

## ORIGINAL ARTICLE

# Global Effect of Modifiable Risk Factors on Cardiovascular Disease and Mortality

The Global Cardiovascular Risk Consortium

## ABSTRACT

**BACKGROUND**

Five modifiable risk factors are associated with cardiovascular disease and death from any cause. Studies using individual-level data to evaluate the regional and sex-specific prevalence of the risk factors and their effect on these outcomes are lacking.

**METHODS**

We pooled and harmonized individual-level data from 112 cohort studies conducted in 34 countries and 8 geographic regions participating in the Global Cardiovascular Risk Consortium. We examined associations between the risk factors (body-mass index, systolic blood pressure, non-high-density lipoprotein cholesterol, current smoking, and diabetes) and incident cardiovascular disease and death from any cause using Cox regression analyses, stratified according to geographic region, age, and sex. Population-attributable fractions were estimated for the 10-year incidence of cardiovascular disease and 10-year all-cause mortality.

**RESULTS**

Among 1,518,028 participants (54.1% of whom were women) with a median age of 54.4 years, regional variations in the prevalence of the five modifiable risk factors were noted. Incident cardiovascular disease occurred in 80,596 participants during a median follow-up of 7.3 years (maximum, 47.3), and 177,369 participants died during a median follow-up of 8.7 years (maximum, 47.6). For all five risk factors combined, the aggregate global population-attributable fraction of the 10-year incidence of cardiovascular disease was 57.2% (95% confidence interval [CI], 52.4 to 62.1) among women and 52.6% (95% CI, 49.0 to 56.1) among men, and the corresponding values for 10-year all-cause mortality were 22.2% (95% CI, 16.8 to 27.5) and 19.1% (95% CI, 14.6 to 23.6).

**CONCLUSIONS**

Harmonized individual-level data from a global cohort showed that 57.2% and 52.6% of cases of incident cardiovascular disease among women and men, respectively, and 22.2% and 19.1% of deaths from any cause among women and men, respectively, may be attributable to five modifiable risk factors. (Funded by the German Center for Cardiovascular Research (DZHK); ClinicalTrials.gov number, NCT05466825.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Blankenberg can be contacted at s.blankenberg@uke.de or at the University Heart and Vascular Center, Department for Cardiology, Center of Population Health Innovation, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany.

A list of the investigators in the Global Cardiovascular Risk Consortium is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Magnussen, Ojeda, and Leong contributed equally to this article.

This article was published on August 26, 2023, at NEJM.org.

This is the *New England Journal of Medicine* version of record, which includes all *Journal* editing and enhancements. The Author Accepted Manuscript, which is the author's version after external peer review and before publication in the *Journal*, is available at PubMed Central.

N Engl J Med 2023;389:1273-85.

DOI: 10.1056/NEJMoa2206916

Copyright © 2023 Massachusetts Medical Society.



**C**ARDIOVASCULAR DISEASES ARE THE most common noncommunicable conditions worldwide and account for approximately one third of all deaths globally.<sup>1</sup> Modifiable risk factors such as body-mass index, systolic blood pressure, low-density lipoprotein cholesterol level, tobacco smoking, and diabetes account for a percentage of the prevalence and incidence of cardiovascular disease; however, the percentage varies according to the populations studied and the methods used.<sup>2,3</sup> These risk factors are used to derive contemporary risk scores<sup>4-6</sup> for the estimation of the 10-year risk of cardiovascular disease, although they are given different weights. These cardiovascular risk factors also have different associations with cardiovascular and non-cardiovascular outcomes. Tobacco use is strongly associated with premature death, whereas elevated blood pressure and non-high-density lipoprotein (HDL) cholesterol level are more specifically related to cardiovascular disease.<sup>7</sup>

A tailored reduction in the burden of cardiovascular disease and death from any cause for persons and populations can be achieved with a better understanding of the region- and sex-specific associations of these cardiovascular risk factors with the development of cardiovascular disease. The Global Cardiovascular Risk Consortium analyzed a global harmonized individual-level data set of population-based cohorts to overcome the limitations of summary data and methodologic heterogeneity.

## METHODS

### STUDY DESIGN AND OVERSIGHT

The study was designed by the Global Cardiovascular Risk Consortium Management Group, whose members are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org. Data were collected by the Hamburg Data Center. Analyses were performed by the second author and reviewed by the Global Cardiovascular Risk Consortium Statistical Working Group. The first draft of the manuscript was prepared by the first, second, and last authors and was reviewed and edited by all the authors. The authors jointly agreed to submit the manuscript for publication and vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

### STUDY POPULATION

We pooled and harmonized individual-level data from 1,518,028 participants in 112 cohort studies conducted in eight geographic regions (North America, Latin America, Western Europe, Eastern Europe and Russia, North Africa and the Middle East, sub-Saharan Africa, Asia, and Australia) participating in the Global Cardiovascular Risk Consortium. Data were harmonized by applying the variable definitions used by the MORGAM (MONICA [Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases] Risk, Genetics, Archiving, and Monograph) project.<sup>8</sup> Investigators in the studies that were not part of the MORGAM project were sent a list of study-related variables with definitions and were asked to provide these data. A description of each study cohort and information about the local ethics committees and participant informed consent are provided in the Supplementary Appendix. The cohorts that were included in the Global Cardiovascular Risk Consortium were selected on the basis of literature review, existing collaborations among investigators, and the availability of the variables of interest (Table S1). The flow of participants through the study is shown in Figure S1 in the Supplementary Appendix.

### CARDIOVASCULAR RISK FACTORS AND OUTCOME DEFINITIONS

Five risk factors (body-mass index, systolic blood pressure, non-HDL cholesterol, current smoking, and diabetes) and two outcomes (cardiovascular disease and death from any cause) were assessed in the study because of the heterogeneity of the effects of the risk factors on outcomes and the widespread availability of these data in the population. Further, these risk factors can be modified with interventions. Information on these five modifiable risk factors was collected at baseline according to the protocols of the respective studies included in the Global Cardiovascular Risk Consortium. The standardized definitions that were used to classify cardiovascular disease events are provided in Table S2, and the representativeness of the study population is shown in Table S3.

### STATISTICAL ANALYSIS

Missing data were imputed by means of multiple imputation with chained equations (Table S4).<sup>9</sup> Both crude and age- and sex-standardized base-

line characteristics were calculated according to region with the use of direct standardization, with the age and sex distribution of the Global Cardiovascular Risk Consortium data set as the standard. Age-standardized event rates stratified according to region were also estimated and reported per 1000 person-years. Cumulative incidence curves were generated for cardiovascular disease and death from any cause. Associations between risk factors and outcome events were evaluated with the use of a two-stage, multivariate, random-effects meta-analysis of individual participant data.<sup>10</sup> Sex-specific Cox models, with age as the time scale,<sup>11</sup> were computed for each study, and coefficients were pooled across studies according to region as well as globally. Covariates (body-mass index, systolic blood pressure, non-HDL cholesterol level, current smoking, diabetes, and the use of antihypertensive medications) were included simultaneously in the models. Both linear and restricted cubic spline models for continuous covariates and models that allowed for time-varying effects were performed. Models that included receipt of lipid-lowering medications as an additional covariate were also computed with the use of data from the studies in which this information was available (these data were missing for approximately 20% of participants).

For the five modifiable risk factors, region- and sex-specific population-attributable fractions were estimated for the 10-year incidence of cardiovascular disease and 10-year all-cause mortality (see the Supplementary Appendix). Population-attributable fraction is an estimate of the proportion of an outcome that could be prevented if the value of a risk factor were replaced by a hypothetical, ideal value. The approach used by Laaksonen and colleagues,<sup>12</sup> which takes into account the time-to-event nature of the data, was applied to calculate the population-attributable fractions. Weibull models were used in the estimation, and their distributional assumptions were assessed graphically. Reference categories for the risk factors are provided in the Supplementary Appendix.

