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Risk Factors for Cardiovascular Disease across the Spectrum of Older Age: The Cardiovascular Health Study

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Abstract

Objective—The associations of some risk factors with cardiovascular disease (CVD) are attenuated in older age; whereas others appear robust. The present study aimed to compare CVD risk factors across older age.

Methods—Participants (n=4,883) in the Cardiovascular Health Study free of prevalent CVD, were stratified into three age groups: 65–74, 75–84, 85+ years. Traditional risk factors included systolic blood pressure (BP), LDL-cholesterol, HDL-cholesterol, obesity, and diabetes. Novel risk factors included kidney function, C-reactive protein (CRP), and N-terminal pro-B-type natriuretic peptide (NT pro-BNP).

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Results—There were 1,498 composite CVD events (stroke, myocardial infarction, and cardiovascular death) over 5 years. The associations of high systolic BP and diabetes appeared strongest, though both were attenuated with age (p-values for interaction = 0.01 and 0.002, respectively). The demographic-adjusted hazard ratios (HR) for elevated systolic BP were 1.79 (95% confidence interval: 1.49, 2.15), 1.59 (1.37, 1.85) and 1.10 (0.86, 1.41) in participants aged 65–74, 75–84, 85+, and for diabetes, 2.36 (1.89, 2.95), 1.55 (1.27, 1.89), 1.51 (1.10, 2.09). The novel risk factors had consistent associations with the outcome across the age spectrum; low kidney function: 1.69 (1.31, 2.19), 1.61 (1.36, 1.90), and 1.57 (1.16, 2.14) for 65–74, 75–84, and 85+ years, respectively; elevated CRP: 1.54 (1.28, 1.87), 1.33 (1.13, 1.55), and 1.51 (1.15, 1.97); elevated NT pro-BNP: 2.67 (1.96, 3.64), 2.71 (2.25, 3.27), and 2.18 (1.43, 3.45).

Conclusions—The associations of most traditional risk factors with CVD were minimal in the oldest old, whereas diabetes, eGFR, CRP, and NT pro-BNP were associated with CVD across older age.

Keywords

aging; epidemiology; risk factors

Over the next 40 years, the population of adults aged 85 years and older is projected to nearly triple in the United States, from 6.6 million in 2010 to 19 million in 2050[1]. Cardiovascular disease (CVD) is the leading cause of death in this population[2], yet adults over 85 have been notably underrepresented in studies of risk factors for CVD. To minimize the burden of CVD in these oldest old, we need an improved understanding of the relative importance among risk factors in this population. Epidemiologic studies have demonstrated that risk factors for CVD are often under-diagnosed and under-treated in older adults, potentially due to the uncertainty regarding the benefits of risk factor reduction in this group.[3, 4] Guidelines reflect this uncertainty; the recent AHA/ACC guideline noted the paucity of data on cholesterol treatment for primary prevention of CVD in adults over 75 years of age.[5]

Substantial research has demonstrated that extrapolating results from middle-aged and young-old adults may not be appropriate in the oldest old. Several traditional risk factors appear to have a diminished association with cardiovascular events in older persons.[6, 7] The association of blood pressure (BP) with stroke and heart disease mortality is robust in younger elders, and appears attenuated in very old adults.[8–10] Elevated total cholesterol appears to have a weaker association with cardiovascular mortality in older adults than younger adults; although, the association of HDL with CVD appears robust across a wide age-range.[11–13] The optimum body mass index (BMI) for older adults is thought to be higher than for the middle-aged population.[14, 15]

We hypothesize that the dominant pathophysiology of CVD may differ in the oldest old compared with younger elders. Physiological processes that are strongly associated with aging appear to have a substantial impact on CVD risk. Recent studies have demonstrated that kidney function and inflammation are important risk factors for CVD in older adults.[16–18] Cystatin C, a measure of kidney function, had among the strongest associations with cardiovascular death of any risk factor in Cardiovascular Health Study (CHS).[17] In

addition, C-reactive protein levels (CRP) are at least as strongly associated with CVD events in older adults as LDL-cholesterol levels.[18, 19] N-terminal pro-B-type natriuretic peptide (NT pro-BNP) concentration, a marker for cardiac strain, has been strongly associated with CVD events in older adults.[20] These three domains – kidney function, inflammation, and cardiac strain - represent potentially important factors in the high burden of CVD observed in the oldest old.

In the present study, we compare the association of risk factors reflecting kidney function, inflammation, and cardiac strain, and traditional risk factors: high BP, dyslipidemia, obesity, diabetes, and smoking, with CVD events in adults across the spectrum of older age.

