

## ORIGINAL RESEARCH ARTICLE

## 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 demoralisation, 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 four US communities. VE was measured using the Maastricht questionnaire between 1990 and 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/centre, participants in the highest VE tertile had an increased risk of SCD (HR 1.48, 95% CI 1.17 to 1.87), but these findings did not remain significant after adjustment for established cardiovascular disease risk factors (HR 0.94, 95% CI 0.73 to 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.

**INTRODUCTION**

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

Studies have demonstrated an association between VE and various cardiovascular disease endpoints.<sup>4–8</sup> VE is hypothesised to be prodromal to SCD<sup>1</sup> based on small studies<sup>9,10</sup> and animal models<sup>11</sup> from the 1950s to 1970s that linked hopelessness, fatigue and depression to SCD. Few studies have examined the association between VE and SCD as an independent endpoint.<sup>12,13</sup> 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 USA. 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.<sup>14</sup> 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 hospitalisations, death certificates and through periodic in-person examinations.<sup>15</sup> The Maastricht questionnaire was administered at the second examination (1990–1992). Participants were excluded if they did not attend the second examination (n=1444), 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 centres 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 31 December 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 31 December 2001<sup>16</sup>; the second phase evaluated CVD deaths between 1 January 2002 and 31 December 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.



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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 non-arrhythmic 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 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 coronary heart disease (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 ischaemic 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 questionnaire<sup>2</sup> was administered to 14 348 participants of the second ARIC examination. Participants attending the Jackson, Mississippi centre 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<sup>2</sup>). Prevalent CHD was defined as prevalent MI using 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 hospitalisation prior to the second examination or on heart failure medication within 2 weeks of the second examination. Diabetes mellitus was defined as fasting glucose  $\geq 126$  mg/dL or

#### 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.

**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
Women, %	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 <sup>2</sup> , mean (SD)	27.3 (4.7)	27.8 (5.3)	28.8 (6.1)	<0.001
Systolic blood pressure, mm Hg, mean (SD)	120.4 (17.6)	121.9 (18.6)	122.3 (20.0)	<0.001
Diastolic blood pressure, mm Hg, mean (SD)	72.4 (9.8)	72.3 (10.3)	71.7 (10.7)	0.002
Antihypertensive 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

non-fasting glucose  $\geq 200$  mg/dL, self-report of diabetes mellitus diagnosis or diabetes medication use within 2 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.<sup>14</sup> Total cholesterol was measured using enzymatic methods and

high-density lipoprotein cholesterol was measured using the dextran sulfate magnesium method.<sup>14</sup>

### Statistical analysis

To be consistent with several studies,<sup>2,5,17</sup> participants were partitioned into tertiles by Maastricht questionnaire score. 'Low VE' participants had VE scores in the first tertile (scores between 0 and 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  $\chi^2$  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 examination date and death or 31 December 2012, whichever was first. Participants who experienced a non-SCD death or were lost to follow-up prior to 31 December 2012 were right censored. The proportional hazards assumption was verified by plotting the standardised 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.<sup>18</sup> A log-rank test tested for equivalence between Kaplan-Meier product-limit cumulative survival estimates for Moderate and High VE tertiles compared with 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/centre. 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

**Table 2** Summary of person-years and incidence by tertile

	Low vital exhaustion	Moderate vital exhaustion	High vital exhaustion	Total
No of participants	4464	4869	4590	13 923
No of person-years	91 715	98 913	90 310	280 938
<i>No of events</i>				
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
<i>Incidence rate per 1000 (95% CI)</i>				
SCD	1.47 (1.22 to 1.72)	1.45 (1.21 to 1.68)	1.98* (1.69 to 2.27)	1.63 (1.48 to 1.78)
FCHD-1	0.85 (0.66 to 1.04)	0.66 (0.5 to 0.82)	1.15* (0.93 to 1.37)	0.88 (0.77 to 0.99)
FCHD-24	1.41 (1.16 to 1.65)	1.22 (1.01 to 1.44)	2.16* (1.86 to 2.46)	1.58 (1.44 to 1.74)
SCD-Union	1.74 (1.47 to 2.01)	1.71 (1.45 to 1.97)	2.6* (2.27 to 2.93)	2.01 (1.85 to 2.18)
SCD-Intersection	0.72 (0.55 to 0.89)	0.54 (0.39 to 0.68)	0.89 (0.69 to 1.08)	0.71 (0.61 to 0.81)

Incidence rate CIs are calculated using a normal approximation to the Poisson distribution.

