

ORIGINAL ARTICLE

Global Effect of Cardiovascular Risk Factors on Lifetime Estimates

The Global Cardiovascular Risk Consortium

ABSTRACT

BACKGROUND

Five risk factors account for approximately 50% of the global burden of cardiovascular disease. How the presence or absence of classic risk factors affects lifetime estimates of cardiovascular disease and death from any cause remains unclear.

METHODS

We harmonized individual-level data from 2,078,948 participants across 133 cohorts, 39 countries, and 6 continents. Lifetime risk of cardiovascular disease and death from any cause was estimated up to 90 years of age according to the presence or absence of arterial hypertension, hyperlipidemia, underweight and overweight or obesity, diabetes, and smoking at 50 years of age. Differences in life span (in terms of additional life-years free of cardiovascular disease or death from any cause) according to the presence or absence of these risk factors were also estimated. Risk-factor trajectories were analyzed to predict lifetime differences according to risk-factor variation.

RESULTS

The lifetime risk of cardiovascular disease was 24% (95% confidence interval [CI], 21 to 30) among women and 38% (95% CI, 30 to 45) among men for whom all five risk factors were present. In the comparison between participants with none of the risk factors and those with all the risk factors, the estimated number of additional life-years free of cardiovascular disease was 13.3 (95% CI, 11.2 to 15.7) for women and 10.6 (95% CI, 9.2 to 12.9) for men; the estimated number of additional life-years free of death was 14.5 (95% CI, 9.1 to 15.3) for women and 11.8 (95% CI, 10.1 to 13.6) for men. As compared with no changes in the presence of all risk factors, modification of hypertension at an age of 55 to less than 60 years was associated with the most additional life-years free of cardiovascular disease, and modification of smoking at an age of 55 to less than 60 years was associated with the most additional life-years free of death.

CONCLUSIONS

The absence of five classic risk factors at 50 years of age was associated with more than a decade greater life expectancy than the presence of all five risk factors, in both sexes. Persons who modified hypertension and smoking in midlife had the most additional life-years free of cardiovascular disease and death from any cause, respectively. (Funded by the German Center for Cardiovascular Research [DZHK]; ClinicalTrials.gov number, NCT05466825.)

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

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CARDIOVASCULAR DISEASES REMAIN THE leading cause of death worldwide, imposing substantial social, economic, and public health burdens. Five modifiable risk factors account for approximately 50% of the global burden of cardiovascular disease, which means that approximately half of all cases of cardiovascular disease could potentially be prevented through effective risk-factor management.¹ Current estimates of lifetime risk of cardiovascular disease increase with accumulated risk-factor load^{2,3} and range from 5 to 50%, depending on the specific cardiovascular disease end point, follow-up duration, population risk-factor profiles, and cardiovascular disease risk in different populations.³⁻⁷ These estimates, however, fail to account for dynamic changes in individual risk profiles over time, which could affect long-term outcomes. Furthermore, the association between individual risk factors and differences in life span remains unclear.

Robust global, individual-level data on lifetime estimates are needed to guide preventive action worldwide. These analyses from the Global Cardiovascular Risk Consortium (GCVRC) aim to estimate the sex-specific lifetime risk of cardiovascular disease and death from any cause; provide the estimated difference in life span between participants without classic risk factors for cardiovascular disease and those with such risk factors and between participants who modified certain risk factors and those who did not; evaluate the difference in life span related to risk-factor modification during a prespecified age decade; and identify the most useful regional targets for effective primary prevention strategies.

The authors jointly agreed to submit the manuscript for publication and vouch for the accuracy and completeness of the data. The study had no formal regulatory sponsor. The study protocol and statistical analysis plan are available at NEJM.org.

STUDY POPULATION

We pooled and harmonized individual-level data from 2,078,948 persons, 18 years of age or older, across 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 GCVRC. The process of data harmonization¹ is summarized in the Supplementary Appendix. The grouping of regions, selecting of cohorts, and handling of data were described previously.¹ For the present analyses, 99,485 persons with cardiovascular disease (defined as a history of myocardial infarction, unstable angina, coronary revascularization, or ischemic or hemorrhagic stroke) at baseline were excluded from analyses in which incident cardiovascular disease was the outcome. Persons with missing information on baseline cardiovascular disease (92,131 [4.4%]) were retained and treated as having no cardiovascular disease at baseline. After further exclusion of persons with missing follow-up information, 1,227,987 persons remained available for analysis of incident cardiovascular disease and 2,042,815 for analysis of death. Figure S1 in the Supplementary Appendix shows the study flow in detail. A description of each cohort, including information on local ethics committees, is provided in the Supplementary Appendix.

METHODS

STUDY DESIGN AND OVERSIGHT

The study was designed by the GCVRC Management Group, whose members are listed in the Supplementary Appendix (available with the full text of this article at NEJM.org). After approval of the statistical analysis plan by the GCVRC Statistical Working Group (as shown in the Supplementary Appendix), analyses were performed by the next-to-last author and again reviewed within the GCVRC Statistical Working Group. The first version of the manuscript was drafted by the first author, the next-to-last author, and the last author and reviewed and edited by all the authors.