METHODS

Study Population

The Cardiovascular Health Study (CHS) is a community-based study of older black and white adults aged 65 years and older at baseline. The primary aim of the CHS is to evaluate risk factors for the development and progression of CVD in older adults.[21] The study recruited 5,201 persons from Medicare eligibility lists in Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania in 1989–1990. An additional 687 black participants were recruited during a supplemental enrollment during 1992–1993. Eligible participants met the following criteria: 1) age > 65 years; 2) not institutionalized; 3) expected to remain in the current community for 3 years or longer; 4) not under active treatment for cancer; and 5) provided informed consent without requiring a proxy respondent. There were 4,883 participants free of CVD (history of myocardial infarction, stroke, coronary bypass surgery, angioplasty, and heart failure) included in the present study. Cardiovascular conditions at enrollment were assessed through a combination of self-report, clinical examination, and survey of the treating physicians.[22]

Participants completed study visits at enrollment and annually during the first 10 years of follow-up; these visits included an interview, health questionnaire, physical examination, and collection of blood specimens. Participants were invited to return for an additional follow-up visit at year 16, which included the same components. Follow-up visits for outcomes were conducted by telephone every six months, and potential events were identified from self-report, review of hospital discharge summaries and Medicare data. The study was approved by institutional review boards at each site and informed consent was obtained from all participants.

Outcomes

The primary outcome used in this analysis was the 5-year risk of a composite outcome including myocardial infarction (MI), stroke, and cardiovascular death. Outcomes were assessed through December 31st, 2010; participants were censored after the first event or at death. Data collected on potential events were reviewed and adjudicated by a CHS outcome-assessment committee. [23] MI was ascertained from hospital records and was indicated by a clinical history of cardiac symptoms, elevated cardiac enzyme levels, and serial

electrocardiographic changes. Stroke cases were adjudicated by a committee of neurologists, neuroradiologists, and internists on the basis of information from interviews with participants, medical records, and brain imaging studies. Deaths were identified by a review of obituaries, medical records, death certificates, and the Centers for Medicare and Medicaid Services health care–utilization database for hospitalizations and from household contacts; 100 percent complete follow-up for ascertainment of mortality status was achieved. Death from cardiovascular causes was defined as death caused by coronary heart disease, heart failure, peripheral vascular disease, cerebrovascular disease, other CVD, and other atherosclerotic disease.

Measures

Age, sex, and race were determined by self-report at year 0; race was categorized as black or white/other because <1% of participants did not identify as black or white. Alcohol consumption, and education were determined by self-report. The risk factors were measured at years 0, 3, 7, and 16, although not all risk factors were measured at each visit (eTable 1). Height, and weight were measured by standard protocol; and body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. BP (systolic and diastolic) was measured in seated participants after a 5-minute rest. Trained study personnel obtained three BP readings, and the average of the last two readings was recorded. High-density lipoprotein (HDL) cholesterol was measured in fasting blood samples, and low-density lipoprotein (LDL) cholesterol was calculated according to the Friedewald equation.[24] Diabetes was defined as a fasting glucose 126 mg/dL or use of insulin or hypoglycemic medications. Smoking status was assessed by self-report. Cystatin C was measured by a BNII nephelometer (Seimens Healthcare Diagnostics, Deerfield, IL) that utilizes a particle enhanced immunonepholometric assay (N Latex Cystatin-C) [25], and estimated glomerular filtration rate (eGFR) was calculated based on the equation including cystatin C, age, sex, and race, developed by the CKD-EPI group.[26] CRP was measured in plasma by immunoassay. NT-proBNP was measured in serum with the Elecsys 2010 system (Roche Diagnostics, Indianapolis, IN).

To simplify the comparisons, we dichotomized the risk factors at cutpoints that are clinically relevant or from prior research in the CHS.[16, 20] Traditional risk factors included systolic BP >140 mmHg, LDL-cholesterol >3.37 mmol/L [130 mg/dL], HDL-cholesterol <1.04 mmol/L [40 mg/dL] in men, <1.29 mmol/L [50 mg/dL] in women, obesity (body mass index > 30 kg/m^2), diabetes (fasting glucose 7.0 mmol/L [126 mg/dL] or use of diabetic medications), and current smoking verses never smoking. Novel risk factors included reduced kidney function (cystatin C based eGFR < 60 ml/min/1.73m^2), CRP > 28.6 nmol/L [3 mg/L], NT-proBNP > 300 ng/L [300 pg/mL] (highest quintile). As an alternative classification we standardized variables by dividing the linear variables by their standard deviations.

Statistical Analysis

Data were pooled across CHS follow-up visits (year 0, 3, 7, and 16) and we examined the 5 year risk of the composite event. Participants were allowed to contribute follow-up time to more than one time interval and to more than one age group. The pooled design allowed us to maximize power to examine risk factors across age categories; this design can be thought

of as multiple cohorts enrolled over time at 3, 7, and 16 years apart. We used clustered robust standard errors for all estimates in regression models; this method adjusts the standard errors appropriately when individuals are included multiple times in an analysis.