\*Denotes a statistically significant (two-sided z-test, p value <0.05) different incidence rate when compared with the corresponding Low VE incidence rate. FCHD-1, fatal CHD within 1 hour of symptom onset; FCHD-24, fatal CHD within 24 hours of symptom onset; SCD, sudden cardiac death.

**Table 3** Cox proportional HRs for the association between vital exhaustion and sudden cardiac death, through 2012

HRs (95% CIs)										
	SCD	p Value	FCHD-1	p Value	FCHD-24	p Value	SCD-Union	p Value	SCD-Intersection	p Value
<b>Model 1</b>										
Low Vital Exhaustion (reference)	1		1		1		1		1	
Moderate Vital Exhaustion	1.02 (0.80 to 1.29)	0.873	0.83 (0.60 to 1.16)	0.275	0.89 (0.70 to 1.15)	0.397	1.00 (0.81 to 1.25)	0.995	0.81 (0.56 to 1.16)	0.253
High Vital Exhaustion	1.48* (1.17 to 1.87)	0.001	1.54* (1.12 to 2.09)	0.005	1.65* (1.31 to 2.08)	<0.001	1.59* (1.29 to 1.96)	<0.001	1.46* (1.04 to 2.07)	0.029
<b>Model 2</b>										
Low Vital Exhaustion (reference)	1		1		1		1		1	
Moderate Vital Exhaustion	0.84 (0.66 to 1.07)	0.145	0.68* (0.49 to 0.96)	0.026	0.76* (0.59 to 0.99)	0.038	0.84 (0.68 to 1.05)	0.136	0.64* (0.44 to 0.93)	0.019
High Vital Exhaustion	0.94 (0.73 to 1.20)	0.609	1.00 (0.72 to 1.37)	0.993	1.11 (0.87 to 1.42)	0.404	1.05 (0.84 to 1.30)	0.697	0.89 (0.63 to 1.28)	0.534

Model 1: adjusted for age, sex, race/centre; model 2: adjusted for age, sex, race/centre, 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.

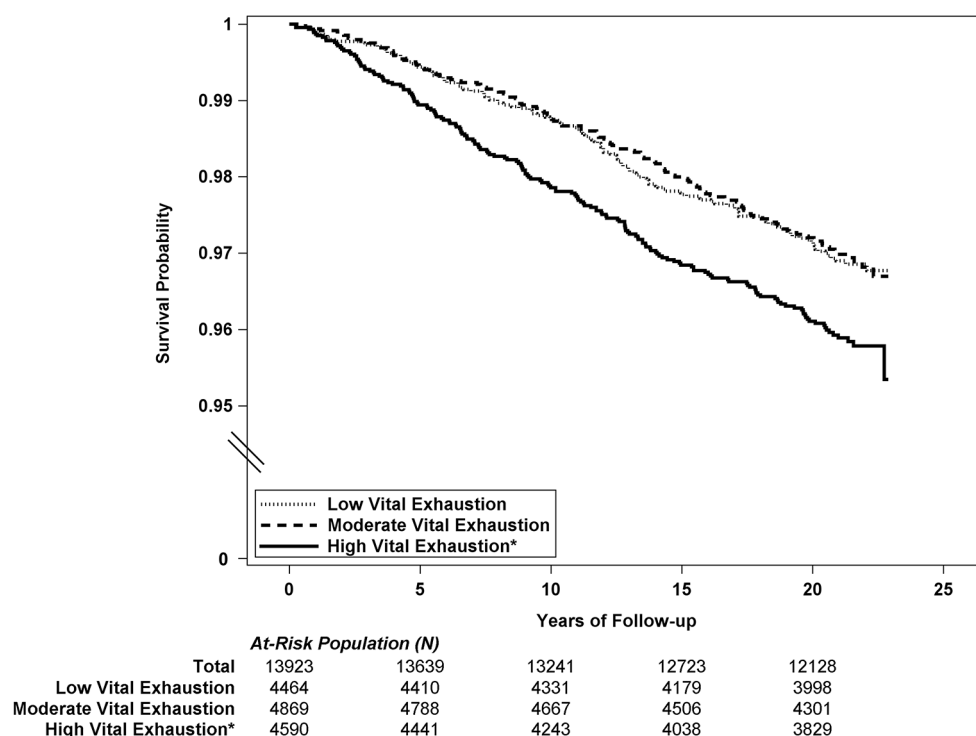
FCHD-1, fatal CHD within 1 hour of symptom onset; FCHD-24, fatal CHD within 24 hours of symptom onset.

test the influence of prevalent CHD on our results, we compared model 1 and model 2 HRs with ratios after refitting these models but excluding participants with prevalent CHD diagnosis at the second examination. We also compared HRs from model 2 with 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.<sup>19</sup> All analyses were performed using SAS V9.3.

