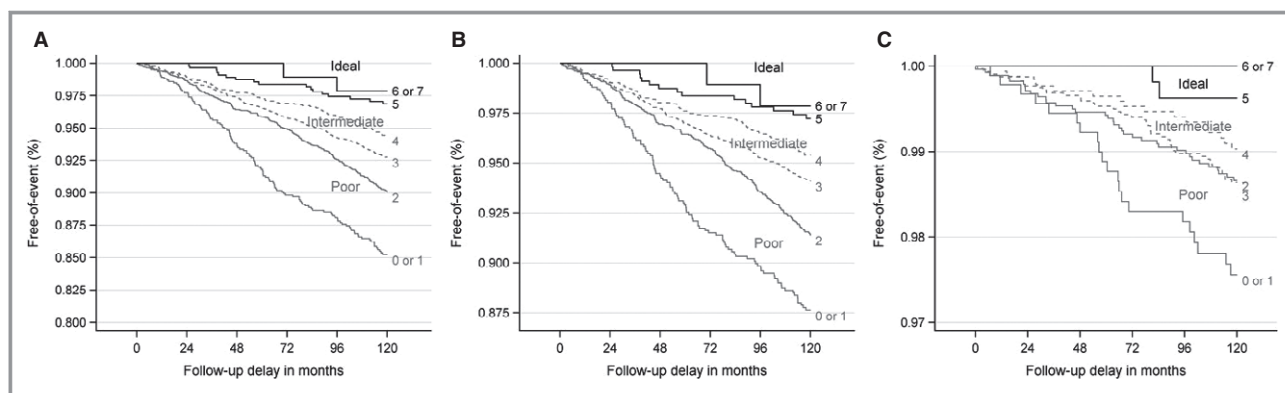


Figure 2. Free-of-event Kaplan–Meier curves of first coronary heart disease and stroke by baseline global cardiovascular health status (N=9312) in the whole PRIME cohort. A, Coronary heart disease+stroke. B, Coronary heart disease. C, Stroke. Cardiovascular health status: Poor: 0 to 2 ideal metrics; Intermediate: 3 to 4 ideal metrics; Ideal: 5 to 7 ideal metrics. PRIME indicates Prospective Epidemiological Study of Myocardial Infarction.

social status, living alone and marital status, family history of CHD, and fibrinogen (which was available for the whole cohort). The HRs for CHD and stroke, and across CHD subtypes (angina, myocardial infarction, and coronary death) and stroke subtypes (ischemic versus nonischemic), were compared by the visual inspection of the HRs and their 95% CIs (no formal statistical test for comparison) to assess heterogeneity. The proportionality assumption of Cox regression analysis was verified graphically by plotting Schoenfeld residuals and further by adding an interaction with time to our Cox model and checking whether it significantly improves our model.

In sensitivity analysis, the possible competing effect of death was evaluated using the Fine and Gray method, with subdistribution HR of ideal and intermediate CVH estimated for CHD and stroke outcomes.²⁵ The HRs per 1-point increment in the score of global cardiovascular health were also calculated.

Blood biomarkers mediating effect: nested case–control study

In the nested case–control study, we first compared the mean concentrations of each blood biomarker across CVH status among the controls in separate linear regression analysis adjusted for age and study centers. Thereafter, blood biomarkers that were significantly associated with CVH status (in the controls) were added separately into a multivariable conditional logistic regression model. First, the relative attenuation (%) of the regression coefficient estimates of CVH status for CHD upon adjustment for a given blood biomarker was calculated (as the difference between the regression coefficient before and after adjustment for the blood biomarker relative to the regression coefficient before adjustment for the blood biomarker). Second, we conducted a mediation analysis for each blood biomarker by evaluating the direct and the indirect effect of CVH status on incident CHD

using an extension of the Baron and Kenny method developed by Valeri et al.²⁶

All statistical analyses were 2-tailed and used a $P < 0.05$ to mean statistically significant associations. SAS software version 9.4 (SAS Institute Inc, Cary, NC) was used for all analyses.

Results

Whole Cohort Analysis

Study population

As shown in the study flowchart (Figure 1), the study population cohort comprises 9312 men free of personal history of CVD including 2292 from Belfast (Northern Ireland) and 7020 from France.

Baseline characteristics by CVH status

At baseline, only 1 participant had the 7 metrics at the ideal level, 96 had 6 metrics at the ideal level, and 557 had 5 metrics at the ideal level, respectively. Altogether, 7.1% of the participants had at least 5 metrics at the ideal level and were referred to as being in ideal CVH. There was a north–south contrast in the distribution of CVH as the prevalence of ideal CVH was 5.0% for Strasbourg and Lille (North and North-East France), 6.8% for Belfast (Northern Ireland), and 11.3% for Toulouse (south France) ($P < 0.001$). Conversely, 39.8% of the population had up to 2 metrics at the ideal level and were referred to as being in poor CVH (46.5% for Lille, 41.3% for Belfast, 39.6% for Strasbourg, and 31.8% for Toulouse, $P < 0.001$). As shown in Table 1, in general, the burden of sociodemographic, cardiovascular risk factors and the concentration of fibrinogen decreased with increasing CVH status. Ideal diet was the least prevalent metric (1.4%) while