CARDIOVASCULAR RISK FACTORS AND OUTCOME DEFINITION

Information on systolic blood pressure, non-high-density lipoprotein (HDL) cholesterol, body-mass index (BMI; the weight in kilograms divided by the square of the height in meters), diabetes, and current smoking was collected at baseline according to the protocols of the respective studies. Data were harmonized with the use of the variable definitions of the MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases) cohorts.⁸ For the main analyses, continuous risk factors were categorized with the use of guideline-based targets: arterial hypertension was identified by a systolic blood pres-

sure of 130 mm Hg or more; hyperlipidemia was determined by non-HDL cholesterol levels of 130 mg per deciliter (3.36 mmol per liter) or more; underweight was defined as a BMI of less than 20; and overweight or obesity was defined as a BMI of 25 or more. Diabetes was determined on the basis of medical history, participant report, or new diagnosis at baseline examination with the use of measures of glycemia, depending on the standard operating procedures of the respective cohorts. Current smoking was defined as regularly (at least once daily) or occasionally (less than once per day) smoking cigarettes, cigars, cigarillos, or pipes. Incident cardiovascular disease was defined as a first fatal or nonfatal myocardial infarction, unstable angina, coronary revascularization, ischemic or hemorrhagic stroke, or death from a cardiovascular or unknown cause. Table S1 summarizes the variables of interest, Table S2 presents the standardized definitions used for the coding system to classify cardiovascular disease events, Table S3 provides the background information of the population studied, and Table S4 details data availability. Information on cohorts with available repeated risk-factor measurements is provided in Table S5.

LIFETIME ESTIMATES

The estimated lifetime risk of cardiovascular disease and death from any cause is based on the estimated cumulative risk of the outcome of interest developing before 90 years of age.⁷ The estimated difference in life span between participants without classic risk factors and those with such risk factors and between participants who modified certain risk factors and those who did not is based on cardiovascular disease–free life expectancy and overall life expectancy and was estimated in terms of median survival time without a cardiovascular disease event or death (i.e., the age at which cumulative survival probability falls below 0.5).⁷ In this analysis, the estimated lifetime difference represents the additional cardiovascular disease–free or death-free life-years associated with the absence of risk factors at a given index age (e.g., 50 or 60 years) and is computed as the difference between the life expectancies of a participant without the risk factors and a participant with all five risk factors. In addition, an analysis of single risk factors is provided. Lifetime difference, or difference in life span, according to risk-factor modification is an estimate of

the additional life-years associated with changes in risk factors (to levels below the above thresholds) and is computed similarly to estimated lifetime difference, with the use of longitudinal risk-factor information in a time interval (e.g., from 50 to 60 years) before the estimation of life expectancies beyond that interval.

The estimated quantities represent differences between subpopulations having distinct risk-factor profiles and capture the degree to which variation in life expectancy is explained by these important factors in a large, global population. In the case of single risk factors, the effect is adjusted for the other four risk factors. The estimated quantities should be interpreted as observational, without implying causality. In other words, the models described below can be used to estimate differences between subpopulations of participants who have one or more risk factors and those who do not or between subpopulations of participants who modify a risk factor and those who do not. Owing to the possibility that participants who have — or modify — one or more risk factors can differ in ways that are explained by unmeasured factors that also predict survival, the estimated effects may not fully capture the within-participant causal effect of modifying a risk factor.

STATISTICAL ANALYSIS

Missing data were imputed with the use of multiple imputation with chained equations or multilevel multiple imputation.^{9,10} Age- and sex-standardized baseline characteristics were calculated according to geographic region with the use of direct standardization, with the use of the age and sex distribution of the GCVRC data set as the standard. Sex-specific Weibull models, with age as the time scale,¹¹ were estimated for each study and pooled across studies according to region as well as globally with the use of multivariate random-effects meta-analysis^{12,13} to allow for between-study heterogeneity. The Weibull models included the following covariates (risk factors): systolic blood pressure, non-HDL cholesterol level, BMI, diabetes, and current smoking.

Initially, systolic blood pressure, non-HDL cholesterol level, and BMI entered the models dichotomized according to the thresholds described above. The distributional assumptions of the Weibull models were assessed graphically (Fig. S2). Additional analyses were performed with various

Table 1. Age- and Sex-Standardized Baseline Characteristics 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
Cohort studies									
Cohort studies — no.	133	11	11	66	16	6	5	12	6
Participants — no.	2,078,948	65,178	192,546	1,049,898	51,133	195,307	19,949	458,028	46,909
Range of survey years	1963–2021	1971–2011	1990–2013	1970–2021	1983–2014	1963–2020	1987–2017	1988–2018	1983–2007
Participants									
Median age (IQR) — yr	53.2 (44.4–62.0)	54.0 (45.0–63.0)	54.0 (45.0–63.0)	53.0 (43.9–61.9)	53.4 (44.4–62.0)	53.8 (45.0–62.0)	53.1 (44.0–62.2)	54.0 (45.0–62.7)	53.5 (44.1–62.2)
Male sex — %	47.3	47.3	47.3	47.3	47.3	47.3	47.3	47.3	47.3
Systolic blood pressure									
Median (IQR) — mm Hg	128.7 (116.7–142.0)	122.0 (111.0–135.0)	126.7 (118.0–138.0)	132.0 (120.0–146.5)	132.0 (120.0–147.5)	116.0 (105.0–130.0)	126.0 (114.0–142.0)	125.0 (112.7–140.0)	127.0 (116.0–139.0)
≥130 mm Hg — %	48.6	34.1	43.6	56.8	56.5	26.6	43.7	43.6	42.8
Median diastolic blood pressure (IQR) — mm Hg	80.0 (72.0–88.0)	74.0 (67.0–81.0)	82.7 (76.7–90.0)	81.0 (74.0–88.5)	82.0 (75.0–90.0)	75.0 (68.0–80.0)	76.0 (69.5–85.0)	80.0 (71.0–89.0)	72.5 (64.5–80.7)
Non-HDL cholesterol									
Median (IQR) — mg/dl	155.6 (127.7–186.8)	149.8 (123.0–179.0)	156.2 (131.1–186.0)	162.4 (133.8–193.4)	161.6 (134.1–191.1)	140.9 (116.0–168.1)	138.8 (111.8–175.8)	140.0 (116.0–165.9)	151.6 (124.9–181.4)
≥130 mg/dl — %	73.1	68.6	75.8	77.9	78.0	61.3	55.6	60.9	70.2
Body-mass index									
Median (IQR)	25.7 (22.8–28.9)	27.2 (24.1–30.9)	28.2 (25.4–31.4)	26.0 (23.5–29.1)	27.1 (24.2–30.5)	27.0 (24.0–30.3)	22.3 (19.9–25.7)	22.6 (20.1–25.4)	26.3 (23.7–29.5)
<20 or ≥25 — %	63.9	71.3	79.6	63.7	71.8	72.9	55.4	51.8	66.5
Diabetes — %	7.7	12.9	15.1	4.8	8.7	17.5	12.9	5.2	4.6
Current smoking — %	22.3	22.7	31.3	20.9	29.9	14.8	25.1	24.7	15.0
Antihypertensive medications — %	17.2	27.2	18.9	17.0	27.9	22.9	15.6	8.6	12.8
Lipid-lowering medications — %	9.0	8.0	2.2	10.7	8.3	10.5	0	4.7	3.8
History of CVD — %	4.9	7.4	3.6	5.1	11.0	5.7	2.2	3.6	6.8

