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Absolute and Attributable Risks of Heart Failure Incidence in Relation to Optimal Risk Factors

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Abstract

Background—Epidemiologic studies have shown that a large proportion of coronary heart disease and stroke events are explained by borderline or elevated risk factors, and that adults with optimal risk factors greatly avoid these events. The degree to which this applies to heart failure incidence is not well documented.

Methods and Results—We categorized baseline (1987–89) risk factors in the Atherosclerosis Risk in Communities Study cohort ($n = 13,460$, aged 45–64) into optimal, borderline, and elevated groups based on national guidelines, using a 4-factor score (blood pressure, plasma cholesterol, diabetes, and smoking) and a 5-factor score (body mass also). Incidence of hospitalized heart failure ($n = 1,344$) was identified over a 16-year period. Only 4.9% of the cohort at baseline had all optimal risk factors based on the 4-factor score and 2.6% using the 5-factor score. Compared to participants with any elevated risk factor using the 4-factor score, the age-, sex-, race-adjusted relative hazard for heart failure events was 0.18 (95% CI 0.10–0.32) for those with all optimal risk factors and 0.35 (95% CI 0.30–0.41) for those with borderline risk factors only. A population attributable fraction estimate suggested that having at least one of the four risk factors, elevated or borderline, accounted for 77.1% of heart failure events. For the 5-factor score, that percentage was 88.8%.

Conclusion—Middle-aged adults with optimal (low) risk factors have low incidence rates of heart failure, which supports redoubled efforts to prevent risk factor development in the first place.

Keywords

epidemiology; heart failure; risk factors

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Disclosures

None.

Much of the United States adult population is at risk of cardiovascular disease (CVD) by virtue of having one or more traditional CVD risk factors – i.e., high blood pressure (BP), high blood cholesterol, cigarette smoking, diabetes, and excess body weight. However, recent epidemiologic studies by Stamler and others have emphasized the potential of primary prevention by showing that adults with no risk factors have a quite low incidence of CVD.^{1–6} We recently showed that this was true for CVD among African Americans and whites in the Atherosclerosis Risk in Communities (ARIC) Study.⁷ Maintaining a life without developing a CVD risk factor therefore should be a universal goal.

Prior studies of optimal CVD risk have generally focused on rates of coronary heart disease (CHD), stroke, or total CVD. Heart failure is a growing public health problem⁸ and affects 1 in 5 U.S. adults eventually.⁹ Although heart failure has several risk factors in common with CHD, and is often a result of CHD, no study has documented the degree to which adults with optimal risk factors avoid heart failure. To examine this issue, we calculated the absolute and attributable risks of heart failure incidence in relation to optimal risk factor levels in the ARIC study. In addition, we performed risk estimates for CHD and stroke separately, as our previous paper pooled these outcomes.

Methods

Study Design and Subjects

The ARIC Study is a prospective cohort study of atherosclerotic diseases in four US communities: Forsyth County, North Carolina; Jackson, Mississippi; Washington County, Maryland; and the northwest suburbs of Minneapolis, Minnesota.¹⁰ The cohort comprised, at baseline in 1987–89, 15,792 men and women aged 45 to 64 years who were selected by list or area probability sampling. Only African Americans were recruited in the Jackson study center. The baseline home interview and clinic examination measured various risk factors and cardiovascular conditions. The ARIC Study protocol was approved by the institutional review board of each participating university.

Baseline Examination

Sitting BP was measured three times using a random-zero sphygmomanometer after five minutes rest.¹¹ The mean of the last two measurements was used for analysis. Use of antihypertensive medications within the past two weeks of baseline interview was self-reported.¹² Fasting plasma total cholesterol was measured by enzymatic methods.¹³ Serum glucose was measured by a hexokinase/glucose-6-phosphate dehydrogenase method. Smoking status (current, former, or never smokers) was derived from interviews. Body mass index (BMI, kg/m²) was computed from weight in a scrub suit and standing height. Pre-existing heart failure at baseline was defined as: (1) an affirmative response to “Were any of the medications you took during the last 2 weeks for heart failure?” or (2) Stage 3 or “manifest heart failure” by Gothenburg criteria.^{14,15} Pre-existing coronary heart disease (CHD) at baseline was defined by self-reported prior physician diagnosis of myocardial infarction (MI) or coronary revascularization, or by prevalent MI by 12 lead electrocardiogram.¹⁶ Pre-existing stroke was defined by any self-reported prior physician diagnosis of stroke.