Table 2. Hazard Ratios for First CHD and Stroke, of Global, Behavioral, and Health Factor CVH Status in the Whole PRIME Study

CVH Status	N	CHD+Stroke			CHD			Stroke		
		n Events	Incidence (CI 95%)	HR (CI 95%)	n Events	Incidence (CI 95%)	HR (CI 95%)	n Events	Incidence (CI 95%)	HR (CI 95%)
Global										
Poor	3699	393	11.7 (10.5–12.8)	1	336	9.92 (8.86–10.98)	1	57	1.63 (1.2–2.05)	1
Intermediate	4957	319	6.9 (6.1–7.6)	0.61 (0.53–0.71)	261	5.60 (4.92–6.28)	0.58 (0.49–0.68)	58	1.22 (0.9–1.53)	0.84 (0.58–1.21)
Ideal	656	19	3.0 (1.7–4.4)	0.28 (0.17–0.44)	17	2.70 (1.42–3.99)	0.28 (0.17–0.46)	2	0.31 (0–0.75)	0.24 (0.06–0.98)
Behavioral										
Poor	4724	452	10.5 (9.5–11.4)	1	380	8.76 (7.88–9.64)	1	72	1.61 (1.24–1.98)	1
Intermediate	3589	235	7.0 (6.1–7.9)	0.71 (0.61–0.83)	198	5.86 (5.05–6.68)	0.71 (0.6–0.84)	37	1.07 (0.73–1.42)	0.75 (0.5–1.12)
Ideal	1010	47	4.9 (3.5–6.2)	0.50 (0.37–0.68)	39	4.02 (2.76–5.28)	0.49 (0.35–0.68)	8	0.81 (0.25–1.37)	0.58 (0.28–1.21)
Health factor										
Poor	6069	560	10.0 (9.2–10.8)	1	475	8.44 (7.68–9.2)	1	85	1.46 (1.15–1.77)	1
Intermediate	2772	151	5.8 (4.9–6.7)	0.58 (0.49–0.70)	122	4.68 (3.85–5.51)	0.55 (0.45–0.67)	29	1.10 (0.70–1.49)	0.79 (0.52–1.22)
Ideal	447	16	3.8 (1.9–5.7)	0.39 (0.23–0.64)	14	3.32 (1.58–5.07)	0.39 (0.23–0.67)	2	0.47 (0–1.12)	0.38 (0.09–1.55)

Incidence rates are given per 1000 person-years. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated in separate Cox proportional hazards regression models using poor status as the reference exposure and were adjusted for age, study center, family history of coronary heart disease, education, social status, living alone status, marital status, and fibrinogen. CHD indicates coronary heart disease; CVH, cardiovascular health status; PRIME, Prospective Epidemiological Study of Myocardial Infarction.

nondiabetic status was the most prevalent (91.2%) (not shown).

HRs of baseline cardiovascular health status for first clinical events

After a median duration of follow-up of 10 years, we observed 731 incident events: 614 CHD including 248 myocardial infarction, 208 stable angina, 130 unstable angina, and 28 coronary deaths; 117 stroke including 94 ischemic and 23 nonischemic strokes.

As shown in Figure 2A through 2C, the crude incidence rates of CHD and stroke (either combined or studied separately) progressively decreased with higher baseline CVH status. The multivariable HRs of CHD and stroke associated with global, behavioral, and health factor CVH are presented in Table 2. In particular, analysis by event subtypes shows a 72% lower risk of CHD (HR=0.28; 95% CI, 0.17; 0.46) and a 76% lower risk of stroke (HR=0.24; 95% CI, 0.06; 0.98) in men with ideal compared with poor CVH at baseline, suggesting no difference between CHD and stroke. Also, the risk of CHD (HR=0.80; 95% CI, 0.77–0.83) and stroke (HR=0.80; 95% CI, 0.74–0.89) decreased similarly by 20% per 1-point increment of the score of global CVH in fully adjusted analysis. Furthermore, analysis by event subtype indicates fairly consistent relative risk reduction across CHD subtypes, whereas relative risk reductions were of lower magnitude for ischemic and nonischemic strokes (Figure 3).

Of note, during follow-up, 414 men had died (see the Kaplan–Meier curves of mortality by CVH status in Figure S1), and in multivariable analysis, the HRs of all-cause mortality for intermediate and ideal CVH versus poor CVH were, respectively, 0.77 (95% CI, 0.65–0.92) and 0.65 (95% CI, 0.42–0.99). However, the association between global CVH and CHD and stroke did not change when competing risk by death was taken into account (Table S1). Furthermore, association between CVH and CHD and stroke combined was consistent across study centers, and no significant interaction was detected (Table S2).