* Percentages, medians, and interquartile ranges (IQRs) according to 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. CVD denotes cardiovascular disease.

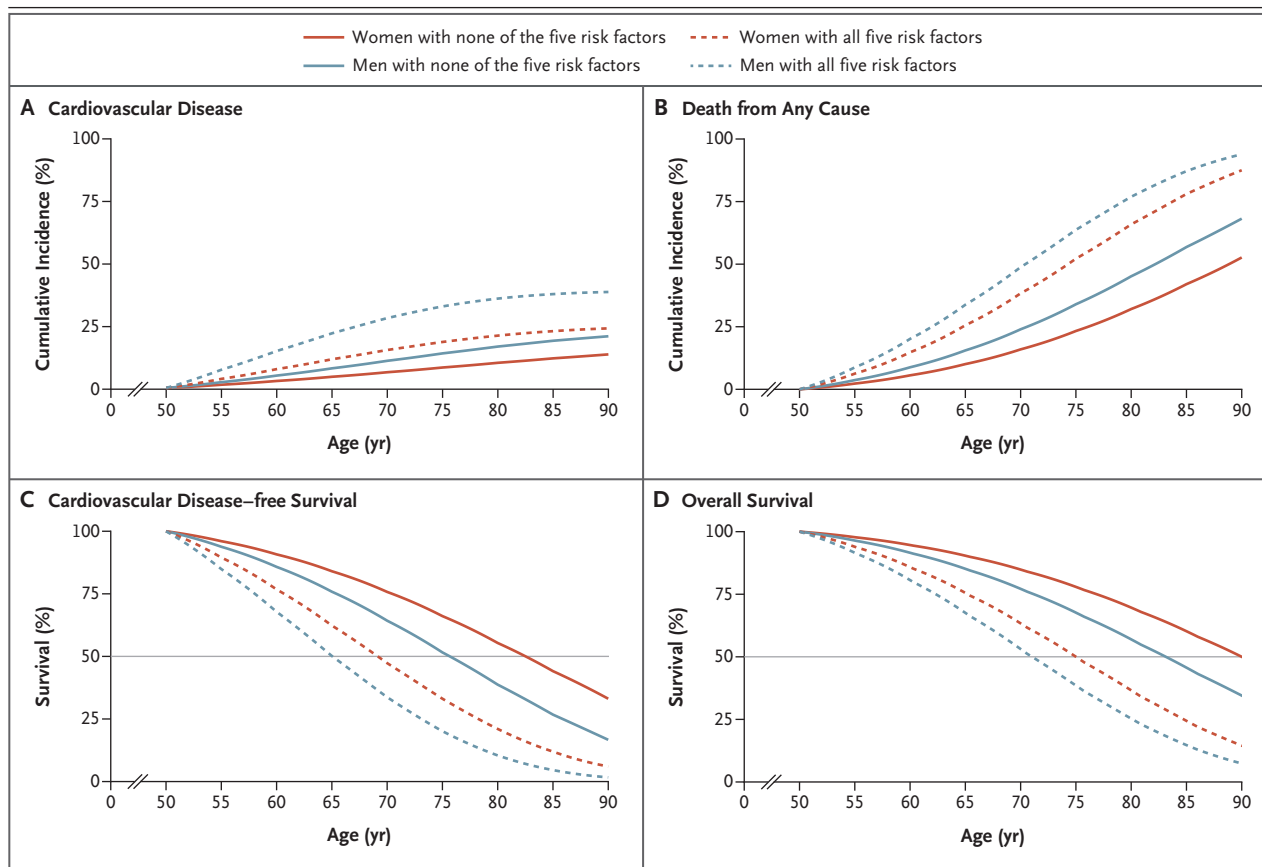


Figure 1. Effect of Five Modifiable Cardiovascular Risk Factors on Lifetime Risk of Cardiovascular Disease and Death from Any Cause.

