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The Impact of Combined Health Factors on Cardiovascular Disease Mortality

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Abstract

Background—The combined effect of modifiable health factors on the risk of cardiovascular disease (CVD) mortality has not been well established. The objective of this study was to determine the association between five modifiable health factors in combination on the risk of CVD mortality in a sample of adult males.

Methods—A cohort of 38,110 men (aged 20 to 84 years and of middle and upper socioeconomic strata) was followed over time until their date of death or December 31, 2003. A health profile score (unweighted and weighted) was developed based on cardiorespiratory fitness (CRF; moderate or high vs. low), self-reported physical activity (active vs. inactive), smoking status (not current vs. current), alcohol consumption (1–14 drinks/wk vs. 0 or >14 drinks/wk), and body mass index (BMI; 18.5–24.9 kg/m^2 vs. ≥25.0 kg/m^2).

Results—During 16.1 ± 8.4 years of follow-up and 613,571 man-years of exposure, there were 949 deaths from CVD. High CRF, normal BMI, being physically active and not currently smoking were individually associated with reduced risk of CVD mortality, after adjusting for confounders. When considered in combination, a minimum of two out of five positive health factors reduced the risk of CVD mortality (HR=0.67; 95% CI 0.49–0.91). The weighted score indicated that a combination of high CRF, not currently smoking and normal BMI is of most clinical importance to CVD mortality (HR=0.31; 95% CI 0.24–0.39).

Conclusions—Exposure to increasing numbers of beneficial health factors in adulthood reduced the risk of CVD mortality in men, and multi-behavioral prevention efforts in adulthood should be encouraged.

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Introduction

Chronic diseases in an aging population are a major public health concern.[1] Cardiovascular disease (CVD) is a leading cause of death and begins to develop in early life.[2–5] Nonetheless, CVD remains a preventable condition and measures taken in early life and maintained over time have been hypothesized to reduce the risk of early CVD mortality.[3, 6]

Modifiable health factors such as low physical fitness, insufficient physical activity, certain dietary exposures, excess adiposity, cigarette smoking, and excess alcohol consumption throughout the lifetime are likely to contribute to CVD mortality.[7–14] At any one time, individuals are exposed to several positive and negative health factors, but few studies have determined the effect of health factors in combination with regard to CVD mortality in adulthood. The studies that have addressed this issue report that greater numbers of beneficial health factors in combination are associated with reduced risk of early mortality and incidence of chronic diseases (type 2 diabetes, stroke, coronary heart disease, and pancreatic cancer).[15–21]

Interestingly, these studies included participants that were middle-aged or older (≥40 years-old) and cardiorespiratory fitness (CRF) was not included as a modifiable health factor. Although physical activity (a behavior) is a primary determinant of CRF (physiological attribute), typical physical activity assessments are only modestly correlated with CRF, primarily due to misclassification in the physical activity measures.[22, 23] The health benefits associated with CRF are substantial, and especially pertinent with regard to CVD risk.[24, 25] We have reported preliminary data demonstrating a negative relationship between a combination of three beneficial health factors (non-smoker, waist circumference and high CRF) and risk of CVD mortality in men.[26] The purpose of this study was to expand on our previous work by determining the association between five health factors in combination with regard to CVD mortality, in a larger cohort of adult men aged 20 to 84 years old, with CRF included as one of the factors.

Methods

Study Participants

The current sample comprises adult males (n=38,110; aged 20 to 84 years-old) participating in the Aerobics Center Longitudinal Study (ACLS)[7], who completed baseline examinations at the Cooper Clinic, Dallas, TX, from 1974–2002. The participants regularly underwent preventive health examinations and received diet, exercise, and other lifestyle counseling with respect to the risk of chronic disease. Many participants were referred by their employers for the examination, with physician-referral and self-referral also taking place. All participants included in the sample were free of known CVD or cancer at baseline, had a body mass index (BMI) ≥18.5 kg/m^2, and achieved 85% of their age-predicted maximal heart rate (220 minus age) on a graded exercise treadmill test. These four criteria serve to create a baseline sample free from important underlying disease conditions. In terms of demographics, the majority of participants were white (96% white, 1% black and 3% other), well-educated, and from middle and upper socioeconomic strata. The study protocol was approved by the Institutional Review Board of the Cooper Institute on an annual basis.