Nested case–control study: Mediating effect of blood biomarkers

This analysis is based on 617 first CHD cases and 1234 matched controls (2 controls per case). Among the controls, the mean concentrations of hs-CRP, IL-6 (inflammatory blood biomarkers), and of fibrinogen (hemostatic blood biomarker) decreased with increasing CVH status (Table 3). This was observed essentially with the behavioral CVH. Blood biomarkers concentrations by level of each metric are given in Table S3. The multivariable HR of intermediate and ideal CVH for CHD were slightly attenuated upon adjustment for each blood biomarker (Table 4 and Table S4). This also applied

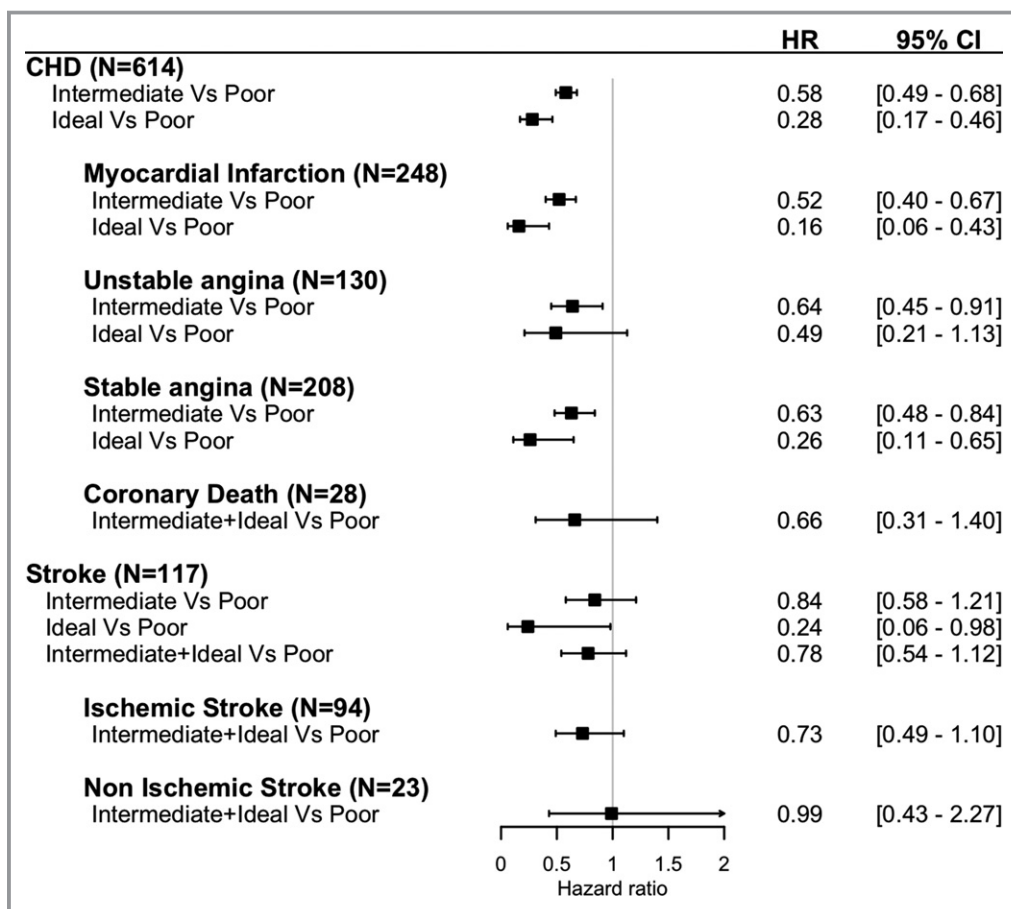


Figure 3. Multivariable hazard ratios of baseline global cardiovascular health status for main coronary heart disease (CHD) and stroke subtypes in the whole PRIME (Prospective Epidemiological Study of Myocardial Infarction) cohort. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated in separate Cox proportional hazards regression model using Poor status as the reference exposure and were adjusted for age, study center, family history of CHD, education, social status, living alone status, cohabiting status, and fibrinogen. Cardiovascular health status: Poor: 0 to 2 ideal metrics; Intermediate: 3 to 4 ideal metrics; Ideal: 5 to 7 ideal metrics.

when looking at each metric separately. Stronger relative attenuation was observed with behavioral CVH after adjustment for hs-CRP (13.28%), IL-6 (8.13%), and fibrinogen (10.73%), respectively. Accordingly, mediation analysis for behavioral CVH (Table 4) indicates statistically significant indirect effect (ie, mediating effect) of hs-CRP (16.69%), IL-6 (8.52%), and fibrinogen (7.30%), respectively.

Discussion

In this multicenter community-based prospective cohort of men aged between 50 and 59, we observed a 72% lower risk of CHD and a 76% lower risk of stroke in men with ideal compared with poor CVH over a median follow-up of 10 years. These risk reductions were consistent for the behavioral and the health factor CVH. There was no heterogeneity across main CHD and main stroke phenotypes, between CHD and

stroke, or between Northern Ireland and France. Finally, lower concentrations of hs-CRP, IL-6, and fibrinogen partly mediated the lower risk of CHD associated with intermediate and ideal CVH, especially behavioral CVH.

