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Vital Exhaustion and Sudden Cardiac Death in The Atherosclerosis Risk in Communities Study

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Abstract

Objective—Vital exhaustion (VE), a construct defined as lack of energy, increased fatigue and irritability, and feelings of demoralization, has been associated with cardiovascular events. We sought to examine the relation between VE and sudden cardiac death (SCD) in the Atherosclerosis Risk in Communities (ARIC) Study.

Methods—The ARIC Study is a predominately biracial cohort of men and women, aged 45–64 at baseline, initiated in 1987 through random sampling in 4 US communities. Vital exhaustion (VE) was measured using the Maastricht questionnaire between 1990–1992 among 13,923 individuals. Cox proportional hazards models were used to examine the hazard of out-of-hospital SCD across tertiles of VE scores.

Results—Through 2012, 457 SCD cases, defined as a sudden pulseless condition presumed due to a ventricular tachyarrhythmia in a previously stable individual, were identified in ARIC by physician record review. Adjusting for age, sex, and race-center, participants in the highest VE tertile had an increased risk of SCD (HR=1.48 95% CI: 1.17–1.87), but these findings did not remain significant after adjustment for established cardiovascular disease risk factors (HR=0.94 95% CI: 0.73–1.20).

Conclusions—Among participants of the ARIC study, VE was not associated with an increased risk for SCD after adjustment for cardiovascular risk factors.

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INTRODUCTION

Vital exhaustion (VE), a construct defined as lack of energy, increased fatigue and irritability, and feelings of demoralization, was conceptualized to explain observed complaints of fatigue and lack of energy preceding myocardial infarction (MI) and sudden cardiac death (SCD).¹ VE is postulated to arise due to chronic physiological overburdening which eventually cannot be counteracted. To quantify VE, the Maastricht questionnaire uses items to maximize its predictive power of MI and cardiac death.^{2,3}

Studies have demonstrated an association between VE and various cardiovascular disease endpoints.⁴⁻⁸ VE is hypothesized to be prodromal to SCD¹ based on small studies^{9,10} and animal models¹¹ from the 1950s to 1970s linked hopelessness, fatigue, and depression to SCD. Few studies have examined the association between VE and SCD as an independent endpoint.^{12,13} These studies are primarily small, retrospective, have short follow-up, and primarily use proxies to assess decedent VE. Additionally, the association between VE and SCD has not been contemporarily examined within the United States. The Atherosclerosis Risk in Communities (ARIC) Study is opportune to prospectively evaluate this association within a large biracial cohort with an extended follow-up period using self-assessed VE. We tested the hypothesis that increased VE is associated with a higher risk of SCD in the ARIC Study.

METHODS

Study Population

Details of the ARIC study are described elsewhere.¹⁴ Briefly, the ARIC Study is a predominately biracial cohort of men and women, aged 45 to 64 at baseline, initiated in 1987 through random sampling in four US communities: Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and Minneapolis, Minnesota. A total of 15,792 participants attended the baseline examination. Follow-up among ARIC cohort participants is conducted annually via telephone interviews, community surveillance of hospitalizations, death certificates, and through periodic in-person examinations.¹⁵ The Maastricht questionnaire was administered at the second examination (1990-1992). Participants were excluded if they did not attend the second examination (n=1,444), were not black or white (n=44), or did not complete the entire Maastricht questionnaire (n=334). Black participants attending Minneapolis, Minnesota and Washington County, Maryland centers were also excluded due to small numbers (n=47).

Definition of Sudden Cardiac Death

Fatal cardiovascular disease (CVD) events occurring out-of-hospital or in emergency rooms through December 31, 2012 were reviewed and adjudicated by a committee of electrophysiologists, general cardiologists, and internists in two phases: the first phase evaluated CVD deaths occurring through December 31, 2001¹⁶; the second phase evaluated CVD deaths between January 1, 2002 and December 31, 2012. In both phases, events were adjudicated independently by two committee members and disagreements were resolved via a third reviewer who participated in both phases to ensure phenotype consistency. Reviewers

examined available data from death certificates, informant interviews, physician questionnaires, coroner reports, prior medical history, hospital discharge summaries, and medical records.