Risk Factor Classification

We created two baseline risk factor scores for analysis. The 4-factor score, which we used previously,⁷ was based on blood pressure, total cholesterol, diabetes, and smoking. The 5-factor score additionally included body mass. We first classified CVD risk factors into optimal (low), borderline, or elevated categories according to national guidelines (Table 1).^{17–20} In this paper, we added impaired fasting glucose (100–125 mg/dL) as a borderline category. Since, in observational studies, participants under medical treatment typically have higher CVD risk

than subjects with borderline risk, we included treated participants in the elevated category. We then summed the number of risk factors to create the 4-factor and 5-factor risk scores. Our main presentation is based on the 4-factor score, but we also mention findings for the 5-factor score.

Incident and Fatal Events

We followed all participants from the baseline examination in 1987–89 to the date of CVD event, death, loss to follow-up, or else through December 31, 2005 (heart failure and CHD) or December 31, 2004 (stroke). CVD events in ARIC were ascertained by contacting participants annually, identifying hospitalizations and deaths during the prior year, and by surveying discharge lists from local hospitals and death certificates from state vital statistics offices for potential CVD events.^{12,21,22} Incident heart failure in ARIC was defined as the first occurrence of either: 1) a hospitalization which included an International Classification of Diseases, 9th revision (ICD-9) discharge code of '428' (428.0–428.9) among the primary or secondary diagnoses or else 2) a death certificate with an ICD-9 code of '428' or an ICD-10 code of 'I50' among the listed or underlying causes of death.¹⁵

For patients hospitalized with a potential MI, trained abstractors recorded the presenting symptoms and related clinical information, including cardiac enzymes, and photocopied up to three 12-lead ECGs for Minnesota coding.^{16,23} Out-of-hospital deaths were investigated by means of death certificates and, in most cases, by an interview with one or more next of kin and a questionnaire filled out by the patient's physician. Coroner reports or autopsy reports, when available, were abstracted for use in validation. A CHD event was defined as a validated definite or probable hospitalized MI or a definite CHD death. The criteria for definite or probable MI were based on combinations of chest pain symptoms, ECG changes, and cardiac enzyme levels.^{21,22} The criteria for definite fatal CHD were based on chest pain symptoms, history of CHD, underlying cause of death from the death certificate, and any other associated hospital information or medical history, including that from an ARIC clinic visit.^{21,22}

The diagnostic classification of stroke was described previously.²⁴ In brief, for potential hospitalized strokes, the abstractors recorded signs and symptoms and photocopied neuroimaging (CT or MRI) and other diagnostic reports. Using criteria adopted from the National Survey of Stroke,²⁵ strokes were classified by computer algorithm and separate review by a physician, with disagreements resolved by a second physician.

Statistical Analyses

Of 15,792 ARIC participants at baseline, we excluded, due to small numbers, participants who were neither white nor African American subjects ($n=48$). We further excluded 1,971 who had a history of heart failure, CHD or stroke, or could not be classified on history. Subjects ($n=313$) who did not have complete information on plasma cholesterol, cigarette smoking, BP value, or serum glucose were also excluded. In all, 13,460 participants were included in the analysis for the 4-factor score and slightly fewer ($n = 13,453$) for the 5-factor score.