Baseline Assessment

At baseline fasting blood withdrawals, detailed accounts of personal and family health history, anthropometric measurements, resting blood pressure measurements, and electrocardiogram tests were performed during a single clinic visit. The baseline examination procedures have been described in more detail elsewhere.[7, 24] In brief, a standard physician's scale and

stadiometer were used to measure weight and height respectively, from which BMI was calculated (kg/m^2). Blood pressure was measured after a quiet period of sitting, specifically as the first and fifth Korotkoff sounds by use of auscultation methods. The fasting blood samples were analyzed for lipids and glucose using automated bioassays in accordance with the Centres for Disease Control and Prevention Lipid Standardization Program. Hypercholesterolemia was defined as total cholesterol ≥240 mg/dL[27], low high density lipoprotein cholesterol (HDL-C) was defined as HDL-C <40 mg/dL, diabetes mellitus was defined as fasting plasma glucose levels ≥126 mg/dL, and hypertension was defined as resting blood pressure ≥ 140/90 mmHg. In addition, hypercholesterolemia, diabetes mellitus and hypertension were also considered present if they had been previously diagnosed by a physician. Standardized Cooper Clinic questionnaires were used to determine smoking habits (never, former or current smoker), alcohol intake (drinks per week; correcting for alcohol content, where one unit of alcohol was defined at 12 ounces of beer, 5 ounces of wine and 1.5 ounces of hard liquor), physical activity, and family history of CVD.

Physical activity was self-reported by participants at the clinic visit, who were asked to recall their usual patterns of regular physical activity in the 3 months prior to the examination. This approach has previously been reported to be a valid measure within the ACLS cohort.[28] From the responses, the participants were classified into one of three categories indicating physical activity level: low (no activity), moderate (walk, jog, or run up to 10 miles per week or participate in sporting or leisure-time physical activity other than walking, jogging or running such as swimming and cycling) or high (walk, jog, or run > 10 miles per week).[24]

Measured CRF was determined by a maximal treadmill exercise test using the modified Balke protocol.7, 29 The total time (minutes) spent on the treadmill was used as an index of aerobic power, which is highly correlated (r > 0.92) with measured maximal oxygen uptake in men.[30] This high correlation is based on men achieving maximal effort, and in order to increase the likelihood that time on treadmill was a good indicator of aerobic power, we excluded men who did not achieve at least 85% of age-predicted maximal heart rate on the test. From the symptom-limited maximal treadmill test, the participants were categorized into thirds depending on age-specific (20–29, 30–39, 40–49, 50–59, and ≥60 years-old) distributions of treadmill time.

Health-risk Profile

A health profile score was developed based on the number of beneficial health factors an individual was exposed to at baseline and both unweighted and weighted scores were considered. For the unweighted health profile score, each beneficial health factor was assigned score of 1 if deemed beneficial. The highest possible score was 5 [moderate alcohol consumption (1–14 drinks per week), moderate or high physical activity, moderate or high CRF (the upper two thirds), BMI between 18.5 and 24.9, and not a current smoker] and the lowest possible score was zero [not moderate alcohol consumption (none or >14 drinks per week), low physical activity, low CRF (the lowest third), BMI ≥25.0, and current smoker].

For the weighted health profile score, the β-coefficients from the full Cox proportional hazard model were transformed using the constant −0.2 to derive a clinical health-risk profile score; this approach has been used previously.[31, 32] Based on these clinical scores, an appropriate weight was given to each of the beneficial health factors.

Outcome Determination

The participants were prospectively followed from the date of their baseline examination until their date of death or December 31, 2003. CVD mortality was determined from the National Death Index (NDI) report or by review of death certificates; the latter being obtained from the department of vital records in the decedent's state of residence. CVD mortality was defined

by *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes 390 to 449.9 before 1999 and *Tenth Revision* (*ICD-10*) codes I00 to I78 during 1999–2003.