SCD was defined as a sudden pulseless condition presumed due to a ventricular tachyarrhythmia in a previously stable individual without evidence of a non-cardiac cause. Non-cardiac causes included acute non-cardiac morbidities such as drug overdose, stroke, aortic aneurysm rupture, other acute bleeding, pulmonary embolism, acute respiratory failure, or trauma. For witnessed cases, SCD was operationally defined as a sudden collapse (pulseless condition) without evidence of a non-cardiac cause of cardiac arrest. For unwitnessed cases, we required evidence of a stable condition within 24 hours preceding death without evidence of a non-cardiac cause of cardiac arrest. We sought to exclude classifying death as SCD in participants with nonarrhythmic characteristics, evidence of progressive hypotension, advanced decompensated congestive heart failure, chronic terminal illnesses or severe dementia, or if the participant was severely debilitated, required long-term care, or in a nursing home at the time of the death. Inter-reviewer agreement was 83.2%, and there was 92.5% agreement in a re-review of a sample of cases from the first phase by second phase committee members.

To permit a robust comparison with prior studies, two additional definitions of sudden cardiac death were examined: fatal CHD within 1 hour of symptom onset (FCHD-1) and fatal CHD within 24 hours of symptom onset (FCHD-24). FCHD-1 is a common definition of sudden cardiac death in longitudinal studies and FCHD-24 was an endpoint examined in prior VE studies. Both FCHD-1 and FCHD-24 were restricted to out-of-hospital definite or possible CHD events, defined as fatal CHD with chest pain 72 hours before death or a history of chronic ischemic heart disease. Known non-atherosclerotic/non-cardiac causes of death were excluded. Informant interviews were used to establish symptom onset within 1 hour (FCHD-1) or 24 hours (FCHD-24) prior to death. All FCHD-1 events were also classified as FCHD-24 events.

We also separately considered the union and intersection of all sudden cardiac death definitions. Deaths were SCD-Union if classified as SCD, FCHD-1, or FCHD-24. Deaths were SCD-Intersection if the criteria for both SCD and FCHD-1 were satisfied. These classifications were derived to understand if the estimated effect of VE on sudden cardiac death varied under a broad (SCD-Union) and a specific (SCD-Intersection) SCD definition.

Vital Exhaustion Measurement

The Maastricht Questionnaire² was administered to 14,348 participants of the second ARIC examination. Participants attending the Jackson, Mississippi center had their questionnaire administered via an interview and all other participants completed a written questionnaire. The questionnaire consists of 21 questions (Figure 1). Each response was scored 0 for “No”, 1 for “Don’t Know” and 2 for “Yes” (reverse scoring for questions 9 and 14). VE scores ranged from 0 to 42 points.

Covariates

Trained interviewers ascertained date of birth, race, sex, and education level at the first examination. Age at the date of the second examination was calculated. All other covariates were determined at the second examination. Interviewers ascertained current cigarette smoking status and medication use. Body mass index was calculated as weight (kg) over height (m^2). Prevalent CHD was defined as prevalent MI using electrocardiogram (ECG) at the second examination, self-reported CHD event preceding baseline, or an adjudicated CHD event between baseline and second examination. Prevalent heart failure was defined as a heart failure hospitalization prior to the second examination or on heart failure medication within two weeks of the second examination. Diabetes mellitus was defined as fasting glucose ≥ 126 mg/dL or non-fasting glucose ≥ 200 mg/dL, self-report of diabetes mellitus diagnosis, or diabetes medication use within two weeks of the examination. Sitting systolic and diastolic blood pressure were measured by calculating the average of the second and third of three measurements using a random zero sphygmomanometer.¹⁴ Total cholesterol was measured using enzymatic methods and high density lipoprotein cholesterol was measured using the dextran sulfate magnesium method.¹⁴