All the models that were used in the analyses of associations and population-attributable fractions were run with the exclusion of first-year follow-up data (1-year landmark analysis). Two-year landmark analyses that excluded data from the first 2 years of follow-up were performed as sensitivity analyses. The widths of the confidence

intervals have not been adjusted for multiple comparisons and should not be used in place of hypothesis testing. All statistical analyses were performed with the use of R software, version 4.1.3.<sup>13</sup>

## RESULTS

### PARTICIPANT CHARACTERISTICS AND PREVALENCE OF RISK FACTORS

The baseline examination for all study cohorts included in the Global Cardiovascular Risk Consortium took place between 1963 and 2020. In the age- and sex-standardized analysis of data from 1,518,028 participants (54.1% of whom were women) with a median age of 54.4 years, the median body-mass index (the weight in kilograms divided by the square of the height in meters) was 26.4 (interquartile range, 23.7 to 29.7), the median systolic blood pressure 130 mm Hg (interquartile range, 118 to 144), and the median non-HDL cholesterol level 156.9 mg per deciliter (4.06 mmol per liter; interquartile range, 128.8 to 187.9 mg per deciliter [3.33 to 4.86 mmol per liter]); 21.6% were current smokers and 8.3% had diabetes. The age- and sex-standardized prevalence of the five risk factors and the use of antihypertensive and lipid-lowering medications across geographic regions are shown in Table 1 and Table S5. Baseline characteristics without age and sex standardization are shown in Table S6, and the distributions of the risk factors according to sex are shown in Tables S7 and S8. The prevalence of modifiable risk factors across contemporary national health examination surveys, which were used in the population-attributable fraction analyses, is shown in Tables S9, S10, and S11.

### CARDIOVASCULAR DISEASE AND DEATH FROM ANY CAUSE

The median duration of follow-up among participants was 7.3 years (interquartile range, 5.9 to 11.8; maximum, 47.3) for incident cardiovascular disease and 8.7 years (interquartile range, 7.0 to 15.9; maximum, 47.6) for death from any cause. The follow-up times for each of the individual cohorts are provided in Table S12. A total of 80,596 cardiovascular disease events (30,033 in women and 50,563 in men) and 177,369 deaths from any cause (78,608 in women and 98,761 in men) were observed during the follow-up period

**Table 1. Characteristics of the Cohort Studies and Age- and Sex-Standardized Characteristics of the Participants at Baseline According to Geographic Region.\***

Characteristic	Global	North America	Latin America	Western Europe	Eastern Europe and Russia	North Africa and the Middle East	Sub-Saharan Africa	Asia	Australia
<b>Cohort studies</b>									
Cohort studies — no.	112	11	10	58	16	5	2	4	6
Participants — no.	1,518,028	65,182	191,244	907,760	51,133	185,608	10,390	59,802	46,909
Range of survey years†	1963–2020	1971–2011	1990–2013	1970–2015	1983–2014	1963–2020	2011–2017	1988–2015	1983–2007
<b>Participants</b>									
Median age (IQR) — yr‡	54.4 (4.2–63.0)	54.0 (45.0–63.0)	54.0 (45.0–63.0)	54.6 (45.5–63.0)	54.1 (45.5–63.0)	54.0 (45.0–62.6)	54.0 (45.0–63.0)	54.0 (45.0–63.0)	54.6 (45.5–63.0)
Male sex — %‡	45.9	45.9	45.9	45.9	45.9	45.9	45.9	45.9	45.9
Median BMI (IQR)	26.4 (23.7–29.7)	27.2 (24.1–31.0)	28.2 (25.4–31.5)	26.1 (23.6–29.2)	27.2 (24.3–30.6)	27.0 (24.0–30.3)	21.0 (19.0–23.4)	22.8 (20.5–25.2)	26.4 (23.7–29.5)
Median SBP (IQR) — mm Hg	130.0 (118.0–144.0)	122.0 (111.0–136.0)	126.7 (118.0–138.7)	134.0 (122.0–148.0)	132.0 (120.0–148.0)	115.0 (105.0–130.0)	125.0 (113.0–140.0)	123.5 (112.0–136.0)	127.0 (116.5–139.0)
Median DBP (IQR) — mm Hg	80.0 (72.0–87.5)	74.0 (67.0–81.0)	82.7 (76.7–90.0)	81.0 (74.0–89.0)	82.0 (75.0–91.0)	75.0 (67.5–80.0)	75.0 (69.0–83.0)	76.0 (68.0–84.0)	72.5 (64.5–80.5)
Median non-HDL cholesterol (IQR) — mg/dl	156.9 (128.8–187.9)	150.0 (123.0–179.4)	156.2 (131.1–185.2)	162.8 (134.8–193.8)	162.4 (135.0–191.8)	140.1 (115.3–167.8)	116.0 (77.3–154.7)	140.0 (117.6–167.0)	151.2 (124.5–181.0)
Current smoking — %	21.6	22.5	30.8	20.9	29.2	14.2	18.6	23.5	14.3
Diabetes — %	8.3	13.0	15.3	4.8	9.0	18.3	2.0	5.1	4.8
Antihypertensive medications — %	19.4	27.5	19.3	17.9	28.8	24.7	18.5	11.6	13.7
Lipid-lowering medications — %	9.6	8.0	2.3	11.5	8.8	11.6	NA	4.4	4.1
History of CVD — %	5.6	7.2	3.6	5.6	11.2	5.6	0	6.3	7.2

\* Percentages are presented for binary variables. Percentages, medians, and interquartile ranges (IQRs) are based on data from the available number of cases per variable. Percentages, medians, and IQRs per geographic region were computed with the use of direct standardization according to age (≤40 years, >40 to ≤45 years, >45 to ≤50 years, >50 to ≤55 years, >55 to ≤60 years, >60 to ≤65 years, >65 to ≤70 years, and >70 years) and sex distribution in the Global Cardiovascular Risk Consortium data set. To convert the values for non-high-density lipoprotein (HDL) cholesterol to millimoles per liter, multiply by 0.02586. BMI denotes body-mass index, CVD denotes cardiovascular disease, DBP denotes diastolic blood pressure. NA data not available, and SBP denotes systolic blood pressure.

† The approximate number of observations according to categorized examination year were 198,517 (13.1%) between 1963 and 1989, 227,002 (15.0%) between 1990 and 1999, 746,074 (49.1%) between 2000 and 2009, and 342,887 (22.8%) between 2010 and 2020.

‡ Similar values for the characteristics of age and sex across the geographic regions are due to the age and sex standardization.

