Meta-Analysis of Relation of Vital Exhaustion to Cardiovascular Disease Events

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To assess the net impact of vital exhaustion on cardiovascular events and all-cause mortality, we conducted a systematic search of PubMed, EMBASE, and PsychINFO (through April 2016) to identify all studies which investigated the relation between vital exhaustion (VE) and health outcomes. Inclusion criteria were as follows: (1) a cohort study (prospective cohort or historical cohort) consisting of adults (>18 years); (2) at least 1 self-reported or interview-based assessment of VE or exhaustion; (3) evaluated the association between vital exhaustion or exhaustion and relevant outcomes; and (4) reported adjusted risk estimates of vital exhaustion/exhaustion for outcomes. Maximally adjusted effect estimates with 95% CIs along with variables used for adjustment in multivariate analysis were also abstracted. Primary study outcome was cardiovascular events. Secondary outcomes were stroke and all-cause mortality. Seventeen studies (19 comparisons) with a total of 107,175 participants were included in the analysis. Mean follow-up was 6 years. VE was significantly associated with an increased risk for cardiovascular events (relative risk 1.53, 95% CI 1.28 to 1.83, p <0.001) and all-cause mortality (relative risk 1.48, 95% CI 1.28 to 1.72, p <0.001). VE also showed a trend for increased incident stroke (relative risk 1.46, 95% CI 0.97 to 2.21, p = 0.07). Subgroup analyses yielded similar results. VE is a significant risk factor for cardiovascular events, comparable in potency to common psychosocial risk factors. Our results imply a need to more closely study VE, and potentially related states of exhaustion, such as occupational burnout. **(Am J Cardiol 2017;119:1211−1216)**

Various psychosocial conditions such as depression, anxiety, chronic stress, and poor social support are well-accepted risk factors that are associated with cardiovascular disease (CVD).[1] A factor that has been poorly studied with respect to CVD, however, is the influence of fatigue and exhaustion. This lack is notable because fatigue and exhaustion are frequent negative complaints in patients presenting to primary care offices.[2,3] The exception has been a line of study initiated by Appels et al[4], following their observation that undue fatigue was a frequent premonitory symptom of cardiac events among their patients. Their investigation led to the delineation of a triad of symptoms, including excessive fatigue, feelings of demoralization, and increased irritability, which they termed "vital exhaustion" (VE). Since then, a variety of longitudinal studies have examined the relation between VE or exhaustion and the occurrence of cardiac events. In this study, we perform a meta-analysis that critically examines this construct and the strength of its relation to cardiac events and other clinical end points.

Methods

The electronic databases PubMed, EMBASE, and PsychINFO (through April 2016) were systematically searched with the following MESH terms "exhaustion," "vital exhaustion," "coronary artery disease," "myocardial infarction," "sudden cardiac death," "ischemic heart disease," "mortality," and "stroke" (Supplementary Table 1). Although some overlap exists between fatigue and exhaustion, fatigue is a more subjective term with variable definitions. Thus, we chose to include only studies involving measures of exhaustion or VE. Similarly, studies concerning burnout, a related construct involving symptoms of mental and physical fatigue of primarily occupational origin, were excluded from the analysis. Compared with burnout, VE represents more well-defined symptomatology which cuts across all aspects of one's life, not just occupation. Only published studies in English from peer-reviewed journals were evaluated. In addition, references of included studies and pertinent review studies were checked to identify additional studies meeting selection criteria.

Studies were considered for inclusion in the meta-analysis if the study[1] consisted of adults (>18 years)[2]; included at least 1 self-reported or interview-based assessment of VE or exhaustion,[3] evaluated the association between VE or exhaustion and any of the following outcomes: cardiovascular events, all-cause mortality, or stroke, and[4] reported adjusted risk estimates of VE/exhaustion for outcomes. We identified studies eligible for further review by performing an initial screen of identified titles or abstracts, followed by a full-text review.

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See page 1215 for disclosure information.

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Table 1
Baseline characteristics of included studies

