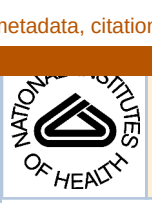

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Vital Exhaustion and Retinal Microvascular Changes in Cardiovascular Disease: The Atherosclerosis Risk in Communities Study

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Abstract

Objective—Negative psychological factors, such as depression, have been implicated in the development of cardiovascular disease. Whether this link is mediated by macrovascular or microvascular disease is unknown. This study aimed to determine whether vital exhaustion, a measure of negative emotion, is associated with microvascular changes in the retina.

Methods—A population-based, cross-sectional study of 10,364 white and African Americans aged 48–73 years. Vital exhaustion scores were determined from the Maastricht questionnaire and categorized into quartiles. Retinopathy signs and retinal vascular caliber were graded from retinal photographs following standardized protocols.

Results—After adjusting for age, gender, race, study center, education, smoking, blood pressure, diabetes, and other risk factors, higher vital exhaustion scores (highest versus lowest quartiles) were modestly associated with the presence of retinopathy (odds ratio [OR] 1.27; 95% confidence intervals [CI]: 1.01, 1.59), particularly retinal hemorrhages (OR 1.71; 95% CI: 1.20, 2.44), and with generalized retinal venular widening (OR 1.19; 95% CI: 1.03, 1.38). Analyzing vital exhaustion as a continuous variable did not change the pattern of the associations.

Conclusions—Middle-aged people with vital exhaustion may be more likely to have retinopathy signs that have been identified as risk predictors of cardiovascular events. Further research is needed to explore the possible adverse effects of negative emotion on the microcirculation.

Keywords

vital exhaustion; depression; microvascular disease; cardiovascular disease; retinopathy; retinal vascular caliber

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CONFICT OF INTEREST: None.

INTRODUCTION

Evidence suggests that negative emotions, such as vital exhaustion, are associated with an increased risk of cardiovascular disease (1–8). However, the underlying mechanistic pathways remain unclear (9,10). Both behavioral and pathophysiological mechanisms have been proposed to explain the associations of vital exhaustion, a measure of negative emotion, with stroke (8,11), coronary heart disease (4,12–14), and diabetes (15).

Nevertheless, existing studies have largely focused on mechanisms that are related to large vessel disease (e.g., atherosclerosis) (10). Little is known about the potential adverse effects of psychological factors on the microcirculation. Limited data from small studies of selected samples have previously associated negative emotions with microvascular angina (16–18) and diabetic microvascular complications (6). These data indicate that the excess cardiovascular risk linked to negative emotions may be mediated, at least in part, by microvascular processes.

The human retina provides a unique window to non-invasively and directly assess the microcirculation *in vivo* (19–22). Using standardized methods to evaluate retinal photographs, population-based studies have shown that retinopathy signs and variations in retinal vascular caliber (e.g., retinal venular widening) predict risks of stroke (23–27), coronary heart disease (26–28) and congestive heart failure (29,30), independent of concomitant risk factors. These findings support the theory that structural alterations in the retinal microvasculature represent systemic microcirculatory dysfunction that predisposes people to develop cardiovascular disease (19–22).

The purpose of this study is to test the hypothesis that negative emotion, measured as vital exhaustion scores, may be related to adverse changes in the microcirculation, as evident in the retinal microvasculature, in a large population-based study in the United States.

METHODS

Study Population

The Atherosclerosis Risk in Communities study has been described previously and included 15,792 persons aged 45–64 years at recruitment in 1987–1989 (31). The study population was selected by probability sampling from four U.S. communities: Forsyth County, NC; Jackson, MS (African-Americans only); suburbs of Minneapolis, MN; and Washington County, MD (32). Of the participants at baseline, 14,348 completed the second examination in 1990–1992 when vital exhaustion was assessed (11,15). Soon after the second examination, 12,887 returned for the third examination in 1993–1995 and 12,794 had retinal photographs taken (23,29). We excluded participants whose race was neither African-American nor white (n=198), who did not complete psychological evaluations (n=253), and whose retinal photographs were not gradable (n=1,979), leaving 10,364 participants for analysis.