Crude incidence rates were calculated separately for each endpoint (heart failure, CHD, or stroke) according to risk factor groups. Persons with multiple endpoints were included with all individual endpoints. Follow-up time went from baseline until the first of: (1) incident endpoint, (2) lost to follow-up, (3) death, or (4) cessation of follow-up. The relative hazards (RH) of incident of heart failure (or CHD or stroke) in relation to risk factor groups were estimated from Cox proportional hazard models adjusted for age, sex, and sometimes race. We treated the participants with at least one elevated risk factor as the reference group. The population attributable fraction (PAF) was calculated as p times [(RH for risk factor category being considered - RH for the optimal risk category) / RH for risk factor category being

considered], where p = proportion of cases that are exposed in whichever risk factor category is being considered.²⁶ In a supplemental analysis, we stratified the heart failure endpoint on whether it occurred after an interim myocardial infarction or coronary revascularization (“ischemic”) or with no such history (“non-ischemic”), and calculated the PAFs for each heart failure stratum relative to those who did not develop heart failure.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Prevalence of Risk Categories

As shown in Table 1, the ARIC Study cohort in 1987–89 had a baseline mean age of 53.9 years. Higher proportions of African Americans than whites had hypertension (53.8% versus 27.9%), diabetes (17.5% versus 8.0%), and obesity (39.3% versus 21.6%). However, more African Americans than whites had an optimal cholesterol level (40.4% versus 36.8%) and had never smoked (47.3% versus 41.4%). As shown in Table 2, based on the 4-factor score involving blood pressure, cholesterol, diabetes, and smoking, only 4.9% of the cohort had all optimal risk factors (3.0% in African Americans and 5.6% in whites). On the other hand, 78.5% of African Americans had at least one of the four risk factors elevated, compared with 60.6% of whites. When we instead used the 5-factor score that included BMI, only 2.6% of the cohort had all optimal risk factors (1.0% in African Americans and 3.2% in whites), and 85.5% of African Americans and 67.1% of whites had at least one elevated risk factor.

Heart Failure Incidence

The mean duration of follow-up was 15.7 years (maximum, 19 years) during which 1,344 incident heart failure events occurred. Compared to participants with any elevated risk factor using the 4-factor score, the age-, sex-, and race-adjusted RH for heart failure events was 0.18 (95% CI 0.10–0.32) for those with all optimal risk factors ($n = 12$ events among 665 participants) and 0.35 (95% CI 0.30–0.41) for those with borderline risk factors only (Table 3). These RHs were 0.28 and 0.31, respectively, in African Americans and 0.16 and 0.36 in whites. The PAF estimate suggested that having at least one elevated risk factor in the 4-factor score accounted for 70.6% of heart failure events; borderline risk factors accounted for just 6.5% more. Thus, elevated and borderline levels of the 4 risk factors, together, seemed to account for a majority heart failure events in African Americans (67.5%) and whites (79.1%).

When we instead computed risks using the 5-factor score (also with BMI), the low prevalence of having only optimal risk factors meant that only 3 heart failure events occurred in whites with optimal risk factors, and 0 in African Americans. The PAF estimates suggested that elevated and borderline levels of the 5 factors accounted for 88.8% of heart failure events overall –100% in African Americans and 85.8% in whites.

Overall, 30% of participants who developed clear “ischemic” heart failure, that is, they had a definite or probable myocardial infarction or coronary revascularization between ARIC baseline and the first heart failure event. This percentage with an interim CHD event was 8% in those with all optimal risk factors, 27% in those with only borderline risk factors, and 31% in those having any elevated risk factor, based on the 4-factor score. The PAF of having non-optimal levels of the 4 factors was 94.2% for “ischemic” heart failure (i.e., after interim CHD) and 69.6% for “non-ischemic” heart failure (i.e., no interim CHD).

CHD and Stroke Incidence

We previously reported the PAF of CVD (CHD plus stroke) for elevated or borderline risk factors using the 4-factor score was 76.4% in ARIC over 13 years.⁷ We have now recalculated these PAFs for CHD and stroke, separately, over 15 to 16 years. Among African Americans, the PAFs were 100% for CHD events (Table 4) and 85.8% for strokes (Table 5). Among whites, these values were 75.0% and 59.9%, respectively.

