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Women's Health in the Lund Area (WHILA) study. Health problems and acute myocardial infarction in women – a 17-year follow-up study

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Abstract

Objectives: The literature has highlighted the importance of identifying symptoms predictive of acute myocardial infarction (AMI) in women, in addition to traditional cardiovascular risk factors. The objective was to study subjective health problems, in relation to later AMI, in a large sample of women, adjusted for age, educational status, smoking, waist/hip ratio, blood pressure, total cholesterol/HDL ratio, diabetes and neighbourhood socioeconomic status.

Study design: From December 1995 to February 2000 a cohort of 6711 women aged 50–59 years in southern Sweden underwent a physical examination and answered a questionnaire that had 18 items on health problems such as stress symptoms, tiredness and pain.

Main outcome measures: Incidence of AMI during a mean follow-up of 17 years, drawn from national registers.

Results: The number of health problems showed a J-shaped relationship with AMI, with the lowest hazard ratio (HR) in women with a median of 4 health problems. The HR for AMI in

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Contributors

Susanna Calling drafted the manuscript.

Sven-Erik Johanssona performed the statistical analyses.

All authors contributed to the conception of the work. All authors contributed to the interpretation of data. All authors critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

The investigations were in accordance with the Declaration of Helsinki. The study was approved by the Ethics committee at Lund University (approval no. 174–95 and 2011/494). Participation in the study was based on informed consent.

Provenance and peer review

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Research data (data sharing and collaboration)

There are no linked research data sets for this submission. The authors do not have permission to share data.

women with 0 health problems was 1.58 (95% CI: 0.95–2.63) and in those with 13 problems HR 1.65 (95% CI 1.16–2.36), after adjusting for potential confounding factors.

Conclusions: The presence of several health problems, including pain and stress symptoms, is associated with an increased risk of later AMI in middle-aged women. Awareness among clinicians of predictive risk factors for AMI is important for the early identification of individuals at higher risk.

Keywords

myocardial infarction; women; risk factors; signs and symptoms

1. Introduction

Although ischemic heart disease including acute myocardial infarction (AMI) has declined during the last decades, it still remains the number one cause of death in most Western countries [1]. Among women, a recent increase of coronary events has been reported in the United States, [2, 3]. Most knowledge on the prevention, diagnosis and treatment of AMI is based on studies conducted predominantly on men [4]. It is well known that the symptomatology of AMI in women differs from that in men, and under-recognition of women's symptoms is a clinical problem [5, 6]. The predictive risk pattern in women also differs, but this area is not fully studied [7]. The literature highlights the importance of identifying symptoms predictive of AMI in women [4, 7].

The development of AMI is multifactorial and complex. In addition to traditional cardiac risk factors adverse pregnancy outcomes, systemic autoimmune disorders and osteoporosis are associated with AMI in women [7]. Previous research studying the predictive cardiac symptomatology in women found that discomfort in jaws/teeth, unusual fatigue, discomfort in arms, general chest discomfort, and shortness of breath were symptoms strongly associated with an increased risk of a cardiac event during 2 years of follow up [5]. In addition to somatic complaints, psychosocial factors have gained an increasing interest as cardiac risk factors in women [8]. Depression and anxiety have been related to AMI [7, 9, 10]. In addition, a previous study from our research group showed that depression was a predictor of developing coronary heart disease strongest for those aged <40; the risk was 2.17 [11]. Also mild mental problems like sleep disturbances, fatigue and self-perceived stress have been related to AMI [12].

Whether common somatic and mental health problems, such as tiredness, stress symptoms and pain are early predictors of AMI in women is not studied thoroughly, and previous studies had only short follow-ups. Another novelty with the present study was that it includes middle aged women with multiple common somatic and mild mental problems, unlike previous studies which include major mental disorders and focus on men.

Accordingly, the aim was to study 18 different subjective health problems, and their association with AMI during a 17 year long follow-up, adjusted for age and traditional cardiac risk factors such as educational status, smoking, waist-hip ratio, blood pressure, total cholesterol/HDL-ratio, diabetes and neighbourhood socioeconomic status measured by Care

Need Index (CNI). The hypothesis was that these health problems are associated with an increased risk of AMI.

