ORIGINAL RESEARCH

Vital exhaustion in women with chest pain and no obstructive coronary artery disease: the iPOWER study

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ABSTRACT

Background More than half of women with symptoms suggestive of myocardial ischaemia have no obstructive coronary artery disease (CAD), yet they face a higher risk of cardiovascular mortality and morbidity. Both vital exhaustion (VE) and depression have been linked to adverse cardiovascular prognosis in patients with CAD. We aimed to assess whether symptomatic women with no obstructive CAD are more vitally exhausted compared with asymptomatic women. Furthermore, we investigated the overlap between the constructs of VE and depression.

Methods Prevalence and burden of VE was assessed in symptomatic women with no obstructive CAD (n=1.266) and asymptomatic women (n=2.390). Among symptomatic women, we also assessed chest pain characteristics and symptoms of Hospital Anxiety and Depression Questionnaire.

Findings Median (IQR) VE score was 4 (1-9) and 2 (0–5) in symptomatic and asymptomatic women, respectively (age adjusted, p<0.001). The risk of severe VE was significantly higher in symptomatic women compared with asymptomatic women (OR 3.3, 95% CI 2.5 to 4.4), independent of age and risk factors, and was associated with symptom severity. VE and depression scores were correlated but principal component cluster analysis (PCCA) showed clear distinctiveness between the two constructs.

Conclusions Women with chest pain and no obstructive CAD are more vitally exhausted compared with asymptomatic women. PCCA showed that VE is distinct from depression in symptomatic women.

Clinical implications Mental health screening focusing on depressive symptomatology in women with chest pain presenting with symptoms of mental and physical exhaustion may overlook VE in these patients.

INTRODUCTION

The majority of women presenting with chest pain suggestive of myocardial ischaemia have no obstructive coronary artery disease (CAD); nevertheless, these women have an increased risk of coronary heart disease (CHD) later in life[1 2] Persistent symptoms, lack of diagnosis and limited treatment options may have a negative impact on quality of life and mental health in these patients.[3]

Vital exhaustion (VE) is a psychological condition perceived as an adaptive response to prolonged and uncontrolled psychological stress. VE is characterised by symptoms of mental and physical exhaustion, including loss of energy, increased irritability and feelings of demoralisation. VE burden can be assessed using the Maastricht Questionnaire (MQ), a tool widely applied in the research setting and not routinely used in the clinical practice. Depression is a mental health disorder currently estimated among the top five leading causes of disability-adjusted life-years lost globally.[4] Depression is a psychopathological condition influenced by genetic, environmental and biological factors, characterised by symptoms of increased fatiguability, persistent sadness and loss of interest and enjoyment. Both VE and depression are more prevalent in women compared with men. Furthermore, both conditions have been independently associated with increased risk of incident CHD, possibly through mechanisms of adverse health behaviours and poor adherence to treatment recommendations.[5 6] Previous research has shown that depression is more prevalent in patients with chest pain and no obstructive CAD compared with asymptomatic controls.[7] Whether VE is more prevalent in symptomatic women with no obstructive CAD compared with asymptomatic women is not known. Despite some similarities between the conditions, prevalence of VE and depression can vary significantly within the same population, leaving the question of whether the constructs capture similar or different aspects of psychological distress. Several smaller studies have investigated the overlap between VE and depression; however, the results have been inconsistent.[8–11]

To address the existing knowledge gap, we performed an observational case–control study to assess the prevalence and burden of VE in women with chest pain and no obstructive CAD compared with asymptomatic women, and to investigate whether quality and burden of chest pain is correlated to VE burden. Furthermore, using a principal component cluster analysis (PCCA), we explored the overlap between VE and depression.