The 7% of middle-aged men in ideal CVH is consistent with rates reported in the literature.^{3,27,28} We did observe some heterogeneity in the prevalence of ideal CVH across study centers. In accordance with the North–South gradient of CVD incidence, the highest rates of ideal CVH were observed in Toulouse (South-East France), whereas the lowest rates were observed in Belfast (Northern Ireland), Strasbourg (North-East France), and Lille (North of France).

Previous studies relating ideal CVH with future CVD were mainly conducted in the United States and in China.^{2–5} So far, only 1 study, the EPIC (European Prospective Investigation into Cancer and Nutrition) Norfolk study, was conducted in a European population.⁶ In this study, a 97% and 84% lower risk

Table 3. Baseline Concentrations of Circulating Blood Biomarkers in Controls by Baseline CVH Status in the Nested Case–Control Study

CVH Status	N	Inflammatory Blood Biomarkers		Hemostatic Blood Biomarker
		Hs-CRP (mg/L)	IL-6 (pg/mL)	Fibrinogen (g/L)
Global				
Poor	472	2.68 (1.42–4.92)	0.29 (0–0.82)	3.21 (2.79–3.77)
Intermediate	632	2.09 (1.04–4.49)	0.22 (0–0.60)	3.10 (2.72–3.64)
Ideal	86	1.61 (0.86–2.98)	0.21 (0–0.52)	2.99 (2.64–3.37)
<i>P</i> for trend		<0.0001	0.08	0.006
Behavioral				
Poor	616	2.74 (1.39–4.94)	0.31 (0–0.75)	3.20 (2.81–3.83)
Intermediate	441	2.05 (1.03–4.38)	0.21 (0–0.62)	3.06 (2.69–3.61)
Ideal	132	1.55 (0.82–2.81)	0.18 (0–0.44)	3.06 (2.64–3.50)
<i>P</i> for trend		<0.0001	0.02	0.005
Health factor				
Poor	757	2.41 (1.24–4.62)	0.23 (0–0.70)	3.14 (2.74–3.68)
Intermediate	367	2.25 (1.10–4.74)	0.29 (0–0.62)	3.11 (2.70–3.68)
Ideal	64	1.71 (0.82–3.91)	0.29 (0–0.62)	3.08 (2.73–3.68)
<i>P</i> for trend		0.036	0.65	0.56

Results are medians (interquartile range)—Comparisons and *P* values for trend derived from linear regression analysis on log-transformed blood biomarkers and were adjusted for age and study center. Blood biomarkers concentrations were obtained on fasting baseline plasma samples. CVH indicates cardiovascular health status; hs-CRP, high-sensitivity C-reactive protein.

of CHD and stroke was found in subjects with ideal compared with poor CVH, respectively. These results are consistent with our findings, although the magnitudes of these risk reductions are apparently higher than ours (97% versus 72% risk reduction for CHD, and 84% versus 39% for stroke). This is likely because of the fact that they contrasted extreme categories of CVH (ie, subjects with 6 or 7 ideal metrics versus subjects with at best 1 metric at the ideal level), whereas in our study, we compared men with 5 to 7 ideal metrics versus men with 0 to 2 ideal metrics, respectively. In the EPIC Norfolk study, however, 61% ($n=15\ 000$) of the participants were excluded from the analysis because of missing covariates, possibly giving a selective picture of the association between CVH and outcomes.

To the best of our knowledge, this is the first study addressing the possible heterogeneity in the association of CVH status with incident CHD and stroke subtypes. The rationale of our approach is that some risk factors that are part of the CVH construct including smoking status, type 2 diabetes mellitus, and blood pressure have demonstrated heterogeneous associations across first manifestations of CVD.^{7–12} For instance, in PRIME, we previously showed differential associations of lipids with incident CHD as compared with stroke over 10 years, and heterogeneous associations of traditional risk factors with incident stable angina as compared with acute coronary syndrome.^{9,10} More recently, data from the CALIBER (Cardiovascular disease

research using linked bespoke studies and electronic health records) study based on nearly 2 million participants from primary care practices in England reported a highly heterogeneous association of smoking status with lifetime risk for 12 first manifestations of CVD.¹¹ In our study, however, we did not observe clear evidence for heterogeneity in the association of CVH between CHD and stroke, or across CHD and stroke subtypes. This supports the uniform application of the AHA ideal CVH tool for health promotion for all subtypes of CVD, at least for CHD and for stroke. It should be noted, however, that coronary death and nonischemic stroke were particularly rare, so that the related HRs should be interpreted with caution. Furthermore, a lifetime risk approach⁸ may offer a more powerful way than the present analysis based on a 10-year risk window to detect heterogeneity across subtypes. An additional source of heterogeneity might have been expected across PRIME study centers, given established differences in lifestyle risk factors including diet²⁰ and alcohol consumption.²⁹ However, the association between CVH and outcomes (CHD and stroke combined) operated equally across study centers, and between France and Northern Ireland. This emphasizes the universal promotion of ideal CVH across populations with different risk factors profile.