2. Methods

Data was retrieved from the Women's Health in the Lund Area (WHILA) study [13], in which women 50–59 years (born between 1935 and 1945) in southern Sweden were invited to take part in a health survey. Between Dec 1995 and Feb 2000, 6916 women underwent a physical and laboratory examination and completed a self-administered questionnaire. The physical examination included measurement of body weight, height, minimal waist and maximal hip circumference. Blood pressure (mmHg) was measured twice in the right arm, after 15 min and 20 min rest in sitting position, and the average of the recordings was used. Non-fasting serum levels of total cholesterol, HDL-cholesterol and LDL cholesterol were measured on capillary whole blood. In the present study, 6,711 women were included, after exclusion of individuals with missing values on education, smoking and diabetes.

The questionnaire has been described previously [13]. In short, after written consent the participants answered a questionnaire including 104 questions about medical history, lifestyle, sociodemographic data and health problems. If any uncertainties, they could ask a nurse. There was no financial reimbursement for participation.

2.1. Follow up and outcome variable

The data was linked to the Hospital Discharge Register, and the women were followed from the day of screening until first hospitalization of AMI, or until the end of the study May 31st 2015. The mean follow-up time was 17 years.

Acute myocardial infarction (AMI) was based on the International Classification of Diseases, i.e. code I21 (ICD-10) or code 410 (ICD-8). Those who had had an AMI before screening were excluded.

2.2. Explanatory variables

The explanatory variables were based on the examinations and questionnaires at baseline. *Agec*, age at screening, continuous, centered around its mean (56 years).

Education; Educational level was categorized into low/middle (≤12 years) and high (university).

Waist hip ratio (WHR) was calculated as waist circumference (cm) divided by hip circumference (cm), and categorized into ≤0.78/>0.78. WHR is a significant predictor of AMI in both men and women [14, 15]. The cut-off point recommended by WHO (0.85) could not be used because of the small sample size and that the women lived in more affluent areas (Care Need Index, CNI = −6.7) than the Swedish population in general (CNI=0). Therefore, we chose the cutoff 0.78 as the optimal limit for this sample.

Ratio between total-cholesterol to HDL (Tch/HDL) was treated as a continuous variable, linearly related to risk of AMI. Tch/HDL ratio has been shown to be the best single predictor of ischemic heart disease risk in the Quebec Cardiovascular Study [16].

Blood pressure was categorized into three levels, based on the distribution: 1) systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg, 2) systolic blood pressure 140–149 mmHg or diastolic blood pressure 90–99 mmHg, and 3) systolic blood pressure ≥150 mmHg or diastolic blood pressure ≥100 mmHg. Due to the small sample size, we could not use the grades of hypertension according to international guidelines [17].

Self-reported diabetes: Yes/No

Smoking was categorized into 1) non-smoker 2) former smoker and 3) daily smoker.

Health problems were based on the questions as follow," Have you been bothered by any of the following conditions during the last three months? (yes/no): dizziness, headache, tiredness, sleeping problems, nervousness, sweating problems, shortness of breath, chest pain, felt irritable, overworked, concentration difficulties, restlessness, down and gloomy, easy to cry, hard to relax, stomach ache, nausea and back pain". For those who didn't answer any of the items, a zero (0) was imputed. A factor analysis (iterated principal factors of 18 health problems (Yes=1/No=0)) based on tetrachoric correlations, resulted in a one-factor solution (Eigenvalue=6.53). All factor loadings, after varimax rotation, were positive and >0.4, supporting that all of the symptoms are indicators of health problems. The factor scores were linearly related to the risk of AMI.

Based on the factor scores health problems were categorized into four levels: (1) −0.53 to −0.48; (2) −0.48 to 0.058; (3) 0.058 to 0.39; (4) 0.39 to 0.93. The mean of the factor scores for the four levels were −0.52, −0.21, 0.22, and 0.57, the higher factor score the more health problems. The median numbers of Health problems in the four categories were 0, 4, 8 and 13, respectively.