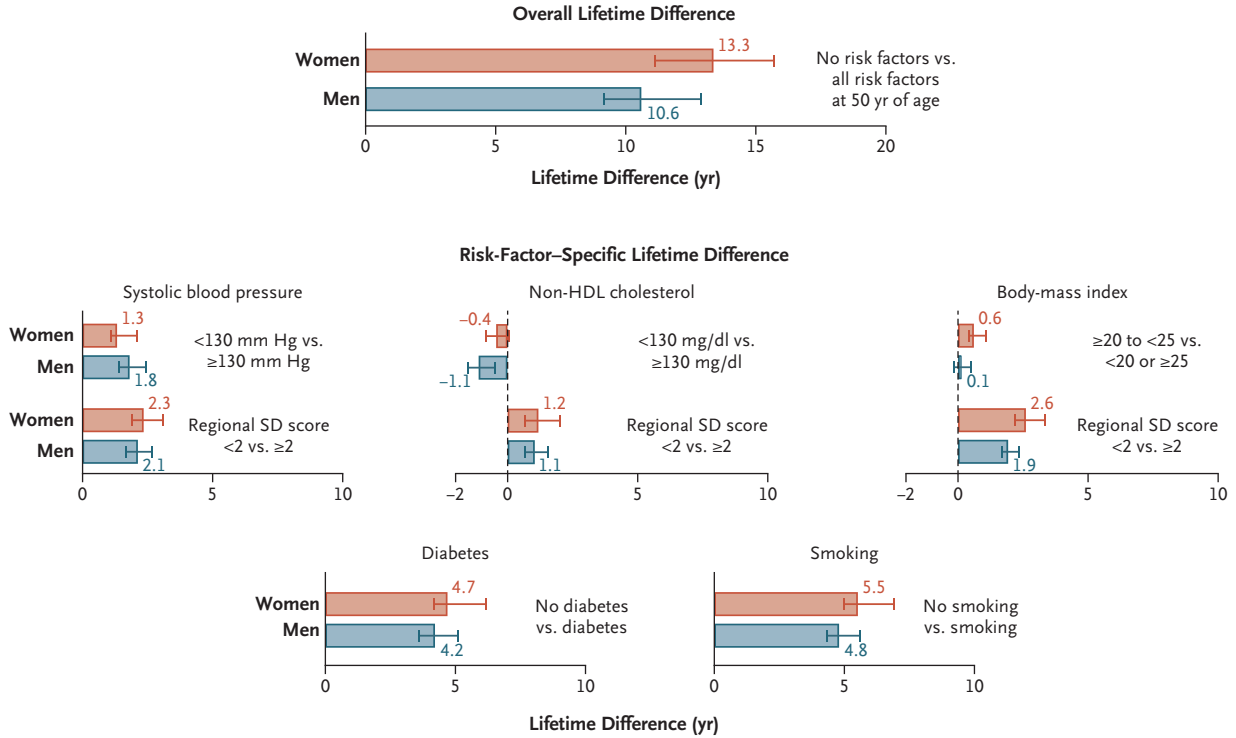
Shown are risk curves for participants without the five cardiovascular risk factors (solid lines) as compared with those with all five risk factors (dashed lines) at an index age of 50 years. Cumulative incidence curves (Panels A and B) and survival curves (Panels C and D) are shown for women (red) and men (blue). Lifetime risk is shown for cardiovascular disease (Panel A) and death from any cause (Panel B), and lifetime difference is shown for cardiovascular disease or death (Panel C) and death from any cause (Panel D). In Panels C and D, cardiovascular disease-free life expectancy and overall life expectancy are indicated by the age at which a given survival curve crosses the horizontal line at 50%. The curves were generated with the use of recalibrated predictions from Weibull models. The five risk factors are a systolic blood pressure of 130 mm Hg or more, a non-high-density lipoprotein (HDL) cholesterol level of 130 mg per deciliter (3.36 mmol per liter) or more, a body-mass index (BMI) of less than 20 or 25 or more, diabetes, and current smoking.

alternative cutoffs. On one such version, sex-specific regional standard-deviation scores were derived for these three variables by subtracting region-specific means and dividing by region-specific standard deviations. One and two standard deviations were used as cutoffs, which effectively allowed for different cutoffs according to region in the analyses. On the basis of these models, cumulative incidence was estimated. The regional standard-deviation scores were used to account for heterogeneity in risk-factor prevalence and distribution among cohorts from different geographic regions to improve comparability.

Owing to the age of some of the included data

sets coupled with secular changes in cardiovascular disease and mortality, the incidence estimated from these models was calibrated with the use of World Health Organization mortality and population data as described previously.^{12,14} Calibrated incidence was used to estimate lifetime risk, life expectancies, and lifetime differences.⁷ More precisely, the calibrated incidence was used to obtain survival probabilities, which then were used to estimate life expectancies for selected combinations of risk factors. The difference in life expectancies for two risk-factor profiles was used to calculate the lifetime difference. For a subset of the data, multiple examination rounds