We stratified the study population into three age groups: 65–74 years, 75–84 years, and 85 years and older, and summarized the participant characteristics across each age group. Next, we calculated the composite event rate over five years in persons with and without each risk factor stratified by age group. We then estimated the association of the risk factors and the composite event over 5 years based on proportional hazards models adjusted for demographic factors (visit year, sex, race, and education level). We tested the proportional hazards assumption based on the Schoenfeld residuals, and demographic adjusted log-log plots. We included multiplicative interaction terms between the risk factors and the age group variable, and used a Wald test for interaction. We next included all risk factors in the demographic adjusted Cox proportional hazard models, and used backwards stepwise elimination (p<0.2) to identify a parsimonious adjusted model. Additionally, we stratified the demographic adjusted models by sex in order to investigate effect modification by sex. We had limited age-stratified sample size to examine effect modification by race. In order to test if the pooled design altered the risk factor associations due to the inclusion of participants at more than one visit, we conducted a sensitivity analysis of the demographic adjusted associations at the 3rd year of follow up only. We also used competing risks regression to account for differences in competing risk due to non-cardiovascular death. Additionally, we estimated the event-specific hazard ratios separately for MI, stroke, and cardiovascular death, adjusted for demographic characteristics.

Finally, we calculated the attributable fraction, adjusted for demographic factors, based on the method described by Greenland and Drescher.[27] This measure takes into account both the prevalence of a risk factor as well as the magnitude of the association with the outcome. The Greenland and Drescher estimator uses maximum likelihood and can include adjustment for covariates. This command (aflogit) was implemented in Stata 10.0. All other analyses were conducted using Stata 12.0 (College Station, TX).

RESULTS

There were 4,883 participants free of CVD (MI, stroke, heart failure, revascularization) included in the present study; they contributed 12,965 visits in which risk factors were assessed. The number of active participants in CHS diminished across time, and at sequential visits, the age distribution shifted toward older categories (eTable 1). At the first visit, there were few participants 85 years and older, and after 16 years of follow-up there were no participants younger than 81 years. (eTable 1)

The mean ages were 70, 79, and 88 years for the three age strata (Table 1). Participants in the older age groups appeared less likely to have a high school education, or smoke. On average, older participants had higher systolic BP, as well as lower diastolic BP, LDL-cholesterol, BMI, eGFR, and CRP levels. Older participants had higher NT pro-BNP levels, and were more likely to be on lipid-lowering and antihypertensive medications. In comparisons of the nine dichotomized risk factors, three were higher in the oldest old

(systolic BP, reduced kidney function, and elevated NT pro-BNP), five were lower in the oldest old (elevated LDL cholesterol, low HDL cholesterol, obesity, current smoking, elevated CRP), and one was nearly equivalent across age groups (diabetes).

Over the 5-year follow-up period from each of the risk factor measurements (at years 0, 3, 7, and 16), there were 1,498 total events included in the composite outcome: 615 MIs, 659 strokes, and 650 cardiovascular deaths (an MI or stroke could also result in a cardiovascular death). (Table 2) The incidence rate of each event type increased across age categories, ranging from 2-fold risk for MI to a 7-fold risk of cardiovascular death in participants 85 years and older compared with participants 65–74 years. The case-fatality rate for MI in participants 85 and older was nearly 3-times that of participants 65–74 years. There was a moderate increase in the case-fatality rate for stroke in participants aged 75 years and older compared with those aged 65–74 years.

We compared event rates among persons with and without risk factors, stratified by age (Figure 1). Among participants under 85 years, the composite event rate in persons with elevated systolic BP or low HDL-cholesterol was greater than in persons without these risk factors. (Figure 1) These differences were attenuated in the oldest age group. There was little difference in the event rates in persons with and without elevated LDL-cholesterol. Likewise, the event rates were similar in persons with and without obesity, except in participants aged 85 and older, where obese participants had a lower event rate than in non-obese persons. The event rate was modestly greater in smokers than in non-smokers in every age group; the difference was largest in those aged 75–84. For diabetes, reduced kidney function, elevated CRP, and elevated NT pro-BNP, there was a general pattern of higher event rates among persons who had each risk factor, irrespective of age category.

The associations were consistent when we estimated hazard ratios and adjusted for demographic characteristics. (Table 3) Only the interactions of age group with systolic BP and diabetes were statistically significantly different (p=0.01 and p=0.002, respectively). Overall, the patterns were similar in the models adjusted simultaneously for the risk factors (Table 3).