**Table 2. Age-Standardized Outcomes According to Geographic Region and Sex.\***

Region	CVD Events among Women			CVD Events among Men			Deaths from Any Cause among Women			Deaths from Any Cause among Men		
	No. of Events	10-yr Incidence (95% CI)	Events per 1000 person-yr (95% CI)	No. of Events	10-yr Incidence (95% CI)	Events per 1000 person-yr (95% CI)	No. of Events	10-yr Incidence (95% CI)	Events per 1000 person-yr (95% CI)	No. of Events	10-yr Incidence (95% CI)	Events per 1000 person-yr (95% CI)
Global	30,033	4.0 (4.0–4.1)	5.2 (5.2–5.3)	50,563	7.8 (7.7–7.9)	9.9 (9.8–10.0)	78,608	6.1 (6.0–6.2)	9.0 (9.0–9.1)	98,761	9.3 (9.2–9.4)	13.4 (13.3–13.4)
North America	4,702	7.4 (7.1–7.8)	10.1 (9.8–10.4)	5,321	13.7 (13.1–14.2)	16.6 (16.2–17.1)	8,674	7.6 (7.3–8.0)	16.7 (16.4–17.0)	8,128	11.3 (10.8–11.8)	21.4 (20.9–21.8)
Latin America†	71	—	2.4 (1.9–3.1)	89	—	4.1 (3.3–5.0)	12,488	6.8 (6.6–7.0)	7.5 (7.4–7.7)	9,733	9.7 (9.5–10.0)	10.7 (10.4–10.9)
Western Europe	22,212	3.7 (3.6–3.8)	4.9 (4.8–4.9)	40,942	7.3 (7.2–7.5)	9.6 (9.5–9.7)	42,676	5.6 (5.5–5.7)	8.9 (8.8–9.0)	59,447	8.4 (8.3–8.5)	12.7 (12.6–12.8)
Eastern Europe and Russia	1,078	5.7 (5.0–6.4)	8.7 (7.9–9.5)	1,508	9.9 (8.9–10.9)	13.5 (12.4–14.6)	3,255	10.1 (9.5–10.7)	12.7 (12.2–13.3)	4,827	17.9 (17.1–18.6)	22.1 (21.4–22.8)
North Africa and the Middle East	1,146	6.4 (5.6–7.2)	4.0 (3.7–4.3)	1,805	9.4 (8.5–10.2)	6.8 (6.5–7.2)	1,650	8.1 (7.2–9.0)	6.1 (5.7–6.5)	8,615	11.9 (11.3–12.5)	16.2 (15.8–16.6)
Sub-Saharan Africa‡	3	—	—	1	—	—	431	27.2 (16.0–36.9)	14.1 (12.7–15.6)	456	34.6 (25.1–42.9)	26.7 (24.1–29.6)
Asia	311	2.5 (1.8–3.2)	2.5 (2.2–2.9)	353	4.2 (3.0–5.4)	5.1 (4.5–5.9)	6,399	11.0 (9.9–12.0)	7.6 (7.1–8.1)	4,751	16.7 (15.1–18.4)	12.0 (11.2–13.0)
Australia	510	4.9 (4.3–5.5)	6.0 (5.4–6.6)	544	9.2 (8.3–10.1)	10.3 (9.4–11.4)	3,035	4.7 (4.5–5.0)	5.6 (5.4–5.9)	2,804	7.2 (6.8–7.6)	8.9 (8.5–9.3)

\* Computations were performed with the use of data from 1,088,670 participants in the analysis of cardiovascular disease and from 1,419,699 participants in the analysis of all-cause mortality. The 10-year incidence of events was estimated with the use of the Kaplan–Meier estimator. Events per 1000 person-years were estimated with the use of data obtained during the complete follow-up, and a Poisson regression with log-transformed follow-up time was used as an offset. Direct standardization according to the age distribution in the Global Cardiovascular Risk Consortium data set (≤40 years, >40 to ≤45 years, >45 to ≤50 years, >50 to ≤55 years, >55 to ≤60 years, >60 to ≤65 years, >65 to ≤70 years, and >70 years) was used in the computation of the 10-year incidence of events and events per 1000 person-years per geographic region. The widths of the 95% confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

† Because the CVD follow-up in Latin America is shorter than 10 years, it is not possible to obtain an estimate of the 10-year incidence of the event with the Kaplan–Meier estimator.

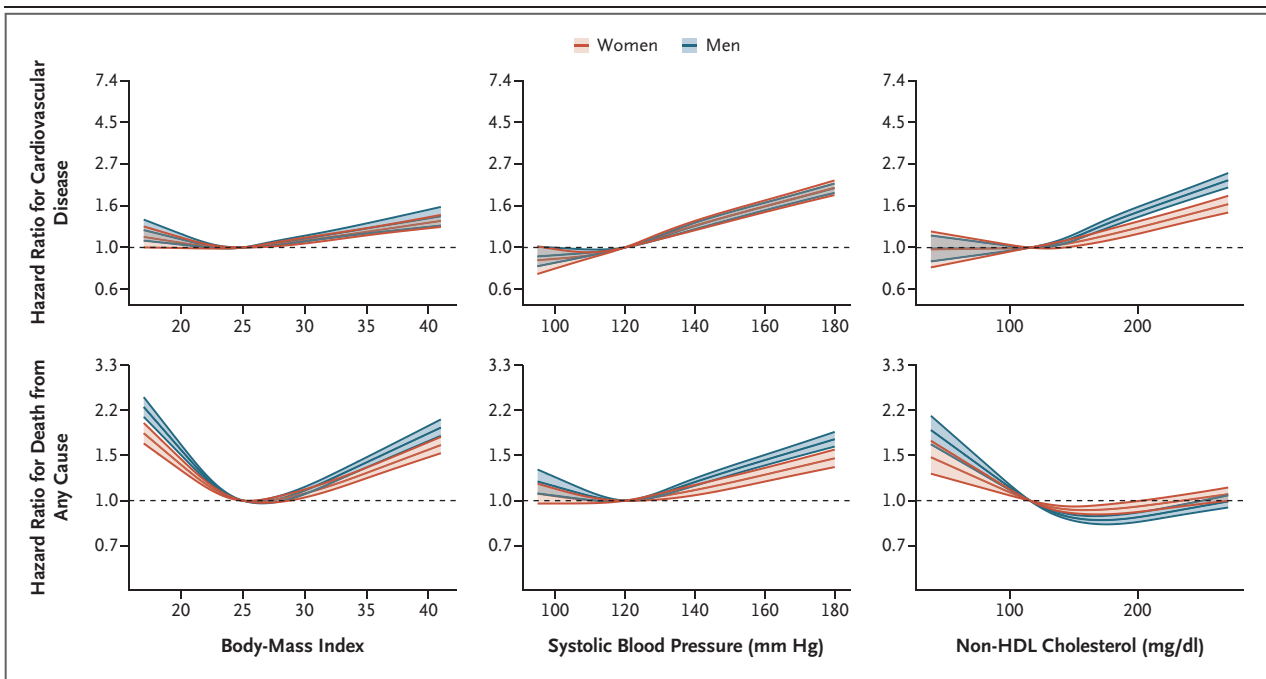
‡ Because of the low number of CVD events recorded, the 10-year incidence of events and events per 1000 person-years were not estimated.

(Table 2). The age-standardized 10-year incidence of cardiovascular disease was 7.4% for women and 13.7% for men in North America, 6.4% for women and 9.4% for men in North Africa and the Middle East, 5.7% for women and 9.9% for men in Eastern Europe and Russia, 3.7% for women and 7.3% for men in Western Europe, and 2.5% for women and 4.2% for men in Asia. The global 10-year incidence of cardiovascular disease was 4.0% among women and 7.8% among men (Table 2). Cardiovascular disease appeared to develop in women at older ages than men (Fig. S2). The age-standardized 10-year all-cause mortality was 27.2% for women and 34.6% for men in sub-Saharan Africa, 10.1% for women and 17.9% for men in Eastern Europe and Russia, 11.0% for women and 16.7% for men in Asia, and 4.7% for women and 7.2% for men in Australia (Table 2).