A Cardiovascular Disease



B Death from Any Cause

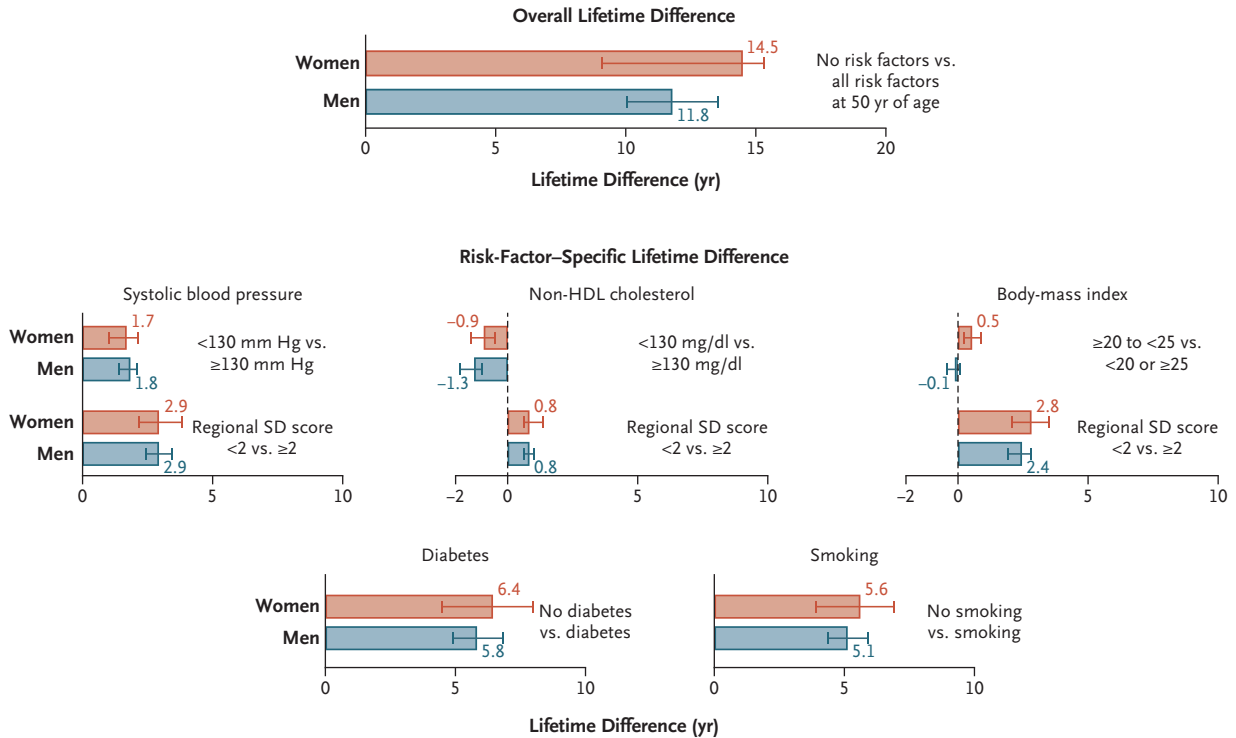


Figure 2 (facing page). Estimated Lifetime Difference between Participants without Risk Factors and Those with Risk Factors.

For both cardiovascular disease (Panel A) and death from any cause (Panel B), lifetime difference is shown for the absence as compared with the presence of all five risk factors at an index age of 50 years and for the absence of a single risk factor as compared with the presence of all other risk factors. Results are shown separately for women (red) and men (blue). Lifetime differences were calculated as the difference between the predicted cardiovascular disease-free or overall life expectancy for persons with all risk factors and those with no risk factors. Lifetime difference for systolic blood pressure, non-HDL cholesterol level, and BMI is presented for two scenarios. Estimates and 95% confidence intervals (error bars) for overall lifetime difference, systolic blood pressure of less than 130 mm Hg as compared with 130 mm Hg or more, a non-HDL cholesterol level of less than 130 mg per deciliter as compared with 130 mg per deciliter or more, a BMI of 20 to less than 25 as compared with less than 20 or 25 or more, no diabetes as compared with diabetes, and no smoking as compared with smoking are based on recalibrated predictions from Weibull models that included these variables as covariates. Estimates and 95% confidence intervals for regional standard-deviation (SD) scores are based on recalibrated predictions from Weibull models including dichotomized regional standard-deviation scores (<2 vs. ≥2) for systolic blood pressure, non-HDL cholesterol level, and BMI as covariates, along with diabetes and smoking.

were available. These data were used to estimate life expectancies and lifetime difference according to risk-factor variation, on the basis of joint models for the longitudinal trajectories of the risk factors and time-to-event data.⁷ Details of the statistical methods are provided in the Supplementary Appendix and statistical analysis plan. Statistical analyses were performed with the use of R statistical software, version 4.3.3.¹⁵

RESULTS

BASILINE CHARACTERISTICS

Among 2,078,948 participants across 133 cohorts, 39 countries, and 6 continents, the median systolic blood pressure was 128.7 mm Hg (interquartile range, 116.7 to 142.0), the median non-HDL cholesterol level was 155.6 mg per deciliter (interquartile range, 127.7 to 186.8 [median, 4.02 mmol per liter; interquartile range, 3.30 to 4.83]), and

the median BMI was 25.7 (interquartile range, 22.8 to 28.9). A total of 7.7% of the participants had diabetes, and 22.3% were current smokers (Table 1). Baseline characteristics in the health examination surveys used for regional calibration are provided in Tables S6A and S6B.

LIFETIME RISK AND DIFFERENCE ACCORDING TO RISK-FACTOR BURDEN

The median follow-up of the cohort studies was 7.6 years (interquartile range, 5.9 to 15.1) for cardiovascular disease and 8.5 years (interquartile range, 6.7 to 15.5) for death. The maximum follow-up time for both outcomes was 47.3 years. At an index age of 50 years, among participants who had none of the five classic risk factors, the estimated lifetime risk of cardiovascular disease before 90 years of age was 13% (95% confidence interval [CI], 12 to 16) among women and 21% (95% CI, 18 to 23) among men; among participants who had all five risk factors, the estimated risk was 24% (95% CI, 21 to 30) among women and 38% (95% CI, 30 to 45) among men (Fig. 1A). The estimated lifetime risk of death before 90 years of age was 53% (95% CI, 36 to 88) among women and 68% (95% CI, 57 to 77) among men with none of the risk factors and was 88% (95% CI, 72 to 99) among women and 94% (95% CI, 87 to 97) among men with all five risk factors (Fig. 1B).

In the comparison between participants with none of the risk factors and those with all the risk factors, the estimated number of additional life-years free of cardiovascular disease was 13.3 (95% CI, 11.2 to 15.7) for women and 10.6 (95% CI, 9.2 to 12.9) for men (Figs. 1C and 2A); the estimated number of additional life-years free of death was 14.5 (95% CI, 9.1 to 15.3) for women and 11.8 (95% CI, 10.1 to 13.6) for men (Figs. 1D and 2B). The estimated lifetime risk and difference between participants without classic risk factors and those with such risk factors for both cardiovascular disease and death from any cause according to geographic region at an index age of 50 years are presented in Figures S3A, S3B, S4A, and S4B. Results for estimated lifetime risk and difference between participants without classic risk factors and those with such risk factors at an index age of 60 years are shown in Figures S5A, S5B, S6A, and S6B.

