Lifetime Risk and Years Lived Free of Total Cardiovascular Disease

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Abstract

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

Objective—To calculate LTR estimates of tCVD by index age [45, 55, 65, 75 years(y)] and risk factor strata and to estimate years lived free of CVD across risk factor strata.

Design, Setting, and Participants—Pooled survival analysis of up to 905,115 person-years of data from 1964 through 2008 from 5 NHLBI-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.

Participants—All participants free of CVD at baseline with risk factor data (blood pressure (BP), total cholesterol (TC), diabetes and smoking status) and tCVD outcome data

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Outcome Measures—Any tCVD event (including fatal and non-fatal coronary heart disease, all forms of stroke, congestive heart failure and other CVD deaths)

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

Conclusions—LTR estimates for tCVD are high (>30%) for all individuals, even those with optimal risk factors in middle age. However, maintenance of optimal risk factor levels in middle age is associated with substantially longer morbidity-free survival.

Keywords

Lifetime Risk; Cardiovascular Disease; Compression of Morbidity

Introduction

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 (LTR) 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 LTR 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 LTR for *total CVD* (including CHD, atherosclerotic and hemorrhagic stroke, CHF and other CVD death). It is unclear how the addition of CHF and other non-atherosclerotic forms of CVD will affect remaining LTR estimates overall, and in the context of aggregate burden of atherosclerosis risk factors.

Risk factor burden at age 50 has been shown to have substantial and significant effects on remaining LTR of atherosclerotic CVD in the Framingham cohort. For example, LTR estimates for atherosclerotic CVD were < 8% for those with optimal risk factor levels at age 50; and >50% for those with two 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.

We conducted a pooled analysis using individual-level data from cohorts included in the Cardiovascular Lifetime Risk Pooling Project. We aimed to estimate LTR for Total CVD (tCVD) in separate models for men and women overall and by aggregate risk factor burden at index ages of 45, 55, 65 and 75 years. We 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 we required cause-specific or cardiovascular mortality data also with ascertainment of non-fatal cardiovascular events. Thus, of the 18 community-based cohorts included in The Cardiovascular Lifetime Risk Pooling Project we included the following 5 cohorts: Framingham Heart Study[7] (FHS), Framingham Offspring Study (FOS), Cardiovascular Health Study (CHS) [8], Atherosclerosis Risk in Communities (ARIC) [9] study, and Chicago Heart Association Detection Project in Industry (CHA)[10] Study. Participants were excluded from the analysis if they had pre-existing CVD. All other cohort participants contributed person-years of follow up to the analysis. This project was approved by the IRB 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, FHS 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] CHS and ARIC utilized similar criteria; myocardial infarction was defined as a new Q-wave on ECG or "cardiac pain" with elevation in cardiac enzymes and new ECG changes defined as: evolving ST or T wave ischemic pattern or a new left bundle branch block. CHF was a physician diagnosis plus confirmatory information from diagnostic procedures, i.e. 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 SHEP criteria[11]: abrupt onset of new neurologic deficit lasting > 24h, with a specific localizing finding with unequivocal confirmatory physical examination findings without evidence of underlying nonvascular cause. Provisional diagnoses for CVD or CVA were reviewed and adjudicated at periodic meetings of a study-wide morbidity review committee. The CHA cohort utilized data from ICD 9 Codes: Morbidity data available from Medicare fee-for-service claims data (age >65yrs) from 1984-2002 include primary discharge diagnosis: with ICD-9 Codes of 430- 438, 410, or 428. Cause of death was assigned using ICD-9 codes for underlying CAD from the National Death Index. [10]

Statistical Analysis

In order to determine whether there were differences in LTR 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 LTR estimates for each cohort were compared; the overall levels of absolute LTR 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 dataset, 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 four years of each index age. LTR 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 LTR 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 tCVD

incidence, adjusted for the competing risk for death free of tCVD were calculated for each index age (45, 55, 65 and 75 years old) and summed for participants up to 95 years old, or to the oldest age with robust person-time. All analyses were stratified by sex.

A separate analysis with participants stratified by risk factor burden at index ages was performed using a previously published algorithm which 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 anti-hypertensive medications, total cholesterol, current smoking, and the presence of diabetes mellitus. Participants were stratified *a priori* into five mutually exclusive categories on the basis of their risk factor burden at each index age (See Table 1).[4,14] Since some of the risk factors used in our stratification scheme may not stratify risk for CHF well (total cholesterol) we conducted secondary analyses using blood pressure strata alone. We chose blood pressure because hypertension (HTN) has a high population prevalence and is associated with all tCVD endpoints included in this study.