**EFFECTS OF MODIFIABLE RISK FACTORS**

The risk factor–associated hazard ratios for cardiovascular disease and death from any cause

according to geographic region and sex, as calculated with the exclusion of data from the first year of follow-up (1-year landmark analysis), are shown in Table S13 and Figures S3 through S7. Subdistribution hazard ratios for cardiovascular disease were calculated with death from noncardiovascular causes as the competing event, and the results were similar to those in the 1-year landmark analysis (Table S14). The associations between the risk factors and cardiovascular disease and death from any cause in the models that used continuous risk factors and allowed for nonlinear effects are shown in Figure 1 and Figure S4. In a 2-year landmark analysis that excluded data from the first 2 years of follow-up, the observed associations appeared to be similar to those in the 1-year landmark analysis (Fig. S5), as were the results of other sensitivity analyses (2-year landmark Cox regression models with a linear exposure–effect assumption, models restricted to cohorts starting in the year 2000 or later, models restricted to participants with data on the use of lipid-lowering medications, and



**Figure 1. Associations of Continuous Risk Factors with Cardiovascular Disease and Death from Any Cause.**

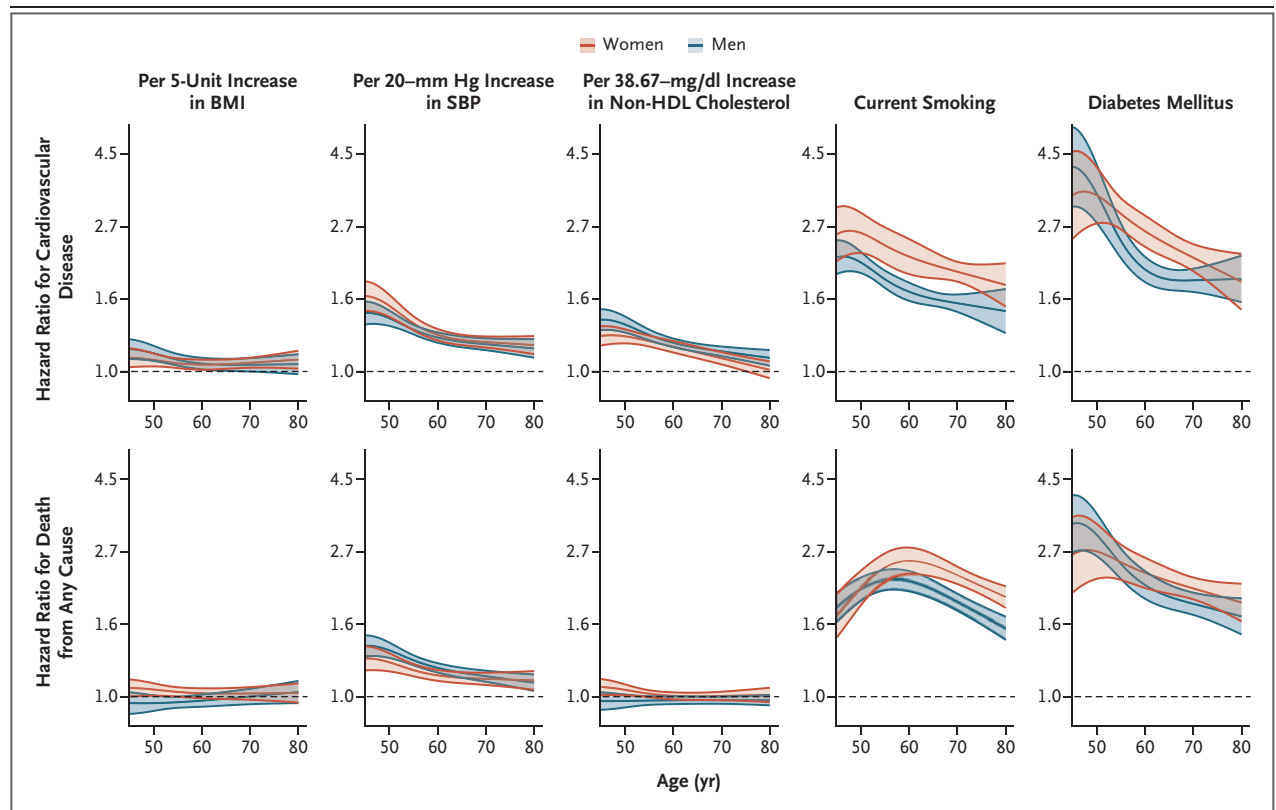
Shown are the results of a global 1-year landmark analysis that allowed for nonlinear effects. Participants with cardiovascular disease at baseline were excluded. Age was used as the time scale. All five risk factors, together with the use of antihypertensive medications, were included as covariates in the models. The widths of the 95% confidence intervals (shaded areas) have not been adjusted for multiplicity and should not be used in place of hypothesis testing. To convert the values for non–high-density lipoprotein (HDL) cholesterol to millimoles per liter, multiply by 0.02586.

models with an alternative definition of cardiovascular disease [a composite of fatal or nonfatal myocardial infarction, ischemic or hemorrhagic stroke, or cardiovascular death] (Tables S15 through S18 and Fig. S6). Unadjusted risk factor–associated hazard ratios for cardiovascular disease and death from any cause are provided in Table S19. For both cardiovascular disease and death from any cause, the association with body-mass index appeared to be consistent across all ages, whereas the strength of the associations with systolic blood pressure, current smoking (after a steady increase up to the second half of life for death from any cause), and diabetes decreased with age (Fig. 2 and Fig. S7). The strength of the association between non-HDL cholesterol level and cardiovascular disease seemed to decline with age but appeared to be stable for death from any cause.

**PREVENTABLE CARDIOVASCULAR DISEASE AND DEATH FROM ANY CAUSE**

The distributional assumptions of the models used in the estimations of the population-attributable fractions were examined graphically (Fig. S8). The five modifiable risk factors accounted for an aggregate global population-attributable fraction of the 10-year incidence of cardiovascular disease of 57.2% (95% confidence interval [CI], 52.4 to 62.1) among women and 52.6% (95% CI, 49.0 to 56.1) among men. In comparison, the five risk factors accounted for an aggregate global population-attributable fraction of 10-year all-cause mortality of 22.2% (95% CI, 16.8 to 27.5) among women and 19.1% (95% CI, 14.6 to 23.6) among men (Fig. 3).

For all modifiable risk factors combined, the aggregate population-attributable fraction of the 10-year incidence of cardiovascular disease was



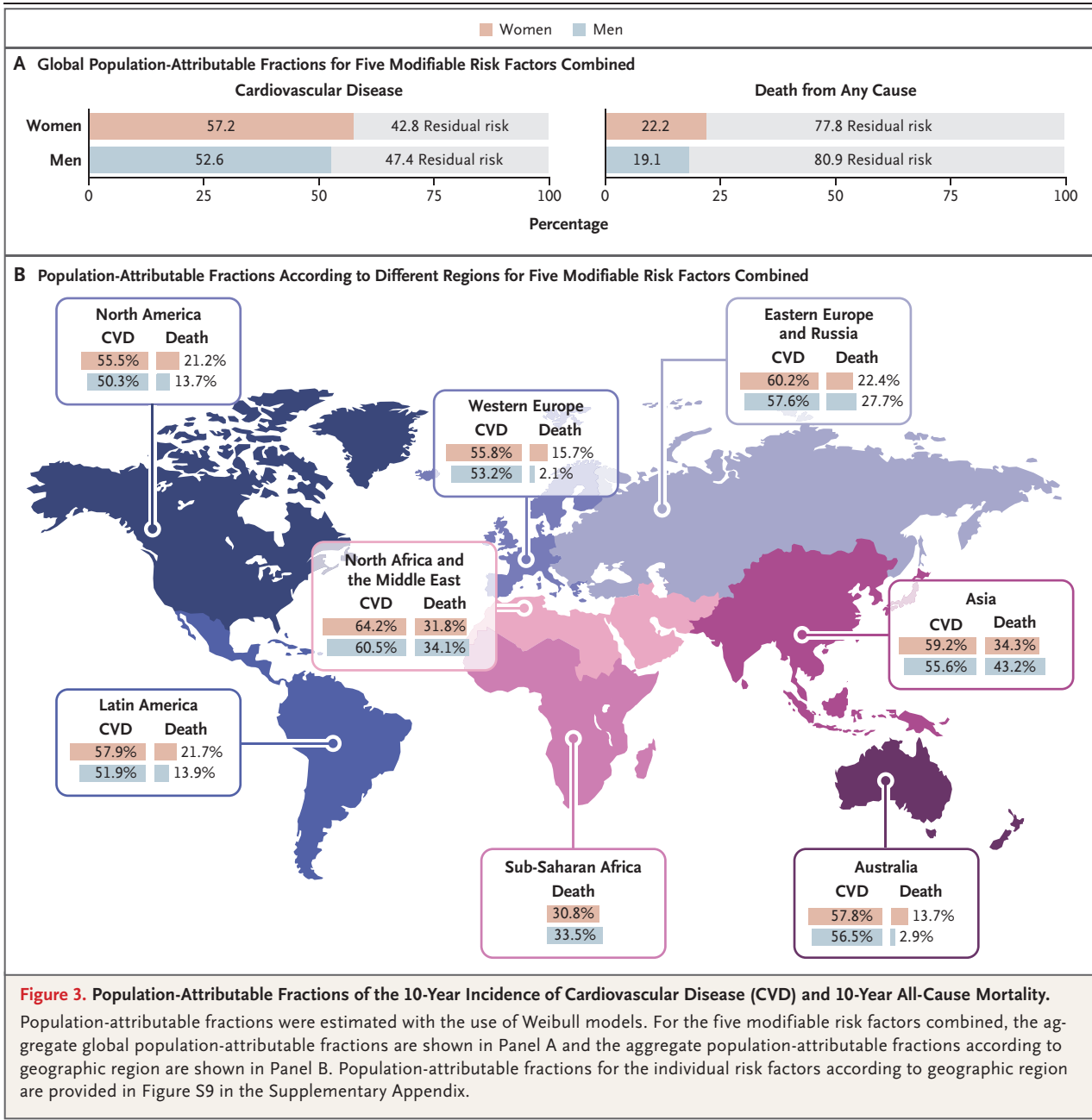
**Figure 2. Associations of Risk Factors with Cardiovascular Disease and Death from Any Cause.**

