The Impact of Traditional Risk Factor Development on the Life Course of Cardiovascular Diseases

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This report discusses the profound impact of established risk factors for coronary heart disease (CHD) and cardiovascular disease (CVD), from the perspective of both short-term and lifetime risks. Emerging data have confirmed the major importance of aggregate risk factor burden in middle and older age on remaining lifetime risks for CVD. The relatively new concept of the ideal cardiovascular health factor profile will play a central role in plans to improve the longevity, healthy longevity, and quality of life and health care costs of all Americans. In this context, the agenda of the Jackson Heart Study should promote understanding of and identify means for enhancing the roles of CVD prevention and health promotion among African Americans. (*Ethn Dis.* 2012; 22[Suppl 1]:S1-30–S1-34)

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Short-term Associations between Risk Factors and CHD

The Framingham Heart Study investigators first coined the term "risk factors" in a seminal report in 1961.[1] This landmark manuscript described the strong prospective associations of cholesterol and hypertension with subsequent coronary heart disease (CHD) events, and also showed the effects of greater aggregate burden of these risk factors on short-term CHD event rates. In that report, Kannel et al showed significant and linear associations between higher levels of cholesterol and blood pressure, as well as electrocardiographic left ventricular hypertrophy (ECG-LVH), and 6-year CHD rates in 40–59 year old men and women. For men with hypertension (then defined as >160/95 mm Hg), the rates were 124 per 1,000 over 6 years, compared with only 41 per 1,000 for men with normal blood pressure. When men had both hypertension and ECG-LVH, the rates were 368 per 1,000. Likewise, for men with high total cholesterol levels (>245 mg/dL), CHD event rates were 120 per 1,000 over 6 years, compared to 35 per 1,000 in men with cholesterol <210 mg/dL. Similar trends were observed among women, who had lower overall event rates. Kannel also observed that event rates were dramatically greater with higher aggregate burden of these risk factors, with rates of 36, 103, 204 and 500 per 1,000 over 6 years for men with 0, 1, 2, or all 3 of the risk factors present, respectively.[1]

Since these early findings, the body of knowledge on risk factors for CHD and cardiovascular disease (CVD) more generally has expanded and offers a better understanding of the associations. Recent evidence now suggests that nine common traditional risk factors, including both physiologic (blood lipids, blood pressure, diabetes, obesity) and lifestyle (smoking, psychosocial factors, fruit and vegetable intake, alcohol intake, physical activity) variables, may explain 90% of CHD events across all races and ethnic groups.[2] It is also clear that the vast majority of individuals who suffer a CHD event have an antecedent elevation in at least one of the major established risk factors of serum cholesterol, blood pressure, blood glucose, or cigarette use.[3]

The current paradigm for preventing CHD, described in the ATP III cholesterol guidelines,[4] relies on the principle that the intensity of prevention efforts should match the absolute risk of the patient. Thus, reliable equations for the estimation of short-term CHD risk have evolved to assist in decision-making under this and similar algorithms. The ATP-III risk assessment tool was derived from Framingham data, and weights the contributions the established risk factors to provide a 10-year estimate of CHD risk; physicians can then make treatment decisions based on the resulting estimated 10-year risk. These equations perform well in discriminating risk and are well calibrated for Caucasian- and African American populations, but they tend to over-estimate risk levels somewhat for Hispanic and Asian American groups.[5,6]

Lifetime Risks for CVD

Short-term associations between established risk factors and CHD are well described. And a growing body of evidence now indicates the even greater associations between risk factor levels across the lifespan and CVD and non-CVD outcomes, as well as longevity. Lifetime risk estimation allows for assessment of an individual's absolute

Table 1. Aggregate risk factor burden stratification for lifetime risks of cardiovascular disease. Adapted from reference 8

	Aggregate Risk Factor Burden			
	All Optimal	**Not Optimal**	**Elevated**	**1 Major /≥2 Major**
SBP / DBP (mm Hg)	<120 / <80	120–139 / 80–89	140–159 / 90–99	≥160 / ≥100
	or	*or*	*or*	*or*
Total cholesterol (mg/dL)	<180	180–199	200–239	≥240
	and	*and*	*and*	*or*
Diabetes	No	No	No	Yes
	and	*and*	*and*	*or*
Smoking	No	No	No	Yes