LIFETIME DIFFERENCE WITH RESPECT TO SINGLE RISK FACTORS

For cardiovascular disease, the absence of diabetes was associated with an estimated lifetime difference of 4.7 years (95% CI, 4.2 to 6.2) for women and 4.2 years (95% CI, 3.6 to 5.1) for men; the absence of smoking was associated with a difference of 5.5 years (95% CI, 5.0 to 6.9) for women and 4.8 years (95% CI, 4.3 to 5.7) for men. (Fig. 2A and Table S7A). A systolic blood pressure of less than 130 mm Hg was related to a lifetime difference of 1.3 years (95% CI, 1.1 to 2.1) for women and 1.8 years (95% CI, 1.4 to 2.4) for men, and the difference increased up to 2.3 years (95% CI, 1.9 to 3.1) for women and 2.1 years (95% CI, 1.7 to 2.7) for men in the comparison between a regional standard-deviation score of less than 2 and a score of 2 or more. The non-HDL cholesterol level was associated with a lifetime difference of -0.4 years (95% CI, -0.8 to 0.1) for women and -1.1 years (95% CI, -1.5 to -0.5) for men if a strict limit of less than 130 mg per deciliter was applied, but the difference increased to 1.2 years (95% CI, 0.7 to 2.0) for women and 1.1 years (95% CI, 0.7 to 1.6) for men if the regional standard-deviation score was applied. Absence of underweight and of overweight or obesity was associated with a lifetime difference of 0.6 years (95% CI, 0.4 to 1.1) for women and 0.1 years (95% CI, -0.2 to 0.5) for men, and the difference increased up to 2.6 years (95% CI, 2.2 to 3.3) for women and 1.9 years (95% CI, 1.7 to 2.3) for men when the regional standard-deviation score was applied.

For death, absence of diabetes was associated with a lifetime difference of 6.4 years (95% CI, 4.4 to 7.9) for women and 5.8 years (95% CI, 4.9 to 6.8) for men, and the absence of smoking was associated with a difference of 5.6 years (95% CI, 3.9 to 7.0) for women and 5.1 years (95% CI, 4.3 to 5.9) for men (Fig. 2B and Table S7B). The lifetime difference between participants who did not have elevated systolic blood pressure, an elevated non-HDL cholesterol level, or underweight, overweight, or obesity and those who had one of these risk factors increased when the regional standard-deviation score was applied, as was seen with cardiovascular disease. The lifetime differences between participants with all risk factors except one of the following — hypertension;

hyperlipidemia; or underweight, overweight, or obesity — and those with all risk factors, when a range of different cutoffs were used, are shown in Table S8. Results did not substantially change in a 1-year landmark analysis that excluded the first year of follow-up (Table S9). Information on the region-specific standard deviations is provided in Table S10.

The lifetime difference between participants without hypertension and those with all other risk factors for both outcomes (cardiovascular disease and death from any cause) and according to geographic region is shown in Figure 3. Globally, the lifetime difference for cardiovascular disease for a standard-deviation score of less than 2 was 2.3 years (95% CI, 1.9 to 3.1) for women and 2.1 years (95% CI, 1.7 to 2.7) for men; the lifetime difference for death was 2.9 years (95% CI, 2.2 to 3.8) for women and 2.9 years (95% CI, 2.4 to 3.4) for men. These values corresponded to regional cutoffs ranging from 155.7 to 175.0 mm Hg for women and from 156.9 to 173.2 mm Hg for men. For both cardiovascular disease and death from any cause, the lifetime difference between participants without hypertension and those with all five risk factors varied according to geographic region. For cardiovascular disease, the greatest difference was observed among Latin American women: 4.9 years (95% CI, 1.5 to 7.6). For death from any cause, the greatest difference was observed among North American women: 5.4 years (95% CI, 0.7 to 7.9).

LIFETIME DIFFERENCE ACCORDING TO RISK-FACTOR MODIFICATION

When all the risk factors were present between 50 and less than 55 years of age and the status of the individual risk factors was modified between 55 and less than 60 years of age, the differences in estimated life-years between those who made modifications and those who did not are shown in Table 2 and Figure S7A and S7B. Modification of hypertension was linked to the most additional life-years free of cardiovascular disease, and modification of smoking was linked to the most additional life-years free of death, followed by modification of hypertension. The number of additional life-years was higher for participants who controlled a greater number of risk factors.