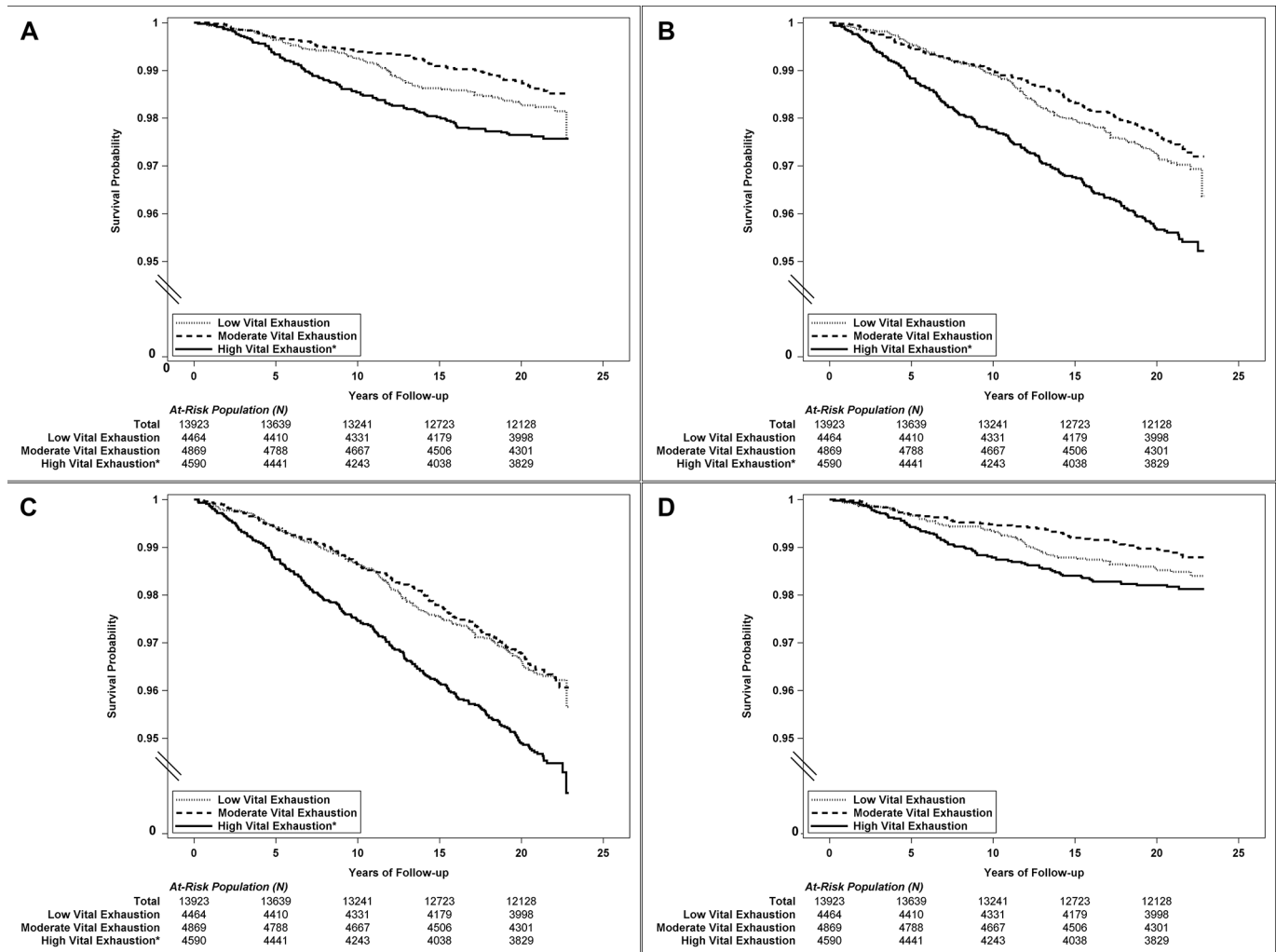
## RESULTS

Of 14 257 participants meeting race/centre inclusion criteria who attended the second examination, 13 923 (97.7%; 24% black and 55% women) completed the Maastricht questionnaire. There were 4464 participants with Low VE, 4869 participants with Moderate VE and 4590 participants with High VE.