Statistical Analysis

To be consistent with several studies,^{2,5,17} participants were partitioned into tertiles by Maastricht questionnaire score. “Low VE” participants had VE scores in the first tertile (scores between 0 to 4), “Moderate VE” participants had scores between 5 and 12, and “High VE” participants were in the third tertile (scores between 13 and 42). “Low VE” served as the reference category. In a sensitivity analysis, we also divided participants by quartiles of VE score. Our primary analysis compared the risk of SCD between participants in the Low and High VE groups. Tests for differences in means were assessed using one-way ANOVA for continuous variables, using chi-squared tests for independence for categorical variables, and using two-sided z-tests for incidence rates.

Separate analyses were performed for SCD, FCHD-1, FCHD-24, SCD-Union, and SCD-Intersection. Cox proportional hazards models were fitted for each definition, and follow-up was the number of days between the participant’s exam date and death or December 31, 2012, whichever was first. Participants who experienced a non-SCD death or were lost to follow-up prior to December 31, 2012 were right censored. The proportional hazards assumption was verified by plotting the standardized cumulative observed martingale residuals versus follow-up and simulating cumulative martingale residuals under the supposition that model assumptions held. Then, the hypothesis that the observed values lie outside of the simulated patterns was tested.¹⁸ A log-rank test tested for equivalence between Kaplan-Meier product-limit cumulative survival estimates for Moderate and High VE tertiles compared to Low VE. Tukey’s method for multiple comparisons was used where appropriate and differences were considered significant at a p -value < 0.05 . We also examined the sensitivity of follow-up duration by assessing a 4-year follow-up period after the participant’s second examination.

Two models were considered. Model 1 adjusts for age, sex, and race-center. Model 2 further adjusts for systolic and diastolic blood pressure, total cholesterol, high density lipoprotein

cholesterol, current smoking status, body mass index, prevalent CHD, diabetes mellitus, education level, and hypertensive medication use. To test the influence of prevalent CHD on our results, we compared Model 1 and Model 2 hazards ratios to ratios after refitting these models but excluding participants with prevalent CHD diagnosis at the second examination. We also compared hazards ratios from Model 2 to ratios from a model without the inclusion of prior CHD diagnosis as a covariate. We replicated these comparisons to examine the influence of heart failure at baseline. Because other outcomes are competing risks for sudden cardiac death, we estimated the risk of subdistribution hazards of VE on the cumulative incidence of sudden cardiac death, using methods described by Fine and Gray.¹⁹ All analyses were performed using SAS 9.3 (Cary, North Carolina).

RESULTS

Of 14,257 participants meeting race/center inclusion criteria who attended the second examination, 13,923 (97.7%; 24% black and 55% female) completed the Maastricht questionnaire. There were 4,464 participants with Low VE, 4,869 participants with Moderate VE, and 4,590 participants with High VE.

Compared to participants with Low VE, participants with High VE were older (56.6 vs. 57.3 years), a higher proportion were female (40.0% vs. 68.8%), a lower proportion were white (81.6% vs. 69.1%), and fewer had completed high school (86.3% vs. 68.7%), and higher proportion exhibited cardiovascular disease risk factors (Table 1). For example, 11.3% of those with Low VE had diabetes compared to 20.0% of those with High VE; 18.3% of Low VE participants were smokers compared to 26.1% of High VE participants; 5.2% of those with Low VE had prevalent CHD compared to 9.9% of High VE participants.

During a median 21.2 years of follow-up (280,938 total person-years), 457 SCD events occurred. SCD incidence was higher among those with High VE compared to Low VE (1.98, 95% CI: 1.69-2.27 vs. 1.47, 95% CI: 1.22-1.72 per 1000 person-years) (Table 2).