Statistical analysis

Baseline characteristics of the population are described by health-risk profile score. Cox proportional hazards regression was used to estimate hazard ratios (HRs), 95% confidence intervals (CIs) and CVD mortality rates (deaths per 10,000 person-years of follow-up) according to exposure categories. Multivariable analyses controlled for baseline measures: age (years) and year of examination (model 1); chronic medical condition (presence of hypertension, diabetes, and hypercholesterolemia) and family history of CVD (model 2). Cumulative hazard plots grouped by exposure suggested no appreciable violations of the proportional hazards assumption. We estimated population attributable risk (PAR) of CVD mortality for the five beneficial health factors to quantify the influence that modifying these factors might have on CVD death rates in our population sample.[33] In addition, we created a weighted health profile score from the transformed Cox proportional hazard model β-coefficients (using the constant −0.2); the Cox proportional hazard model included all five health factors and the covariates in models 1 and 2 described above. All *P* values were calculated assuming 2-sided alternative hypotheses; *P* values <.05 were taken to indicate statistically significant comparisons. All analyses were performed using SAS statistical software, version 9.1 (SAS Inc., Cary, NC).

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Results

The baseline characteristics of the 38,110 men included in our study are described in Table I. The majority of the participants attained 3 to 4 beneficial health factors (n=21,270). The associations between established CVD risk factors and health profile scores at baseline are presented in Table II. Apart from family history of CVD, all established CVD risk factors were inversely associated with increasing health profile scores at baseline.

There were 949 CVD deaths identified during an average of 16.1 ± 8.4 years of follow-up and 613,571 man-years of exposure. The relative risks of death from CVD for the five individual health factors are listed in Table III; the health factors that were associated with a higher risk of CVD mortality included being overweight or obese, currently smoking, low physical activity and low CRF.

The analyses regarding the association between the unweighted health profile scores with respect to CVD mortality are shown in Table IV. It was observed that the CVD mortality rate decreased with increasing health profile scores. A minimum score of two was shown to reduce the risk of CVD mortality. The strength of the protection increased per additional beneficial health factor attained and achieving a health risk profile score of five corresponded to a 67% reduced risk of CVD mortality. In terms of PAR, it is estimated that 42% (95% CI: 24%, 55%) of all CVD deaths in this population could potentially be eliminated if all men had been physically fit, refrained from smoking, were light alcohol consumers, were physically active, and had a normal weight. Sensitivity analyses were performed, excluding men who died within the first 2-years of their baseline visit. The results with these exclusions were similar to those presented.

The weighted health profile scores in Table IV were derived from the findings in Table V. The transformation of the β-coefficients (using the constant −0.2) ranked the health factors, and revealed the importance of moderate or high CRF (score=3), not currently smoking (score=2) and normal BMI (score=1) in terms of the risk of early CVD mortality (Table V). A weighted score of two was required to reduce the risk of CVD mortality. The highest weighted health profile score was 6 (moderate or high CRF, BMI between 18.5 and 24.9, and not a current smoker) and this was associated with a 69% reduced risk of early CVD mortality in our sample of men (Table IV).

Discussion

The results in the present study indicated that having at least two of the five beneficial health factors reduced the risk of CVD mortality by 33% in adult men compared to those having no beneficial health factors. Furthermore, the risk of CVD mortality was reduced incrementally per increase in health profile score, and attaining all five beneficial health factors reduced the risk of CVD mortality by 67% in our sample of adult males. Our weighted analysis, which accounts for the five health factors having varying degree of importance, showed that a combination of moderate to high CRF, not currently smoking and being normal BMI is of high clinical importance (reduced the risk of CVD mortality by 69%).