METHODS

Symptomatic women

Women with a history of chest pain (angina) or angina-equivalent symptoms (dyspnoea), no obstructive CAD and completed MQ were enrolled from the ImProve diagnOsis and treatment of Women with angina pEctoris and micRovessel disease (iPOWER) cohort. iPOWER is a Danish prospective multicentre study investigating prevalence and prognostic significance of coronary microvascular disease in women with chest pain. A detailed description of the main study inclusion and exclusion criteria has been published elsewhere.[12] In brief, women (age 18–80 years) with stable chest pain and/or dyspnoea and no obstructive CAD (<50% stenosis) on clinically indicated invasive angiography, performed within a year of study enrolment, were recruited from a national register between March 2012 and November 2015. Participants were excluded if other cause of chest pain/dyspnoea than myocardial ischaemia was deemed more likely. Furthermore, pregnant women, and women with a history of CHD, left ventricular ejection fraction <45%, significant valvular heart disease, congenital heart disease, cardiomyopathy, severe lung disease or significant comorbidity with <1 year expected survival were excluded.

Asymptomatic women

A cohort of asymptomatic women (age 18–80 years) without a history of chest pain or heart disease (CHD, heart failure, significant valvular heart disease, congenital heart disease or cardiomyopathy), and a complete MQ, was randomly selected from the Copenhagen City Heart Study database.[13] Seattle Angina Questionnaire (SAQ) or Hospital Anxiety and Depression Questionnaires (HADS) were not available for this population.

Self-administrated questionnaires

Prior to examination, self-administered questionnaires were sent to all participants, including questions about medical history, current medication, family history of CHD and history of tobacco and alcohol consumption. Excessive alcohol use was defined as >7 alcohol units per week. All information was confirmed by a trained health professional during a personal interview.

Quality and burden of chest pain

Symptoms of chest pain (angina) were classified into three categories using the established criteria: (1) typical angina requiring (A) chest/jaw/shoulder/arm discomfort, (B) provoked by exertion and (C) relieved by rest or nitroglycerine, (2) atypical angina, requiring two of the above characteristics and (3) non-anginal chest pain with one or none of the above characteristics. In accordance with the guidelines, dyspnoea was regarded as an angina equivalent symptom.[14]

Women's physical status and chest pain characteristics, experienced in the past 4 weeks prior to the personal interview, were assessed using a 19-item SAQ translated to Danish.[15] SAQ is a prognostic disease-specific tool evaluating 5 dimensions of functional status: physical limitation (nine items), chest pain stability (one item), chest pain frequency (two items), treatment satisfaction (four items) and disease perception (three items). SAQ score was calculated in accordance with the recommendations.[15] Total score was calculated for every dimension of SAQ and a high subscale score indicated high functional status. No overall questionnaire score was generated. Missing values within a dimension were excluded from the analysis.

Vital exhaustion

Assessment of VE was performed using a 17-item MQ translated to Danish.[13] This questionnaire was derived from the original MQ presented by Appels *et al*.[16] Possible answers for each of the 17 items were 'yes', 'no' and 'I don't know'. Total item score ranged between 0 and 17. The sum of all positive answers ('yes'), except from question 11 'I feel fine', which was reversed, was calculated and grouped into 4 VE categories: normal (0), mild (1–4), moderate (5–9),and severe (10-17).

Hospital Anxiety and Depression Qquestionnaire

Assessment of anxiety and depression disorders was performed using a 14-item HADS in Danish. HADS is validated for assessment of emotional disorders among patients in non-psychiatric hospital and outpatient setting.[17] HADS consists of a 7-item anxiety subscale (HADS-A) and a 7-item depression subscale (HADS-D). Each item scores between 0 and 3 (3 indicating higher symptom frequency), with a total subscale score ranging between 0 and 21. Final subscale scores were grouped into four anxiety/depression categories: normal (0–7), mild (8–10), moderate (11–14) and severe (15–21). A total scale score range between 0 and 42, with higher scores indicating greater levels of emotional distress. Participants with missing values within a subscale were excluded from the analysis.

All participants provided written informed consent after receiving written and oral information about the study.