Care Need Index (CNI) was used as a proxy for socioeconomic status of the neighborhood area, and has previously been described in detail [18]. Information on CNI was obtained from Swedish public registers on 31 December 1995, with individual information on the entire adult population. The CNI included proportions of seven material, sociodemographic, and cultural variables for each neighborhood: elderly people living alone, children under age 5, unemployed people, people with low educational status, single parents, residents who have moved house during the past year, and foreign born people from Southern and Eastern Europe, Asia, Africa, and South America. The higher the CNI score, the more deprived the neighbourhood. In the present study, CNI was dichotomized into affluent (0) and deprived (1) areas. As there was a relatively high number of missing values for CNI (e.g. individuals who were registered in other areas than they lived in), this variable was analysed in a reduced sample of 6,234 women. In the sample, 71 % of the women lived in more affluent areas (CNI<0). In the statistical analyses, the variable was treated at the same level as the other individual variables in the statistical analyses, as the small sample size was not suited for multi-level analysis.

The following variables were analysed as potential confounders: postmenopausal therapy use, age at menopause, alcohol use and family history of cardiovascular disease. None of them was associated with acute myocardial infarction. When added to the multivariate full model, the result were almost identical. They were therefore not included as covariates in the models.

2.3. Statistical method

In order to compensate for missing we weighted data by age and county: N_i/nresponders per one-year age-group (50–59) and municipality. The response rate varied in the different age-groups between 58.9 (youngest) and 66.7 % (oldest), in average 64.2 %. The weights sum up to population size 1995.

We estimated incidence rates of AMI (formed from the number of failures divided by the person-time, per 10,000 person years at risk) with 95 % confidence intervals (STPTIME in STATA) per variable.

In order to analyse the association between health problems and AMI, we applied a Cox regression model, adjusted for potential confounders. All included variables satisfied the proportional hazard assumption. There were no interactions between number of health problems and any of the other included covariates. In a reduced sample the same analyses were conducted including education and CNI.

STATA version 13 was used for the statistical analyses.

2.4. Ethics

The investigations were in accordance with the Declaration of Helsinki. The study was approved by the Ethics committee at Lund University (approval no. 174–95 and 2011/494). Participation in the study was based on informed consent.

3. Results

The women were on average 56 years old at the screening (Table 1). Eight percent reported a median number of 0 health problems, 50% 4 problems, 25% 8 problems and 17% 13 problems. Those who reported 13 health problems were more frequent smokers and diabetics and they had higher WHR and Tch/HDL-ratio, compared with those who reported fewer problems. The prevalence of diabetes was 2.2%, which is probably an under-reporting even if the cohort is quite young. The overall prevalence of diabetes in Sweden has been reported to over 4% [19].

During the mean follow-up period of 17 years, 205 women had an AMI. The number of health problems showed a J-shaped relationship with AMI, with the lowest incidence rate (IR) in women with a median of 4 health problems (IR 15.0 [95% confidence interval, CI: 12.1–18.7]) and the highest in those with 13 problems (IR 25.3 [95% CI: 19.2–34.1]) (Table 2). The J-shaped relationship with AMI remained in the multivariate models (Table 3), even after adjusting for all other variables, for example the HR of future AMI for women with 0 health problems was 1.58 (95% CI: 0.95–2.63) and for women with 13 health problems 1.65

(95% CI 1.16–2.36). After including education and CNI in the model, the increased HR for women with 13 health problems remained statistically significant [HR 1.55 (1.06–2.24)] (Table 4, based on reduced sample). Furthermore, an increased future risk for AMI was associated with age, smoking, large WHR, high blood pressure, high Tch/HDL and diabetes. Low education and deprived area were also associated with increased risk of AMI, however not statistically significant.