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

cumulative risk of developing CVD (or other common diseases) before dying of another condition. This statistical approach accounts for the risk of CVD, as well as remaining life expectancy and competing causes of death. Therefore, it tends to reflect real-life risks and population burden of disease better than traditional methods such as the Kaplan-Meier cumulative incidence.[7] The lifetime risk concept is useful for clinicians, researchers and policy-makers in that lifetime risk can assist in assessing the burden of disease in a population, comparing lifetime risks between common diseases, and allocating resources for competing causes of morbidity and mortality. In working with the Framingham Heart Study (FHS) data, we have been able to illustrate lifetime cumulative risks for atherosclerotic CVD (ASCVD) events based on cholesterol levels. We found that 50-year-old men with the lowest cholesterol levels of <180 mg/dL had a 39% remaining lifetime risk for developing an ASCVD event; in comparison, for men with total cholesterol level ≥240 mg/dL, risk for an ASCVD event was 65% during their remaining lifespan. For women, we found similar associations, with a nearly 2.5 fold difference in risk from 19% in the lowest cholesterol levels up to almost 50% in women with cholesterol ≥240 mg/dL.[8] Yet, the risk stratification in this example, while significant, only accounts for a single risk factor, cholesterol level, and ignores the presence or absence of others such as hypertension, diabetes, or smoking.

Our next approach was to stratify individuals based on their aggregate burden of risk factors.[8] Using the Framingham Heart Study cohort of individuals at aged 50 years, we created five mutually exclusive categories of aggregate risk factor burden, as shown in Table 1, and estimated remaining lifetime risks for ASCVD events after age 50 for men and women. Men and women with two or more major risk factors at age 50 years had markedly elevated lifetime risks for ASCVD, at 69% and 50%, respectively. Even with one or more risk factors at not quite optimal levels, the chance of having an ASCVD event was elevated, at 36% for males; 27% for females. However, for those who reached aged 50 years with all optimal levels of risk factors (i.e., untreated cholesterol <180 mg/dL, untreated blood pressure <120/<80 mm Hg, no diabetes, and non-smoking), the remaining lifetime risks for developing ASCVD were extremely low (5% for men and 8% for women.[8]

More recently, we expanded these observations across diverse age, race and sex groups by pooling data from 18 large epidemiologic, US community-based cohort studies in the Cardiovascular Lifetime Risk Pooling Project.[9] This dataset includes approximately 620,000 unique individuals with more than 10 million person-years of follow-up and more than 55,000 deaths attributed to CVD, and including data on tens of thousands of African American participants. We observed that the same general associations between aggregate risk factor burden and remaining lifetime risks for CVD events hold true. As shown in Table 2, those with all optimal risk factors have very low remaining lifetime risks, and there is a gradient of increasing lifetime risk with higher aggregate risk factor burden across all ages, in both men and women, similarly in whites and African-Americans, and regardless of birth cohort or type of CVD event studied.[9] In the future, after further follow up, the projected inclusion of the Jackson Heart Study data into this pooling project would allow for more in-depth study about the associations between lifetime risks and fatal and non-fatal events among African Americans.

Ongoing studies are using competing Cox models to analyze the differential effect of risk factor burdens over time on CVD lifetime risks after adjustment for competing risks of non-cardiovascular death. This may be particularly important when considering race/ethnic disparities in CVD event rates, since non-CVD death rates differ between races and those who die of non-CVD death first may not live to experience a CVD event for which they were destined. Using this approach, we have examined different combinations of risk factors from the all-optimal risk group to those with elevations of all 4 major risk factors (cholesterol, blood pressure, diabetes and smoking. Figure 1 illustrates the case for 45-year-old men and projects lifetime risk until age 90. In this analysis, a 45-year-old man with all 4 major risk factors

Table 2. Lifetime risks* (95% confidence intervals) for all atherosclerotic cardiovascular disease events in men and women in the Cardiovascular Lifetime Risk Pooling Project (adapted from reference 9)