**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<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 and (D) Sudden Cardiac Death-Intersection. Asterisks indicate that the corresponding curve statistically differs from Low Vital Exhaustion ( $p < 0.05$ ).

Compared with participants with Low VE, participants with High VE were older (56.6 vs 57.3 years), a higher proportion were women (40.0% vs 68.8%), a lower proportion were white (81.6% vs 69.1%), fewer had completed high school (86.3% vs 68.7%) and a higher proportion exhibited cardiovascular disease risk factors (table 1). For example, 11.3% of those with Low VE had diabetes compared with 20.0% of those with High VE; 18.3% of Low VE participants were smokers compared with 26.1% of High VE participants; 5.2% of those with Low VE had prevalent CHD compared with 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 with Low VE (1.98, 95% CI 1.69 to 2.27 vs 1.47, 95% CI 1.22 to 1.72 per 1000 person-years) (table 2).

On 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 to 1.87), and the Kaplan-Meier survival function differed significantly between the two groups (figure 2). However, on additional adjustment (model 2), no significantly different relative risk was observed (table 3, HR 0.94, 95% CI 0.73 to 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 (online supplementary table 1). Overall, results for these definitions were similar to our primary SCD endpoint: model 1 HRs 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 (4 years); however, High VE was positively associated with FCHD-24 in model 2 (online supplementary table 2). Using a competing risks approach to assess subdistribution hazards over the longer follow-up period (through 2012) also produced similar results (online 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 on 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 with 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. Appels<sup>1</sup> reported that men 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<sup>2,3</sup> to maximise its predictive power for hard coronary outcomes (MI/cardiac death) during a case-control study of Dutch men over 4 years, but the majority of these events were non-fatal MIs.<sup>2</sup> 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 used. A non-significant age-adjusted association between fatal cardiac events and VE (relative risk 1.39, 95% CI 0.59 to 3.25) was also reported in the same population.<sup>4</sup> 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 HRs for CHD of 2.36 (95% CI 1.70 to 3.26) in men and 2.07 (95% CI 1.48 to 2.88) for women,<sup>8</sup> but these effects may be inflated since a stepwise selection method was employed without applying shrinkage methods.<sup>20</sup> 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 to 1.79), but fatal and non-fatal events were not examined separately.<sup>7</sup> Our study is a natural extension to Williams *et al*,<sup>7</sup> as we evaluate a subset of fatal CHD events within the same population. Fully adjusted HRs 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 HRs 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.<sup>19</sup> 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).<sup>13</sup> VE scores were significantly higher for SCD (within 24 hours) victims compared with deceased controls with history of CHD. On multivariate adjustment, 'emotionally closed' vitally exhausted participants had a sevenfold increase in SCD risk. VE also increased the risk of SCD (OR 2.81, 95% CI 1.1 to 7.3) compared with controls without CHD.<sup>12</sup> There are several limitations of these studies,<sup>12,13</sup> 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 scores<sup>6</sup> and lower rates of SCD than men,<sup>21,22</sup> 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.<sup>23</sup>

We note that High VE was associated with FCHD-24 even after adjustment, which may corroborate other studies using a 24-hour definition.<sup>12,13</sup> We also note that Moderate VE was associated with multiple endpoints after adjustment, but this effect was modest (HRs 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 electrophysiological 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.<sup>24</sup> 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 unwitting. SCD in studies by Appels *et al*<sup>12,13</sup> 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 behavioural and psychosocial risk factors related to

## Key messages

## What is already known on this subject?

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

## What might 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-term or long-term follow-up on adjustment. This is the first study to examine vital exhaustion specifically in relation to sudden cardiac death in a biracial, prospective cohort within the USA. 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 conceptualisation 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.

VE,<sup>25 26</sup> including depression,<sup>27</sup> anger,<sup>17</sup> stress and fatigue.<sup>28</sup> Depression has been linked to a reduced heart rate variability,<sup>29</sup> which is associated with arrhythmias and sudden cardiac death.<sup>30</sup> It is not well understood if these conditions influence the development of coronary heart disease or acutely induce the arrest.<sup>26</sup>

In deriving the Maastricht questionnaire, MI and SCD were combined into a common outcome, but only a small portion were SCD.<sup>2</sup> 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 optimising 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.