Of the traditional risk factors, the attributable fraction for elevated systolic BP was highest (approximately 20%) among persons less than 85 years owing to both the high prevalence of this risk factor and the strength of the association with the outcome. (Figure 2) There was a modest attributable fraction associated with low HDL-cholesterol and diabetes (approximately 13 and 15%, respectively), in persons less than 75 years of age, and the attributable fraction was attenuated at older ages. The attributable fraction of reduced kidney function and elevated NT pro-BNP increased with age, and reached 23% and 28%, respectively, in participants 85 and older. The attributable fraction of elevated CRP was moderate (10–20%) across the spectrum of older age.

We conducted multiple sensitivity analysis to evaluate the robustness of our findings. First, we examined the association of the risk factors modeled as continuous risk factors and found a similar pattern across the age groups (eTable 2). Subsequently, we examined the hazard ratios of the risk factors based on sex-stratified models, and overall patterns were similar,

although the estimates were more variable (eTable 3). There was some variation between women and men; the 3-way interaction terms that had a p-value of <0.05 were as follows: 1) HDL-cholesterol and sex and 65–74, 2) BMI and sex and 65–74, 3) CRP and sex and 85+, and 4) BNP and sex and 65–74 years. Similarly, when we restricted to risk factor measures at a single visit year (1992–1993), we observed similar relationships of the risk factors and composite outcome (eTable 4); a notable exception was the attenuation of the magnitude of the association for high CRP and the composite event in older age. Additionally, we used competing risk regression to account for death due to non-cardiovascular causes and also observed similar relationships to our initial models (eTable 5); one difference was the change in the direction of the association of smoking and the composite outcome in the very old, although this association was not statistically significant. Neither adjustment for antihypertensive medication use nor lipid lowering medications had a substantial effect on the estimates for systolic BP or LDL-cholesterol; HR for elevated systolic BP: 1.64 (95% CI: 1.36, 1.97), 1.52 (95% CI: 1.30, 1.77), and 1.01 (95% CI: 0.79, 1.31) for 65–74, 75–84 and 85+ years, and for elevated LDL-cholesterol: 1.17 (95% CI: 0.96, 1.44), 0.99 (95% CI: 0.81, 1.20), and 1.16 (95% CI: 0.80, 1.69). Finally, we examined the event-specific hazard ratios, and while the patterns of risk factor associations were similar to those with the composite outcome, we again had limited power to identify associations with precision. (eFigure 1).

DISCUSSION

Diabetes, kidney function, inflammation, and cardiac strain were associated with the five-year risk of a composite cardiovascular outcome into very old age. In contrast, certain traditional risk factors, including elevated systolic BP, and low HDL cholesterol were associated with cardiovascular events only in persons <85 years. Elevated LDL cholesterol and obesity were not associated with cardiovascular events in persons older than 65 years. Current smoking appeared to be associated with cardiovascular events across older age, although there were few current smokers age 85 and older. The highest attributable fraction was associated with high systolic BP and inflammation in adults 65–74 years, high systolic BP and cardiac strain in adults 75–84 years, and cardiac strain and reduced kidney function in adults ages 85 and older.

Our findings are consistent with several studies examining individual cardiovascular risk factors in older adults. Prior research has demonstrated a robust association of high BP and outcomes in younger elders and an attenuated association in the very old.[8–10, 28, 29] An earlier analysis in CHS found an association between elevated systolic and diastolic BP and MI, stroke, and mortality.[10] The authors assessed BP at baseline, at which time the mean age of the participants was 73 years, and there were few participants over 85 years of age. In the Framingham Heart Study, the association of high BP with cardiovascular mortality was inverse among persons > 75 years.[8] Additionally, several studies have demonstrated an attenuated association of total or LDL cholesterol and outcomes in older adults;[4, 5, 12, 30] and a robust association of HDL cholesterol and outcomes across older age.[11, 13] Substantial evidence has demonstrated an attenuated or even inverted association of higher BMI and poor outcomes in older adults,[31, 32] although this may be due to weight loss at older ages. [33]

There are two main explanations for the attenuated association of the traditional risk factors and CVD in older age; both likely contribute to the observed findings. First, there is a differential selection of survivors in the oldest age group. Persons who are susceptible to a risk factor are more likely to have events earlier in life; and survival to old age with a risk factor may be an indicator that an individual is less susceptible to the ill-effects of that particular risk factor. This theory is often described as the "depletion of susceptibles" in epidemiologic literature. Second, the effect of some risk factors may be modified due to physiologic changes that occur during the aging process; these changes may be amplified in frail or multimorbid older adults, whom are often excluded from clinical trials. For example, in some elders, high BP may have no effect or may even help combat the consequences of vascular stiffness and maintain adequate perfusion of the central organs.[34] In previous research, we found that BP was associated with mortality only in faster walkers (a marker of functional status), whereas the association was null or inverted in slower walkers.[35, 36] Additionally, researchers have suggested that some cholesterol may be necessary to maintain neuronal function; [37] a theory supported by recent evidence demonstrating a negative effect of statin use on cognitive function in some adults.[38, 39] Greater body weight at older age may reflect lower frailty and loss of physiologic reserve.[31]