So far, only the Framingham study has explored how much novel blood biomarkers could contribute to the associations between ideal CVH and outcomes.¹⁷ In that study, the relative attenuation of the HRs was 33% upon simultaneous

Table 4. HR for First CHD of Global, Behavioral, and Health Factor CVH Status Without and With Adjustment for Inflammatory and Hemostatic Blood Biomarkers in the Nested Case–Control Study

CVH Status	n/N	Model 1	Model 1+hs-CRP	Model 1+IL-6	Model 1+Fibrinogen
		HR (CI 95%)	HR (CI 95%)	HR (CI 95%)	HR (CI 95%)
Global	587/1777				
Poor	317/789	1	1	1	1
Intermediate	254/886	0.58 (0.47–0.72)	0.58 (0.47–0.73)	0.58 (0.46–0.72)	0.60 (0.48–0.74)
Ideal	16/102	0.26 (0.15–0.47)	0.29 (0.16–0.52)	0.28 (0.16–0.50)	0.27 (0.15–0.49)
% Relative attenuation			8.09	5.50	2.80
% Mediated			9.57	4.91	3.61
Behavioral	590/1779				
Poor	360/976	1	1	1	1
Intermediate	194/635	0.75 (0.60–0.93)	0.76 (0.61–0.95)	0.75 (0.60–0.93)	0.77 (0.62–0.96)
Ideal	36/168	0.46 (0.31–0.69)	0.51 (0.34–0.77)	0.49 (0.33–0.74)	0.50 (0.33–0.75)
% Relative attenuation			13.28	8.13	10.73
% Mediated			16.69	8.52	7.30
Health factor	584/1772				
Poor	454/1211	1	1	1	1
Intermediate	117/484	0.49 (0.38–0.64)	0.48 (0.37–0.62)	0.45 (0.35–0.60)	0.50 (0.39–0.65)
Ideal	13/77	0.33 (0.18–0.62)	0.34 (0.18–0.63)	0.35 (0.19–0.66)	0.31 (0.17–0.59)
% Relative attenuation			2.69	5.31	5.64
% Mediated			3.85	0.03	1.27

Hazard ratios were estimated by conditional logistic regression and model M1 included age, study center and family history of CHD, education, social status, living alone status, and marital status as covariates. Mediating effect was estimated using an extension of the Baron and Kenny method developed by Valeri et al.²⁶ CHD indicates coronary heart disease; CI, confidence interval; CVH, cardiovascular health status; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein.

adjustment for brain natriuretic peptides, PAI-1, and growth differentiation factor 15, and a further 20% relative attenuation upon subsequent adjustment for subclinical markers of vascular disease, yielding an almost 47% relative attenuation when all blood biomarkers were combined in the same model. The relative attenuations were much lower in our study and ranged from 8.13% to 3.28% when exploring behavioral CVH. Beyond the fact that we did not evaluate the same blood biomarkers (except hs-CRP), these differences may also partly be because of the fact that our study sample comprised exclusively men, unlike the Framingham study. Indeed, women are twice to 4 times more likely to have ideal CVH^{28,30} but often have higher concentrations of inflammatory and hemostatic blood biomarkers than men. Compared with the Framingham study, we investigated the impact of IL-6, which is a strong and potentially causal predictor of CVD, and additionally provided a mediation analysis. In our study, hs-CRP and to a lesser extent IL-6 and fibrinogen had a significant mediating effect on the association between CVH status and incident CHD events. These mediating effects were relatively small in magnitude, ranging from 3.61% to 9.57%, but were of stronger magnitude in the analysis of behavioral CVH, ranging from 7.3% to 16.69%. Repeated measurements

of blood biomarkers could help to better quantify their mediating effect. Additional mediating pathways should also be explored. In a recent cross-sectional analysis, we demonstrated significant differences in subclinical carotid structural and functional parameters across CVH status.³¹ The extent to which these alterations contribute to the association between ideal CVH and CVD needs to be investigated in future prospective analysis.

We acknowledge the following limitations. Generalization to women and other age groups cannot be made. CVH status was evaluated in the early 1990s, when statins were not commonly prescribed and when the distribution of risk factors, especially with respect to smoking, differed from what we observe currently. This may affect the prevalence estimates but not the associations under investigation. As in many studies, the definition of the diet metric was not optimal. This might contribute to the lack of significant association of the diet metric with combined CHD or stroke. We also acknowledge the incomplete definition of the glycemic metric. By investigating treated diabetes mellitus only, we missed undiagnosed diabetes mellitus and possibly underestimated the association of diabetes mellitus with outcomes. CVH was available at baseline only, so that change

in CVH over time could not be related to incident CVD. Finally, we acknowledge that the AHA life 7 metrics tool is intended to be a simple one to promote an ideal CVH, but we should keep in mind that each of the 7 metrics may not have the same weight regarding their association with CVD.

In summary, in this large European study of middle-aged men, men with 5 ideal metrics or more had a substantially lower risk of CHD and stroke as compared with those with up to 2 metrics at the ideal level. Risk reductions were of comparable magnitude between CHD and stroke, and across CHD subtypes and possibly across stroke subtypes, indicating that there was no clear heterogeneity in the association of baseline cardiovascular health with the main subtypes of CVD. This supports a universal promotion of ideal CVH to prevent all types of CVD. Furthermore, these risk reductions were partly mediated by lower concentrations of inflammatory (hs-CRP and IL-6) and hemostatic (fibrinogen) blood biomarkers.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Data S1.

