Scan for Author Video Interview

Lifetime Risk and Years Lived Free of Total Cardiovascular Disease

John T. Wilkins, MD, MS
Hongyan Ning, MD, MS
Jarett Berry, MD, MS
Lihui Zhao, PhD
Alan R. Dyer, PhD
Donald M. Lloyd-Jones, MD, ScM

Context Estimates of lifetime risk for total cardiovascular disease (CVD) may provide projections of the future population burden of CVD and may assist in clinician-patient risk communication. To date, no lifetime risk estimates of total CVD have been reported.

Objectives To calculate lifetime risk estimates of total CVD by index age (45, 55, 65, 75 years) and risk factor strata and to estimate years lived free of CVD across risk factor strata.

Design, Setting, and Participants Pooled survival analysis of as many as 905 115 person-years of data from 1964 through 2008 from 5 National Heart, Lung, and Blood Institute–funded community-based cohorts: Framingham Heart Study, Framingham Offspring Study, Atherosclerosis Risk in Communities Study, Chicago Heart Association Detection Project in Industry Study, and Cardiovascular Health Study. All participants were free of CVD at baseline with risk factor data (blood pressure [BP], total cholesterol [TC], diabetes, and smoking status) and total CVD outcome data.

Main Outcome Measures Any total CVD event (including fatal and nonfatal coronary heart disease, all forms of stroke, congestive heart failure, and other CVD deaths).

Results At an index age of 45 years, overall lifetime risk for total CVD was 60.3% (95% CI, 59.3%-61.2%) for men and 55.6% (95% CI, 54.5%-56.7%) for women. Men had higher lifetime risk estimates than women across all index ages. At index ages 55 and 65 years, men and women with at least 1 elevated risk factor (BP, 140-149/90-99 mm Hg; or TC, 200-239 mg/dL; but no diabetes or smoking), 1 major risk factor, or at least 2 major risk factors (BP, ≥160/100 mm Hg or receiving treatment; TC, ≥240 mg/dL or receiving treatment; diabetes mellitus; or current smoking) had lifetime risk estimates to age 95 years that exceeded 50%. Despite an optimal risk factor profile (BP, <120/80 mm Hg; TC, <180 mg/dL; and no smoking or diabetes), men and women at the index age of 55 years had lifetime risks (through 85 years of age) for total CVD of greater than 40% and 30%, respectively. Compared with participants with at least 2 major risk factors, those with an optimal risk factor profile lived up to 14 years longer free of total CVD.

Conclusions Lifetime risk estimates for total CVD were high (>30%) for all individuals, even those with optimal risk factors in middle age. However, maintenance of optimal risk factor levels in middle age was associated with substantially longer morbidity-free survival.

JAMA. 2012;308(17):1795-1801 www.jama.com

TEN-YEAR ABSOLUTE RISK ESTIMATES for coronary heart disease (CHD) have been developed and well validated in multiple cohorts; they are used in current treatment guidelines for lipid-lowering therapy in primary prevention.[1,2] In an effort to better characterize the current and future public health burden of CHD, and improve communication of risk between patients and clinicians, lifetime risk estimates for atherosclerotic cardiovascular disease (CVD) (angina pectoris, coronary insufficiency, myocardial infarction, atherosclerotic stroke, or death from CVD) and congestive heart failure (CHF) have been reported separately.[3-5] Recently, we demonstrated that lifetime risk estimates for stroke and CHD were very low for individuals with optimal risk factor burden in middle and older age, and risks increased in a stepwise fashion with greater risk factor burden.[6] To date, there have been no published data on the lifetime risk for total CVD (including CHD, atherosclerotic and hemorrhagic stroke, CHF, and other CVD death). It is unclear how the addition of CHF and other nonatherosclerotic forms of CVD will affect remaining lifetime risk estimates overall and in the context of aggregate burden of atherosclerosis risk factors.

Risk factor burden at age 50 years has been shown to have substantial and significant effects on remaining lifetime risk of atherosclerotic CVD in the Framingham cohort. For example, lifetime risk estimates for atherosclerotic CVD were less than 8% for individuals with optimal risk factor levels at age 50 years; and more than 50% for individuals with 2 or more substantially elevated risk factors.[4] However, there are no estimates of years lived free of CVD, a measure of healthy longevity, by risk factor burden in middle and older age.

CME available online at www.jamaarchivescme.com and questions on p 1815.

Author Audio Interview available at www.jama.com.