Author/Ref	Country	N	Mean Age (Years)	% Male	Follow Up (Years)	Measure	Instrument	Baseline CVD	End Points
Appels [11]	Netherlands	3,365	53	100	10	Exhaustion	Single Question	No	Cardiac death
Kop [12]	NR	127	56	83	1.5	VE	MQ	Yes	Recurrent CVD Event
Cole [13]	USA	5,053	65	100	12	Exhaustion	Single Question	No	CHD Death; ACM
Koertge [14]	Sweden	292	55	0	5	VE	MQ	Yes	Recurrent CVD Event
Prescott [15]	Denmark	9,202	58	43	9	VE	MQ	No	Fatal/Non-Fatal MI; ACM
Schuitemaker [16]	Netherlands	2,433	41-66	49	4.25	VE	MQ	Yes	Fatal/Non-Fatal MI
Macleod [17]	USA	5,191	48	100	10	VE	Single Question	No	CHD Death
Williams [18]	USA	12,895	57	43	13	VE	MQ	No	Fatal/Non-Fatal MI
Smith [19]	Netherlands	704	NR	77	2.1	VE	MQ	Yes	CVD readmission and/or death
Ekmann [20]	Denmark	5,210	54	100	2	Fatigue	SF-36 Vitality Scale	No	Non-Fatal MI; ACM
Lindeberg [6]	Sweden	11,795	57	43	1	Exhaustion	SF-36 Vitality Scale	No	Fatal/Non-Fatal MI or Revascularization
Lundgren [21]	Sweden	981	57	49	8	VE	MQ	No	Fatal/Non-Fatal MI or Revascularization
Sergi [22]	USA	1,567	74	49	4.4	Exhaustion	Single Question	No	All CVD Events
Bowling [23]	USA	23,669	≥45	40	7	Exhaustion	SF-12	Yes	All-Cause Mortality
Schuitemaker [24]	Netherlands	2,432	41-66	50	4.25	VE	MQ	Yes	CVA
Kornerup [7]	Denmark	9,186	22-99	57	6-9	VE	MQ	No	CVA
Schwartz [25]	USA	13,066	48-67	60	6.3	VE	MQ	No	Incident CVA

ACM = all-cause mortality; CHD = coronary heart disease; CVA = cerebrovascular accident; CVD = cardiovascular disease; MI = myocardial infarction; MQ = Maastricht Questionnaire; SF = Short Form.

The data were independently extracted by 3 investigators (C.B., S.H., and J.T.) using a standardized protocol. Disagreements were resolved by arbitration (R.C.). We extracted the following information: study characteristics (study name, first author, publication year, country of origin, sample size, study design, and follow-up duration), patient characteristics (mean age, gender, co-morbidities, and participation ratio), main exposure (VE/exhaustion), method of assessment of VE/exhaustion, and outcomes reported. Maximally adjusted effect estimates with 95% CIs, and variables used for adjustment in multivariate analysis were also abstracted. Our primary study outcome was cardiovascular events as defined by the included studies (cardiac death, recurrent myocardial infarction [MI] and/or revascularization, CHD death, fatal/nonfatal MI, coronary revascularization, CVD readmission, and/or death). Secondary outcomes were stroke and all-cause mortality.

Only adjusted relative risks or hazards ratios reported by individual studies were used. Because of known clinical and methodologic heterogeneity of the studies, effect estimates were pooled using DerSimonian and Laird random effects models.[5] Lindeberg et al[6] and Kornerup et al[7] reported separate relative risks for men and women and hence were considered as 2 separate studies. Heterogeneity was assessed using Higgins and Thompson with I-squared (I^2) and tau-squared (τ^2) statistics. I^2 is the proportion of total variation observed between the trials attributable to differences between trials rather than sampling error (chance) with I^2 values of <25%, 25% to 75%, and >75% corresponding to low, moderate, and high levels of heterogeneity, respectively.[8] τ^2 represents a point estimate of the between-study variance of true effects. Reasons for heterogeneity in study results were further explored using subgroup analysis. To study the effect of various covariates on the association between VE/exhaustion and cardiovascular events, we performed meta-regression analysis. We also performed a sensitivity analysis to investigate the influence of each individual study on the overall meta-analysis results. Publication bias was tested using Egger's regression test[9] and visual inspection of funnel plot. The Duval and Tweedie nonparametric trim-and-fill procedure was used to further assess the possible effect of publication bias in our meta-analysis.[10]

Results

A flow diagram of the literature search is shown in Supplementary Figure 1. Twenty-three studies met our initial selection criteria, of which 17 studies (with 19 comparisons) were included in the meta-analysis. The baseline characteristics of the included studies are listed in Table 1.[6,7,11–25] In total, there were 107,175 subjects with a mean follow-up of 6.0 years (range of 1 year to 12 years). Eleven studies evaluated VE, whereas 5 studies evaluated exhaustion. One study (Ekmann et al) evaluated fatigue but used questions from the Short Form-36 vitality scale which was used in other studies to measure exhaustion and was thus included in the analysis. All the studies were of low-bias risk per Newcastle-Ottawa Scale (Supplementary Table 2).

Thirteen studies evaluated the association between VE/exhaustion and cardiovascular events. VE/exhaustion was significantly associated with an increased risk for cardiovascular events (relative risk [RR] 1.53, 95% CI 1.28 to 1.83, p <0.001; Figure 1). A moderate degree of heterogeneity was found in the analysis (I^2 = 55.8%, τ^2 = 0.05). Meta-influence analysis showed a possibly higher influence by 2 studies,[15,17] but their removal did not alter the effect estimate (RR 1.52, 95% CI 1.34 to 1.73, p <0.001; Supplementary Figure 2). Visual inspection of funnel plot suggested the presence of publication bias (Supplementary