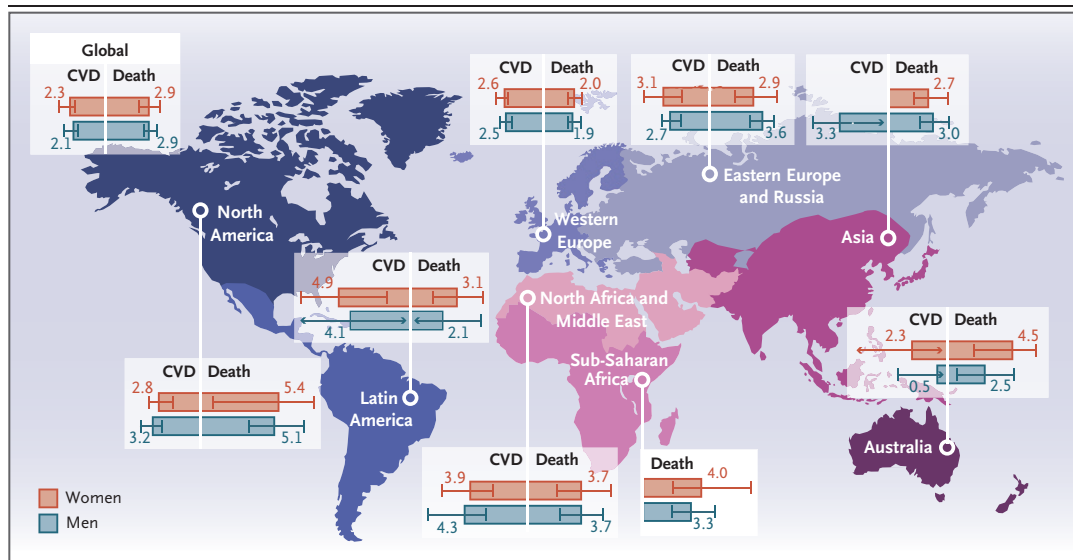


Figure 3. Estimated Lifetime Difference with Respect to Arterial Hypertension, According to Geographic Region. The values shown are the number of additional life-years free of cardiovascular disease (CVD) or death from any cause among participants without hypertension, but with all other risk factors, as compared with those with all five risk factors. Hypertension was selected as the risk factor globally contributing the highest population-attributable fraction to cardiovascular disease development. Results are shown at an index age of 50 years and separately for women (red) and men (blue). Estimates and 95% confidence intervals (error bars) are for a dichotomized regional standard-deviation score (<2 vs. ≥2) for systolic blood pressure and are based on recalibrated predictions from Weibull models including dichotomized regional standard-deviation scores (<2 vs. ≥2) for systolic blood pressure, non-HDL cholesterol level, and BMI as covariates, along with diabetes and smoking. The use of regional standard-deviation scores allows for different regional cutoffs. Clipped confidence intervals are indicated with arrows. For sub-Saharan Africa, insufficient data were available for cardiovascular disease. For Asia, no lifetime difference is shown for cardiovascular disease in women because values could not be estimated owing to high life expectancy.

DISCUSSION

Using harmonized individual-level data from 2,078,948 participants across 133 cohorts, 39 countries, and 6 continents, we analyzed the lifetime risk of cardiovascular disease and death from any cause and estimated the lifetime difference between participants without classic cardiovascular risk factors and those with such factors, as well as the effect of modifying certain risk factors. We report five key findings. First, even among participants who had none of the classic risk factors, as defined here, the lifetime risk of cardiovascular disease remained substantial, estimated at 13% (95% CI, 12 to 16) among women and 21% (95% CI, 18 to 23) among men. Second, the absence of all five risk factors at 50 years of age was associated with a maximum lifetime difference of 13.3 years (95% CI, 11.2 to 15.7) in women and 10.6 years (95% CI, 9.2 to 12.9)

in men as compared with participants who had all the risk factors. Third, the extent of lifetime difference between participants without classic risk factors for cardiovascular disease and those with such risk factors varied depending on which specific risk factor was absent. Fourth, regional heterogeneity was seen in the magnitude of lifetime difference, as illustrated for hypertension, the leading global contributor to cardiovascular disease. Fifth, using risk-trajectory analyses, we found that among all the risk factors assessed, modifying the presence of hypertension was related to the most additional life-years free of cardiovascular disease.

A person's lifetime risk of cardiovascular disease has been associated with the accumulation of risk factors.² Previous studies have estimated lifetime risks exceeding 55%³ while considering more severe, uncontrolled risk-factor levels than those examined in our study. Existing estimates

Table 2. Life Expectancy and Lifetime Difference According to Risk-Factor Modification between 55 and Less than 60 Years of Age.*

Risk Factor or Factors Modified	Cardiovascular Disease				Death from Any Cause			
	Life Expectancy (95% CI)†		Lifetime Difference (95% CI)‡		Life Expectancy (95% CI)§		Lifetime Difference (95% CI)‡	
	Women	Men	Women	Men	Women	Men	Women	Men
	years		additional years free of cardiovascular disease		years		additional years free of death	
Hypertension	72.0 (69.7 to 74.3)	69.7 (69.0 to 70.4)	2.4 (1.3 to 3.6)	1.2 (0.8 to 1.7)	74.9 (72.8 to 76.9)	71.8 (70.6 to 73.1)	1.7 (1.1 to 2.3)	1.7 (0.8 to 2.6)
Hyperlipidemia	69.7 (67.3 to 72.2)	68.5 (67.7 to 69.3)	0.1 (-0.7 to 1.0)	0.0 (-0.7 to 0.7)	73.0 (71.3 to 74.7)	69.9 (68.3 to 71.5)	-0.2 (-1.1 to 0.7)	-0.3 (-0.9 to 0.2)
Underweight, overweight, or obesity	69.9 (67.4 to 72.4)	68.5 (67.5 to 69.4)	0.3 (-0.2 to 0.8)	0.0 (-0.3 to 0.3)	73.2 (71.1 to 75.2)	70.1 (68.6 to 71.7)	0.0 (-0.5 to 0.5)	-0.1 (-0.4 to 0.2)
Diabetes	70.7 (68.1 to 73.4)	69.0 (68.1 to 69.8)	1.1 (0.5 to 1.8)	0.5 (0.2 to 0.8)	74.7 (73.0 to 76.3)	71.4 (70.0 to 72.8)	1.5 (0.8 to 2.2)	1.2 (0.6 to 1.8)
Smoking	71.3 (68.5 to 74.1)	69.5 (68.4 to 70.6)	1.7 (1.1 to 2.3)	1.0 (0.5 to 1.6)	75.2 (73.1 to 77.3)	72.6 (71.2 to 74.0)	2.1 (1.1 to 3.0)	2.4 (1.9 to 2.9)
Hypertension and hyperlipidemia	72.0 (69.7 to 74.3)	69.4 (68.6 to 70.1)	2.4 (0.9 to 3.9)	0.9 (0.0 to 1.8)	74.9 (72.9 to 76.8)	71.5 (70.3 to 72.8)	1.7 (0.9 to 2.6)	1.3 (0.7 to 2.0)
Hypertension, hyperlipidemia, and diabetes	72.9 (71.0 to 74.8)	70.0 (69.2 to 70.7)	3.3 (1.9 to 4.7)	1.5 (0.4 to 2.6)	76.5 (74.8 to 78.2)	72.7 (71.7 to 73.6)	3.3 (2.3 to 4.4)	2.5 (1.6 to 3.4)
Hypertension, hyperlipidemia, diabetes, and smoking	74.7 (72.6 to 76.7)	71.5 (70.8 to 72.3)	5.1 (3.7 to 6.4)	3.1 (2.1 to 4.0)	78.4 (76.8 to 79.9)	74.7 (73.8 to 75.6)	5.2 (4.1 to 6.3)	4.5 (3.5 to 5.6)