Author Affiliations: Departments of Preventive Medicine (Drs Wilkins, Ning, Zhao, Dyer, and Lloyd-Jones), and Medicine, Division of Cardiology (Drs Wilkins and Lloyd-Jones), Northwestern University Feinberg School of Medicine, Chicago, Illinois; and Division of Cardiovascular Disease, University of Texas Southwestern School of Medicine, Dallas (Dr Berry). **Corresponding Author:** John T. Wilkins, MD, MS, Department of Preventive Medicine, Northwestern University, 680 N. Lakeshore Dr, Suite 1400, Chicago, IL 60611 (j-wilkins@fsm.northwestern.edu).

Table 1. Definitions of Risk Factor Strata[a]

	Systolic and Diastolic Blood Pressure, mm Hg	Total Cholesterol, mg/dL	Diabetes	Tobacco Smoking
All optimal	<120 and <80 and	<180 and	No and	No
≥1 Not optimal	120-139 or 80-89 or	180-199 and	No and	No
≥1 Elevated	140-159 or 90-99 or	200-239 and	No and	No
1 Major	≥160 or ≥100 or treated or	≥240 or treated or	Yes or	Yes
≥2 Major	≥160 or ≥100 or treated and/or	≥240 or treated and/or	Yes and/or	Yes

SI conversion: To convert total cholesterol to mmol/L, multiply by 0.0259.
[a]Risk factors are additive. Table must be interpreted left to right.

This study conducted a pooled analysis using individual-level data from cohorts included in the Cardiovascular Lifetime Risk Pooling Project. The aim was to estimate lifetime risk for total CVD in separate models for men and women overall and by aggregate risk factor burden at index ages of 45, 55, 65, and 75 years. This study also sought to examine the potential compression of morbidity and longer disease-free survival that might be associated with lower aggregate risk factor burden at these same ages.

METHODS

Participants

Details of the selection of cohorts and the pooling of data in The Cardiovascular Lifetime Risk Pooling Project are presented elsewhere.[6] For the present analysis cause-specific or cardiovascular mortality data was required as well as ascertainment of nonfatal cardiovascular events. Thus, of the 18 community-based cohorts included in the Cardiovascular Lifetime Risk Pooling Project, this study included the following 5 cohorts: the Framingham Heart Study,[7] Framingham Offspring Study, Cardiovascular Health Study,[8] Atherosclerosis Risk in Communities[9] study, and the Chicago Heart Association Detection Project in Industry[10] study. Participants were excluded from the analysis if they had preexisting CVD. All other cohort participants contributed person-years of follow-up to the analysis. This project was approved by the institutional review board at Northwestern University.

Case Ascertainment

The criteria for ascertainment and adjudication of CVD events for each of the cohorts have been described elsewhere.[7-11] Briefly, the Framingham Heart Study adjudicated CVD events using medical history, physical examinations, and electrocardiograms. Interim medical records, including hospital and attending physicians' records and chest radiograph reports, were reviewed. All suspected CVD events were reviewed by a panel of 3 physicians who applied established criteria for such events.[12] Criteria for the development of CHF in the Framingham cohort have been described elsewhere.[13]

The Cardiovascular Health Study and the Atherosclerosis Risk in Communities study used similar criteria; myocardial infarction (defined as a new Q-wave showing on electrocardiogram or cardiac pain with elevation in cardiac enzymes) and new electrocardiogram changes (defined as evolving ST-segment or T-wave ischemic pattern or a new left bundle branch block). CHF was defined by a physician diagnosis plus confirmatory information from diagnostic procedures, ie, cardiomegaly or pulmonary edema on chest radiograph, a dilated ventricle with wall motional abnormalities on echocardiographic examination, or a physician diagnosis plus medical therapy for CHF. Stroke was adjudicated by Systolic Hypertension in the Elderly Program (SHEP) criteria[11]: abrupt onset of new neurologic deficit lasting more than 24 hours, with a specific localizing finding with unequivocal confirmatory physical examination findings without evidence of underlying nonvascular cause. Provisional diagnoses for CVD or cerebrovascular accident were reviewed and adjudicated at periodic meetings of a study-wide morbidity review committee.