Baseline examination:

At baseline, men answered to standardized and detailed questionnaires regarding past medical history, demographic and socioeconomic factors, tobacco and alcohol consumption, psychological factors including depressive mood.¹ Physical activity was assessed for the year preceding recruitment by means of the MONICA Optional Study of Physical Activity Questionnaire (MOSPA-Q)², while information on diet was obtained through a food frequency questionnaire.³ Height and body weight were measured by nurses during physical examination in subjects with light clothing and no shoes. Diabetes was defined by current diet for diabetes or current intake of oral hypoglycemic treatment. Blood pressure was measured in a sitting position after 5 min of rest with the same automatic device (Spengler SP9, Spengler, Cachan, France).

Blood was drawn after an overnight fast. A subset of biological measurements was performed in fresh plasma in the entire cohort. Plasma lipid analyses were centralized (SERLIA INSERM U325, Institut Pasteur de Lille, France). Total cholesterol (Total-C) and high-density lipoprotein cholesterol (HDL-C) were measured by enzymatic methods using commercial kits in an automatic analyzer (Boehringer, Mannheim, Germany). Fibrinogen was assessed at the Laboratory of Hemostasis of La Timone Hospital in Marseilles, France, using commercially available ELISAs from Diagnostica Stago (Asnières-sur-Seine, France). Aliquots of serum and plasma were then frozen in liquid nitrogen until analysis of biomarkers in nested case control studies (see corresponding paragraph).

Cardiovascular health metric definition

Cardiovascular health metrics were defined according to the American Heart Association criteria.⁴

Behavioural metrics

Body mass index

Anthropometric factors were measured in subjects with light clothing and no shoes by nurses during physical examination. Height was measured to the nearest cm while body weight was determined to the nearest 200g. Body mass index (BMI) was quantified as body weight divided by the square of height (kg/m^2). Poor, intermediate and ideal BMI were defined by values $> 30 \text{ kg}/\text{m}^2$, between 25 and $29.9 \text{ kg}/\text{m}^2$ and below $25 \text{ kg}/\text{m}^2$ respectively.

Smoking habits

In the general self-administrated questionnaire, participants reported their current smoking status (never smoker/ex smoker/current smoker) and the time since smoking cessation (for ex-smokers). Poor, intermediate and ideal smoking status corresponded to current smokers, ex-smokers that have stopped for less than 12 months, and never smokers or ex-smokers that have stopped for at least 12 months respectively.

Physical Activity

Physical activity was assessed for the year preceding recruitment by means of the MONICA Optional Study of Physical Activity Questionnaire (MOSPA-Q), whose validity and reliability have been reported.² This administered questionnaire evaluated time and mean energy expenditure during leisure time, at work, and during walking or cycling to and from work. Leisure-time walking and the two activities that were most frequently performed (sport or others, such as gardening) were taken into account. The intensities of the activities were derived from the Compendium and expressed in metabolic equivalents (MET)⁵. Sports comprised between 4 and 6 MET were considered as moderate, and sports equal or more than 6 MET as vigorous. Times per week for moderate and vigorous activities considered the time spent at

work, way to work, leisure and sport. This time took into account the annual practice. Ideal status was defined as moderate activities ≥ 150 minutes per week, or vigorous activities > 75 minutes per week, or combined moderate and vigorous activities ≥ 150 minutes per week. Intermediate status was defined as moderate or vigorous (or combined moderate and vigorous) activities ≥ 1 minute / week. Poor status was defined as no moderate or vigorous activities of ≥ 1 minute/week. Subjects who reported no work no leisure and no sport activities but who declared having an intense physical activity at least 20 minutes one time or more per week were classified as intermediate status.

Diet

Two items of the original diet metric including fibers and sodium intake could not be computed, so that the diet metric was computed on 3 out of the original 5 items. A food frequency questionnaire allowed us to estimate the frequency of fruits, vegetables and fish consumption.³ A detailed questionnaire on alcohol consumption (including wine, cider, beer and spirits) permitted us to estimate sugar intake in alcohol and to convert it into kcal/week. Then, the item fruits and vegetables was considered healthy if 4.5 portions of fruits and vegetables were consumed per day; for the fish item, if consumed twice or more per week; for the sugar item, if consumed equal or less than 450 kcal/week.

Altogether, ideal diet includes 3 healthy items, intermediate 2 healthy items and poor diet as having one or zero healthy items.

Biological metrics

Blood pressure

Blood pressure was measured in a quiet room in the sitting position with the right arm on a desk at the heart level after a 5-min rest using an automatic sphygmomanometer (Spengler SP9;

Springler, Cachan, France). Poor, intermediate and ideal blood pressure corresponded to values (SBP/DBP) \geq 140/90 mm-Hg, values $<$ 140/90 mm-Hg or $<$ 120/80 mm-Hg on medications, and untreated $<$ 120/80 mm-Hg respectively.