Upon adjustment for demographic covariates only (Model 1), we found that participants with High VE had a significant increase in SCD risk (Table 3, HR: 1.48, 95% CI: 1.17-1.87), and the Kaplan-Meier survival function differed significantly between the two groups (Figure 2). However, upon additional adjustment (Model 2), no significantly different relative risk was observed (Table 3, HR: 0.94, 95% CI: 0.73-1.20). Moderate VE participants did not have a relatively increased risk for SCD.

Other Sudden Cardiac Death Definitions

During follow-up, 247 FCHD-1, 445 FCHD-24, 564 SCD-Union, and 199 SCD-Intersection events occurred. The positive predictive value of FCHD-1 to classify SCD was 80.6% and was 76.1% for FCHD-24 (Supplementary Table 1). Overall, results for these definitions were similar to our primary SCD endpoint: Model 1 hazards ratios were significantly higher for High VE participants but was not under Model 2 (Table 3). The Kaplan-Meier product-limit survival functions for High VE statistically differed from Low VE for every definition except for SCD-Intersection (Figure 3).

Sensitivity Analyses

Excluding those with prevalent CHD or heart failure at baseline or adjusting for those conditions in Model 2 did not significantly influence any conclusions. Using quartiles instead of tertiles of VE score did not alter results. We observed similar results over a shorter follow-up (four-years); however, High VE was positively associated with FCHD-24 in Model 2 (Supplementary Table 2). Using a competing risks approach to assess subdistribution hazards over the longer follow-up period (through 2012) also produced similar results (Supplementary Table 3).

DISCUSSION

Among ARIC participants, we observed a modest increase in SCD risk among those scoring in the highest tertile of VE in analyses adjusted for demographic characteristics, but this was attenuated upon adjustment for cardiovascular risk factors. This suggests that VE at mid-life, as measured by the Maastricht questionnaire, is not associated with an increased risk of SCD. This conclusion is robust to various definitions of SCD.

While a larger proportion of High VE participants experienced SCD compared to those with lower scores, they also exhibited a higher burden of cardiovascular disease risk. Therefore, it was not surprising that adjustment for these variables attenuated the modest association between VE and SCD.

Most studies exploring the association between VE and cardiac events do not separately report SCD. Appels¹ reported that males who experienced MI or SCD over 10 months had higher baseline VE scores than participants who did not experience SCD or MI. Maastricht questionnaire items were selected^{2,3} to maximize its predictive power for hard coronary outcomes (MI/cardiac death) during a case-control study of Dutch men over four years, but the majority of these events were nonfatal MIs.² The relative risk of coronary events was the highest for those scoring in the highest tertile of VE, but multivariate adjustment for risk factors was not utilized. A non-significant age-adjusted association between fatal cardiac events and VE (relative risk: 1.39, 95% CI: 0.59-3.25) was also reported among.⁴ Although this result is most similar to our findings, the temporal nature of death was not ascertainable because fatal events were obtained only via death certificate. The Copenhagen City Heart Study reported hazards ratios for CHD of 2.36 (95% CI: 1.70–3.26) in men and 2.07 (95% CI: 1.48–2.88) for women,⁸ but these effects may be inflated since a stepwise-selection method was employed without applying shrinkage methods.²⁰ Williams et al. observed an increased risk for acute MI or fatal CHD among ARIC participants with the highest quartile of VE scores (HR=1.46, 95% CI:1.20-1.79) but fatal and nonfatal events were not examined separately.⁷ Our study is a natural extension to Williams et al.,⁷ as we evaluate a subset of fatal CHD events within the same population. Fully adjusted hazards ratios in our study are significantly lower than those reported by Williams et al. This suggests that VE may increase the risk of CHD in general but may not be specific to SCD. One limitation to our study is that truly elevated hazards ratios may have not been detected since our study, like many longitudinal studies with rare events, may have a low statistical power.