The Chicago Heart Association Detection Project in Industry cohort used data from *International Classification of Diseases, Ninth Revision (ICD-9)* codes: and morbidity data available from Medicare fee-for-service claims data (age >65 years) from 1984-2002 including primary discharge diagnoses with *ICD-9* codes of 430 through 438, 410, or 428. Cause of death was assigned using *ICD-9* codes for underlying coronary artery disease from the National Death Index.[10]

Statistical Analysis

To determine whether there were differences in lifetime risk by cohort due to differences in sampling, geography, calendar year of inception, size, follow-up, and definition of outcome, we first performed cohort-specific analyses. Sex- and risk factor–stratified lifetime risk estimates for each cohort were compared; the overall levels of absolute lifetime risk were similar so individual-level data from the cohorts were pooled. After obtaining all of the data, risk factor and end point variables were examined from each cohort data set. Similar variables were identified and renamed using a standardized protocol to allow for ease of use in the analysis.[14] We grouped participants by sex and risk factor profile as measured within 4 years of each index age. Lifetime risk estimates were calculated from the pooled data cohort.

We used a modified Kaplan-Meier analysis, which accounts for competing risks from non-CVD death, to avoid lifetime risk overestimation as described previously.[3] In brief, the modified Kaplan-Meier analysis counts non-CVD death as a separate event, not a withdrawal (as a traditional Kaplan-Meier analysis would) at the time of the event.[15] Rates of total CVD incidence, adjusted for the competing risk for death free of total CVD, were calculated for each index age (45, 55, 65, and 75 years) and summed for participants as old as 95 years, or to the oldest age with robust person-time. All analyses were stratified by sex.

Table 2. Study Sample Characteristics

	Index Age of Participants, y							
	45		55		65		75	
	Men	Women	Men	Women	Men	Women	Men	Women
No. of participants	24 031	25 459	18 211	20 969	10 408	12 586	4109	5909
Person-years of follow-up	440 612	464 503	287 061	349 496	121 084	158 839	36 213	61 775
Total deaths, No. (%)	11 099 (46.2)	8943 (35.1)	8700 (47.8)	7606 (36.3)	4869 (46.8)	4747 (37.7)	2096 (51.0)	2685 (45.4)
CVD events, No. (%)	8472 (35.2)	6703 (26.3)	6553 (36.0)	5730 (27.3)	3675 (35.3)	3566 (28.3)	1513 (36.8)	1965 (33.2)
Survival time, median (IQR), y	35.2 (24.0-43.6)	41.2 (29.4-50.7)	24.0 (15.9-31.5)	29.3 (21.4-37.3)	17.6 (11.3-24.0)	21.9 (15.0-28.4)	11.8 (6.8-16.8)	14.8 (9.3-20.3)

Abbreviations: CVD, cardiovascular disease; IQR, interquartile range.

Table 3. Distribution of Risk Factor Burden Strata[a]

	Index Age of Participants, y							
	45		55		65		75	
Prevalence of Selected Aggregate Risk Factor Burden, %	Men	Women	Men	Women	Men	Women	Men	Women
All optimal	4.2	7.9	4.2	4.2	3.8	2.1	3.6	1.7
≥1 Not optimal	10.9	14.6	9.2	8.7	9.8	7.3	11.9	6.5
≥1 Elevated	23.0	22.1	20.7	21.6	20.0	19.3	19.9	18.7
1 Major	39.9	38.8	39.3	39.1	39.4	39.5	42.1	42.5
≥2 Major	22.0	16.6	26.6	26.5	27.0	31.8	22.5	30.6

[a] See Table 1 for risk factor category definitions.

A separate analysis with participants stratified by risk factor burden at index ages was performed using a previously published algorithm that has been validated in multiple cohorts.[6,16] National guidelines were used to define optimal and elevated risk factor levels.[17,18] Variables included in risk factor analysis were blood pressure, use of antihypertensive medications, total cholesterol, current smoking, and the presence of diabetes mellitus. Participants were stratified a priori into 5 mutually exclusive categories on the basis of their risk factor burden at each index age (TABLE 1).[4,14] Since some of the risk factors used in our stratification scheme may not stratify risk for CHF well (total cholesterol), secondary analyses were conducted using blood pressure strata alone. We chose blood pressure because hypertension has a high population prevalence and is associated with all total CVD end points included in this study.

To examine the potential compression of morbidity associated with lower aggregate risk factor burden, this study examined potential differences among different strata of aggregate risk factor burden in both mean CVD-free survival time and mean overall survival time. Because censoring precludes estimation of these mean survival times, Irwin's restricted mean was used, which is the mean of the survival time restricted to a given time point.[19] The restricted mean is mathematically equivalent to the area under the survival curve up to the selected restriction time point. For each index age (45, 55, 65, and 75 years), the restriction time point was set as 95 years old or the oldest age such that the standard error of the survival estimate at the restriction time point is 10% or less.[20] The results for risk factor strata were then compared to determine whether one is associated with prolonged mean overall survival time, whether the gain in mean overall survival is due to prolonged CVD-free survival time or overall survival time after CVD, or both. We used a *P* value of less than .05 for 2-sided significance test. All statistical calculations were performed using SAS version 9.1.