Statistics

Data normality was assessed both graphically and by Shapiro-Wilk test for normality. Normally distributed continuous variables were expressed as mean±SD. Skewed continuous variables were presented as median and IQR. Number of observations (N) and percentage (%) were used for categorical variables. Symptomatic women were older compared with asymptomatic women; thus, the intergroup differences were tested using age-adjusted linear (continuous dependent variables) or logistic regression analyses (categorical dependent variables). Skewed numerical variables, including VE, SAQ and HADS scores, were transformed using natural logarithm (ln) prior to performing intrascale correlation estimation using Pearson's correlation. The correlation coefficient was interpreted as weak (0.10–0.39), moderate (0.40–0.69), strong (0.70–0.89) or very strong (0.90–1.00). ORs with 95% CI was calculated using logistic regression. OR of severe VE between symptomatic and asymptomatic women was adjusted for age, body mass index (BMI), hypertension, diabetes, hypercholesterolaemia, family history of CHD, history of smoking (present or previous) and excessive alcohol use. The relationship between chest pain, VE severity and cardiovascular risk factors was assessed using multivariate linear regression analysis.

To assess the distinctiveness of the constructs of VE and HADS-D subscale, we performed individual and combined PCCA using the SAS command 'proc varclus'. The command is closely related to the principal component analysis (PCA) with oblique rotation and uses clusters to group variables that are as correlated as possible among themselves and as uncorrelated as possible with variables in other clusters.[18] We calculated correlation of each variable with its own cluster ($R^2_{\text{own cluster}}$) and with any other cluster ($R^2_{\text{closest cluster}}$). Furthermore, 1-$R^2$ ratio was calculated as $\frac{1-\text{R2 own cluster}}{1-\text{R2 closest cluster}}$.[18] Variables with the lowest 1-R^2 ratio were considered to be good representatives for the cluster, because of their maximum correlation with own cluster and minimum correlation with the next cluster.[19] A two-sided $p \leq 0.05$ was considered statistically significant. All analyses were performed using STATA/IC .13.1 (StataCorp LP) and SAS software (V.9.4, SAS Institute).

Table 1 Participant characteristics

	Symptomatic women	Asymptomatic women	
	n=1266	n=2390	P value
Age, years	64 (55–70)	57 (44–68)	<0.001
BMI, kg/m^2*	26 (23–30)	24 (22–27)	<0.001
Hypertension†	681 (54)	400 (17)	<0.001
Diabetes*	159 (13)	50 (2)	<0.001
Hypercholesterolaemia‡	786 (62)	60 (3)	<0.001
CHD in the family	675 (53)	557 (23)	<0.001
Current or ex-smoker	710 (56)	1.481 (62)	0.001
Excessive alcohol use	211 (17)	813 (34)	<0.001
Chest pain classification			
Typical angina	402 (32)		
Atypical angina or non-anginal chest pain.	864 (68)		
Vital exhaustion			
Total score	4 (1–9)	2 (0–5)	<0.001
Normal	197 (16)	658 (28)	<0.001
Mild	458 (36)	1.119 (47)	
Moderate	354 (28)	437 (18)	
Severe	257 (20)	176 (7)	
Hospital Anxiety Scale			
Total score	6 (3–9)		
Normal	732 (65)		
Mild	212 (19)		
Moderate	141 (13)		
Severe	34 (3)		
Hospital Depression Scale			
Total score	2 (0–5)		
Normal	970 (87)		
Mild	104 (9)		
Moderate	37 (3)		
Severe	8 (1)		
Seattle Angina Questionnaire			
Physical limitation	64±19		
Angina stability	64±28		
Angina frequency	78±20		
Treatment satisfaction	71±20		
Disease perception	54±21		

Data are presented as median (IQR), n (%) or mean±SD. P values from Wilcoxon rank-sum test or χ^2 test.
*Participants diagnosed with diabetes type 2.
†Participants diagnosed with hypertension or receiving antihypertensive medication.
‡Participants diagnosed with hypercholesterolaemia or receiving treatment with lipid-lowering medication, BMI, CHD.
§P value from age-adjusted ordered logistic regression analysis.
BMI, body mass index; CHD, coronary heart diseas.

FINDINGS

Participant characteristics

Overview of the participants with completed questionnaires are displayed in the flow diagram (online supplemental appendix figure 2). Symptomatic women (n=1.266) were older and had a higher burden of cardiovascular risk factors compared with asymptomatic women (n=2.390; all p≤0.001; table 1). Thirty-two per cent (n=402) of symptomatic women had typical angina, 39% (n=492) had atypical angina and 29% (n=372) had non-anginal chest pain. Among women with non-anginal chest pain, 80% were enrolled due to having retrosternal chest pain, and 9% have had dyspnoea as the primary symptom. The rest of the symptomatic women with non-anginal chest pain presented with discomfort in the jaw, shoulder or arm.