If instead we used the 5-factor score, among African Americans the PAFs were 100% for CHD and 55.5% for strokes, and among whites were 76.9% for CHD and 75.9% for strokes.

Discussion

The main findings of this study of middle-aged adults recruited in the late 1980s and followed an average of 15 years were that (1) incidence of heart failure, especially “ischemic” heart failure, seemed explained to large degree (77% or more) by traditional CVD risk factors and (2) the few subjects with optimal risk factors rarely developed heart failure. This was true for both African Americans and whites. Previous studies, for example, the Framingham Heart Study^{8,9,27} have documented the absolute and relative risks of heart failure in relation to traditional risk factors. Lifetime risk of heart failure in Framingham was 20%.⁹ Hypertension was a key risk factor; PAFs suggested it accounted for 39% of heart failure events in Framingham men and 59% in women.²⁸ Previous studies have also demonstrated that subjects with a favorable CVD risk profile rarely develop CHD and/or stroke.^{1–7} Others have reported that those with CVD-healthy behaviors also are at very low CVD risk.^{29,30} However, our report seems to be the first to show that approximately 77% of heart failure events in middle-aged adults might also be prevented with the avoidance of risk factors. It therefore further emphasizes the need for preventing the development of risk factors in the first place, in addition to other recommended strategies for the primary and secondary prevention of heart failure.³¹

The prevalence of an optimal risk factor profile in this sample, and in previous reports, was very low. Only 3.0% of these middle-aged African Americans and 5.6% of whites had optimal levels of blood pressure, plasma cholesterol, and serum glucose, and had never smoked. Only 1.0% and 3.2%, respectively, had optimal risk factors if BMI was also included in the profile. The lower prevalence of optimal risk factors in African Americans than whites was also reported by the Multiple Risk Factor Intervention Study⁴ and Third National Health and Nutrition Examination Survey.³² Although the prevalences of several risk factors have declined in recent years in the U.S., prevalences of diabetes and obesity are rising, and the ethnic pattern remains. Meanwhile, CHD and stroke mortality are declining in the U.S., but heart failure hospitalizations and health care costs are increasing. Clearly, population and individual approaches to CVD risk factor prevention need to remain a priority.

Study Strengths and Limitations

The strengths of this study include the careful assessment of CVD risk factors and cardiovascular incidence for an extended follow-up period. One limitation is that heart failure incidence, which was based on unvalidated hospital discharge and death certificate codes for heart failure, did not include outpatient events. However, heart failure hospital discharge codes have moderately good sensitivity and specificity.^{33,34} Moreover, surveillance of Rochester, MN, indicates that 74% of heart failure cases identified in the outpatient setting are hospitalized within 1.7 years.³³ A second limitation is that we could not differentiate between systolic and diastolic heart failure. A third limitation is that our classification into ischemic and non-ischemic heart failure was based only on interim occurrences of myocardial infarction or coronary revascularization. A fourth limitation is that few events occurred in the optimal risk factor group, leading to imprecision in the heart failure incidence rate. However, this is the

crux of our findings – that people with no risk factors rarely develop heart failure or other CVD events.

The use of PAF values also has strengths and limitations. The PAF offers an estimate on a population-wide basis of the proportion of cases that may be due to risk factors. It is best used when the risk factors being considered are causally related to the disease endpoint. This is believed to be the case for major cardiovascular risk factors. The PAF offers an estimate of the health potential of maintaining optimal risk factors life-long, but, of course, is idealistic because few Americans at present are able to do this.

Conclusions

Our data indicate that middle-aged adults with optimal (low) risk factor levels have low incidence rates of heart failure, in addition to their low rates of CHD and stroke. Efforts need to continue not only for primary prevention of CVD, but also for “primordial” prevention of CVD risk factors in the first place.