Table 4. Lifetime Risk Estimates for Total CVD by Sex and Selected Index Age[a]

	% (95% CI)	
Index Age, y	Men	Women
45	60.3 (59.3-61.2)	55.6 (54.5-56.7)
55	60.2 (59.1-61.2)	56.3 (55.2-57.4)
65	59.0 (57.6-60.4)	56.1 (54.7-57.5)
75	54.5 (52.2-56.9)	52.3 (50.3-54.3)

Abbreviation: CVD, cardiovascular disease.
[a] Lifetime risk estimates represent the percentage of cohort participants who would experience a total CVD event from the index age to the end of follow-up if the last participant in the cohort were to die at the last age of follow-up (95 years).

RESULTS

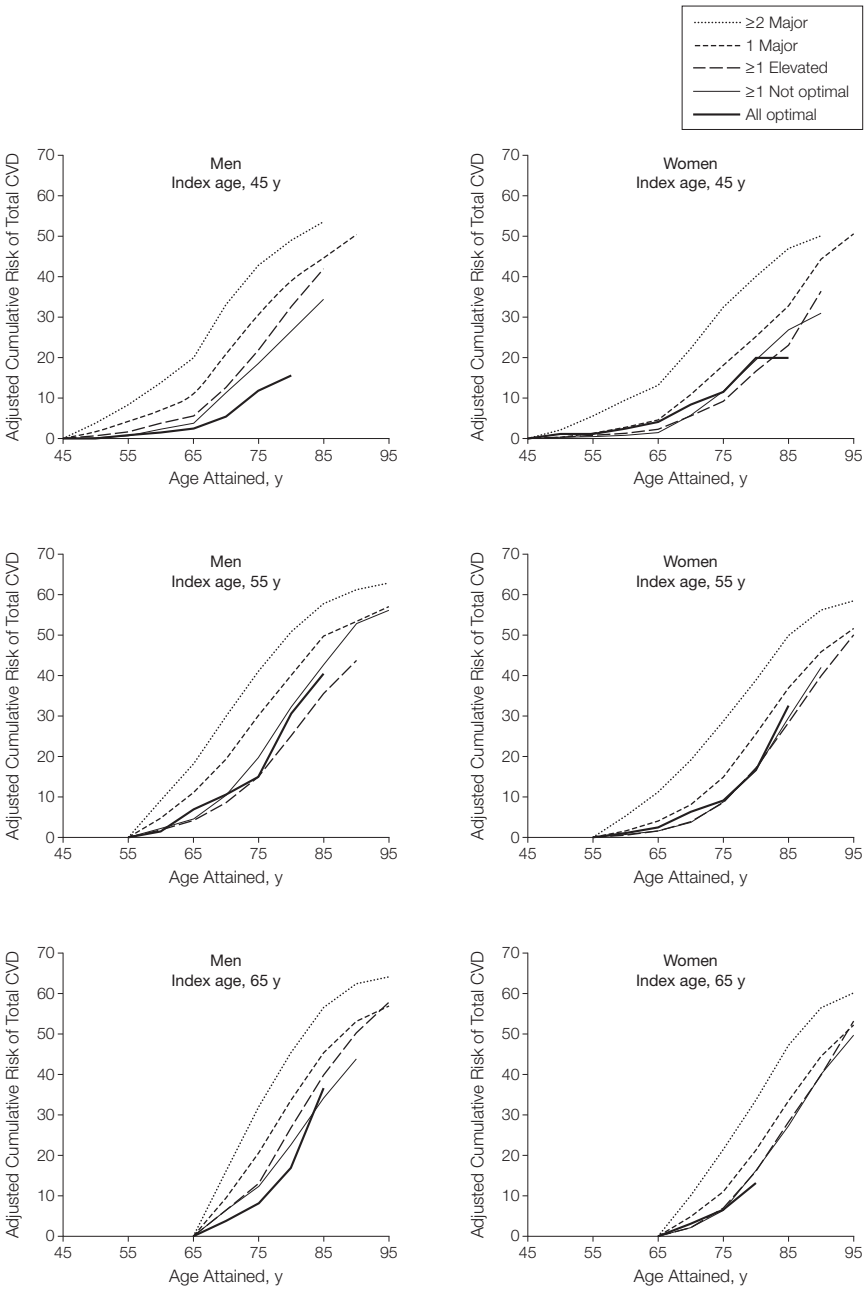
Study Sample

Person-years of follow-up, total deaths, and CVD events during follow-up at each index age are displayed in TABLE 2. For example, for index age 45 years, we observed 49 490 men and women for 905 115 person-years. During follow up, there were 20 042 deaths and 30.7% of participants (15 175) experienced a CVD event. There were fewer person-years of follow-up for older index ages. Approximately 30% to 35% of indi-

viduals experienced CVD events at some time during follow-up across all index age groups.