Median (IQR) VE score was higher in symptomatic compared with asymptomatic women (age adjusted, p<0.001). Prevalence and severity of VE differed between populations, with 20% (n=257) of symptomatic women having severe VE (VE score >10) vs only 7% (n=176) of asymptomatic women (age adjusted, p<0.001; table 1 and figure 1). Increasing VE severity was associated with younger age (p<0.001), higher BMI (p<0.001) and a higher prevalence of diabetes (p=0.041). In a multivariable logistic regression analysis, risk of severe VE was greater in symptomatic than asymptomatic women (OR 3.3, 95% CI 2.5 to 4.4]; p<0.001), independent of age and risk factors presented in table 1.

VE and chest pain

Symptomatic women who scored higher on the VE scale were more likely to have typical angina (age adjusted, p≤0.001). SAQ subscale scores decreased with increasing VE severity (age adjusted, p<0.01; online supplemental appendix table 4). Correlations between ln-transformed SAQ and VE scores were weak to moderate, indicating lower level of functioning (r=−0.25; p<0.001), increasing (r=−0.27; p<0.001) and more frequent symptoms (r=−0.30; p<0.001), worse treatment compliance and less overall treatment satisfaction (r=−0.28; p<0.001) and more worrying about symptom implication (r=−0.43; both p<0.001) with increasing VE burden.

Anxiety, depression and chest pain

Twelve per cent of symptomatic women received antidepressant medication. Moderate or severe anxiety and depression according to HADS (score ≥11) were present in 16% and 4% of symptomatic women, respectively. Women with typical angina had slightly higher depression score than women with atypical or non-anginal chest pain (median (IQR) HADS-D score 3 [1–6] vs 2 (1–5); p=0.006), while anxiety score was comparable (median (IQR) HADS-A score 6 [3–9] for both groups; p=0.061). As for VE, weak to moderate negative correlations were found between ln-transformed SAQ and HADS scores, indicating lower level of functioning (r_{HADS-A}=−0.15; r_{HADS-D}=−0.24 ; both p<0.001), increasing (r_{HADS-A}=−0.18; r_{HADS-D}=−0.20; both p<0.001) and more frequent symptoms (r_{HADS-A}=−0.25; r_{HADS-D}=−0.25; both p<0.001), worse treatment compliance and less overall treatment satisfaction (r_{HADS-A}=−0.22; r_{HADS-D}=−0.26; both p<0.001), and more worrying about symptom implication (r_{HADS-A}=−0.44; r_{HADS-D}=−0.42; both p<0.001) with increasing anxiety or depression burden.

Inter-relationship between psychological constructs

Overview of the relationship between VE, depression and anxiety is presented in table 2. We found moderate correlations between ln-transformed HADS-A and VE scores (r=0.54; p<0.001) and HADS-D and VE scores (r=0.68; p<0.001). Symptomatic women with moderate and severe anxiety were more likely to be vitally exhausted (VE score ≥5; OR 9.5, 95% CI 6.0 to 15.1; p<0.001). Similarly, symptomatic women with moderate and severe VE scored higher on the depression scale (HADS-D score ≥11; OR 5.9, 95% CI 2.6 to 13.4); p<0.001). In a subanalysis, including symptomatic women with completed MQ and HADS (n=1.119), moderate or severe VE, anxiety or depression was present in 49%, 16% and 4% of women, respectively. Twenty-eight per cent and 7% of women with moderate or severe VE