The lack of studies specifically examining SCD is intriguing considering how early hypotheses postulated fatigue or exhaustion as prodromal to SCD.^{1,9} To our knowledge, there are only two studies that do so and both differ from our study design. In a retrospective case-control study, next-of-kin completed the Maastricht questionnaire for decedents and judged if decedents were “emotionally closed” (socially inhibited).¹³ VE scores were significantly higher for SCD (within 24 hours) victims compared with deceased controls with history of CHD. Upon multivariate adjustment, “emotionally closed” vitally exhausted participants had a seven-fold increase in SCD risk. VE also increased the risk of SCD (OR: 2.81, 95% CI: 1.1-7.3) compared to controls without CHD.¹² There are several limitations of these studies^{12,13}, including a limited ability to assess temporal associations due to retrospective design. Proxy-completed Maastricht questionnaires may be inaccurate because items are introspective and personal. Women have demonstrably higher VE scores⁶ and lower rates of SCD than men,^{21,22} but few women were included in older studies, possibly biasing the reported relationship between VE and SCD in the general population.

To our knowledge, our study is among the few that assess the relationship between VE and SCD, and the only to do so prospectively with long follow-up. We observed similar results for short- and long follow-up, suggesting that the association of VE with SCD is not influenced by time. Although results from short follow-up should be cautiously interpreted due to the small number of events, they diverge from previous reports suggesting a monotonic decrease over time in risk of cardiac death due to exhaustion.²³

We note that High VE was associated with FCHD-24 even after adjustment, which may corroborate other studies using a 24-hour definition.^{12,13} We also note that Moderate VE was associated with multiple endpoints after adjustment, but this effect was modest (hazards ratios nearly intersected 1) and was not observed for the most rigorously adjudicated SCD definition.

Clinical and autopsy studies have demonstrated a predominant, common pathophysiology of SCD in Western populations: the most common electrophysiologic mechanism for SCD is ventricular fibrillation and the most common pathogenesis is coronary artery disease. Nonetheless, SCD is difficult to ascertain and there is no uniform agreement on how to operationally define SCD.²⁴ Without autopsy and clinical data, it is nearly impossible to have assurance regarding the cardiac nature of the event. Furthermore, time of death must be estimated if unwitnessed. SCD in studies by Appels et al.^{12,13} was defined as unexpected cardiac death within 24 hours of symptom onset, but adjudication and exclusions were not described. SCD ascertainment is well-documented in ARIC. While it is possible that our differing conclusions may be attributable to the outcome definition, our conclusions were predominately consistent for several SCD endpoints.

Despite our findings, several studies report positive associations between sudden cardiac death or ventricular arrhythmias and behavioral and psychosocial risk factors related to VE,^{25,26} including depression,²⁷ anger,¹⁷ stress, and fatigue.²⁸ Depression has been linked to a reduced heart rate variability,²⁹ which is associated with arrhythmias and sudden cardiac death.³⁰ It is not well understood if these conditions influence the development of coronary heart disease or acutely induce the arrest.²⁶

In deriving the Maastricht questionnaire, MI and SCD were combined into a common outcome but only a small portion were SCD.² Thus, the questionnaire may be composed of items that are not optimally predictive of SCD. A subset of existing questions or questions removed in earlier versions may be more strongly associated with SCD. We leave analysis of item-specific association and optimizing the questionnaire for SCD to future work. Although contrary to expectation, our findings, combined with the strengths of the ARIC Study design, justify a further examination of the relation of psychosocial stressors with sudden cardiac death.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY QUESTIONS**What is already known about this subject?**

Vital exhaustion, a construct defined as lack of energy, increased fatigue and irritability, and feelings of demoralization, has been associated with cardiovascular events.

What does this study add?