The participant distribution of risk factor strata is shown in TABLE 3. Across all index ages, 1.7% to 7.9% of individuals were in the all optimal risk factor stratum. In contrast, more than 55% of individuals were in the 1 major or at least 2 major risk factor strata at all index ages. The baseline characteristics by cohort for index age 65 years are presented in eTable 1 (available at http://www.jama.com).

Figure 1. Lifetime Risk Estimates for Total CVD Stratified by Sex, Index Age, and Aggregate Risk Factor Burden



For risk factor category definitions, see Table 1. CVD indicates cardiovascular disease.

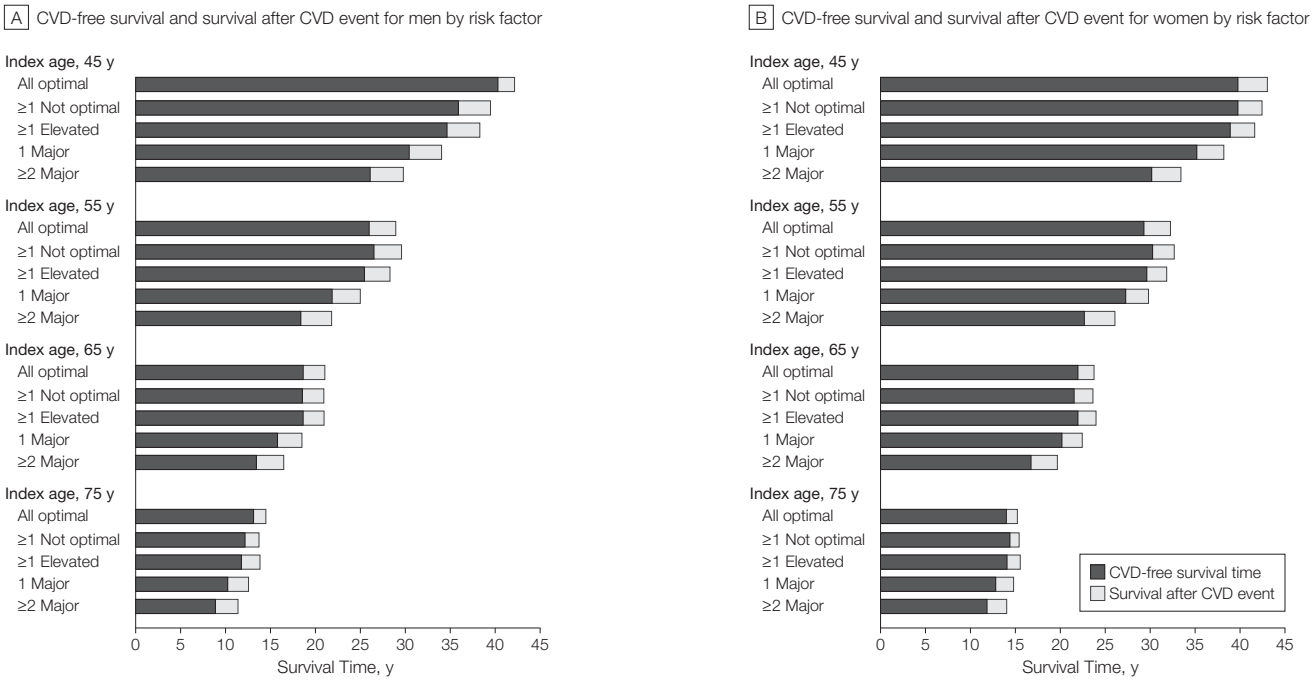
Lifetime Risk Estimates for Total CVD Stratified by Index Age

Remaining lifetime risk estimates for total CVD for the selected index ages are displayed in TABLE 4. At an index age of 45 years, overall lifetime risk estimates for total CVD through age 95 years were 60.3% (95% CI, 59.3%-61.2%) for men, and 55.6% (95% CI, 54.5%-56.7%) for women. Women had significantly lower lifetime risk estimates than men at all index ages. Even at an index age of 75 years, when median (interquartile range [IQR]) survival in our cohort was 11.8 (6.8-16.8) years for men and 14.8 (9.3-20.3) years for women, the remaining lifetime risk for total CVD remained high at 52% for women and 54.5% for men.