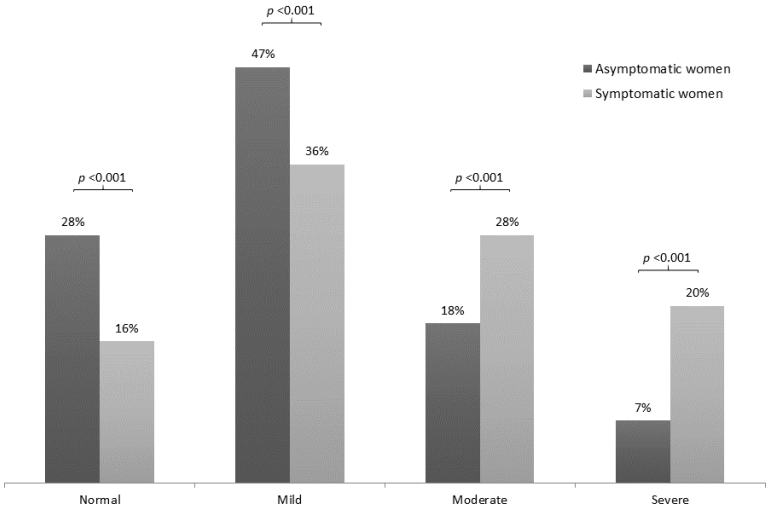

Figure 1 Burden of vital exhaustion in symptomatic and asymptomatic women. P values from age-adjusted logistic regression model.

had moderate or severe anxiety or depression, respectively. Moreover, among the 229 patients with severe VE, 56% had a normal HADS-D score.

Are VE and depression distinct constructs?

To explore whether MQ and HADS-D measure distinguishable entities, we performed a two-step PCCA. First, to assess scale heterogeneity and internal factor composition, individual PCCAs were performed separately for 17-items of MQ and 7 items of HADS-D. PCCA of MQ yielded two distinct clusters, characterised by (1) symptoms of fatigue and exhaustion; (2) symptoms of depression, hopelessness, irritation and difficulty concentrating (online supplemental appendix table 5). PCCA of HADS-D yielded only one factor (data not shown).

Second, to assess whether factor composition is distinct between the concepts, we performed PCCA combining all 24 items from both scales. The procedure yielded three clusters (table 3). Cluster 1 (6 MQ variables and one HADS-D variable) was dominated by somatic symptoms, fatigue and exhaustion. Cluster 2 (6 HADS-D variables) was represented by depressive cognitive symptoms. Cluster 3 (11 MQ variables) comprised a combination of somatic and cognitive symptoms, including hopelessness, depression and difficulty concentrating. For both analyses, grouped variables displayed high correlation with their own cluster and a low correlation with the other clusters. The presented moderate to high 1-R^2 ratios indicated good variable selection within the cluster. In summary, combined PCCA yielded almost the same factor pattern as the PCA performed separately on each scale, demonstrating heterogeneity within the VE scale, homogeneity within the HADS-D scale and heterogeneity between the two scales.

DISCUSSION

In a large cohort of women with chest pain and no obstructive CAD, we found a high prevalence of VE compared with asymptomatic women without a prior history of CHD, independent of age and risk factors. In symptomatic women, increasing levels of VE, depression and anxiety were associated with frequent and

Table 2 Psychological risk factors

	Vital exhaustion categories				
	Normal	Mild	Moderate	Severe	Age adjusted
	(n=156)	(n=411)	(n=323)	(n=229)	P value
Hospital Anxiety Scale					
Normal	147 (94)	338 (82)	182 (56)	65 (28)	
Mild	7 (4)	53 (13)	89 (28)	63 (28)	
Moderate	2 (1)	15 (4)	46 (14)	78 (34)	
Severe	0	5 (1)	6 (2)	23 (10)	
Total score	3 (1–5)	4 (2–7)	7 (4–9)	10 (7–13)	<0.001
Hospital Depression Scale					
Normal	154 (99)	399 (97)	289 (89)	128 (56)	
Mild	0	7 (2)	23 (7)	74 (32)	
Moderate	2 (1)	3 (1)	11 (3)	21 (9)	
Severe	0	2 (1)	0	6 (3)	
Total score	1 (0–1)	1 (0–2)	3 (2–5)	7 (5–9)	<0.001

Data are presented as n (%) or median (IQR). P values from age-adjusted linear regression analysis.