Among Atherosclerosis Risk in Communities Study participants, we did not find an association between vital exhaustion and any definition of sudden cardiac death over either short- or long-term follow-up upon adjustment. This is the first study to examine vital exhaustion specifically in relation to sudden cardiac death in a biracial, prospective cohort within the United States. It is also the first to examine the association of vital exhaustion with sudden cardiac death as the primary endpoint over a long follow-up period.

How might this impact on clinical practice?

Sudden death events supported the original conceptualization and questionnaire used to assess vital exhaustion. However, based on our findings, it may be more accurate to view vital exhaustion as possible precursor to more prevalent cardiovascular disease events than as a predictor specific to sudden cardiac death.

Instructions:

For the next series of questions, please answer Yes or No, whichever best describes you. If you cannot decide or don't know, please indicate "Don't Know".

1. Do you often feel tired?
2. Do you often have trouble falling asleep?
3. Do you wake up repeatedly during the night?
4. Do you feel weak all over?
5. Do you have the feeling that you haven't been accomplishing much lately?
6. Do you have the feeling that you can't cope with everyday problems as well as you used to?
7. Do you believe that you have come to a "dead end"?
8. Do you lately feel more listless than before?
9. I enjoy sex as much as ever.
10. Have you experienced a feeling of hopelessness recently?
11. Does it take more time to grasp a difficult problem than it did a year ago?
12. Do little things irritate you more lately than they used to?
13. Do you feel you want to give up trying?
14. I feel fine.
15. Do you sometimes feel that your body is like a battery that is losing its power?
16. Would you want to be dead at times?
17. Do you have the feeling these days that you just don't have what it takes any more?
18. Do you feel dejected?
19. Do you feel like crying sometimes?
20. Do you ever wake up with a feeling of exhaustion and fatigue?
21. Do you have increasing difficulty in concentrating on a single subject for long?

FIGURE 1.

Maastricht Questionnaire Administered to Atherosclerosis Risk in Communities Study Participants.

FIGURE 2.

Kaplan-Meier Product-Limit Survival Estimates for Sudden Cardiac Death, by Tertile.

Asterisks indicate that the corresponding curve statistically differs from Low Vital Exhaustion (p-value < 0.05).

FIGURE 3.

Kaplan-Meier Product-Limit Survival Estimates by tertile for: (a) Fatal Coronary Heart Disease within 1 hour, (b) Fatal Coronary Heart Disease within 24 hours, (c) Sudden Cardiac Death-Union, (d) Sudden Cardiac Death-Intersection. Asterisks indicate that the corresponding curve statistically differs from Low Vital Exhaustion (p -value < 0.05).

TABLE 1

Characteristics of participants by tertile of vital exhaustion score

Variable	Low vital exhaustion N=4464	Moderate vital exhaustion N=4869	High vital exhaustion N=4590	p-value
Age, years	56.6 (5.6)	57.0 (5.7)	57.3 (5.8)	<0.001
Female, %	40.0%	56.0%	68.8%	<0.001
White, %	81.6%	75.9%	69.1%	<0.001
Completed high school, %	86.3%	80.5%	68.7%	<0.001
Current smoker, %	18.3%	22.6%	26.1%	<0.001
Diabetes, %	11.3%	13.8%	20.0%	<0.001
Body Mass Index, kg/m ² , mean (SD)	27.3 (4.7)	27.8 (5.3)	28.8 (6.1)	<0.001
Systolic blood pressure, mmHg, mean (SD)	120.4 (17.6)	121.9 (18.6)	122.3 (20.0)	<0.001
Diastolic blood pressure, mmHg, mean (SD)	72.4 (9.8)	72.3 (10.3)	71.7 (10.7)	0.002
Anti-hypertensive medication use, %	25.6%	31.8%	41.3%	<0.001
Total cholesterol, mg/dL, mean (SD)	207.5 (37.3)	209.4 (39.0)	212.2 (41.6)	<0.001
High density lipoprotein cholesterol, mg/dL, mean (SD)	48.0 (16.1)	50.0 (17.2)	50.3 (17.0)	<0.001
Prevalent heart failure, %	0.3%	0.5%	1.5%	<0.001
Prevalent coronary heart disease, %	5.2%	6.6%	9.9%	<0.001
Vital exhaustion score, mean (SD)	2.0 (1.6)	8.4 (2.2)	20.7 (6.6)	<0.001
Follow-up, years, mean (SD)	20.5 (3.3)	20.3 (3.7)	19.7 (4.6)	<0.001
<i>SD: standard deviation</i>				