The robust associations of the novel risk factors studied here are striking, and may provide insight into the pathophysiology of CVD at older age. Kidney function is strongly associated with cardiovascular outcomes[17]; potentially mediated through increased inflammation, altered homeostasis in the blood, altered regulation of intravascular volume and waste products, and increased vascular stiffness resulting in cardiac strain. A previous study from the CHS demonstrated that the association of albuminuria and CVD and death was also robust across the spectrum of older age.[40] Inflammation plays an important role in the atherogenic process and plaque formation, and likely is influenced by the presence of atherosclerosis.[41] Cardiac strain markers reflect preclinical and clinical heart failure, and portend higher arrhythmia risk. While these biomarkers reflect age-related processes with deleterious consequences, they may also reflect the cumulative exposure to traditional risk factors and other deleterious exposures across the life course. These novel factors may thus capture a lifetime of insults to the cardiovascular system, and demonstrate the importance of a life-course perspective in cardiovascular prevention.

Strengths of our study include the comparison of several important cardiovascular risk factors across a wide age range of older adults. Additionally, we examined the risk factor associations across ages on both an additive and multiplicative scale;[30] and present the attributable fraction, a measure which takes into account the both the prevalence and the magnitude of association of the risk factor. Our study also has limitations which need to be considered. As noted above, the survivors to older age are a unique population, and we cannot separate the effects of selective survival from age-related changes in the effects of the risk factors. We believe both of these factors contribute to the observed results. Second, to simplify the comparison across risk factors, we dichotomized the risk factors based on relevant cutpoints. While this is an oversimplification of the association of the risk factors and outcomes, we found a similar pattern of associations when we explored the risk factors as continuous variables. Additionally, we did not examine the cumulative exposure to risk factors over time. Finally, we did not estimate treatment effects of pharmacological agents

used to treat these risk factors, so we cannot make inferences regarding the effectiveness of therapies used to treat these risk factors.

In summary, the traditional targets for CVD prevention do not appear to be important risk factors when measured late in life among the oldest old. In contrast, risk factors associated with the aging process are associated with cardiovascular risk across the spectrum of older age; these factors may reflect cumulative exposure to risk factors. If confirmed in other studies, this research underscores the importance of CVD prevention across the life course. Additionally, these results highlight that the optimal factors for CVD risk assessment may differ in the very old.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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- We compared risk factors for cardiovascular disease across older age.

- Participants were 65 and older adults in the Cardiovascular Health Study(n=4,883).

- The associations of blood pressure and diabetes were attenuated in older age.

- Lipids and obesity did not appear to be risk factors in the very old.