4. Discussion

In this prospective cohort study of middle-aged women with a mean follow-up of 17 years, a novel finding was the J-shaped relationship between number of health problems (e.g. tiredness, pain, sleeping problems, nervousness and feeling overworked) and incidence of AMI, even after adjusting for traditional cardiovascular risk factors, i.e. age, education, smoking, WHR, blood pressure, Tch/HDL-ratio, diabetes and CNI. To our knowledge, no earlier studies have studied the impact of several health problems on future risk of AMI in women during a longer follow up. McSweeney et al found that fatigue and other symptoms were related to an increased cardiac risk, however during a shorter follow-up of 2 years [5]. The reasons behind the J-shaped relationship cannot be explained by our current data. Possible explanations may be that those who reported 0 health problems may belong to a group of individuals who neglect their symptoms and seek health care at a later stage, when their health problems have already developed into intractable diseases. It is also possible that individuals who neglect their health have a poorer lifestyle and poorer adherence to medical treatment.

Several of the reported problems in the questionnaire used in the present study could be related to stress and mental illness, i.e. sleeping problems, tiredness, nervousness, irritability, concentration difficulties, hard to relax etc. There is considerable evidence that mental illness, including depression, anxiety and psychological distress, is associated with an increased risk of AMI [7, 9, 10, 20–23]. The present study supports that even mild symptoms of psychological distress is associated with increased cardiovascular risk. A study of more than 1 million Swedish young men from conscription registers showed an increased risk of later coronary heart disease in men with a range of mental disorders diagnosed at young age [20], which means that mental illness is an early predictive cardiovascular risk factor in itself, and not a result of CVD. However, the mechanisms are not fully understood and previous data on women are scarce. Both biological and behavioral mechanisms may be involved. For example, explanatory mechanisms between depression and AMI include poorer heart rate variability, impaired vascular function and antidepressant cardiotoxicity [21, 24]. High levels of psychological distress have been shown to influence atherosclerotic mechanisms, e.g. elevated inflammatory markers and dysregulation of the hypothalamic-pituitary-adrenal axis [25, 26]. People with mental illness may also have a higher prevalence of poor lifestyle and other modifiable risk factors, such as obesity and hypertension, and poorer adherence to medication of cardiovascular risk factors [7]. Moreover, mental illness may be associated with lack of social support and socioeconomic disadvantage. In the present study, the increased risk of AMI in women with 13 health problems was attenuated by the other included cardiovascular risk factors, but still remained significant.

Increased cardiovascular risk attributed to psychological distress is similar in men and women, but since women are more prone to stress their burden of disease related to stress may be greater [8]. Two recent Swedish longitudinal studies showed that poor self-rated health and self-reported anxiety have increased in younger individuals during the last decades, especially in women [27, 28]. The WHILA cohort consists of a relatively young cohort and the present study indicates that this worsening trend in self-rated and mental health may have a poor impact on cardiovascular health in women.

4.1. Strengths and limitations

The strengths of the present study are the prospective design and the large sample of women drawn from the general population. The women could be followed for AMI during a long follow-up period and the data has been adjusted for several potential cardiovascular confounders. Another strength is the design with a thorough self-reported questionnaire including a range of health problems, completed with a clinical baseline examination.

The study also has some limitations. The grouping of the different physical and psychological symptoms may have affected the results as the different symptoms may reflect different groups of diseases. However, the aim of the study was to create a predictor variable, i.e., Health problems, including a broad variety of common symptoms and to analyse how these common physical and psychological symptoms are related to incident myocardial infarction. Psychological distress may manifest as physical symptoms like chest pain and stomach ache. Furthermore, people may describe symptoms related to psychological illness very differently, and the comprehensive list of health problems in the questionnaire gave the participants an opportunity to choose between several symptoms. The 18 symptoms included in the variable Health problems were selected from the factor analysis and all factor loadings were positive, supporting that all 18 symptoms were good indicators of health problems. The factor scores were linearly related to the risk of AMI. Another limitation is that even if we were able to control for several potential confounding factors, residual factors may have affected the association. For example, we did not have access to data on sleep apnea or depression. Because of several missing values on CNI and education, we had to analyse these variables in a reduced sample. Moreover, self-reported data is limited by the individuals' will to report, and can be influenced by several factors, including social context and social desirability [29]. Individuals who reported 0 health problems may in fact have several problems that they did not report. A problem of using baseline questionnaires in prospective studies with a long follow-up is also that the data may change over time. We had no data on potential changes in the participants' medical condition during the follow-up. This is an inherent problem when the follow-up time from baseline is long. However, to be able to analyse the association between health problems and AMI in women who were middle-aged at base-line, it is important that the follow-up is not too short.