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TABLE 1
Distribution of Individual Baseline Cardiovascular Disease Risk Factors in the ARIC Study, 1987–1989

Risk Factor	Definition	Total (n=13,460)	African-Americans (n = 3,441)	Whites (n = 10,019)
<i>Age, mean ± standard deviation, y</i>				
		53.9 ± 5.7	53.3 ± 5.8	54.2 ± 5.7
<i>Hypertension, %*</i>				
Optimal	SBP of <120 mmHg and DBP <80 mmHG	41.2	22.7	47.5
Borderline	SBP of 120–139 mmHg and/or DBP of 80–89 mmHg (prehypertension)	24.3	23.5	24.6
Elevated	SBP of ≥140 mmHg, DBP of ≥90 mmHg, and/or treatment for hypertension (hypertension)	34.5	53.8	27.9
<i>Total cholesterol level, %[†]</i>				
Optimal	Total cholesterol levels of <200 mg/dL	37.7	40.4	36.8
Borderline	Total cholesterol levels of 200–239 mg/dL	36.7	32.8	38.0
Elevated	Total cholesterol levels of ≥240 mg/dL (hypercholesterolemia) and/or treatment for hypercholesterolemia	25.7	26.8	25.3
<i>Diabetes, %[‡]</i>				
Optimal	No diabetes	52.7	47.5	54.5
Borderline	Fasting serum glucose 100–125 mg/dL	36.9	35.0	37.5
Elevated	Fasting serum glucose ≥126 mg/dL, non fasting serum glucose ≥200 mg/dL (diabetes), and/or physician's diagnosis of or treatment for diabetes	10.4	17.5	8.0
<i>Smoking, %</i>				
Optimal	Never	42.9	47.3	41.4
Borderline	Former	31.6	23.5	34.4
Elevated	Current	25.5	29.3	24.2
<i>Excess body mass, %</i>				
Optimal	Normal, <25 kg/m ²	34.4	23.0	38.3
Borderline	Overweight, 25–29.99 kg/m ²	39.5	37.7	40.1
Elevated	Obese, ≥30 kg/m ²	26.1	39.3	21.6

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure.

* According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

† According to the executive summary of the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.

† According to the American Diabetes Association diagnosis and classification of diabetes mellitus.

TABLE 2

Prevalence of Baseline Risk Factor Categories in the ARIC Study, 1987–1989

4-Factor Risk Factor Category*	No. of Elevated Risk Factors	No. of Borderline Risk Factors	Total, % (n=13,460)	African-Americans, % (n = 3,441)	Whites, % (n=10,019)
All optimal	0	0	4.9	3.0	5.6
Borderline risk factors only	0	1	11.2	6.9	12.7
	0	2	10.9	7.0	12.3
	0	3	6.4	3.8	7.3
	0	4	1.4	0.8	1.6
		Total	29.9	18.5	33.8
Elevated risk factors	1	Any	39.8	39.8	39.8
	2	Any	20.1	29.2	17.0
	3	Any	4.8	8.7	3.5
	4	Any	0.4	0.8	0.3
	Total		65.1	78.5	60.6

* This 4-factor score included blood pressure, plasma cholesterol, diabetes and smoking, as categorized in Table 1. When BMI was added to create a 5-factor score, the prevalence of “all optimal” risk factors fell to 2.6% (1.0% African Americans, 3.2% whites), the prevalence of “borderline risk factors only” decreased to 25.6% (13.6% African Americans, 29.8% whites), and the prevalence of any “elevated” risk factor increased to 71.8% (85.5% African Americans, 67.1% whites).

TABLE 3

Incidence Rate, Relative Hazard (RH), and Population Attributable Fraction (PAF) for Heart Failure Among Risk Groups, the Atherosclerosis Risk in Communities (ARIC) Study, 1987–2005