These findings expand upon our earlier work which included 14,453 fewer participants (aged 30–79 years), with 643 fewer CVD deaths, over a shorter period of follow-up. This earlier study reported that there was a 45–77% risk reduction in CVD mortality among men with a health score ranging from 1 to 3 (high CRF, normal waist girth, and non-smoker), in comparison to men with a health score of zero.[26]

It should be noted that there was no plateau in the reduced risk between health profile scores of four and five (unweighted) or five and six (weighted), and it is unknown if further beneficial health factors considered in combination would continue to reduce the risk of CVD mortality. A plateau effect is likely at some point since beneficial exposures in adulthood alone would have to overcome genetic predispositions, potential epigenetic mechanisms associated with CVD[34], and exposures *in utero*[6], and during childhood or adolescence that have been linked to CVD in later life.[3]

Our results also complement previous studies, which found that increasing numbers of beneficial health factors in combination reduce the risk of early mortality or the incidence of chronic disease.[15–17, 19–21] In addition, all of the previous studies have reported reduced risks of early mortality, or chronic disease incidence, per increase in health profile score, which aligns with our findings.[15–17, 19–21]

The strengths of associations reported do vary between studies, and a reason for this may be due to the different outcomes being investigated. Some adopt all-cause mortality or a cause-specific mortality, whereas others have adopted the incidence of a specific chronic disease as the dependent variable. Furthermore, each health profile score varies in terms of the health factors included and the definition of comparable health factors.

A recent study by Ford et al. found that out of 4 health factors (smoking status, BMI, physical activity and diet), never smoking and having a BMI <30 kg/m^2 were especially important with regard to the incidence of chronic disease in general.[35] We observed similar results from our weighted health score analysis, with CRF being additionally important with regard to CVD mortality. From a clinical standpoint, individuals should be counseled to achieve a health profile score of at least two and priority combinations of health factors should include moderate or high CRF, not smoking and normal BMI to protect against CVD mortality in men.

The major strengths of our study include the use of laboratory determined CRF as a health factor, the large number of participants, the prospective study design, and the extensive man-years of follow-up. No studies, other than our earlier work, have included CRF as a health factor. [26] This objective measure has been shown to be strongly, and independently, associated with reduced risk of CVD mortality.[24, 25] As such, its inclusion as a health factor is important given the outcome variable. Nonetheless, there are limitations that need to be considered. Our sample comprised adult men, who were predominantly white and from high socio-economic backgrounds; this of course limits the generalizability of our findings only to such demographic groups, but strengthens the internal validity. Self-reported physical activity and alcohol consumption can be somewhat difficult to accurately recall, and there is a potential for social desirability that may lead to over-reporting of physical activity and under-reporting of alcohol consumed.[36] Self-reported smoking status does not take into account the number of cigarettes smoked by past and present smokers. Each of the five health factors were given equal weight when determining the health-risk profile score, which does not take into account the possibility that the health factors may have a varying degrees of impact on CVD mortality. However, this most likely leads to a conservative effect size. Our health risk profile score was lacking a well measured dietary variable; however, the inclusion of an objective measure of CRF is unique to our study. Our health profile score was determined from five variables measured at a single point in time and did not take into account any change in these variables over time. Finally, residual confounding is likely as this was an observational study and such studies are unable to adjust for all known and unknown confounding variables.

In conclusion, there are multiple points throughout the lifetime where adverse exposures can contribute to the development of CVD. A health profile score of at least two can reduce the risk of CVD mortality in men, and moderate to high CRF, not smoking and normal weight are of most clinical importance to reduce the risk of CVD mortality.

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Table I

Baseline characteristics of the male participants combined and by unweighted health profile score