Table 3 Cluster structure for the 17 items of Maastricht Questionnaire and 7 items of Hospital Depression Scale according to the oblique principal component cluster analysis

	R^2 own cluster	R^2 closest cluster	1-R^2 ratio
Cluster 1			
HADS-D Q4: I feel as if I am slowed down	0.534	0.238	0.612
MQ1: Do you often feel tired?	0.423	0.136	0.668
MQ2: Do you feel altogether weak?	0.455	0.213	0.692
MQ3: Do you feel you have not accomplished much recently?	0.525	0.245	0.628
MQ12: Do you sometimes feel your body is like a battery running out?	0.482	0.237	0.679
MQ14: Are you feeling 'not worth a scrap' at present?	0.538	0.322	0.681
MQ17: Do you ever wake up with a feeling of exhaustion?	0.401	0.181	0.731
Cluster 2			
HADS-D Q1: I still enjoy the things I used to enjoy	0.681	0.270	0.437
HADS-D Q2: I can laugh and see the funny side of things	0.658	0.198	0.427
HADS-D Q3: I feel cheerful	0.654	0.264	0.469
HADS-D Q5: I have lost interest in my appearance	0.321	0.180	0.828
HADS-D Q6: I look forward with enjoyment to things	0.637	0.260	0.490
HADS-D Q7: I can enjoy a good book or radio or TV programme	0.303	0.138	0.809
Cluster 3			
MQ4: Do you, at the moment feel that you do not have what it takes?	0.435	0.246	0.749
MQ5: Do you believe you have come to a dead end?	0.320	0.144	0.795
MQ6: Do you lately feel listless?	0.480	0.313	0.757
MQ7: Do you feel dejected?	0.573	0.234	0.558
MQ8: Do you lately have difficulties in concentrating?	0.299	0.193	0.868
MQ9: Do little things irritate you more than they used to?	0.415	0.201	0.732
MQ10: Do you feel that you want to give up?	0.452	0.164	0.656
MQ11: I feel fine(reversed).	0.373	0.235	0.819
MQ13: Do you sometimes wish you were dead?	0.263	0.097	0.817
MQ15: Do you have feelings of hopelessness recently?	0.529	0.223	0.606
MQ16: Do you sometimes just feel like crying?	0.418	0.179	0.708

HADS-D, Hospital Depression Scale; MQ, Maastricht Questionnaire; TV, television.

typical symptoms, lower level of functioning, poorer treatment compliance, less treatment satisfaction and more symptom related concerns. Increasing VE also correlated to increasing depression score; however, less than 10% of women with moderate or severe VE had moderate or severe depression. Despite the inter-relationship between the constructs and their correlation to chest pain characteristics, we showed a distinct, mainly non-overlapping cluster composition using PCCA, suggesting that these scales capture different aspects of psychological distress.

Comparison of VE prevalence across studies is challenging due to (1) use of different MQ versions with a different set of questions / number of items; (2) no consensus regarding the cut-off for 'true' exhaustion; and (3) heterogeneous patient populations with various stages of CHD. Prevalence of VE assessed by the 17-item MQ has previously been reported in partially overlapping populations.[13 20] In two previously published studies of asymptomatic individuals without a history of CHD, the mean±SD VE scores were 30.2±7.6 on a 19–56 point scale and 10.3±8.6 on a 0–42 point scale, both indicating normal or mild VE on average.[21 22] These results are in line with our findings for the asymptomatic women. No comparable studies were identified with regard to VE prevalence in symptomatic women with no obstructive CAD.

In the present study population, 16% and 4% of symptomatic women had moderate or severe anxiety or depression, respectively. Similar prevalence of anxiety (18%) and depression (6%), assessed by HADS, was reported by Jespersen *et al* in a study of symptomatic women with no obstructive CAD.[3] The same group reported SAQ subscores within the same range as our findings. The study concluded that persistent angina symptoms were associated with long-term anxiety, depression, impaired physical functioning, and lower quality of life irrespective of the degree of CAD. Our study confirms that angina burden is associated with several indices of psychosocial distress.

Prolonged exposure to stress has previously been associated with chest pain and development and progression of CHD. Recently, two independent meta-analyses concluded that VE is a significant risk factor for cardiovascular events.[6 23] Several studies have looked at the relationship between chest pain and VE. In his original research, Appels and Mulder[24] found a positive association between chest pain and VE in a large cross-sectional study investigating a heterogeneous cohort of men. Pedersen and Middel[25] showed a positive correlation between chest pain burden and VE scores in patients with CAD.