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## REFERENCES

- Appels A. Psychological prodromata of myocardial infarction and sudden death. *Psychother Psychosom* 1980;34(2-3):187-95.
- Appels A, Höppener P, Mulder P. A questionnaire to assess premonitory symptoms of myocardial infarction. *Int J Cardiol* 1987;17:15-24.
- Appels A, Mulder P. Excess fatigue as a precursor of myocardial infarction. *Eur Heart J* 1988;9:758-64.
- Appels A, Mulder P. Fatigue and heart disease. The association between 'vital exhaustion' and past, present and future coronary heart disease. *J Psychosom Res* 1989;33:727-38.
- Schwartz SW, Carlucci C, Chambless LE, et al. Synergism between smoking and vital exhaustion in the risk of ischemic stroke: evidence from the ARIC study. *Ann Epidemiol* 2004;14:416-24.
- Prescott E, Holst C, Grønbaek M, et al. Vital exhaustion as a risk factor for ischaemic heart disease and all-cause mortality in a community sample. A prospective study of 4084 men and 5479 women in the Copenhagen City Heart Study. *Int J Epidemiol* 2003;32:990-7.
- Williams JE, Mosley TH, Kop WJ, et al. Vital exhaustion as a risk factor for adverse cardiac events (from the Atherosclerosis Risk In Communities [ARIC] study). *Am J Cardiol* 2010;105:1661-5.
- Schnohr P, Marott JL, Kristensen TS, et al. Ranking of psychosocial and traditional risk factors by importance for coronary heart disease: the Copenhagen City Heart Study. *Eur Heart J* 2015;36:1385-93.
- Alonzo AA, Simon AB, Feinleib M. Prodromata of myocardial infarction and sudden death. *Circulation* 1975;52:1056-62.
- Kuller L. Sudden death in arteriosclerotic heart disease; the case for preventive medicine. *Am J Cardiol* 1969;24:617-28.
- Richter CP. On the phenomenon of sudden death in animals and man. *Psychosom Med* 1957;19:191-8.
- Appels A, Golombek B, Gorgels A, et al. Psychological risk factors of sudden cardiac arrest. *Psychol Health* 2002;17:773-81.
- Appels A, Golombek B, Gorgels A, et al. Behavioral risk factors of sudden cardiac arrest. *J Psychosom Res* 2000;48(4-5):463-9.
- The ARIC investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am J Epidemiol* 1989;129:687-702.
- White AD, Folsom AR, Chambless LE, et al. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: methods and initial two years' experience. *J Clin Epidemiol* 1996;49:223-33.
- Kucharska-Newton AM, Couper DJ, Pankow JS, et al. Diabetes and the risk of sudden cardiac death, the Atherosclerosis Risk in Communities study. *Acta Diabetol* 2010;47(Suppl 1):161-8.
- Wattanakit K, Williams JE, Schreiner PJ, et al. Association of anger proneness, depression and low social support with peripheral arterial disease: the Atherosclerosis Risk in Communities Study. *Vasc Med* 2005;10:199-206.
- Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. *Biometrika* 1993;80:557-72.
- Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496-509.
- Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15:361-87.
- Ni H, Coady S, Rosamond W, et al. Trends from 1987 to 2004 in sudden death due to coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J* 2009;157:46-52.
- Bogle BM, Ning H, Mehrotra S, et al. Lifetime risk for sudden cardiac death in the community. *J Am Heart Assoc* 2016;5:e002398.
- Appels A, Otten F. Exhaustion as precursor of cardiac death. *Br J Clin Psychol* 1992;31(Pt 3):351-6.
- Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. *Circulation* 2016;133:e38-60.
- Levy D, Labib SB, Anderson KM, et al. Determinants of sensitivity and specificity of electrocardiographic criteria for left ventricular hypertrophy. *Circulation* 1990;81:815-20.
- Hemingway H, Malik M, Marmot M. Social and psychosocial influences on sudden cardiac death, ventricular arrhythmia and cardiac autonomic function. *Eur Heart J* 2001;22:1082-101.
- Ahern DK, Gorkin L, Anderson JL, et al. Biobehavioral variables and mortality or cardiac arrest in the Cardiac Arrhythmia Pilot Study (CAPS). *Am J Cardiol* 1990;66:59-62.
- Irvine J, Basinski A, Baker B, et al. Depression and risk of sudden cardiac death after acute myocardial infarction: testing for the confounding effects of fatigue. *Psychosom Med* 1999;61:729-37.
- Carney R, Saunders R, Freedland K. Association of depression with reduced heart rate variability in coronary artery disease. *Am J* 1995.
- Maheshwari A, Norby FL, Soliman EZ, et al. Low heart rate variability in a 2-minute electrocardiogram recording is associated with an increased risk of sudden cardiac death in the general population: the Atherosclerosis Risk in Communities study. *PLoS One* 2016;11:e0161648.