Institutional review boards at study sites approved the study. Informed consent was obtained from all participants and the study was conducted in accordance with the Declaration of Helsinki.

Evaluation of Negative Emotions

Vital exhaustion was measured by the Maastricht questionnaire, which was empirically developed to capture symptoms of unusual fatigue and feelings of dejection that preceded myocardial infarction. The questionnaire, which has been published previously (11,15), consists of 21-items focusing on fatigue, irritability, stress, and feelings of demoralization.

Retinal Photography and Definition of Retinal Microvascular Signs

The assessment and definition of retinal microvascular signs has been described in detail elsewhere (23,24,29,33–35). In brief, one randomly selected eye was photographed using a non-mydriatic camera, and evaluated by trained graders in a masked fashion according to standardized protocols (33). We defined five categories of retinal microvascular signs: any retinopathy (which included presence of retinal hemorrhages, microaneurysms, cotton wool spots and other less common signs), arterio-venous nicking and focal arteriolar narrowing.

Generalized retinal arteriolar narrowing and venular widening were defined from measuring retinal vascular caliber using a computer-based program based on a standardized protocol (23,24,29,33–35). In brief, for each photograph, retinal arterioles and venules coursing through an area half to one optic disc diameter from the optic disc margin were measured and summarized as the central retinal arteriolar and venular equivalents, which represented the average of projected calibers for the central retinal vessels (36). Generalized arteriolar narrowing was defined as the narrowest 20% of the central retinal arteriolar equivalents, and generalized venular widening as the widest 20% of central retinal venular equivalents.

Quality control data regarding the assessment of retinal signs have been previously reported, showing good reliability of measurements for retinal vascular caliber (inter- and intra-grader correlation coefficients for arteriolar and venular caliber ranged from 0.69–0.89) and retinopathy (inter- and intra-grader kappa of 0.89 and 0.99) (33).

Definition of Other Variables

Participants had standardized questionnaires and evaluation of cardiovascular risk factors at all examinations (23,29,37). Diabetes mellitus was defined as a fasting glucose ≥7.0 mmol/L (≥126 mg/dl), a non-fasting glucose ≥11.1 mmol/L (≥200mg/dl), or a self-reported history of physician-diagnosed diabetes or treatment for diabetes. Fasting blood samples were obtained for lipid profile, fibrinogen, white blood cell, von Willibrand factor and factor VIII. Carotid artery intima-media thickness was also measured by high-resolution B-mode ultrasound (38).

Statistical Analysis

Vital exhaustion was analyzed as a continuous variable as well as defined according to quartiles (the number in each quartile differs as the scale consists of integer scores) (15). Logistic regression was used to determine the odds ratios (OR) and 95% confidence intervals (CI) for retinal vascular signs in association with vital exhaustion, initially adjusting for age, gender, race and study center (Model 1), and further adjusted for other risk factors measured at the second examination (Model 2), including socioeconomic status (education) and lifestyle (cigarette smoking and alcohol drinking status) and cardiovascular risk factors (systolic blood pressure, body mass index, diabetes, and serum total cholesterol). First-order interaction terms between age, gender, systolic blood pressure and diabetes were assessed pair wise. Interactions were included in Model 2 if they improved the model (assessed by Bayesian Information Criterion). In supplementary analyses, we further adjusted Model 2 for inflammatory markers (white cell count and fibrinogen levels), endothelial dysfunction markers (von Willibrand factor and factor VIII), and large artery atherosclerosis (carotid intima-media thickness).

RESULTS

The participants' characteristics across vital exhaustion quartiles in the ARIC have been reported elsewhere (15), and are summarized in Table 1. In general, participants with higher vital exhaustion scores were more likely to be women, African-Americans, current smokers, former alcohol consumers, and to have lower education, diabetes and hypertension than those with lower vital exhaustion scores.