Causal association between chest pain and VE is difficult to establish. Persistent symptoms may reflect on the somatic component of the VE scale; however, an underlying common mechanism affecting both factors is a plausible explanation. Further research is warranted to establish whether VE is a marker of poor prognosis in symptomatic patients independent of CAD severity and comorbidities, and whether effective symptom treatment will have a beneficial effect on VE prevalence in these patients.

It has been discussed whether the psychometric scales for VE and depression measure the same underlying construct or whether they assess different and distinguishable entities. In the original study by Appels *et al*,[26] a study of men without previous CAD, 37-item MQ loaded on three factors representing unusual fatigue, depressive affect and irritability, respectively. Following this a number of studies have identified several factors within the VE construct: in patients with myocardial infarction using the 21-item MQ, 4 factors were identified, fatigue, depression, lack of concentration and sleep difficulties; in patients admitted for percutaneous coronary intervention, using the 21-item MQ, 2 factors were identified, fatigue and depressive symptoms.[11 27] In a study of patients with chronic heart failure, factor analysis by Smith *et al*[28] revealed 4 factors of VE, including fatigue, cognitive–affective depressive symptoms, sleep difficulties and lack of concentration. Patterns of MQ clustering in the current study, characterised by fatigue and depressive symptoms, are in line with the existing research. In contrast, in a study of myocardial infarction patients by Vroege *et al*, factor analysis using a 21-item MQ yielded only one factor, which was highly correlated to the somatic/affective dimension of depression assessed by the Beck Depression Inventory.[8] In the current analysis, we found that VE and HADS-D, although correlated, broke down to three distinct clusters, characterised by somatic symptoms (fatigue and

exhaustion), depressive cognitive symptoms and a combination of somatic and cognitive symptoms (hopelessness, depression and difficulty concentrating). This findings is in line with the results published by Kudielka *et al*, supporting the notion that depressive symptoms captured by HADS-D are distinct from the VE captured by MQ.[29]

HADS-D captures cognitive and emotional depressive symptoms, while MQ represents a combination of somatic and cognitive symptoms, including fatigue/exhaustion, feelings of worthlessness, hopelessness and depression[8 30] This might explain the 'exhaustion/depression paradox'—patients often fulfil criteria for one of the constructs, but not both, as seen in the current study population. Whether VE captures a subclinical form of depression, which eventually will develop into a major depressive disorder, is yet to be established.

Strengths and limitations

The main strength of the current study is the inclusion of a reference population, allowing us to compare prevalence of VE between women with and without angina. Furthermore, both symptomatic and asymptomatic women were systematically screened using well-defined inclusion and exclusion criteria. Significant CAD was ruled out by invasive angiography in the symptomatic population.

There are some limitations to this study. The current study is female focused; however, it is important to emphasise that angina in the absence of obstructive CAD is common in both sexes. Thus, future prognostic studies on VE in angina populations should include both female and male angina patients. The majority of women included were of Caucasian origin. Whether the current study findings can be extrapolated to other ethnicities is not known. Prevalence and burden of depression and anxiety assessed by HADS questionnaire was only available for the symptomatic population.

History of clinical depression was not available for neither symptomatic nor asymptomatic women. However, assuming that women with well-managed clinical depression score low on HADS-D, and women with resistant depression/medication nonadherence score high on HADS-D, adjustment for clinical depression is unlikely to affect the current study results.

CLINICAL IMPLICATIONS

Women with chest pain and no obstructive CAD have higher prevalence and burden of VE, an independent risk factor for incident CHD, compared with asymptomatic women. Quality and severity of chest pain are the likely contributing factors of VE burden in these women. Despite interscale similarities and correlation to chest pain characteristics, this study confirms that the constructs of VE (MQ) and depression (HADS-D) represent separate psychological risk factors, capturing different aspects of psychological distress in women with chest pain and no obstructive CAD. The heterogeneity of the constructs explains the discrepancy in prevalence of depression and VE. Hence, mental health screening focusing on cognitive and emotional depressive symptomatology in women presenting with mental and physical exhaustion may overlook VE in these patients.

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