Risk Factor Burden	Index Age							
	Age 45[a]		Age 55[a]		Age 65[b]		Age 75[b]	
	Men	Women	Men	Women	Men	Women	Men	Women
All optimal	**1.4%** (0–3.4)	**4.1%** (0–8.2)	**14.6%** (1.0–28.3)	**10.1%** (0–25.0)	**29.5%** (17.0–42.0)	**12.4%** (2.8–22.0)	**17.5%** (3.0–32.0)	**12.4%** (0–25.6)
≥1 Not optimal	**31.2%** (17.6–44.7)	**12.2%** (4.6–19.7)	**19.7%** (11.9–27.4)	**13.3%** (5.5–21.1)	**29.4%** (20.7–38.1)	**25.0%** (15.4–34.5)	**22.8%** (14.4–31.2)	**19.9%** (10.9–29.0)
≥1 Elevated	**35.0%** (26.8–43.2)	**15.6%** (10.3–20.9)	**33.9%** (27.9–39.8)	**15.3%** (11.3–19.3)	**38.2%** (32.4–43.9)	**29.3%** (23.8–34.7)	**28.9%** (22.7–35.2)	**21.8%** (16.8–26.8)
1 Major	**39.6%** (35.7–43.6)	**20.2%** (17.2–23.2)	**32.2%** (29.1–35.2)	**16.7%** (14.5–19.0)	**37.2%** (33.7–40.8)	**31.9%** (28.8–34.9)	**36.1%** (31.6–40.5)	**29.4%** (26.1–32.7)
≥2 Major	**49.5%** (45.0–53.9)	**30.7%** (26.3–35.0)	**46.8%** (43.0–50.7)	**29.2%** (26.2–32.3)	**49.5%** (45.2–53.8)	**38.7%** (35.3–42.1)	**38.5%** (32.0–45.0)	**36.3%** (32.2–40.4)

[a] To age 80; [b] to age 90

has a 64% chance of having a CVD event and a 35% chance of dying from non-CVD causes by age 90, with almost none surviving to age 90 years and being free from CVD. Conversely, for 45-year-old men with all optimal risk factors, there is a 43% chance of surviving to age 90 and being CVD-free, with 33% suffering a non-CVD death and 23% having a CVD event by age 90. These data all point to the importance of achieving and maintaining the ideal cardiovascular risk profile well into middle age.

Implications of the Ideal Cardiovascular Health Factor Profile

Whereas death is inevitable, evidence is strongly suggesting that promoting a pattern of ideal cardiovascular health in middle age will result in a longer life lived free of CVD and other diseases, including cancer.[10] Our research confirms that most single risk factors tend to stratify lifetime risk for cardiovascular disease moderately well, but imperfectly if considered alone. However, aggregate risk factor burden in adults at all ages appears to stratify lifetime risk extremely well.[8,9] Maintenance of this ideal cardiovascular health factor profile into middle and older age is clearly associated with minimal and dramatically reduced remaining lifetime risk for cardiovascular disease. In addition, individuals who have two or more major risk factors at age 50 years have a median life expectancy at least 12 years shorter than the all-optimal risk factor group.[8]

In other research from the Chicago Heart Association Detection Project in Industry,[1] these risk projections are also being replicated. The data also emphasize the point that increased risk factors not only increase the risk of CVD events, but also the risk of non-CVD death,[11] illustrating the importance of addressing risk factors that affect the total chronic disease burden in the remaining lifespan. Taking this research a step further, Daviglus et al found that those who had high risk factor burden in middle age (compared to those who had no risk factors in middle age) had significantly lower health-related quality of life 25 years later at aged 73 years.[12]

The financial implications of this risk factor/disease burden should also be considered in understanding the importance of maintaining all-optimal risk factors at middle age in terms of health care policy. Lower risk factor burden translates to substantially lower medical costs; thus as individuals become eligible for Medicare, their risk factor burden at age 45-50 will determine average annual and lifetime Medicare expenditures.[13]

Trends in Prevalence of Ideal Cardiovascular Health Factor Profile

Current research efforts are underway to define and quantify the prevalence of the ideal cardiovascular health factor profile and to determine if this ideal health pattern is more than the sum of the parts of the absence of any individual risk factor. From NHANES data (1970 – early 2000s), Ford et al found that, while prevalence of the ideal health factor pattern (low cholesterol, low blood pressure, no diabetes, no smoking, low BMI) increased in the early 1990s, the current obesity epidemic and ensuing increased rates of diabetes have contributed to trends making the ideal CV health factor profile less prevalent between 1999-2004 than between 1988–1994.[14] Ford et al also observed a greater decrease in the prevalence of the ideal CV health factor profile among the younger age group (25- to 44-year olds) compared to the older groups between the same two time periods. Ford also found that prevalence of the ideal CV health factor profile was greater among Whites and Mexican Americans compared to African Americans. The same trend of decreasing prevalence of the ideal profile in 1999-2004 vs 1988-1994 was seen among all the three groups.[14]