Compared to excluded participants, our study population was generally younger, more likely to be men, whites, non-diabetic, non-hypertensive, former cigarette smoker, current alcohol drinker, and have higher education status, lower systolic blood pressure, lower serum fasting glucose, serum total and HDL cholesterols (data not shown).

Table 2 shows that after adjusting for age, gender, race, and study center (Model 1), higher vital exhaustion scores were monotonically associated with any retinopathy, retinal hemorrhages, and generalized retinal venular widening. These associations remained significant after further adjustment for other risk factors (Model 2); odds ratio for any retinopathy was 1.27, retinal hemorrhages was 1.71, and retinal venular widening was 1.19, comparing highest versus lowest quartiles of vital exhaustion scores. Analysis of vital exhaustion as a continuous variable (per 2-point increase), the pattern of the results was similar.

In supplementary analyses, the observed associations remained after additional adjustment for biomarkers of inflammation (white cell count and fibrinogen levels) and endothelial dysfunction (von Willebrand factor and factor VIII), as well as large artery atherosclerosis (carotid intima-media thickness) (ORs for retinal signs in association with each 2 points increase in vital exhaustion score were: 1.03 [95% CI: 1.01, 1.05] for any retinopathy; 1.05 [95% CI: 1.03, 1.08] for retinal hemorrhages; 1.00 [0.98, 1.01] for generalized retinal arteriolar narrowing; 1.01 [95% CI: 1.00, 1.03] for generalized retinal venular widening). Furthermore, first-order interaction terms between age, gender, systolic blood pressure and diabetes were assessed pair wise. None of these interaction terms were significant and their inclusion did not improve the model (assessed by comparison of Bayesian Information Criterion), thus Models 1 and 2 remain as described in the original manuscript and do not include interaction terms.

DISCUSSION

There is increasing recognition that psychological factors are important determinants of an individual's risk of cardiovascular disease (1–8,11–15). Previous studies have mostly focused on large vessel disease in search of explanations for the association between psychological factors and cardiovascular disease risk. However, recent large prospective studies show that negative psychological factors are not associated with coronary artery calcification, a measure of large artery atherosclerotic burden (39,40). These findings raise the possibility that the association of negative psychological factors with cardiovascular risk may be mediated by other mechanisms, such as processes involved in small vessel disease (41). In our current study of a large population-based sample of middle-aged individuals, we show that persons with higher levels of vital exhaustion (unusual fatigue and feelings of dejection) were more likely to have retinopathy signs, independent of demographic, lifestyle and cardiovascular risk factors.

We are not aware of any directly comparable studies. Limited data from previous studies among small numbers of highly selected patient samples have reported associations of negative emotions with small vessel diseases, such as microvascular angina without epicardial coronary stenosis (16–18) and diabetic microvascular complications (6). A case-control study showed that women with microvascular angina suffered higher levels of psychological morbidity, including depression and anxiety, as compared to the control group or those with coronary heart disease (16). In addition, a previous meta-analysis has demonstrated a significant and consistent association of depressive symptoms with risk of diabetic microvascular complications, including both retinopathy and nephropathy (6). Our data now extend previous observations to a larger community and suggest possible adverse impact of negative emotion, measured as vital exhaustion scores, on the microcirculation. Since retinopathy signs and retinal venular widening have been consistently shown to predict future cardiovascular events independently of conventional risk factors (21–30), the findings in our current study raise the

possibility that microvascular characteristics may contribute to or be markers for processes that lead to the association between vital exhaustion and excess cardiovascular risk.