There is also a possibility that non-responders are different from the responders and non-responders may have an increased risk of AMI [30].

4.2. Conclusions

The present study indicates that common health problems including pain and stress symptoms are associated with an increased risk of later AMI in middle-aged women. Awareness among clinicians of predictive risk factors for AMI in women is important for early identification of risk individuals.

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Highlights

- The cardiovascular predictive risk pattern in women has not been fully studied.
- Somatic and mental health problems, including pain and stress, were the subject of the present study.
- The presence of several health problems was associated with myocardial infarction.
- Knowledge of early predictive cardiac risk factors is important for clinicians.

Table 1

Distribution (%) of the variables by number of health problems, n=6,711.

Distribution of the sample (%)					
Variable		**Median number of health problems (%)**			
	Totals	**0 (8.2)**	**4 (50.1)**	**8 (25.0)**	**13 (16.7)**
Age					
Mean (years)	56.4	56.7	56.6	56.2	56.0
50–54	31.7	29.1	30.0	33.4	35.6
55–59	49.7	49.1	49.9	49.4	49.7
60–64	18.6	21.8	20.1	17.2	14.7
Education *1)*					
Low-Middle	65.1	70.5	65.6	62.7	65.4
High	34.9	29.5	34.4	37.8	34.6
Smoking					
Non-smoker	59.1	67.0	59.9	57.4	55.3
Former smoker	20.2	17.4	19.5	21.4	21.6
Daily smoker	20.7	15.6	20.6	21.2	23.1
WHR					
Small (≤0.78)	54.5	61.9	55.4	53.0	50.2
Large (>0.78)	45.5	38.9	44.6	47.0	49.8
Blood pressure					
SBP < 140 & DBP < 90 mmHg	52.1	47.0	51.8	54.0	50.6
SBP 140–149 or DBP 90–99 mmHg	27.1	29.0	26.9	26.6	28.5
SBP ≥ 150 or DBP ≥ 100 mmHg	20.8	24.0	21.3	19.4	20.9
Ratio total- cholesterol/HDL					
mean	3.7	3.5	3.6	3.7	3.9
Diabetes					
No	97.8	98.7	97.8	97.9	97.3
Yes	2.2	1.3	2.2	2.1	2.7
CNI *1)*					
Affluent areas	61.7	64.8	61.6	61.0	62.6
Deprived areas	38.3	35.2	38.4	39.0	37.4

WHR, waist-hip-ratio, SBP, systolic blood pressure, DBP, diastolic blood pressure, CNI, Care Need Index

1) Reduced sample n=6,234

Table 2

Incidence rates (IR) per 10,000 person-years at risk. n=6,711; # AMI=205;

AMI (n=205)		
Variable	**IR**	**95 % CI**
Age		
50–54	14.7	11.3–19.4
55–59	17.3	14.2–21.2
60–64	28.7	21.9–37.1
Education *1)*		
Low-Middle	20.4	17.4–24.1
High	14.4	11.2–19.0
Smoking		
Non-smoker	13.0	10.6–16.2
Former smoker	17.7	13.1–24.5
Daily smoker	34.6	27.9–43.5
WHR		
Small (<=0.78)	13.1	10.6–16.4
Large (>0.78)	24.8	20.9–29.7
Blood pressure		
SBP < 140 & DBP < 90 mmHg	15.0	12.2–18.6
SBP 140–149 or DBP 90–99 mmHg	19.6	15.3–25.6
SBP ≥ 150 or DBP ≥ 100 mmHg	25.2	19.6–33.0
Ratio total-cholesterol/HDL		
0.3–3.4	12.4	9.9–15.9
3.5–4.5	16.4	12.7–21.6
4.6–21	36.6	29.5–45.9
Health problems (median)		
0	20.5	13.3–33.4
4	15.0	12.1–18.7
8	19.8	15.3–26.1
13	25.3	19.2–34.1
Diabetes		
No	17.7	15.4– 20.4
Yes	51.9	29.7– 99.0
CNI *1)*		
Affluent areas	16.5	13.7– 20.0
Deprived areas	21.7	17.6–27.0