Shown are the results of a global 1-year landmark analysis that allowed for effects to change with age. Participants with cardiovascular disease at baseline were excluded. Age was used as the time scale. All five risk factors, together with the use of antihypertensive medications, were included as covariates in the models. The widths of the 95% confidence intervals (shaded areas) have not been adjusted for multiplicity and should not be used in place of hypothesis testing. BMI denotes body-mass index, and SBP systolic blood pressure.

64.2% (95% CI, 59.8 to 68.6) among women and 60.5% (95% CI, 57.2 to 63.9) among men in North Africa and the Middle East and 55.5% (95% CI, 50.7 to 60.3) and 50.3% (95% CI, 46.8 to 53.8), respectively, among those in North America. The aggregate population-attributable fraction of 10-year all-cause mortality was 34.3% (95% CI, 29.7 to 38.9) among women and 43.2% (95% CI, 39.8 to 46.6) among men in Asia; 13.7% (95% CI, 7.1 to 20.3) and 2.9% (95% CI, -3.7 to 9.5), respectively,

among those in Australia; and 15.7% (95% CI, 9.3 to 22.0) and 2.1% (95% CI, -4.3 to 8.6), respectively, among those in Western Europe (Fig. 3).

The population-attributable fractions calculated for the individual five modifiable risk factors are shown in Figure S9. The population-attributable fraction of the 10-year incidence of cardiovascular disease associated with systolic blood pressure was 29.3% (95% CI, 25.4 to 33.2) among women and 21.6% (95% CI, 18.7 to 24.5) among



**Figure 3. Population-Attributable Fractions of the 10-Year Incidence of Cardiovascular Disease (CVD) and 10-Year All-Cause Mortality.**

Population-attributable fractions were estimated with the use of Weibull models. For the five modifiable risk factors combined, the aggregate global population-attributable fractions are shown in Panel A and the aggregate population-attributable fractions according to geographic region are shown in Panel B. Population-attributable fractions for the individual risk factors according to geographic region are provided in Figure S9 in the Supplementary Appendix.



men; the corresponding values were 15.4% (95% CI, 10.9 to 19.8) and 16.6% (95% CI, 12.6 to 20.6) for cardiovascular disease associated with non-HDL cholesterol level and 15.2% (95% CI, 13.3 to 17.1) and 10.2% (95% CI, 9.2 to 11.2) for cardiovascular disease associated with diabetes. The population-attributable fraction of the 10-year incidence of cardiovascular disease among women was 6.7% (95% CI, 5.8 to 7.6) for current smoking and 7.6% (95% CI, 5.1 to 10.1) for body-mass index; the corresponding values among men were 10.7% (95% CI, 9.6 to 11.7) and 7.6% (95% CI, 5.6 to 9.7). Among women, the population-attributable fraction of 10-year all-cause mortality associated with diabetes was 12.2% (95% CI, 11.1 to 13.3), whereas among men, the population-attributable fraction of 10-year all-cause mortality associated with current smoking was 14.4% (95% CI 13.3 to 15.4). The population-attributable fractions of the 10-year incidence of cardiovascular disease and 10-year all-cause mortality, according to modifiable risk factor level or status, are shown in Tables S20 and S21.

## DISCUSSION

The Global Cardiovascular Risk Consortium harmonized individual-level data from 1,518,028 participants who participated in 112 cohort studies conducted in 34 countries in North America, Latin America, Western Europe, Eastern Europe and Russia, North Africa and the Middle East, sub-Saharan Africa, Asia, and Australia to assess the effect of five modifiable risk factors on the incidence of cardiovascular disease and all-cause mortality. The study showed that the prevalence of the five modifiable risk factors and the incidence of cardiovascular disease and all-cause mortality varied across geographic regions worldwide, and women had consistently lower event rates than men. The association between individual modifiable risk factors and both incident cardiovascular disease and death from any cause also varied across regions. The five modifiable risk factors accounted for an aggregate population-attributable fraction of the 10-year incidence of cardiovascular disease of 57.2% among women and 52.6% among men, and the corresponding values for 10-year all-cause mortality were 22.2% and 19.1%. Population-attributable fractions of the incidence of cardiovascular disease and all-cause mortality varied according to geographic

region. Elevated systolic blood pressure appeared to be the largest contributor to the population-attributable fraction of incident cardiovascular disease events in all regions.

The Global Cardiovascular Risk Consortium and other studies<sup>14-16</sup> confirmed apparent differences in cardiovascular risk factor profile and event rates between women and men, irrespective of geographic region. Differences in risk factor level have been shown to translate into lifetime risk of cardiovascular disease<sup>17</sup> but not necessarily to affect other fatal outcomes. Cardiovascular risk factors are known to increase cardiovascular disease risk differently across various geographic regions.<sup>2,18</sup> Among them, high blood pressure is associated with up to 13.5% of all deaths annually worldwide and is considered to be the leading risk factor for cardiovascular disease.<sup>19</sup> Strict blood-pressure control to a systolic blood pressure of less than 120 mm Hg has been associated with lower rates of cardiovascular events and all-cause mortality.<sup>20</sup> Our data corroborate this observation; of the five risk factors studied, systolic blood pressure may offer the greatest potential for the prevention of cardiovascular disease. Although there is a strong continuous association between non-HDL cholesterol level and incident cardiovascular disease,<sup>21</sup> we and others<sup>3,22,23</sup> observed an inverted J-shaped association of non-HDL cholesterol level with all-cause mortality. Although very low levels of non-HDL cholesterol are related to a reduction in cardiovascular disease events,<sup>24,25</sup> some observations point toward higher all-cause mortality among participants with very low levels, at least in longer-term follow-up.<sup>26</sup> In contrast to what was previously reported,<sup>3</sup> body-mass index and current smoking (at least in some parts of the world) were associated with comparatively modest population-attributable fractions of cardiovascular disease events in the populations participating in the Global Cardiovascular Risk Consortium. These associations may be related to underlying differences in population characteristics, risk-factor definition and prevalence, or methods used to estimate population-attributable fractions.