Blood total cholesterol

Fasting plasma total cholesterol and HDL cholesterol levels were measured at the Central Laboratory in Lille by enzymatic methods using reagents from Boehringer-Mannheim (Mannheim, Germany) Poor, intermediate and ideal total cholesterol corresponded to values \geq 240 mg/dL, values $<$ 240 mg/dL or $<$ 200 mg/dL on medications and untreated values $<$ 200 mg/dL respectively.

Glucose

In PRIME, fasting glycaemia was unavailable for the whole cohort. Thus, men were categorized as poor if they were on diet for diabetes or under medications for diabetes, intermediate if they had a history of diabetes but were no longer on medication and ideal if they had no history of diabetes, no diet and no medications for diabetes.

Cardiovascular health status and cardiovascular health score

Participants who had 0-2, 3-4 or 5-7 ideal metrics were categorized as having poor, intermediate or ideal *global* cardiovascular health, respectively. We maximized the information at hand to assign a CVH status when some metrics were missing. While participants with missing data on individual metrics were excluded from analysis for that metric, this was not the case when the available information on the other metrics was sufficient to assign a CVH status. For example a participant with 5 metrics at the ideal level and missing data on 2 metrics had the possibility of remaining in the analysis as he could be categorized as having an ideal global CVH. In contrast, in those with data on only 2 metrics, a global CVH status could not be assigned and the participant was excluded from analysis. This explains that the study sample size varies

between the metrics analysis and the analysis of CVH. (see flow chart on Figure 1). Instead, the score of cardiovascular health was calculated only in men with available information on the 7 metrics.

Table S1. Sub distribution hazard ratios for first Coronary Heart Disease (CHD) and Stroke associated with cardiovascular health (CVH) status in the whole PRIME cohort taking into account competition by all-cause mortality.

Global CVH status	CHD+stroke		CHD		Stroke	
	N events	sHR	N events	sHR	N events	sHR
	(95% CI)		(95% CI)		(95% CI)	
Poor (N=3699)	393		336		57	1
	1		1			
Intermediate (N=4957)	319	0.61	261	0.58	58	0.84
	[0.53-0.71]		[0.49-0.68]		[0.58-1.21]	
Ideal (N=656)	19	0.28	17	0.29	2	0.24
	[0.18-0.44]		[0.18-0.47]		[0.06-0.99]	

Sub distribution HR (sHR) of ideal and intermediate CVH for CHD and stroke were estimated using the Fine and Gray method ⁶ and were adjusted for age, study centre, family history of CHD, education, social status, living alone, marital status, and fibrinogen.

Table S2. Hazard ratios for first Coronary Heart Disease or Stroke associated with cardiovascular health (CVH) status stratified by study centre in the whole PRIME cohort

CVH Component	Status	Belfast	Strasbourg	Lille
		HR [CI95%]	HR [CI95%]	HR [CI95%]
Global	Poor	1	1	1
	Intermediate	0.56 [0.43-0.72]	0.65 [0.47-0.90]	0.64 [0.46-0.88]
	Ideal	0.26 [0.12-0.59]	0.41 [0.15-1.12]	0.21 [0.05-0.85]
Behavioural	Poor	1	1	1
	Intermediate	0.66 [0.49-0.87]	0.75 [0.53-1.05]	0.86 [0.62-1.2]
	Ideal	0.47 [0.27-0.83]	0.77 [0.43-1.38]	0.26 [0.1-0.63]
Health factor	Poor	1	1	1
	Intermediate	0.60 [0.45-0.81]	0.66 [0.44-1]	0.54 [0.35-0.84]
	Ideal	0.36 [0.16-0.8]	-	-

* p for interaction between study centres and CVH status; Hazards ratios (HR) are adjusted

for age, family history of CHD, education, social status, living alone status, marital status, and

fibrinogen. CVH stands for cardiovascular health status

Table S3. Baseline concentrations of blood biomarkers in controls by baseline cardiovascular health metrics in the case control study nested within the PRIME cohort.

		N	Inflammatory blood biomarkers		Haemostatic blood biomarker
Metrics		N	Hs-CRP (mg/L)	IL6 (pg/mL)	fibrinogen (g/L)
Smoking	Poor	316	2.67 (1.43-5.69)	0.37 (0.05-0.83)	3.28 (2.82-3.84)
	Intermediate	42	2.98 (1.03-4.64)	0.32 (0-0.8)	3.21 (2.9-3.78)
	Ideal	808	2.14 (1.09-4.35)	0.21 (0-0.59)	3.09 (2.69-3.64)
P for trend			<0.0001	<0.0001	0.002
Body mass Index	Poor	143	3.59 (2.04-5.67)	0.41 (0.05-0.82)	3.23 (2.82-3.72)
	Intermediate	653	2.44 (1.28-4.76)	0.23 (0-0.68)	3.11 (2.73-3.68)
	Ideal	370	1.77 (0.82-3.74)	0.21 (0-0.61)	3.09 (2.71-3.64)
P for trend			<0.0001	0.07	0.21
Physical Activity	Poor	380	2.63 (1.32-4.89)	0.32 (0-0.81)	3.21 (2.83-3.87)
	Intermediate	240	2.25 (1.06-4.6)	0.14 (0-0.48)	3.1 (2.71-3.64)
	Ideal	542	2.07 (1.1-4.51)	0.25 (0-0.64)	3.06 (2.69-3.61)
P for trend			0.12	0.89	0.05
Healthy Diet	Poor	1019	2.36 (1.15-4.74)	0.25 (0-0.68)	3.11 (2.73-3.68)
	Intermediate	135	2.2 (1.16-4.42)	0.21 (0-0.68)	3.11 (2.73-3.69)
	Ideal	12	2.27 (1.51-2.98)	0.17 (0-0.62)	3.14 (2.45-3.69)
P for trend			0.69	0.97	0.85
Diabetes	Poor	32	3.55 (2.31-6.79)	0.37 (0-1.15)	3.25 (2.64-3.76)
	Intermediate	56	2.06 (0.98-4.3)	0.26 (0-1)	3 (2.63-3.4)
	Ideal	1078	2.29 (1.15-4.59)	0.24 (0-0.64)	3.13 (2.75-3.68)
P for trend			0.03	0.81	0.53