Risk Profile based on 4-factor score*	No. of Subjects at Risk	No. of Subjects Developing Heart Failure	Incidence Rate [†]	Adjusted RH (95% CI) [‡]	PAF, %
<i>Total sample</i>					
All optimal risk factors	665	12	1.1	0.18 (0.10–0.32)	0.0
Borderline risk factors only	4,028	177	2.7	0.35 (0.30–0.41)	6.5
Having any elevated risk factors	8,767	1,155	8.6	1.0 [§]	70.6
<i>African Americans</i>					
All optimal risk factors	103	4	2.4	0.28 (0.10–0.74)	0.0
Borderline risk factors only	638	33	3.2	0.31 (0.22–0.44)	0.8
Having any elevated risk factors	2,700	444	11.2	1.0 [§]	66.7
<i>Whites</i>					
All optimal risk factors	562	8	0.8	0.16 (0.08–0.31)	0.0
Borderline risk factors only	3,390	144	2.6	0.36 (0.30–0.43)	9.5
Having any elevated risk factors	6,067	711	7.6	1.0 [§]	69.6

* This 4-factor score included blood pressure, plasma cholesterol, diabetes and smoking, as categorized in Table 1.

[†] Crude incidence rate per 1000 person-years

[‡] RH adjusted for age and sex, plus race for the total sample.

[§] The reference group for the RH is those having any elevated risk factor.

TABLE 4

Incidence Rate, Relative Hazard (RH), and Population Attributable Fraction (PAF) for Coronary Heart Disease (CHD) Among Risk Groups, the Atherosclerosis Risk in Communities (ARIC) Study, 1987–2005

Risk Profile based on 4-factor score*	No. of Subjects at Risk	No. of Subjects Developing CHD	Incidence Rate [†]	Adjusted RH (95% CI) [‡]	PAF, %
<i>Total sample</i>					
All optimal risk factors	665	10	0.9	0.15 (0.08–0.28)	0.0
Borderline risk factors only	4,028	160	2.4	0.33 (0.28–0.39)	7.5
Having any elevated risk factors	8,767	995	7.5	1.0 [§]	72.5
<i>African Americans</i>					
All optimal risk factors	103	0	0.0	0.00	0.0
Borderline risk factors only	638	11	1.1	0.14 (0.08–0.25)	3.3
Having any elevated risk factors	2,700	327	8.2	1.0 [§]	96.7
<i>Whites</i>					
All optimal risk factors	562	10	1.1	0.18 (0.10–0.34)	0.0
Borderline risk factors only	3,390	149	2.7	0.37 (0.31–0.45)	9.1
Having any elevated risk factors	6,067	668	7.2	1.0 [§]	65.9

* This 4-factor score included blood pressure, plasma cholesterol, diabetes and smoking, as categorized in Table 1.

[†] Crude incidence rate per 1000 person-years

[‡] RH adjusted for age and sex, plus race for the total sample.

[§] The reference group for the RH is those having any elevated risk factor.

Incidence Rate, Relative Hazard (RH), and Population Attributable Fraction (PAF) for Stroke Among Risk Groups, the Atherosclerosis Risk in Communities (ARIC) Study, 1987–2004

TABLE 5

Risk Profile based on 4-factor score*	No. of Subjects at Risk	No. of Subjects Developing Stroke	Incidence Rate [†]	Adjusted RH (95% CI) [‡]	PAF, %
<i>Total sample</i>					
All optimal risk factors	665	7	0.7	0.25 (0.12–0.53)	0.0
Borderline risk factors only	4,028	87	1.4	0.42 (0.33–0.52)	5.7
Having any elevated risk factors	8,767	517	4.0	1.0 [§]	63.6
<i>African Americans</i>					
All optimal risk factors	103	1	0.6	0.12 (0.02–0.86)	0.0
Borderline risk factors only	638	19	1.9	0.33 (0.21–0.52)	4.6
Having any elevated risk factors	2,700	243	6.4	1.0 [§]	81.2
<i>Whites</i>					
All optimal risk factors	562	6	0.7	0.31 (0.14–0.71)	0.0
Borderline risk factors only	3,390	68	1.3	0.45 (0.35–0.59)	5.9
Having any elevated risk factors	6,067	274	3.0	1.0 [§]	54.0

* This 4-factor score included blood pressure, plasma cholesterol, diabetes and smoking, as categorized in Table 1.

[†] Crude incidence rate per 1000 person-years

[‡] RH adjusted for age and sex, plus race for the total sample.

[§] The reference group for the RH is those having any elevated risk factor.