Lifetime Risk Estimates Stratified by Index Age, Sex, and Aggregate Risk Factor Strata

For index ages 45, 55, and 65 years, the cumulative risk for total CVD (adjusted for the competing risk of non-CVD death) in those with at least 2 major risk factors was higher after 5 years of follow-up, but appeared to reach the maximum difference compared with lower risk strata after about 20 years of follow-up (FIGURE 1). At index ages 45, 55, and 65 years, the lifetime risk for total CVD through age 95 years exceeded 50% in participants with 1 major or at least 2 major risk factors for men and women. Lifetime risks for total CVD were more than 40% for men and more than 30% for women with 1 or more not optimal risk factor levels at index ages 55 and 65 years. At an index age of 55 years, men with optimal risk factor profiles had remaining lifetime risks for total CVD that exceeded 40% and women had risks that approached 30% to aged 85 years. The use of blood pressure categories alone for lifetime risk stratification resulted in less separation of lifetime risk estimates than the multiple risk factor scheme used previously. At index ages 45 and 55 years, when we used data from the same participants but ignored heart failure as an end point, lifetime risk rates were

Figure 2. CVD-Free Survival and Survival After CVD Events for Men and Women by Index Age and Aggregate Risk Factor Burden



CVD indicates cardiovascular disease.

approximately 5% to 10% lower across all risk factor strata.

Years Lived Free of Total CVD by Aggregate Risk Factor Strata

Across all index ages, longer survival time free of total CVD was experienced by individuals with optimal risk factor levels when compared with participants with at least 2 major risk factors (FIGURE 2A and 2B). For example, at an index age of 45 years, individuals with optimal risk factor profiles lived up to 14 years longer free of total CVD than individuals with at least 2 risk factors. The differences in years lived free of total CVD between risk factor strata were less pronounced at older index ages. Survival after a total CVD event was more similar across risk factor strata, ranging from 1.1 to 3.8 years across all index ages and both sexes.

COMMENT

After age 45 years, overall remaining lifetime risk estimates for total CVD to age 95 years exceed 60% for men and 55% for women. Risks for total CVD were greater in men than women across all ages. Lifetime risks for total CVD were high regardless of index age, indicating that achieving older age free of total CVD does not guarantee escape from remaining lifetime risk for total CVD. However, lower aggregate risk factor burden at any index age is associated with a lower lifetime risk for total CVD through age 95 years. Even those with optimal risk factor profiles had lifetime risk for total CVD that exceeded 30%, but maintenance of low risk factor burden at middle age is associated with a substantial delay in age at onset of total CVD by as much as 14 years for younger adults.

In previous research, lifetime risk estimates for CHD alone (to age 95 years) were 48% for men and 32% for women.[3] Estimates for atherosclerotic CVD at an index age of 50 years were approximately 50% for men and 39% for women.[4] Lloyd-Jones et al[5] reported an estimated lifetime risk for CHF of 21% for men and 20.3% for women at an index age of 40 years in the Framingham cohort. Lifetime risk estimates for total CVD reported in this study are greater than any of these individual estimates, which is not surprising given that total CVD is a composite end point that includes CHD and CHF, as well as other CVD end points. Furthermore, the sex-specific differences in total CVD were consistent with previous observations as well.

Lifetime risk for total CVD in participants with optimal risk factor profiles exceeded 30% to 40%. This is in contrast to previous work by Lloyd-Jones et al,[5] that reported a 5% to 8% lifetime risk of atherosclerotic CVD at index age 50 years to age 95 years in Framingham participants with optimal risk factor profiles.[4] The difference in these 2 estimates may be attributed in part to the addition of CHF and hemorrhagic stroke to the end point of the current study, as well as the more diverse composition of the current study sample, which includes participants at higher atherosclerotic CVD risk such as African Americans. The results of this study

suggest that despite optimal risk factor levels in middle age, lifetime risk may still be elevated and may be driven largely by aging and the accumulation of downstream risk factors. For example, Vasan et al[15] estimated that lifetime risk for developing hypertension is greater than 90% for men and women free of hypertension in middle age; thus, almost everyone will become hypertensive, giving them a major risk factor for incident CVD.