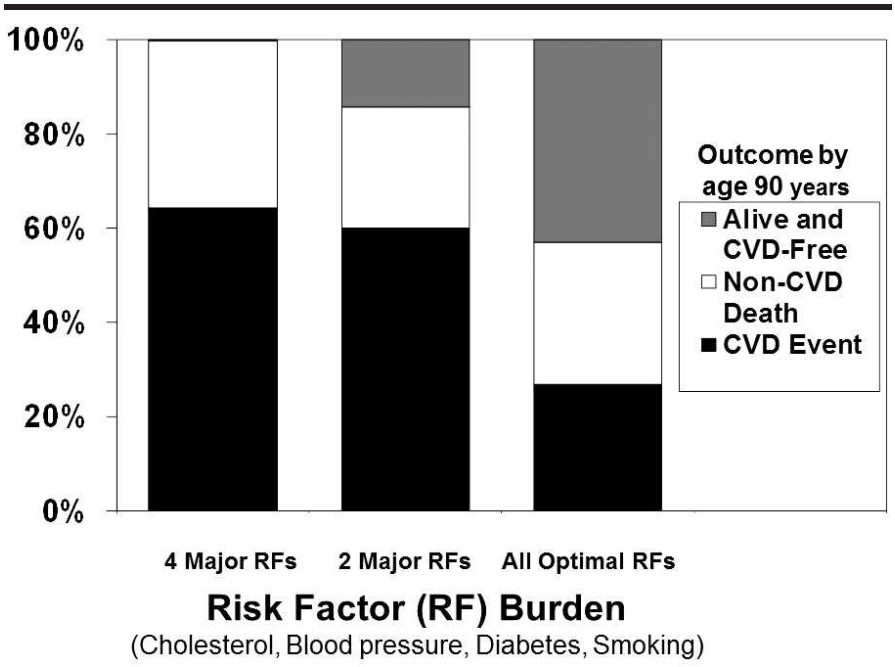

Fig 1. Remaining lifetime risks for CVD-free survival, CVD events or non-CVD death through age 90 for a 45-year-old male with selected risk factor burdens

An important question regarding the ideal CV health factor profile is whether its maintenance into middle age is due solely to genetics or more to environmental and behavioral influences. Our recent data from the Framingham Heart Study estimate that the heritability of having an ideal CV health factor profile in middle age is only 17%,[15] suggesting that the major influences from environment and lifestyle are largely responsible for maintaining an ideal CV health factor profile. New data from the CARDIA study[16] have shown the profound association between health behaviors in early adulthood and maintenance of the ideal health pattern into middle age. For example, in examining five health behaviors of a cohort aged <30 years (lean body mass index, no or only modest alcohol intake, top two quartiles of a healthy diet score, top two quartiles of physical activity and never having been a cigarette smoker), we found that, of those with no or only one of the ideal health factors before age 30, only approximately 3% reached middle age with the ideal health factor pattern. For those with all five healthy lifestyle factors, almost 60% reached middle age with the ideal health factor.[16] Similar associations were observed for white and African-American men and women.

A CALL TO ACTION: TURNING SCIENCE INTO POLICY

The concept of ideal cardiovascular health has become the centerpiece of the American Heart Association's (AHA) prevention efforts for the next decade.[17] AHA defines ideal cardiovascular health as "the presence of both ideal health behaviors (nonsmoking, body mass index <25 kg/m^2, physical activity at goal levels, and pursuit of a diet consistent with current guideline recommendations) and ideal health factors (untreated total cholesterol <200 mg/dL, untreated blood pressure <120/<80 mm Hg, and fasting blood glucose <100 mg/dL)."[17] For the first time in its history, the AHA 2020 strategic impact goals, while still working toward reducing CVD and stroke by 20%, also feature a commitment to ***improving the cardiovascular health*** of **all** Americans by 20%. Importantly, the AHA emphasizes that, to succeed, we must improve the cardiovascular health of **all** Americans – including Whites, Blacks, Hispanics, other minorities, underserved populations, and those with special needs.

While traditional risk factors will continue to be of major import in CV health, emerging science will help us understand and develop a solid research agenda for CVD prevention in African Americans. First, we must continue to examine and validate the importance of the ideal CV health factor profile for African Americans through the Jackson Heart Study data. Next, we must define genetic and lifestyle factors and their contributions to ideal cardiovascular health in African Americans, while exploring novel or unique gene interactions among people of African ancestry (eg, susceptibility to high sodium intakes). And, finally, we must design tests and implement public health and clinical policies that are aimed at primordial prevention (prevention of risk factor development in the first place, not just prevention of disease once risk factors develop).

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