Case-control studies such as INTERHEART may have overestimated the population-attributable fraction of the incidence of cardiovascular disease subtypes by attributing 90% of the risk of myocardial infarction to nine targetable risk factors.<sup>2</sup> Data from 155,722 participants who were

evaluated prospectively in the Prospective Urban Rural Epidemiology (PURE) study suggested that 71% of cardiovascular disease cases are attributable to 14 potentially modifiable metabolic and behavioral risk factors, a result that is consistent with our findings.<sup>3</sup> Our study focused on five modifiable risk factors for which strict control could potentially prevent 57.2% of all cases of cardiovascular disease in women and 52.6% of all cases in men globally. The varying effect of individual risk factors across different regions could enable ranking and prioritization of risk-factor control for public health action within those regions. However, there is substantial scope for a more complete characterization of the risk of cardiovascular disease. Environmental and exposure-related factors such as physical activity,<sup>2</sup> alcohol consumption,<sup>27</sup> air pollution,<sup>28</sup> climate and noise,<sup>29</sup> educational level,<sup>3</sup> or psychosocial risk factors, including depression,<sup>30</sup> have an effect on the risk of cardiovascular disease. Biomarkers<sup>31,32</sup> and genetic variants most likely would add to the prediction of cardiovascular disease risk.

The analysis by the Global Cardiovascular Risk Consortium differs from other global initiatives that combine different data sources such as registries, population surveys, and health system administrative data to produce meta-analytic summaries.<sup>33,34</sup> The Global Cardiovascular Risk Consortium maintains a large and comprehensive database of harmonized, observational, individual-level, prospectively collected data. This database allows for multiple prespecified statistical analyses on large-scale individual-level data. This study relates major modifiable cardiovascular risk factors to the incidence of cardiovascular disease and all-cause mortality. The inclusion of cohorts with a large spectrum of follow-up times enabled robust sex-specific analyses and the evaluation of differences across geographic regions.

Our study has several limitations. The Global Cardiovascular Risk Consortium database includes cohorts with varying representativeness, data quality and quantity, dates of baseline assessments, follow-up times, end-point definitions, and use of clinical interventions. Variation in the adjudication of causes of death or surrogates of non-fatal myocardial infarction is plausible across regions, but an analysis that included the use of a secondary definition of cardiovascular disease that excluded unclassifiable death, unstable angina, and coronary revascularization did not change the results. Structured harmonization

was used to reduce variation, and sensitivity analyses provided results similar to those for the overall study population. Standardized event rates should be interpreted as descriptive measures rather than actual incidences in a population. To overcome bias resulting from deaths from non-cardiovascular diseases that were present at the time of the baseline examination, analyses were performed with the exclusion of first-year follow-up data. Information about modifiable risk factors was available from the baseline examination, and the effect of changes in exposure over time are not known; the analyses were not corrected for regression dilution bias. Residual confounding cannot be completely excluded. The effects of overweight and obesity may be mediated by hyperlipidemia, hypertension, and diabetes.<sup>35</sup> Models that included body-mass index, systolic blood pressure, and diabetes attribute the share of the effect of body-mass index to systolic blood pressure and diabetes, even if overweight or obesity is the real underlying cause. The definition of current smoking may not capture the entire spectrum and dose of tobacco exposure, and smoking cessation during follow-up might have led to an underestimation of tobacco smoking as a risk factor. It was also assumed that risk factor effects and prevalence within a region are homogeneous; however, intraregional differences may exist. Information about ethnic group is not provided, because definitions differed among the cohorts or collection of the variable was incomplete or not available to a comparable standard. The categorization of geographic regions by the World Health Organization and United Nations was adapted to accommodate cohort size and representativeness of a geographic region, so a different categorization of regions may produce different results.

In our study, harmonized individual-level data from the Global Cardiovascular Risk Consortium showed that 57.2% and 52.6% of cases of incident cardiovascular disease among women and men, respectively, and 22.2% and 19.1% of deaths from any cause among women and men, respectively, may be attributable to five modifiable risk factors. The prevalence and effect of these risk factors on the incidence of cardiovascular disease and all-cause mortality vary according to sex and geographic region.

Supported by the German Center for Cardiovascular Research (DZHK).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

## APPENDIX

The authors' full names and academic degrees are as follows: Christina Magnussen, M.D., Francisco M. Ojeda, Ph.D., Darryl P. Leong, M.B., B.S., Ph.D., Jesus Alegre-Diaz, M.D., Philippe Amouyel, M.D., Ph.D., Larissa Aviles-Santa, M.D., Dirk De Bacquer, Ph.D., Christie M. Ballantyne, M.D., Antonio Bernabé-Ortiz, M.D., Ph.D., Martin Bobak, Ph.D., Hermann Brenner, M.D., Rodrigo M. Carrillo-Larco, M.D., Ph.D., James de Lemos, M.D., Annette Dobson, Ph.D., Marcus Dörr, M.D., Chiara Donfrancesco, Ph.D., Wojciech Drygas, M.D., Ph.D., Robin P. Dullaart, M.D., Ph.D., Gunnar Engström, M.D., Ph.D., Marco M. Ferrario, M.D., Ph.D., Jean Ferrières, M.D., Ph.D., Giovanni de Gaetano, M.D., Ph.D., Uri Goldbourt, Ph.D., Clicerio Gonzalez, M.D., Guido Grassi, M.D., Allison M. Hodge, Ph.D., Kristian Hveem, M.D., Ph.D., Licia Iacoviello, M.D., Ph.D., M. Kamran Ikram, M.D., Ph.D., Vilma Irazola, M.D., Ph.D., Modou Jobe, M.D., Pekka Jousilahti, M.D., Ph.D., Pontiano Kaleebu, M.D., Ph.D., Maryam Kavousi, M.D., Ph.D., Frank Kee, M.D., Davood Khalili, M.D., Ph.D., Wolfgang Koenig, M.D., Anna Kontsevaya, M.D., Ph.D., Kari Kuulasmaa, Ph.D., Karl J. Lackner, M.D., David M. Leitner, M.D., Lars Lind, M.D., Ph.D., Allan Linneberg, M.D., Ph.D., Thiess Lorenz, M.A., Magnus Nakrem Lyngbakken, M.D., Ph.D., Reza Malekzadeh, M.D., Sofia Maljutina, M.D., Ph.D., Ellisiv B. Mathiesen, M.D., Ph.D., Olle Melander, M.D., Ph.D., Andres Metspalu, M.D., Ph.D., J. Jaime Miranda, M.D., Ph.D., Marie Moitry, M.D., Joseph Mugisha, Ph.D., Mahdi Nalini, M.D., Ph.D., Vijay Nambi, M.D., Ph.D., Toshiharu Ninomiya, M.D., Ph.D., Karen Oppermann, M.D., Ph.D., Eleonora d'Orsi, Ph.D., Andrzej Pająk, M.D., Ph.D., Luigi Palmieri, Ph.D., Demosthenes Panagiotakos, M.D., Ph.D., Arokiasamy Perianayagam, Ph.D., Annette Peters, Ph.D., Hossein Poustchi, M.D., Ph.D., Andrew M. Prentice, Ph.D., Eva Prescott, M.D., Ulf Risérus, M.D., Ph.D., Veikko Salomaa, M.D., Ph.D., Susana Sans, M.D., Ph.D., Satoko Sakata, M.D., Ph.D., Ben Schöttker, Ph.D., Aletta E. Schutte, Ph.D., Sadaf G. Sepanlou, Ph.D., Sanjib Kumar Sharma, M.D., Jonathan E. Shaw, M.D., Leon A. Simons, M.D., Stefan Söderberg, M.D., Ph.D., Abdonas Tamosiunas, M.D., Barbara Thorand, Ph.D., Hugh Tunstall-Pedoe, M.D., Raphael Twerenbold, M.D., Diego Vanuzzo, M.D., Giovanni Veronesi, Ph.D., Julia Waibel, M.Sc., S. Goya Wannamethee, Ph.D., Masafumi Watanabe, M.D., Ph.D., Philipp S. Wild, M.D., Yao Yao, M.D., Ph.D., Yi Zeng, M.D., Andreas Ziegler, Ph.D., and Stefan Blankenberg, M.D.