Of note, even though approximately 40% of individuals with all optimal risk factor levels in middle age eventually developed a total CVD event by age 95 years, their age at onset of total CVD was an average of 8 to14 years later than individuals with at least 2 major risk factors. Thus, the maintenance of optimal risk factors through ages 45, 55, and 65 years may not guarantee a life free from total CVD, but it increases the probability that more years will be lived free of CVD. In addition, for some index ages in men and women in our analyses, we observed that individuals with optimal risk factors who developed total CVD at much older ages, appeared to have a shorter post-CVD event survival, consistent with the phenomenon of compression of morbidity posited by Fries.[21]

Our study benefited from a large sample size from multiple well-phenotyped, community-based cohorts with broad representation across age, race, sex, geography, and birth cohorts.

There may be several limitations to our study. First, differences in outcome ascertainment between cohorts could lead to some degree of misclassification, which could affect the accuracy of the lifetime risk estimate. However, data from individual cohorts prior to pooling yielded similar absolute lifetime risk results, suggesting there was not significant outcome misclassification. In addition, although there was diversity in the composition cohorts, prior work from the Cardiovascular Lifetime Risk Pooling Project suggests that birth cohort and racial differences are very modest in comparison with the consistent effects of risk factors on CVD event rates.[6]

Second, we evaluated lifetime risk of a composite end point of atherosclerotic CVD, CHF, and hemorrhagic CVA, yet in our risk factor–stratified analysis, we included risk factors that may not stratify all of the components of our composite end point similarly (eg, total cholesterol and incident CHF or stroke). Similarly, several well-validated risk markers for CHD events were not included in our stratification, notably high-density lipoprotein cholesterol, a family history of premature CHD events, and waist circumference since these data were not available across all cohorts included in the analysis. However, the strongest determinants of incident CHF risk were included, notably age and hypertension. Furthermore, stratifying exclusively by blood pressure strata (and not aggregate risk factor burden) did not result in substantial differences in the lifetime risk estimates for our composite end point. Also of note, the stratification method we used has been validated in multiple cohorts as a method for examining lifetime risk in the context of aggregate risk factor burden.[4,6,22]

As with all previous studies involving lifetime risk estimates for CVD-related outcomes we used a modified Kaplan-Meier model adjusted to account for competing risks of non-CVD death. An unmodified Kaplan-Meier model would result in overestimation of lifetime risk for total CVD. For example, for a man with an index age of 45 years, an unmodified Kaplan-Meier model yields a lifetime risk estimate of 83.5%, whereas a modified model, adjusted for competing risks of non-CVD death, yields an estimate of 60.3%.

In this study of participants from community-based cohorts, lifetime risk estimates (to age 95 years) for total CVD exceeded 60% for men and 55% for women overall. Risks for total CVD appear substantially greater in individuals with greater risk factor burden; however lifetime risk still exceeded 30% in men and women with an optimal risk factor profile, highlighting the large public health burden and opportunities for prevention of total CVD. These results also highlight the association of low levels of traditional risk factors in midlife with substantially increased CVD-free survival and may suggest compression of morbidity in older ages.

Author Contributions: Dr Wilkins had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Wilkins, Dyer, Lloyd-Jones.
Acquisition of data: Lloyd-Jones.
Analysis and interpretation of data: Wilkins, Ning, Berry, Zhao, Lloyd-Jones.
Drafting of the manuscript: Wilkins, Lloyd-Jones.
Critical revision of the manuscript for important intellectual content: Wilkins, Ning, Berry, Zhao, Dyer, Lloyd-Jones.
Statistical analysis: Wilkins Ning, Zhao, Lloyd-Jones.
Obtained funding: Dyer, Lloyd-Jones.
Study supervision: Wilkins, Lloyd-Jones.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.
Funding/Support: Dr Lloyd-Jones and this work were supported in part by grant R21 HL085375 from the National Heart, Lung, and Blood Institute (NHLBI). Dr Berry reports receipt of funding from: the Dedman Family Scholar in Clinical Care endowment at UT Southwestern Medical Center; the NHLBI (grant K23 HL092229); and the American Heart Association (grant 10BG1A4280091). The data reported from Cardiovascular Health Study in this article were supported by contracts from the NHLBI (grants HHSN268201200036C, N01-HC-85239, N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01-HC-15103, N01 HC-55222, N01-HC-75150, N01-HC-45133, and HL080295), with an additional contribution from the National Institute of Neurological Disorders and Stroke. Additional support was provided from the National Institute on Aging (grants AG-023629, AG-15928, AG-20098, and AG-027058).
Role of Sponsor: The funding agency had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.
Cardiovascular Health Study Investigators: A full list of principal Cardiovascular Health Study Investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm.
Disclaimer: This study was conducted with the use of limited-access datasets obtained by the NHLBI and does not necessarily reflect the opinions or views of the study investigators or the NHLBI. The Atherosclerosis Risk in Communities Study, Framingham Heart Study, and the Framingham Offspring Study are conducted and supported by the NHLBI in collaboration with the study investigators.
Online-Only Material: Author Audio Interview and the eTable are available at http://www.jama.com
Additional Contributions: We thank the investigators of all the cohort studies included in this analysis for their hard work and dedication in collecting the underlying data, and especially the study participants, whose dedication and commitment have formed the basis of profound observations regarding health and disease that have contributed to improved health, longevity, and quality of life for millions of persons.