- Kidney function, inflammation, and cardiac strain were important at all ages.
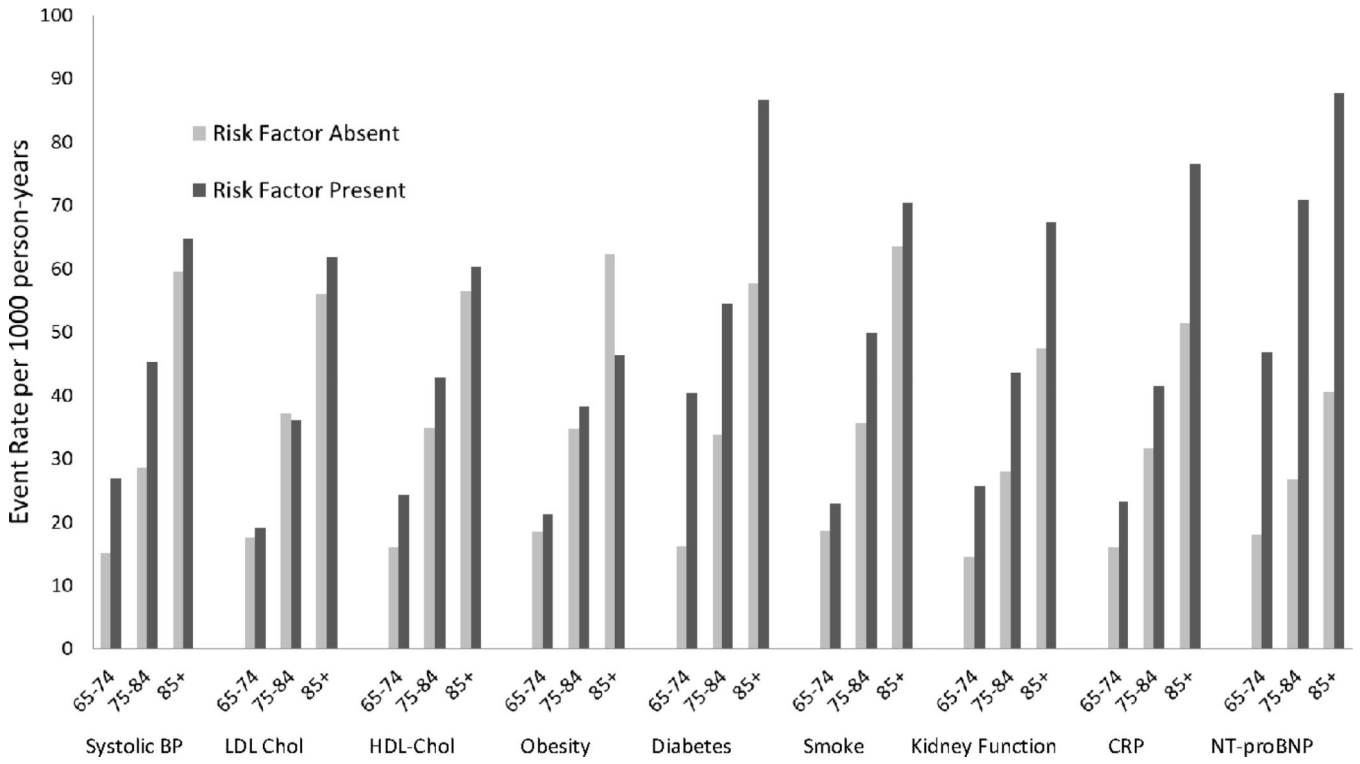
Figure 1.
Absolute composite event rates vary by risk factor and age group. BP = blood pressure, LDL Chol = Low-density lipoprotein cholesterol, HDL Chol = High-density lipoprotein cholesterol, CKD = chronic kidney disease, CRP = C-reactive protein, NT-proBNP = N-terminal pro-B-type natriuretic peptide
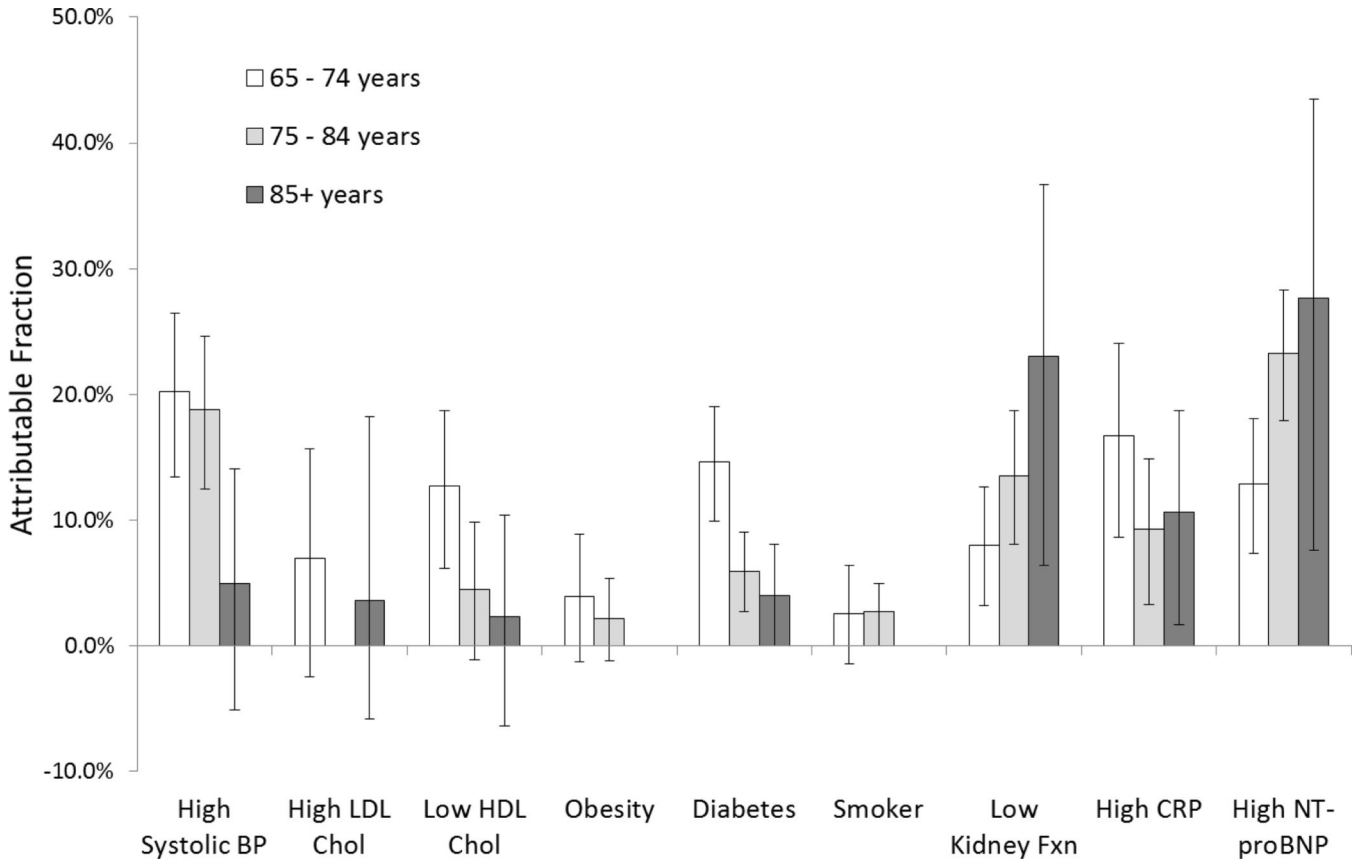
Figure 2.
Population attributable fraction associated with the risk factors by age group. Missing bars indicate that the estimate for the risk factor was in the protective direction. BP = blood pressure, LDL Chol = Low-density lipoprotein cholesterol, HDL Chol = High-density lipoprotein cholesterol, CKD = chronic kidney disease, CRP = C-reactive protein, NT-proBNP = N-terminal pro-B-type natriuretic peptide