In order to examine the potential compression of morbidity associated with lower aggregate risk factor burden, we examined potential differences among different strata of aggregate risk factor burden in both mean CVD-free survival time and mean overall survival time. As censoring precludes estimation of these mean survival times, we used Irwin's restricted mean, 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), we set the restriction time point as 95 years old, or the oldest age such that the standard error of the survival estimate at the restriction time point is 10%.[20] We then compared results for risk factor strata to determine whether one is associated with prolonged mean overall survival time, and 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 <0.05 for two-sided significance test. All statistical calculations were carried out in SAS v9.1 (Cary, NC). The study was approved by the IRB at Northwestern University.

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 followed 49,490 men and women for 905,115 person years; during follow up there were 20,042 deaths and 30.6% of participants experienced a CVD event. There were fewer person years of follow-up for older index ages. Approximately 30% to 35% of individuals 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, in excess of 55% of individuals were in the 1 major or 2 major risk factor strata at all index ages. The baseline characteristics by cohort for index age 65 years are presented in appendix table 1.

Lifetime Risk Estimates for Total CVD stratified by Index Age

Remaining lifetime risk estimates for tCVD for the selected index ages are displayed in Table 4. At an index age of 45 years, overall LTR estimates for tCVD through age 95 were 60.3% (95% CI, 59.3 to 61.2) for men, and 55.6% (95% CI, 54.5 to 56.7) for women. Women had significantly lower LTR estimates than men at all index ages. Even at an index age of 75 years, when median survival in our cohort was 11.8 years for men and 14.8 years

for women, the remaining LTR for tCVD 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 tCVD (adjusted for the competing risk of non-CVD death) in those with 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 LTR for tCVD through age 95 years exceeded 50% in participants with 1 or more elevated, 1 major, and 2 major risk factors for men and women. Lifetime risks for tCVD were >40% for men and >30% for women with 1 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 tCVD that exceed 40%, and women had risks that approached 30% to age 85 years of age. The use of blood pressure categories alone for LTR stratification resulted in less separation of LTR estimate ubyhb s than the multiple risk factor scheme used above. At index ages 45 and 55 years when we used data from the same participants but ignored heart failure as an endpoint LTR were approximately 5-10% lower across all risk factor strata. (Data not shown)

Years Lived Free of tCVD by Aggregate Risk Factor Strata

Across all index ages, when compared to participants with 2 major risk factors, those with optimal risk factor levels had longer CVD-free and overall survival (Figures 2A and 2B). For example, at an index age of 45y, individuals with optimal risk factor profiles lived up to 14 years longer free of tCVD and up to 12 years longer overall than individuals with 2 risk factors. The differences in years lived free of tCVD between risk factor strata were less pronounced at older index ages. Survival after a tCVD event was more similar across RF strata, ranging from 1.1 to 3.8 years across all index ages and sexes.

Discussion

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

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

LTR for tCVD in participants with optimal risk factor profiles exceeded 30-40%. This is in contrast to previous work by Lloyd-Jones et al., that reported 5-8% lifetime risk of *atherosclerotic* CVD at index age 50 to age 95 in Framingham participants with optimal risk

factor profiles.[4] The difference in these two estimates may be attributed in part to the addition of CHF and hemorrhagic stroke to the endpoint 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. Our results suggest that, despite optimal risk factor levels in middle age, LTR may still be elevated and may be driven largely by aging and the accumulation of downstream risk factors. For example, Vasan et al. estimated that LTR for developing hypertension is >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.[15]

Of note, even though approximately 40% of individuals with all optimal risk factor levels in middle age eventually developed a tCVD event by age 95 years, their age at onset of tCVD was an average of 8 to14 years later than individuals with   2 major risk factors. Thus, the maintenance of optimal risk factors through age 45, 55, and 65 may not guarantee a life free from tCVD, 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 tCVD 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 LTR estimate. However, data from individual cohorts prior to pooling yielded similar absolute LTR 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 to the consistent effects of risk factors on CVD event rates.[6] Second, we evaluated LTR of a composite endpoint 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 endpoint similarly (e.g. total cholesterol and incident CHF or stroke). Similarly, several well-validated risk markers for CHD events were not included in our stratification, notably HDL 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 our LTR estimates for our composite endpoint. Also of note, the stratification method we used has been validated in multiple cohorts as a method for examining LTR in the context of aggregate risk factor burden.[4,6,22]

As with all previous studies involving LTR 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 LTR for tCVD. For example, for a man at an index age of 45 years, an unmodified Kaplan-Meier model yields a LTR 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, LTR estimates (to age 95) for tCVD exceeded 60% for men and 55% for women overall. Risks for tCVD 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 tCVD. These results also highlight the association of low levels of traditional risk factors in mid-life with substantially increased CVD-free survival and may suggest compression of morbidity in older ages.