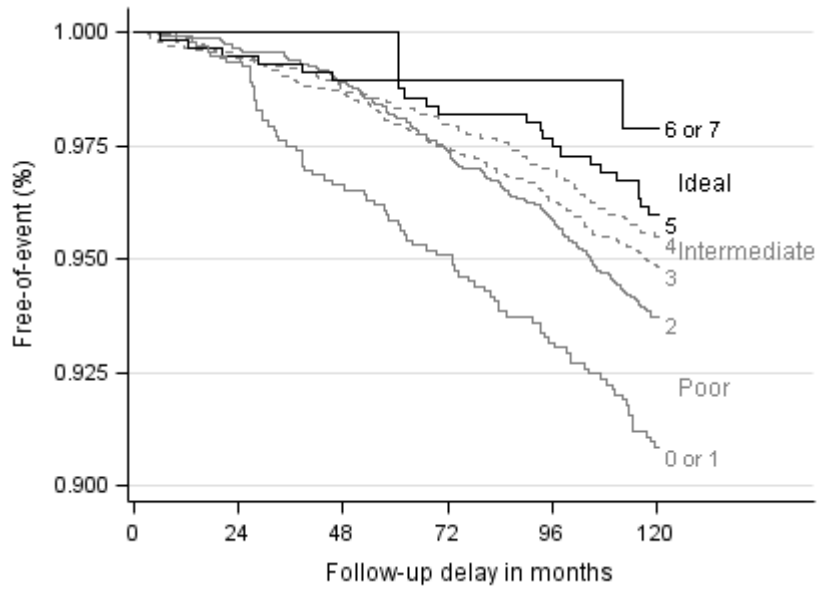
Fasting Total Cholesterol	Poor	347	2.44 (1.32-4.77)	0.29 (0-0.75)	3.22 (2.83-3.76)
	Intermediate	519	2.15 (1.11-4.37)	0.2 (0-0.57)	3.11 (2.72-3.64)
	Ideal	295	2.35 (1.09-4.93)	0.31 (0-0.71)	3.08 (2.71-3.68)
P for trend			0.11	0.92	0.20
Blood Pressure	Poor	467	2.74 (1.49-5.11)	0.31 (0-0.78)	3.1 (2.78-3.68)
	Intermediate	477	2.11 (1.09-3.92)	0.22 (0-0.64)	3.14 (2.71-3.64)
	Ideal	222	1.94 (0.95-4.25)	0.22 (0-0.56)	3.13 (2.73-3.68)
P for trend			<0.0001	0.016	0.88

Table S4. Hazard ratios for first coronary heart disease associated with global cardiovascular health before and after adjustment for inflammatory and haemostatic blood biomarkers in the case control study nested within the PRIME cohort

	CVH status			Per 1 unit increase of Log-transformed blood biomarker
	Poor	Intermediate	Ideal	
n/N=587/1777	317/789	254/886	16/102	
Model 1	1	0.58 [0.47-0.72]	0.26 [0.15-0.47]	
Model 1+hs-CRP	1	0.58 [0.47-0.73]	0.29 [0.16-0.52]	1.05 [1.02-1.08]
Model 1+IL-6	1	0.58 [0.46-0.72]	0.28 [0.16-0.50]	1.07 [1.02-1.11]
Model 1+Fibrinogen	1	0.60 [0.48-0.74]	0.27 [0.15-0.49]	2.11 [1.38-3.25]

Hazard ratios and 95% confidence intervals (CI) were estimated in separate conditional logistic regression analysis that accounted for the matching variables and using Poor status as the reference exposure. Model 1 includes family history of CHD, education, social status, living alone status and marital status as covariates.

Figure S1. Free of all-cause mortality Kaplan-Meier curves by baseline cardiovascular health status in the whole PRIME cohort (N=9312).



Cardiovascular health status: Poor: 0 to 2 ideal metrics; Intermediate: 3-4 ideal metrics;

Ideal: 5 to 7 ideal metrics

Supplemental References:

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