Table 1

Characteristics of participants without a history of CVD

Characteristics[†]		65 – 74 age group (5,944 observations[*])	75 – 84 age group (5,479 observations[*])	85+ age group (1,542 observations[*])
		Mean ± SD or Median (IQR) or N (%)		
Age (years)		70 ± 2.5	79 ± 2.9	88 ± 3.1
Female		3787 (64)	3511 (64)	965 (63)
Black race		816 (14)	676 (12)	183 (12)
High school education		4504 (76)	3981 (73)	1096 (71)
Smoking	Current	864 (15)	506 (9)	92 (6)
	Former	2440 (41)	2129 (39)	528 (34)
	Never	2633 (44)	2837 (52)	919 (59)
Systolic BP (mmHg)		134 ± 20	138 ± 21	139 ± 23
Diastolic BP (mmHg)		72 ± 11	70 ± 11	68 ± 12
LDL Cholesterol (mmol/L) [mg/dL]		3.39 ± 0.91 [131 ± 35]	3.24 ± 0.91 [125 ± 35]	2.90 ± 0.88 [112 ± 34]
HDL Cholesterol (mmol/L) [mg/dL]		1.42 ± 0.39 [55 ± 15]	1.42 ± 0.39 [55 ± 15]	1.42 ± 0.39 [55 ± 15]
BMI (kg weight/m^2)		27 ± 4.8	26 ± 4.5	25 ± 4.1
eGFR-cystatin C (mL/min/1.73 m^2)		82 ± 23	71 ± 21	60 ± 21
CRP (mmol/L) [mg/L]		23.8 (35.3) [2.5 (3.7)]	21.9 (34.3) [2.3 (3.6)]	17.1 (28.5) [1.8 (3.1)]
NT pro-BNP (ng/L) [pg/mL]		97 (127) [97 (127)]	158 (198) [158 (198)]	322 (520) [322 (520)]
Lipid-Lowering Medication		408 (7)	474 (9)	177 (12)
Antihypertensive medication		2487 (42)	2704 (50)	824 (56)
High systolic BP (>140 mmHg)		2013 (35)	2182 (44)	484 (44)
High LDL Cholesterol (>3.37 mmol/L) [>130 mg/dL]		2429 (48)	1222 (41)	195 (27)
Low HDL Cholesterol (<1.04 mmol/L [<40 mg/dL] –men, <1.25 mmol/L [<50 mg/dL] - women)		1457 (29)	816 (27)	183 (25)
Obesity (BMI >30 kg/m^2)		1338 (23)	864 (18)	115 (11)
Diabetes[‡]		787 (14)	680 (14)	152 (12)
Current Smoking		864 (15)	506 (9)	92 (6)
Reduced kidney function[§]		781 (14)	1,356 (30)	497 (52)
High CRP (> 28.6 mmol/L) [>3 mg/L]		2,444 (43)	1,858 (40)	327 (33)
High NT pro-BNP (>300 ng/L) [>300 pg/mL]		285 (11)	676 (23)	213 (52)