Acknowledgments

Appendix

Appendix Table 1

Baseline Characteristics by Cohort Among Index Age 65 Participants

|	ARIC (n=9375)	CHA (n=2966)	CHS (n=4455)	FHS (n=4047)	FOS (n=2151)
Non His White, No (%)	7211 (76.9)	2868 (96.7)	3780 (84.8)	4047 (100.0)	2151 (100.0)
Male, No (%)	4321 (46.1)	1616 (54.5)	1740 (39.1)	1715 (42.4)	1016 (47.2)
Systolic Blood Pressure, mmHg	126 (19)	148 (22)	136 (20)	140 (22)	132 (18)
Diastolic Blood Pressure, mmHg	72 (11)	85 (12)	72 (11)	83 (12)	78 (9)
Total Cholesterol, mg/dL	213.4 (40.1)	220.1 (38.8)	212.2 (38.1)	243.8 (44.7)	215.3 (40.7)
Rx for Hypertension, No (%)	3186 (34.2)	440 (14.8)	1750 (39.3)	544 (14.2)	615 (28.6)
Smoker, No (%)	1820 (19.4)	784 (26.4)	553 (12.4)	1112 (35.3)	426 (19.8)
Diabetes, No (%)	1434 (15.4)	161 (5.5)	161 (7.5)	173 (4.3)	201 (9.3)
Total CVD Event, No (%)	1296 (13.8)	1727 (58.2)	1830 (41.1)	2126 (52.5)	262 (12.2)