AMI, acute myocardial infarction, WHR, waist-hip-ratio, SBP, systolic blood pressure, DBP, diastolic blood pressure, CNI, Care Need Index

1) Reduced sample

Table 3

Hazard ratios (HR) with 95% confidence interval (CI) for AMI, age-adjusted and main effect model. n=6,711; # AMI=205.

AMI (age-adjusted model)			AMI (main effects model)		
Variable	**HR**	**95 % CI**	**Variable**	**HR**	**95 % CI**
Agec (age-56) only age	1.089	1.04–1.14	**Agec** (age-56)	1.09	1.04– 1.14
Education			**Education** *1)*		
Low-Middle	1.33	0.97– 1.82	Low-Middle	‘	
High	1	Ref	High	‘	
Smoking			**Smoking**		
Non-smoker	1	Ref	Non-smoker	1	Ref
Former smoker	1.39	0.95–2.02	Former smoker	1.37	0.94– 2.00
Daily smoker	2.84	2.09–3.86	Daily smoker	2.66	1.95– 3.64
WHR			**WHR**		
Small (<=0.78)	1	Ref	Small (<=0.78)	1	Ref
Large (>0.78)	1.84	1.39– 2.45	Large (>0.78)	1.43	1.06– 1.93
Blood pressure			**Blood pressure**		
SBP < 140 & DBP < 90 mmHg	1	Ref	SBP < 140 & DBP < 90 mmHg	1	Ref
SBP 140–149 or DBP 90–99 mmHg	1.26	0.91–1.76	SBP 140–149 or DBP 90–99 mmHg	1.22	0.87–1.70
SBP ≥ 150 or DBP ≥ 100 mmHg	1.57	1.12–2.19	SBP ≥ 150 or DBP ≥ 100 mmHg	1.43	1.02–2.02
Ratio Tch/HDL			**Ratio Tch/HDL**		
Per 1 unit increase	1.24	1.16–1.32	Per 1 unit increase	1.16	1.08–1.24
Diabetes			**Diabetes**		
No	1		No	1	
Yes	2.85	1.56– 5.21	Yes	2.43	1.30–4.54
Health problems (median)			**Health problems**		
0	1.35	0.82–2.34	0	1.58	0.95– 2.63
4	1	Ref	4	1	Ref
8	1.36	0.97–1.91	8	1.35	0.96–1.89
13	1.78	1.25–2.54	13	1.65	1.16–2.36

1) Reduced sample, see Table 4.

Table 4

Hazard ratios (HR) with 95% confidence interval (CI) for AMI, including also education and CNI. Main effect model also adjusted for all other variables. AMI: n=6,234; # AMI=192.

AMI (age-adjusted)			AMI (main effects model)		
Variable	**HR**	**95 % CI**	**Variable**	**HR**	**95 % CI**
Education			**Education**		
Low-Middle	1.30	0.95– 1.79	Low-Middle	1.08	0.79– 1.49
High	1	Ref	High	1	
CNI			**CNI**		
Affluent areas	1		Low	1	
Deprived areas	1.30	0.98-1-74	High	1.25	0.94–1.66
Health problems (median)			**Health problems**		
0	1.37	0.82–2.29	0	1.58	0.94–2.65
4	1	Ref	4	1	Ref
8	1.36	0.96–1.93	8	1.35	0.95–1.92
13	1.66	1.14–2.40	13	1.55	1.06–2.24

AMI, acute myocardial infarction, CNI, Care Need Index