The exact pathophysiological pathways underlying our findings need to be further delineated. Here, we propose two possible mechanisms. First, endothelial dysfunction is one of the pathogenic factors involved in the link between negative emotion and cardiovascular disease (10). There is evidence that endothelial dysfunction also contributes to the development of retinopathy signs (42–44) and possibly retinal venular widening (26,45). Nevertheless, while controlling for non-specific markers of endothelial function, such as von Willebrand factor and factor VIII, our observed associations remained significant. Second, by virtue of its effect on the cardiac autonomic tone, excessive activation of the sympathetic nervous system is another mechanism by which negative emotions may be related to cardiovascular risk (10). Interestingly, it has also been suggested that prolonged stress-related sympathetic response, via its altered regulation of neurotransmitters (e.g., neuropeptide Y), could induce vascular remodeling and abnormal angiogenesis, leading to the development of retinopathy (46,47). However, it is important to note that the cross-sectional design of our study does not provide information regarding the temporal sequence of events. Thus, reverse causality cannot be totally excluded. For example, it is also possible that higher levels of negative emotion could also be a result of the unmeasured discomfort, inconvenience and co-morbidity associated with visual impairment from retinopathy.

Strengths of our study include a large population-based sample and standardized grading of retinopathy signs and retinal vascular caliber using a previously validated protocol. However, for proper interpretation of our results, several limitations must be taken into consideration. First, although vital exhaustion is a standardized tool to determine the degree of negative emotion, it is not a commonly used method to assess depression in clinical settings. It is believed that, nonetheless, vital exhaustion score serves as an appropriate surrogate measure of clinical depression (15). Second, the magnitude of the associations in our study was generally modest (OR ranging from 1.19 to 1.70) and attenuated after factoring the effects of potential confounders in the multivariate analyses (Table 2). Therefore, the possibility of residual confounding from both measured (e.g., chronic hypertension) and unmeasured (e.g., C-reactive protein) factors cannot be totally excluded. While the effect size of our findings, in general, is not large, their significance highlights the need for additional studies to examine the potential adverse effects of psychological factors on the microvascular system. Future studies, in conjunction with ours, may shed light into the link between negative psychological factors and cardiovascular disease.

In summary, our study provides some evidence to suggest a cross-sectional association between vital exhaustion, a measure of negative emotion that includes fatigue, irritability and demoralization, and retinal microvascular signs that are risk markers of cardiovascular disease. If our findings are confirmed by other studies, the role of small vessel disease in the link between psychological factors and cardiovascular disease development may warrant further investigation.

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Table 1

Characteristics of Included Participants, By Vital Exhaustion Score

	All included participants	Quartiles of Vital Exhaustion Score				
		Q1	Q2	Q3	Q4	
	(n=10,364)	(n=2457)	(n=2354)	(n=2528)	(n=3025)	*p* *
Vital Exhaustion score	10.1 (8.5) 8 (4, 14)†	Range 0–3	Range 4–7	Range 8–13	Range 14–42	-
Age (years)	56.5 (5.6)	56.1 (5.5)	56.6 (5.6)	56.6 (5.7)	56.7 (5.7)	<0.001
Gender (% male)	44.8	61.4	51.2	41.0	29.5	<0.001
Race (% African-American)	20.4	15.2	18.4	20.9	25.7	<0.001
Education (% completed high school)	81.7	89.4	85.2	81.8	72.9	<0.001
Diabetes (%)	9.5	6.7	7.7	9.9	13.0	<0.001
Smoking						<0.001
- Former (%)	38.6	42.5	41.6	38.1	33.7	
- Current (%)	20.6	17.1	17.3	22.3	24.5	
Alcohol						<0.001
- Former (%)	19.3	16.5	18.8	18.8	22.5	
- Current (%)	59.0	66.7	61.3	59.2	50.8	
Systolic blood pressure (mmHg)	120.4 (17.9)	119.3 (16.9)	120.8 (17.4)	120.5 (18.2)	120.8 (18.9)	0.008
Hypertension (%)	38.4	31.1	37.2	37.9	45.5	<0.001
Body mass index (kg/m^2)	27.9 (5.2)	27.2 (4.5)	27.6 (4.9)	27.9 (5.2)	28.7 (5.9)	<0.001
Total cholesterol (mg/dl)	209.3 (38.5)	206.7 (36.3)	208.5 (38.2)	209.1 (38.0)	212.1 (40.5)	<0.001

Values are means (SD) or proportions, unless otherwise stated.