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Figure 1: Lifetime Risk Estimates for Total CVD stratified by Sex and Risk Factor Burden
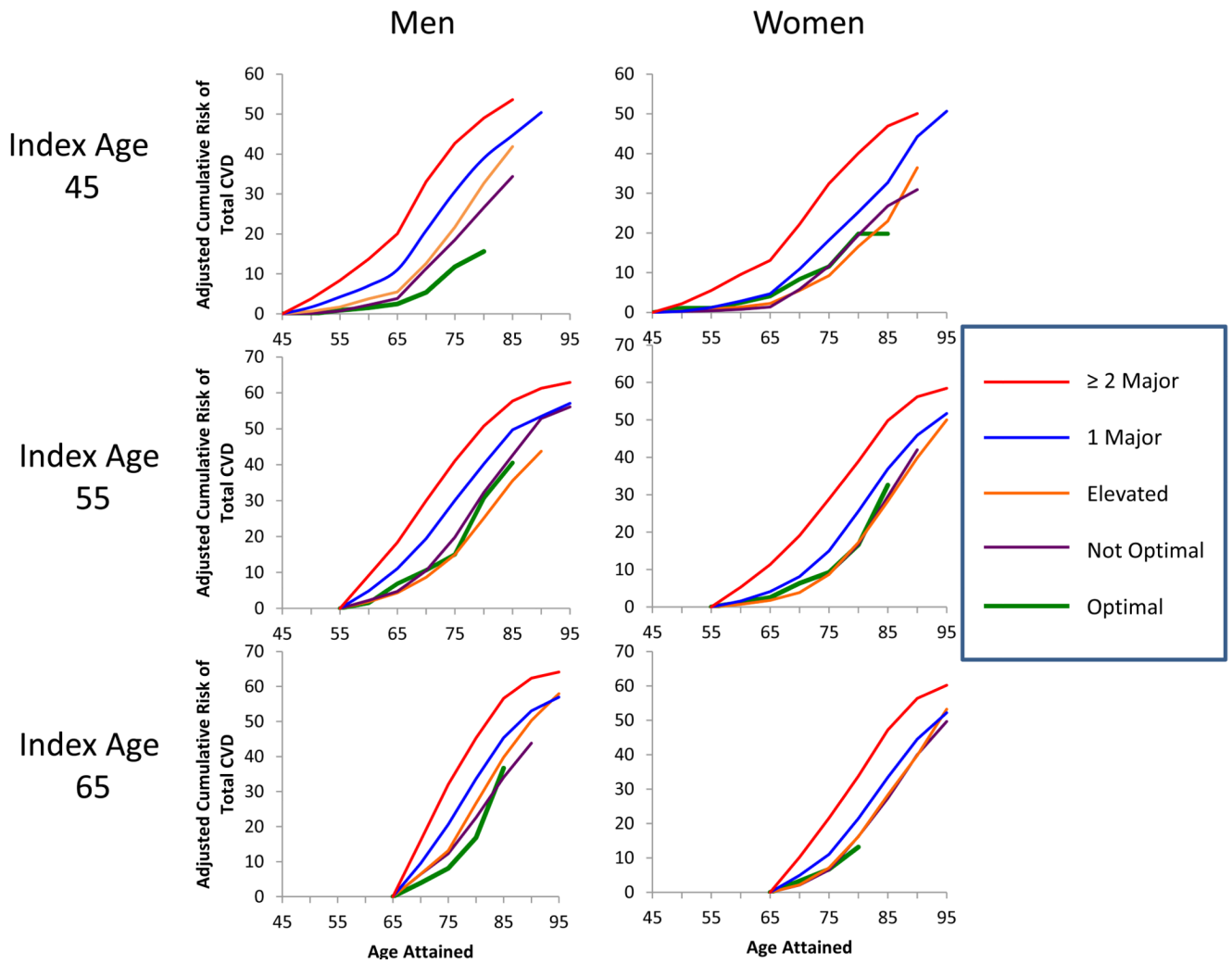
Figure 1.
Lifetime risk estimates for total CVD stratified by sex, index age and aggregate risk factor burden[a].
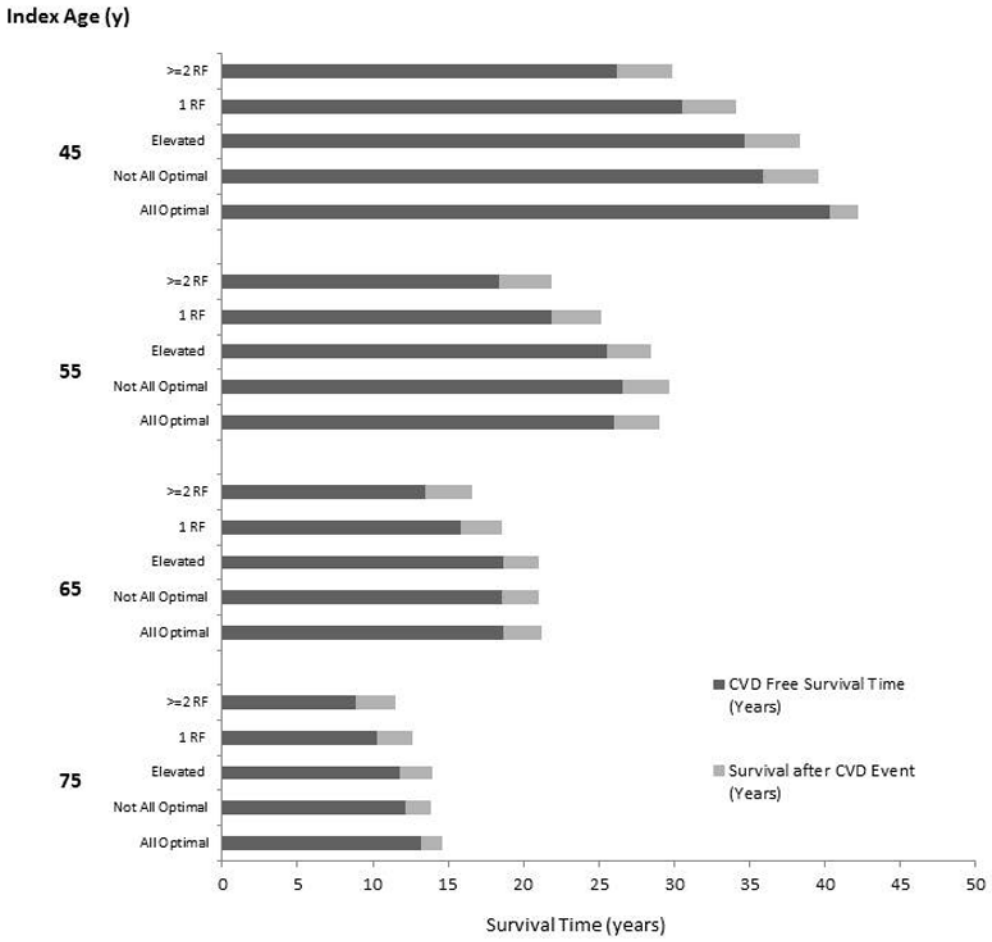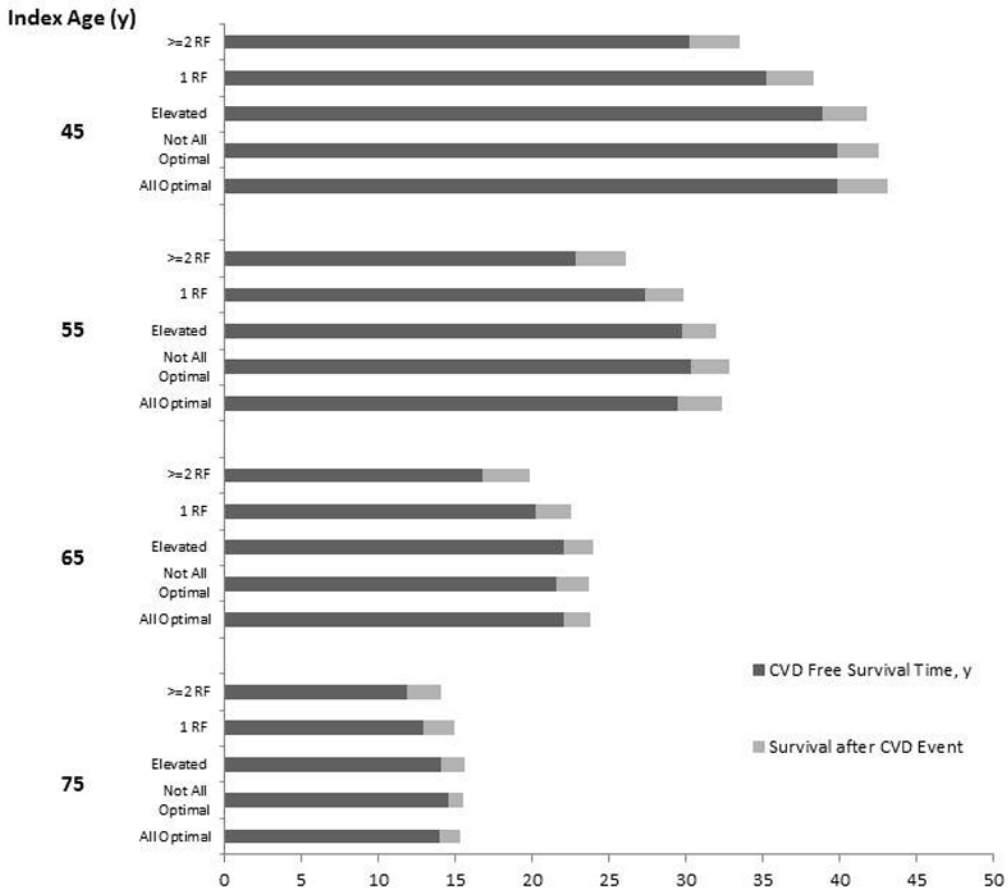[a]See table 1 for risk factor category definitions.