REFERENCES

1. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P; CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. 2001;286(2):180-187.

2. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA*. 2001;285(19):2486-2497.

3. Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. *Lancet*. 1999;353(9147):89-92.

4. Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation*. 2006; 113(6):791-798.

5. Lloyd-Jones DM, Larson MG, Leip EP, et al; Framingham Heart Study. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation*. 2002;106(24):3068-3072.

6. Berry JD, Dyer A, Cai X, et al. Lifetime risks of cardiovascular disease. *N Engl J Med*. 2012;366(4): 321-329.

7. Dawber TR, Kannel WB, Lyell LP. An approach to longitudinal studies in a community: the Framingham Study. *Ann N Y Acad Sci*. 1963;107:539-556.

8. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol*. 1991;1(3):263-276.

9. The Atherosclerosis Risk in Communities (ARIC) study, design and objectives: the ARIC investigators. *Am J Epidemiol*. 1989;129(4):687-702.

10. Stamler J, Dyer AR, Shekelle RB, Neaton JD, Stamler R. Relationship of baseline major risk factors to coronary and all-cause mortality, and to longevity: findings from long-term follow-up of Chicago cohorts. *Cardiology*. 1993;82(2-3):191-222.

11. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA*. 1991;265(24):3255-3264.

12. Dawber TR, Meadors GF, Moore FE Jr. Epidemiologic approaches to heart disease: the Framingham study. *Am J Public Health*. 1951;41(3):279-286.

13. Kannel WB, D'Agostino RB, Silbershatz H, Belanger AJ, Wilson PWF, Levy D. Profile for estimating risk of heart failure. *Arch Intern Med*. 1999;159(11):1197-1204.

14. Berry JD, Garside DB, Cai X, Dyer AR, Lloyd-Jones DM. Remaining lifetime risks for cardiovascular disease death by risk factor burden at selected ages in black and white men and women [AHA abstract 3666; scientific sessions 2007]. *Circulation*. 2007;116 (I6 suppl):832.

15. Vasan RS, Beiser A, Seshadri S, et al. Residual lifetime risk for developing hypertension in middle-aged women and men: the Framingham Heart Study. *JAMA*. 2002;287(8):1003-1010.

16. Berry JD, Liu K, Folsom AR, et al. Prevalence and progression of subclinical atherosclerosis in younger adults with low short-term but high lifetime estimated risk for cardiovascular disease: the coronary artery risk development in young adults study and multiethnic study of atherosclerosis. *Circulation*. 2009; 119(3):382-389.

17. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. Circulation. 2002;106(25):3143-3421. http://http://circ.ahajournals.org/content/106/25/3143.full.pdf+html.

18. National Heart, Lung, and Blood Institute. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.* Bethesda, MD: National Institutes of Health; 1989.

19. Irwin J. The standard error of an estimate of expectation of life, with special reference to expectation of tumourless life in experiments with mice. *J Hyg (Lond)*. 1949;47(2):188-189.

20. Karrison TG. Use of Irwin's restricted mean as an index for comparing survival in different treatment groups—interpretation and power considerations. *Control Clin Trials*. 1997;18(2):151-167.

21. Fries JF. Aging, natural death, and the compression of morbidity. *N Engl J Med*. 1980;303 (3):130-135.

22. Lloyd-Jones DM, Dyer AR, Wang R, Daviglus ML, Greenland P. Risk factor burden in middle age and lifetime risks for cardiovascular and noncardiovascular death (Chicago Heart Association Detection Project in Industry). *Am J Cardiol*. 2007; 99(4):535-540.