The authors' affiliations are as follows: the Center for Population Health Innovation, University Heart and Vascular Center Hamburg (C.M., F.M.O., T.L., R.T., J.W., A.Z., S.B.), University Medical Center Hamburg-Eppendorf (C.M., F.M.O., T.L., R.T., J.W., A.Z., S.B.), the German Center for Cardiovascular Research (DZHK) Partner Site Hamburg-Kiel-Lübeck (C.M., T.L., R.T., J.W., S.B.), the Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, and Network Aging Research, Heidelberg University, Heidelberg (H.B., B.S.), the Department of Internal Medicine B, University Medicine Greifswald, and DZHK Partner Site Greifswald, Greifswald (M.D.), DZHK Partner Site Munich Heart Alliance (W.K., A. Peters), the German Heart Center, Technical University of Munich (W.K.), and the Institute for Medical Information Processing, Biometry, and Epidemiology, Medical Faculty, Ludwig Maximilians Universität München (A. Peters, B.T.), Munich, the Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm (W.K.), the Institute of Clinical Chemistry and Laboratory Medicine (K.J.L.), Preventive Cardiology and Preventive Medicine (P.S.W.), and Clinical Epidemiology and Systems Medicine, Center for Thrombosis and Hemostasis (P.S.W.), University Medical Center of the Johannes Gutenberg-University Mainz, DZHK Partner Site Rhine-Main (K.J.L., P.S.W.), and Institute for Molecular Biology (P.S.W.), Mainz, the University Heart and Vascular Center Frankfurt, DZHK Partner Site Rhine-Main, Frankfurt (D.M.L.), the Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health (A. Peters, B.T.), and German Center for Diabetes Research (DZD) Partner Site Munich-Neuherberg (A. Peters, B.T.), Neuherberg — all in Germany; the Department of Medicine (Cardiology), McMaster University, Hamilton, Canada (D.P.L.); the Experimental Medicine Research Unit, School of Medicine, National Autonomous University of Mexico, Mexico City (J.A.-D.), and Centro de Estudios en Diabetes, Centro de Investigación en Salud Poblacional, Instituto Nacional de Salud Pública, Cuernavaca (C.G.) — both in Mexico; Université de Lille, INSERM, Centre Hospitalier University de Lille, Institut Pasteur de Lille, UMR1167-RID-AGE-Risk Factors and Molecular Determinants of Aging-Related Diseases, Epidemiology and Public Health Department, Lille (P.A.), the Department of Cardiology, INSERM UMR1295, Toulouse Ranguel University Hospital, Toulouse (J.F.), and the Department of Public Health, Strasbourg University Hospital, University of Strasbourg, Strasbourg (M.M.) — all in France; the Division of Clinical and Health Services Research, National Institute on Minority Health and Health Disparities (L.A.-S.), and the Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute (M.N.), National Institutes of Health, Bethesda, MD; the Department of Public Health and Primary Care, Ghent University, Ghent, Belgium (D.D.B.); the Department of Medicine, Baylor College of Medicine (C.M.B.), and Michael E. DeBakey Veterans Affairs Hospital and Baylor College of Medicine (V.N.), Houston, and the Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas (J.L.) — all in Texas; the CRONICAS Center of Excellence in Chronic Diseases, Universidad Peruana Cayetano Heredia, Lima, Peru (A.B.-O., J.J.M.); the Department of Epidemiology and Public Health (M.B.) and the Research Department of Primary Care and Population Health (S.G.W.), University College London, London, the Centre for Public Health, Queens University Belfast, Belfast (F.K.), and the Cardiovascular Epidemiology Unit, Institute of Cardiovascular Research, University of Dundee, Dundee (H.T.-P.) — all in the United Kingdom; the Emory Global Diabetes Research Center and Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta (R.M.C.-L.); the School of Public Health, University of Queensland, Brisbane (A.D.), the Division of Cancer Epidemiology, Cancer Council Victoria (A.M.H.), the Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, the University of Melbourne (A.M.H.), and Baker Heart and Diabetes Institute (J.E.S.), Melbourne, the Sydney School of Public Health, Faculty of Medicine and Health, University of Sydney (J.J.M.), and the George Institute for Global Health (A.E.S.), Sydney, and the School of Population Health (A.E.S.), University of New South Wales, Kensington (L.A.S.) — all in Australia; the Department of Cardiovascular and Endocrine-Metabolic Diseases and Aging, Istituto Superiore di Sanità, Rome (C.D., L.P.), the Research Center in Epidemiology and Preventive Medicine, Department of Medicine and Surgery, University of Insubria, Varese (M.M.F., L.I., G.V.), the Department of Epidemiology and Prevention, IRCCS Neuromed, Pozzilli (G. de Gaetano, L.I.), Clinica Medica, University of Milano-Bicocca, Milan (G. Grassi), and the MONICA (Monitoring Cardiovascular Diseases)-Friuli Study Group, Udine (D.V.) — all in Italy; the Department of Epidemiology, Cardiovascular Disease Prevention and Health Promotion, National Institute of Cardiology, and Lazarski University, Warsaw (W.D.), and the Department of Epidemiology and Population Studies, Institute of Public Health, Faculty of Health Sciences, Jagiellonian University Medical College, Krakow (A. Pająk) — all in Poland; the Department of Endocrinology, University Medical Center Groningen, University of Groningen, Groningen (R.P.D.), and the Departments of Neurology (M.K.I.) and Epidemiology (M.K.I.), Erasmus University Medical Center Rotterdam, Rotterdam — both in the Netherlands; the Department of Clinical Sciences Malmö, Lund University, Malmö (G.E., O.M.), the Department of Public Health and Caring Sciences, Clinical Nutrition and Metabolism, Uppsala University (U.R.), and the Department of Medical Sciences, Uppsala University, Uppsala (L.L.), and the Department of Public Health and Clinical Medicine, University of Umea, Umea (S. Söderberg) — all in Sweden; the Department of Epidemiology, Tel Aviv University School of Public Health, Tel Aviv, Israel (U.G.); HUNT (Trøndelag Health Study) Research Center, Department of Public Health and Nursing, Norwegian University of Science and Technology, Levanger (K.H.), the