Figure 2A: CVD-Free Survival and Survival After CVD Event for Men by Risk Factor Burden

Figure 2.
CVD-free survival and survival after CVD events for men (Panel A) and women (Panel B)
by index age and aggregate risk factor burden.

Table 1

Definitions of Risk Factor Strata

	All Optimal	1 Not Optimal	1 Elevated	1 Major	2 Major
Systolic/Diastolic Blood Pressure (mmHg)	<120 and <80	120-139 or 80-89	140-159 or 90-99	160 or 100 or treated	160 or 100 or treated
	AND	OR	OR	OR	AND/OR
Total Cholesterol (mg/dL)	<180	180-199	200-239	240 or treated	240 or treated
	AND	AND	AND	OR	AND/OR
Diabetes	No	No	No	Yes	Yes
	AND	AND	AND	OR	AND/OR
Tobacco Smoking	No	No	No	Yes	Yes

Table 2

Study Sample Characteristics

Index Age		N	P-Y of follow up	Total Deaths, No (%)	CVD Events, No (%)	Median survival time (Y)
45	Men	24031	440612	11099 (46.2)	8472 (35.2)	35.2
	Women	25459	464503	8943 (35.1)	6703 (26.3)	41.2
55	Men	18211	287061	8700 (47.8)	6553 (36.0)	24.0
	Women	20969	349496	7606 (36.3)	5730 (27.3)	29.3
65	Men	10408	121084	4869 (46.8)	3675 (35.3)	17.6
	Women	12586	158839	4747 (37.7)	3566 (28.3)	21.9
75	Men	4109	36213	2096 (51.0)	1513 (36.8)	11.8
	Women	5909	61775	2685 (45.4)	1965 (33.2)	14.8

Table 3

Distribution of risk factor burden strata[a]

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

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

Table 4

Lifetime risk estimates[a] for total CVD, by sex and selected index age

Index Age	Men % (95% CI)	Women % (95% CI)
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)

[a]The lifetime risk estimates reported above represent the percentage of cohort participants who would experience a tCVD 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).