	Health Profile Score						
	All	**0**	**1**	**2**	**3**	**4**	**5**
	(n=38,110)	**(n=663)**	**(n=3,490)**	**(n=6,654)**	**(n=9,686)**	**(n=11,584)**	**(n=6,033)**
Age (y)	43.8±9.6	43.9±8.8	44.1±9.2	44.2±9.5	44.5±9.6	43.8±9.6	42.0±9.7
BMI (kg/m^2)	26.5±14.9	28.9±3.7	29.0±4.3	28.6±3.5	27.1±3.4	25.6±2.8	23.2±1.3
Maximal METs	11.7±2.4	8.8±1.3	9.2±1.3	9.9±1.6	11.3±1.9	12.8±2.0	13.9±2.1
SBP (mmHg)	122±13	124±14	124±14	123±14	122±13	121±13	119±13
DBP (mmHg)	81±10	83±10	83±10	83±10	82±9	81±9	78±9
Total cholesterol (mg/dL)	208.9±40.5	219.4±39.5	220.3±41.3	215.7±39.2	211.8±40.0	204.6±41.2	196.8±36.8
HDL-C (mg/dL)	46.2±12.3	39.4±11.2	40.9±11.0	42.6±11.3	45.0±11.7	47.8±12.4	51.3±12.3
Fasting glucose (mg/dL)	100.2±16.7	104.0±12.3	104.2±25.4	102.7±21.4	100.4±15.2	98.6±12.4	97.1±11.6
Physical activity (%)*							
Low	29.2	100	88.1	60.0	25.9	7.6	0
Moderate	52.3	0	11.4	35.8	59.2	65.3	63.7
High	18.5	0	0.5	4.3	14.9	27.1	36.3
Smoking status (%)							
Never	48.1	0	23.9	36.3	46.9	58.6	62.4
Former	32.9	0	22.6	32.3	33.9	34.9	37.6
Current	19.0	100	53.6	31.4	19.2	6.5	0
Alcohol intake (drinks/wk)	5.0±7.1	6.2±12.3	5.1±9.4	5.1±8.4	5.3±7.8	4.7±5.7	4.7±3.5
Family history of CVD (%)	26.5	31.7	30.1	29.1	26.9	25.1	23.1

Data are means ± standard deviations unless indicated otherwise.

BMI, body mass index; METs, metabolic equivalents derived from graded treadmill test; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; CVD, cardiovascular disease;

*Leisure-time physical activity in the 3 months before the examination

Table II

Baseline associations between CVD risk factors and unweighted health profile scores

Health Profile Score	Hypertension*	Hypercholesterolemia†	Diabetes‡	Low HDL-C§	Family history of CVD
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
0	1.00	1.00	1.00	1.00	1.00
1	0.92 (0.78–1.10)	1.11 (0.91–1.34)	0.87 (0.65–1.15)	0.83 (0.68–1.02)	0.95 (0.79–1.14)
2	0.82 (0.70–0.97)	0.90 (0.75–1.08)	0.73 (0.55–0.95)	0.68 (0.56–0.83)	0.95 (0.79–1.13)
3	0.68 (0.57–0.80)	0.77 (0.64–0.92)	0.59 (0.45–0.78)	0.50 (0.41–0.60)	0.88 (0.74–1.05)
4	0.52 (0.45–0.62)	0.55 (0.46–0.67)	0.49 (0.37–0.64)	0.32 (0.27–0.39)	0.86 (0.72–1.03)
5	0.36 (0.30–0.43)	0.35 (0.29–0.43)	0.55 (0.41–0.74)	0.22 (0.18–0.27)	0.85 (0.71–1.02)

CVD, cardiovascular disease; OR, odds ratio; CI, confidence interval; HDL-C, high density lipoprotein cholesterol.

All models are adjusted for age (years), examination year, and each of the other CVD risk factors.

*Hypertension, SBP/DBP of 140/90 mmHg or history of physician diagnosis;

†Hypercholesterolemia, total cholesterol ≥240 mg/dL or history of physician diagnosis;

‡Diabetes, fasting glucose ≥126 mg/dL or history of physician diagnosis;

§Low HDL-C, HDL-C <40 mg/dL.

Table III

Hazard ratios relating to CVD mortality according to the five health risk factors