K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, Trondheim(K.H.), the Department of Cardiology, Division of Medicine, Akershus University Hospital, Lørenskog (M.N.L.), the K.G. Jebsen Center for Cardiac Biomarkers, Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo (M.N.L.), and the Department of Clinical Medicine, University of Tromsø the Arctic University of Norway, Tromsø (E.B.M.) — all in Norway; the Department of Chronic Diseases, Institute for Clinical Effectiveness and Health Policy, Buenos Aires (V.I.); Medical Research Council Unit The Gambia at London School of Hygiene and Tropical Medicine, Banjul, Gambia (M.J., A.M.P.); the Department of Public Health and Welfare, Finnish Institute for Health and Welfare, Helsinki (P.J., K.K., V.S.); Medical Research Council–Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda (P.K., J.M.); the Prevention of Metabolic Disorders Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences (D.K.), the Liver and Pancreaticobiliary Disease Research Center (R.M.), the Digestive Oncology Research Center (R.M., H.P.), and the Digestive Disease Research Center (R.M., M.N., H.P., S.G.S.), Digestive Disease Research Institute, Shariati Hospital, Tehran University of Medical Sciences — all in Tehran, Iran; the National Research Center for Therapy and Preventive Medicine, Ministry of Healthcare of the Russian Federation, Moscow (A.K.), and the Research Institute of Internal and Preventive Medicine—Branch of the Federal Research Center Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences, Novosibirsk (S.M.) — both in Russia; the Department of Clinical Medicine, Faculty of Health and Medical Sciences (A.L.), and the Department of Cardiology, Bispebjerg Hospital (E.P.), University of Copenhagen, and the Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital (A.L.) — both in Copenhagen; the Estonian Genome Center, Institute of Genomics, University of Tartu, Tartu, Estonia (A.M.); the Department of Epidemiology and Public Health, Graduate School of Medical Sciences, Kyushu University, Fukuoka (T.N., S. Sakata), and the Global Center of Excellence Program Study Group, Yamagata University School of Medicine, Yamagata (M.W.) — both in Japan; the School of Medicine, University of Passo Fundo, Passo Fundo (K.O.), and the Department of Public Health, Postgraduate Program in Public Health, Federal University of Santa Catarina, Florianopolis (E.O.) — both in Brazil; the School of Health Sciences and Education, Harokopio University, Athens, Greece (D.P.); the National Council of Applied Economic Research, Delhi (A. Perianayagam), and the International Institute for Population Sciences, Mumbai (A. Perianayagam) — both in India; the Catalan Department of Health, Barcelona (S. Sans); the Hypertension in Africa Research Team, South African Medical Research Council Unit for Hypertension and Cardiovascular Disease, North-West University, Potchefstroom (A.E.S.), and the School of Mathematics, Statistics, and Computer Science, University of KwaZulu-Natal, Pietermaritzburg (A.Z.) — both in South Africa; the Department of Internal Medicine, B.P. Koirala Institute of Health Sciences, Dharan, Nepal (S.K.S.); the Laboratory of Population Studies, Institute of Cardiology, and the Department of Preventive Medicine, Faculty of Public Health, Lithuanian University of Health Sciences, Kaunas, Lithuania (A.T.); the China Center for Health Development Studies (Y.Y.) and Center for Healthy Aging and Development Studies, National School of Development (Y.Z.), Peking University, and the Key Laboratory of Epidemiology of Major Diseases, Peking University, Ministry of Education (Y.Y.) — both in Beijing; the Center for the Study of Aging and Human Development and Geriatrics Division, Medical School of Duke University, Durham, NC (Y.Z.); and Cardio-CARE, Davos (A.Z., S.B.), and the Swiss Institute of Bioinformatics, Lausanne (A.Z.) — both in Switzerland.

## REFERENCES

- Joseph P, Leong D, McKee M, et al. Reducing the global burden of cardiovascular disease, part 1: the epidemiology and risk factors. *Circ Res* 2017;121:677-94.
- Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937-52.
- Yusuf S, Joseph P, Rangarajan S, et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet* 2020;395:795-808.
- SCORE2 working group and ESC Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. *Eur Heart J* 2021;42:2439-54.
- Yadlowsky S, Hayward RA, Sussman JB, McClelland RL, Min YI, Basu S. Clinical implications of revised pooled cohort equations for estimating atherosclerotic cardiovascular disease risk. *Ann Intern Med* 2018;169:20-9.
- World Health Organization. World health statistics 2011 (<https://web.archive.org/web/20111116011154/http://www.who.int/whosis/whostat/2011/en/>).
- Jaspers NEM, Blaha MJ, Matsushita K, et al. Prediction of individualized lifetime benefit from lowering, blood pressure lowering, antithrombotic therapy, and smoking cessation in apparently healthy people. *Eur Heart J* 2020;41:1190-9.
- Evans A, Salomaa V, Kulathinal S, et al. MORGAM (an international pooling of cardiovascular cohorts). *Int J Epidemiol* 2005;34:21-7.
- van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *J Stat Softw* 2011;45:1-67.
- Riley RD, Tierney JF, Stewart LA. Individual participant data meta-analysis: a handbook for healthcare research. Medford, MA: Wiley, 2021.
- Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. *Am J Epidemiol* 1997;145:72-80.
- Laaksonen MA, Virtala E, Knekt P, Oja H, Härkönen T. SAS macros for calculation of population attributable fraction in a cohort study design. *J Stat Softw* 2011;43:1-25.
- R Foundation for Statistical Computing. The R project for statistical computing (<http://www.r-project.org/index.html>).
- Pencina MJ, D'Agostino RB Sr, Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: the Framingham heart study. *Circulation* 2009;119:3078-84.
- Joseph P, Kutty VR, Mohan V, et al. Cardiovascular disease, mortality, and their associations with modifiable risk factors in a multi-national South Asia cohort: a PURE substudy. *Eur Heart J* 2022;43:2831-40.
- Walli-Attaei M, Joseph P, Rosengren A, et al. Variations between women and men in risk factors, treatments, cardiovascular disease incidence, and death in 27 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet* 2020;396:97-109.
- Berry JD, Dyer A, Cai X, et al. Lifetime risks of cardiovascular disease. *N Engl J Med* 2012;366:321-9.
- Ueshima H, Sekikawa A, Miura K, et al. Cardiovascular disease and risk factors in Asia: a selected review. *Circulation* 2008;118:2702-9.
- Lawes CM, Vander Hoorn S, Rodgers A; International Society of Hypertension. Global burden of blood-pressure-related disease, 2001. *Lancet* 2008;371:1513-8.
- SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;373:2103-16.
- Brunner FJ, Waldeyer C, Ojeda F, et al. Application of non-HDL cholesterol for

- population-based cardiovascular risk stratification: results from the Multinational Cardiovascular Risk Consortium. *Lancet* 2019;394:2173-83.
22. Johannesen CDL, Langsted A, Mortensen MB, Nordestgaard BG. Association between low density lipoprotein and all cause and cause specific mortality in Denmark: prospective cohort study. *BMJ* 2020;371:m4266.
23. Liu Y, Liu F, Zhang L, et al. Association between low density lipoprotein cholesterol and all-cause mortality: results from the NHANES 1999-2014. *Sci Rep* 2021;11:22111.
24. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376:1713-22.
25. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;372:1489-99.
26. van Bruggen FH, Luijendijk HJ. Evolocumab's long-term mortality risk unclear due to shortened follow-up of FOURIER. *Am J Cardiovasc Drugs* 2022; 22:5-8.
27. GBD 2020 Alcohol Collaborators. Population-level risks of alcohol consumption by amount, geography, age, sex, and year: a systematic analysis for the Global Burden of Disease Study 2020. *Lancet* 2022; 400:185-235.
28. Schraufnagel DE, Balmes JR, Cowl CT, et al. Air Pollution and noncommunicable diseases: a review by the Forum of International Respiratory Societies' Environmental Committee, part 2: air pollution and organ systems. *Chest* 2019;155: 417-26.
29. Basner M, Babisch W, Davis A, et al. Auditory and non-auditory effects of noise on health. *Lancet* 2014;383:1325-32.
30. Walli-Attaei M, Rosengren A, Rangarajan S, et al. Metabolic, behavioural, and psychosocial risk factors and cardiovascular disease in women compared with men in 21 high-income, middle-income, and low-income countries: an analysis of the PURE study. *Lancet* 2022;400:811-21.
31. Blankenberg S, Salomaa V, Makarova N, et al. Troponin I and cardiovascular risk prediction in the general population: the BiomarCaRE consortium. *Eur Heart J* 2016;37:2428-37.
32. Neumann JT, Twerenbold R, Ojeda F, et al. Application of high-sensitivity troponin in suspected myocardial infarction. *N Engl J Med* 2019;380:2529-40.
33. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. *J Am Coll Cardiol* 2020;76:2982-3021.
34. Vaduganathan M, Mensah GA, Turco JV, Fuster V, Roth GA. The global burden of cardiovascular diseases and risk: a compass for future health. *J Am Coll Cardiol* 2022;80:2361-71.
35. Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. *Lancet* 2014;383:970-83.

Copyright © 2023 Massachusetts Medical Society.