TABLE 2

Summary of Person-Years and Incidence by Tertile. Incidence Rate confidence intervals are calculated using a normal approximation to the Poisson distribution.

	Low Vital Exhaustion	Moderate Vital Exhaustion	High Vital Exhaustion	Total
#Participants	4,464	4,869	4,590	13,923
#Person-Years	91,715	98,913	90,310	280,938
#Events:				
SCD	135	143	179	457
FCHD-1	78	65	104	247
FCHD-24	129	121	195	445
SCD-Union	160	169	235	564
SCD-Intersection	66	53	80	199
Incidence rate per 1000 (95% CI):				
SCD	1.47 (1.22, 1.72)	1.45 (1.21, 1.68)	1.98* (1.69, 2.27)	1.63 (1.48, 1.78)
FCHD-1	0.85 (0.66, 1.04)	0.66 (0.5, 0.82)	1.15* (0.93, 1.37)	0.88 (0.77, 0.99)
FCHD-24	1.41 (1.16, 1.65)	1.22 (1.01, 1.44)	2.16* (1.86, 2.46)	1.58 (1.44, 1.74)
SCD-Union	1.74 (1.47, 2.01)	1.71 (1.45, 1.97)	2.6* (2.27, 2.93)	2.01 (1.85, 2.18)
SCD-Intersection	0.72 (0.55, 0.89)	0.54 (0.39, 0.68)	0.89 (0.69, 1.08)	0.71 (0.61, 0.81)

* denotes a statistically significant (two-sided z-test, p-value <0.05) different incidence rate when compared to the corresponding Low VE incidence rate

TABLE 3
Cox proportional hazard ratios for the association between vital exhaustion and sudden cardiac death, through 2012

		Hazard Ratios (95% Confidence Intervals)					
	SCD	p-value	FCHD-1	p-value	FCHD-24	p-value	SCD-Union SCD-Intersection p-value
Model 1							
Low Vital Exhaustion (reference)	1		1		1		1
Moderate Vital Exhaustion	1.02 (0.80, 1.29)	0.873	0.83 (0.60, 1.16)	0.275	0.89 (0.70, 1.15)	0.397	1.00 (0.81, 1.25) 0.995
High Vital Exhaustion	1.48* (1.17, 1.87)	0.001	1.54* (1.12, 2.09)	0.005	1.65* (1.31, 2.08)	<0.001	1.59* (1.29, 1.96) <0.001
Model 2							
Low Vital Exhaustion (reference)	1		1		1		1
Moderate Vital Exhaustion	0.84 (0.66, 1.07)	0.145	0.68* (0.49, 0.96)	0.026	0.76* (0.59, 0.99)	0.038	0.84 (0.68, 1.05) 0.136
High Vital Exhaustion	0.94 (0.73, 1.20)	0.609	1.00 (0.72, 1.37)	0.993	1.11 (0.87, 1.42)	0.404	1.05 (0.84, 1.30) 0.697
							0.89 (0.63, 1.28) 0.534

Model 1: Adjusted for Age, sex, race/center

Model 2: Adjusted for age, sex, race/center, systolic and diastolic blood pressure, total cholesterol, high density lipoprotein cholesterol, current smoking status, body mass index, prior coronary heart disease diagnosis, diabetes mellitus, education level, and hypertensive medication use.

* denotes p-value <0.05