Quartiles of Vital Exhaustion: Q1 (score ≤3), Q2 (score 4–7), Q3 (score 8–14), Q4 (score ≥15)

* *p* values relate to the difference between categories assessed by one-way analysis of variance or *chi*-squared test statistics, as appropriate..

† values presented are median (interquartile range).

Table 2

Relationships between Vital Exhaustion Score and Retinal Microvascular Signs

	N	N (prevalence %)	Odds Ratio (95% CI) for Retinal Sign Model 1*	Odds Ratio (95% CI) for Retinal Sign Model 2†
Any retinopathy				
VE per 2-point increase	10364	765 (7.4)	1.05 (1.03, 1.07)	1.03 (1.01, 1.05)
VE quartile 1	2457	142 (5.8)	1.0	1.0
VE quartile 2	2354	144 (6.1)	1.03 (0.81, 1.31)	0.99 (0.77, 1.26)
VE quartile 3	2528	195 (7.7)	1.31 (1.04, 1.65)	1.16 (0.92, 1.47)
VE quartile 4	3025	284 (9.4)	1.56 (1.25, 1.94)	1.27 (1.01, 1.59)
p for trend			<0.001	0.017
Retinal hemorrhages				
VE per 2-point increase	10364	360 (3.5)	1.08 (1.06, 1.11)	1.05 (1.03, 1.08)
VE quartile 1	2457	49 (2.0)	1.0	1.0
VE quartile 2	2354	60 (2.6)	1.21 (0.83, 1.78)	1.13 (0.76, 1.68)
VE quartile 3	2528	98 (3.9)	1.82 (1.29, 2.60)	1.52 (1.05, 2.19)
VE quartile 4	3025	153 (5.1)	2.25 (1.60, 3.16)	1.71 (1.20, 2.44)
p for trend			<0.001	0.001
Generalized retinal arteriolar narrowing				
VE per 2-point increase	10339	2051 (19.8)	0.99 (0.98, 1.00)	1.00 (0.98, 1.01)
VE quartile 1	2450	536 (21.9)	1.0	1.0
VE quartile 2	2352	487 (20.7)	0.95 (0.83, 1.09)	0.95 (0.82, 1.09)
VE quartile 3	2523	462 (18.3)	0.84 (0.73, 0.97)	0.85 (0.74, 0.98)
VE quartile 4	3014	566 (18.8)	0.90 (0.79, 1.04)	0.94 (0.82, 1.09)
p for trend			0.072	0.258
Generalized retinal venular widening				
VE per 2-point increase	10339	2079 (20.1)	1.03 (1.02, 1.04)	1.01 (1.00, 1.03)
VE quartile 1	2450	436 (17.8)	1.0	1.0
VE quartile 2	2352	442 (18.8)	1.09 (0.94, 1.26)	1.08 (0.93, 1.26)
VE quartile 3	2523	527 (20.9)	1.27 (1.10, 1.47)	1.14 (0.98, 1.32)

	N	N (prevalence %)	Odds Ratio (95% CI) for Retinal Sign Model 1*	Odds Ratio (95% CI) for Retinal Sign Model 2†
VE quartile 4	3014	674 (22.4)	1.40 (1.21, 1.61)	1.19 (1.03, 1.38)
p for trend			<0.001	0.016

Quartiles of Vital Exhaustion (VE): Q1 (score ≤3), Q2 (score 4–7), Q3 (score 8–14), Q4 (score ≥15); *p* for trend relates to test for linear trend across the quartiles

*Model 1 was adjusted for age, gender, race, study center

†Model 2 was adjusted for age, gender, race, study center, high school education, systolic blood pressure, cigarette smoking, diabetes, total cholesterol and body mass index.