Conventional units in brackets

[*] Participants could contribute repeated observations at more than one follow-up visit and to more than one age group; the study population includes 3,324 unique participants aged 65–74 years, 3,629 aged 75–84 years, and 1,257 aged 85+

[†] See eTable 1 for description of total N for each risk factor

[‡] Fasting glucose 7.0 mmol/L or use of diabetic medications,

[§] Cystatin C based estimated glomerular filtration rate < 60 ml/min/1.73m2

Table 2

Descriptive characteristics of events

		Myocardial Infarction[*]	Stroke[*]	Cardiovascular Death	Composite Outcome
Number of Events		615	659	650	1,498
	65–74 years	218	200	132	462
	75–84 years	300	343	311	724
	85+ years	197	116	207	312
Event Rate (per 1000 person-years)		10.5	11.2	10.9	26.1
	65–74 years	7.7	7.1	4.6	16.6
	75–84 years	12.2	14.0	12.3	30.2
	85+ years	16.7	20.2	34.7	55.4
Case-Fatality		10.9%	15.8%	n/a	30.8%
	65–74 years	7.3%	11.0%	n/a	22.9%
	75–84 years	10.3%	18.4%	n/a	29.3%
	85+ years	20.6%	16.4%	n/a	45.2%

[*] Fatal myocardial infarctions and fatal strokes were also included as cardiovascular deaths

Table 3

Adjusted association of risk factors with composite outcome

Risk Factors	Model*	65 – 74 years (5,773 observations)		75 – 84 years (5,479 observations)		85+ years (1,542 observations)		p-value for interaction
		HR (95% CI)†	p-value	HR (95% CI)†	p-value	HR (95% CI)†	p-value	
Elevated Systolic BP	I	1.79 (1.49, 2.15)	<0.001	1.59 (1.37, 1.85)	<0.001	1.10 (0.86, 1.41)	0.43	0.01
	II	1.51 (1.12, 2.03)	0.006	1.38 (1.14, 1.68)	0.001	-		
Elevated LDL–Cholesterol	I	1.16 (0.95, 1.43)	0.14	0.97 (0.80, 1.18)	0.80	1.12 (0.77, 1.63)	0.55	0.68
	II	-		-		-		
Low HDL–Cholesterol	I	1.57 (1.28, 1.93)	<0.001	1.22 (0.99, 1.50)	0.06	1.07 (0.74, 1.54)	0.72	0.18
	II	1.51 (1.10, 2.08)		-		-		
Obesity	I	1.18 (0.95, 1.47)	0.13	1.13 (0.93, 1.38)	0.20	0.70 (0.45, 1.10)	0.12	0.14
	II	-		-		-		
Diabetes	I	2.36 (1.89, 2.95)	<0.001	1.55 (1.27, 1.89)	<0.001	1.51 (1.10, 2.09)	0.01	0.002
	II	1.83 (1.27, 2.64)	0.001	1.63 (1.25, 2.12)	<0.001	-		
Current Smoking	I	1.23 (0.96, 1.59)	0.11	1.41 (1.12, 1.76)	0.003	1.16 (0.72, 1.87)	0.54	0.63
	II	-		1.43 (1.04, 1.95)	0.03	2.14 (0.96, 4.76)	0.06	
Reduced kidney function	I	1.69 (1.31, 2.19)	<0.001	1.61 (1.36, 1.90)	<0.001	1.57 (1.16, 2.14)	0.004	0.65
	II	-		1.35 (1.10, 1.65)	0.003	1.53 (0.90, 2.60)	0.12	
Elevated CRP	I	1.54 (1.28, 1.87)	<0.001	1.33 (1.13, 1.55)	<0.001	1.51 (1.15, 1.97)	0.003	0.51
	II	1.28 (0.94, 1.73)	0.12	-		1.76 (1.17, 2.66)	0.007	
Elevated NT pro-BNP	I	2.67 (1.96, 3.64)	<0.001	2.71 (2.25, 3.27)	<0.001	2.18 (1.43, 3.45)	<0.001	0.64
	II	2.12 (1.46, 3.09)	<0.001	2.40 (1.97, 2.93)	<0.001	2.05 (1.32, 3.18)	0.001	

HR = hazard ratio, LDL = low-density lipoprotein, HDL = high-density lipoprotein, NT pro-BNP = N-terminal pro-B-type natriuretic peptide

*
Model I adjusted for visit year, cohort, sex, race, and education; Model II adjusted for visit, cohort, sex, race, education and risk factors with p<0.20 for retention of risk factor in the model

† A missing estimate Indicates the risk factor was not selected for the final adjusted model because p 0.20.