Health Factor	No. at risk (# deaths)	Model 1* HR (95% CI)	Model 2† HR (95% CI)
BMI (kg/m^2)			
18.5–24.9	14,728 (312)	1.00	1.00
25.0–29.9	18,007 (457)	1.41 (1.22–1.62)	1.26 (1.10–1.47)
≥30.0	5,375 (180)	2.76 (2.30–3.33)	2.20 (1.82–2.66)
Smoking Status			
Never	18,342 (283)	1.00	1.00
Former	12,531 (405)	1.10 (0.95–1.28)	1.04 (0.90–1.22)
Current	7,237 (261)	1.79 (1.51–2.12)	1.76 (1.49–2.09)
Alcohol intake (drinks per week)			
None	10,554 (466)	1.00	1.00
Light (1–14)	24,371 (444)	0.89 (0.78–1.02)	0.88 (0.77–1.00)
Moderate and heavy (>14)	3,185 (39)	0.94 (0.67–1.31)	0.87 (0.63–1.22)
Physical activity‡			
High	7,066 (126)	1.00	1.00
Moderate	19,925 (411)	0.97 (0.80–1.19)	0.94 (0.77–1.15)
Low	11,119 (412)	1.33 (1.08–1.63)	1.22 (1.00–1.50)
Cardiorespiratory fitness			
Highest third	12,576 (150)	1.00	1.00
Middle third	12,818 (229)	1.31 (1.07–1.61)	1.22 (0.99–1.50)
Lowest third	12,716 (570)	2.56 (2.14–3.07)	2.22 (1.85–2.67)

BMI, body mass index; HR, hazard ratio; CI, confidence interval.

*Adjusted for age (years), and examination year;

†adjusted for age (years), examination year, hypertension, diabetes, hypercholesterolemia, low HDL-C, and family history of CVD;

‡leisure-time physical activity in the 3 months before the examination.

Table IV

Hazard ratios related to CVD mortality according to health profile scores

Unweighted Health Profile Score				Weighted Health Profile Score			
Health Profile Score	**Rate* (#deaths)**	**Model1† HR (95% CI)**	**Model 2‡ HR (95% CI)**	**Health Profile Score**	**Rate* (#deaths)**	**Model1† HR (95% CI)**	**Model 2‡ HR (95% CI)**
0	33.0 (49)	1.00	1.00	0	32.8 (145)	1.00	1.00
1	26.9 (193)	0.82 (0.60–1.12)	0.86 (0.63–1.18)	1	26.3 (54)	0.80 (0.59–1.10)	0.87 (0.64–1.19)
2	20.5 (255)	0.62 (0.46–0.84)	0.67 (0.49–0.91)	2	22.1 (288)	0.67 (0.55–0.82)	0.65 (0.53–0.80)
3	14.5 (216)	0.44 (0.32–0.60)	0.50 (0.36–0.68)	3	16.2 (119)	0.50 (0.39–0.63)	0.56 (0.44–0.72)
4	10.8 (171)	0.33 (0.24–0.45)	0.39 (0.28–0.53)	4	11.5 (26)	0.35 (0.23–0.53)	0.43 (0.28–0.65)
5	8.9 (65)	0.27 (0.19–0.39)	0.33 (0.22–0.47)	5	12.0 (168)	0.37 (0.29–0.46)	0.39 (0.31–0.48)
				6	8.6 (149)	0.26 (0.21–0.33)	0.31 (0.24–0.39)

CVD, cardiovascular disease; HDL cholesterol, high density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval;

*Rate per 10,000 person-years adjusted for age, and examination year;

†Adjusted for age (years), and examination year;

‡Adjusted for age (years), examination year, hypertension, diabetes, hypercholesterolemia, low HDL cholesterol, and family history of CVD.

Weighted health profile score is derived from the beta coefficients from Table V. The beta coefficients were transformed using the constant −0.2; the weighted health profile score ranges from 0 to 6 where moderate alcohol=0, moderate-to-high PA=0, normal weight=1; non-current smoker=2; and moderate-to-high cardiorespiratory fitness=3

Table V

Clinical health profile points for the reduced risk of CVD mortality

Health Factor	β-coefficient*	Health profile points†
Normal BMI (18.5–24.9 kg/m^2)	−0.19283	1
Not current smoker	−0.42131	2
Light alcohol intake (1–14 drinks/week)	−0.09230	0
Physical activity (moderate or high)	0.09274	0
Cardiorespiratory fitness (moderate or high)	−0.60082	3

CVD, cardiovascular disease;

*Adjusted for age (years), examination year, hypertension, diabetes, hypercholesterolemia, low HDL cholesterol, family history of CVD, and each of the individual health factors;

†Health profile points were determined by transforming the β-coefficient, using the constant −0.2 (higher score is better)