* Life expectancy is estimated from survival curves obtained from recalibrated predictions based on joint models for longitudinal data (systolic blood pressure ≥ 130 mm Hg, non-HDL cholesterol levels ≥ 130 mg per deciliter, body-mass index < 20 or ≥ 25 , diabetes, and smoking) and time-to-event data (cardiovascular disease or death from any cause). Life expectancy and lifetime difference with 95% confidence intervals are provided.
 † Shown is the cardiovascular disease-free life expectancy for persons who had all risk factors present between 50 and less than 55 years of age and then modified the risk factor or factors in question between 55 and less than 60 years of age.
 ‡ Lifetime differences are computed against life expectancies of persons with all risk factors present between 50 and less than 60 years of age. Lifetime difference according to risk-factor modification is predicted up to age 90.
 § Shown is the overall life expectancy for persons who had all risk factors present between 50 and less than 55 years of age and then modified the risk factor or factors in question between 55 and less than 60 years of age.

of a person's lifetime risk of cardiovascular disease have been derived largely from data collected from U.S.³ or European¹⁴ populations. By leveraging a global data set, our findings highlight that there is geographic variability in lifetime cardiovascular risk, extending previous observations that showed similar lifetime risk of cardiovascular disease across different ethnic groups with similar risk-factor profiles.² Although only approximately 50% of cardiovascular disease events are attributable to the five classic risk factors,¹ nonclassic risk factors may account for residual cardiovascular disease risk¹⁶ and may be related to myocardial infarction among persons without standard modifiable cardiovascular risk factors.¹⁷

Pooled data from five U.S. population-based cohorts suggested that persons with an optimal risk profile at 45 years of age had a 14-year difference in life expectancy as compared with persons with two or more traditional risk factors.³ In our study, using contemporary definitions for cardiovascular disease risk factors, we found a lifetime difference of more than a decade between persons without risk factors and those with risk factors. Notably, the association of non-HDL cholesterol level and BMI with cardiovascular disease has a J- or U-shaped pattern,^{1,18} which complicates direct estimates of their contribution. The interaction among obesity, diabetes, and hypertension¹⁹ could have influenced results related to BMI. Our analyses also suggest that achievement of favorable risk-factor levels during midlife was associated with a higher probability of living more years free of cardiovascular disease.³ When hypertension was present between 50 and less than 55 years of age and absent between 55 and less than 60 years of age, this modification was associated with most additional life-years free of cardiovascular disease in our analysis. Smoking cessation was associated with the most additional life-years free of death, followed by modification of hypertension.

Existing risk-prediction tools rely primarily on regionally focused studies, which may limit their broad applicability.^{7,14} Some models offer static estimates over prespecified time intervals, such as 10 years, and do not account for changes in risk-factor burden over time. Our study contributes to current knowledge in several important ways. First, we improved the generalizability of findings beyond locally focused studies by

presenting results from a large and diverse global data set of individual-level, prospectively collected, harmonized data. Second, our comparative analysis of participants who modified one or more risk factors during a critical midlife decade, as compared with those who did not, suggests that modifying a risk factor could change the association with lifetime years in the presence or absence of a risk factor. Third, to promote the empowerment of individual persons, we extended traditional lifetime risk assessments by shifting the wording from simply acknowledging risk toward exploring the potential association between risk-factor modification and additional years of healthy life.

This study has several limitations. The GCVRC data includes cohorts with varying representativity, data quality and quantity, dates of baseline assessments, follow-up times, end-point definitions, and use of clinical interventions. Although the regression model quantifies important associations between risk factors and survival, the associations do not have a causal interpretation; in particular, the estimated effects may be partially driven by unmeasured factors that are associated with both the risk factor and outcome. For example, we found that lower blood pressure is associated with additional life-years after controlling the other risk factors in the model: non-HDL cholesterol level, BMI, diabetes, and smoking. The overall effect could have been influenced by unmeasured factors that are associated with both lower blood pressure and overall survival, such as physical activity, nutrition, and access to health care. We cannot rule out the possibility that an entry age into the time-to-event analyses, which may differ from 50 years, could have introduced bias into the estimates of incidence. Limited data density in a few regions may influence the effect sizes of lifetime estimates at the regional level. However, structured harmonization was used to reduce variation, and sensitivity and additional analyses yielded results similar to those for the overall study population.

In this study, we examined how the presence or absence of classic cardiovascular risk factors affects lifetime estimates of cardiovascular disease and death from any cause on a global scale. Modification of arterial hypertension from present to absent during midlife was related to the most additional life-years free of cardiovascular disease.

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