ORIGINAL ARTICLE

Accumulation of psychosocial risk factors and incidence of cardiovascular disease: a prospective observation of the Polish HAPIEE cohort

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ABSTRACT

BACKGROUND   Psychosocial risk factors for cardiovascular disease (CVD) are known to cluster in individuals, but the effect of cumulative exposure has not been thoroughly described in terms of CVD risk.

AIMS   The aim of the study was to assess the relationship between accumulation of psychosocial risk factors such as low education, material deprivation, depressive symptoms, and low perceived control and the risk of incident CVD.

METHODS   This cohort study with 11-year follow-up included a random population sample (age, 45–69 years). Psychosocial factors were assessed using standard tools. Accumulation of psychosocial risk factors was determined by summing up the number of psychosocial factors experienced. The risk of incident CVD depending on the number of psychosocial factors was estimated (reference, no psychosocial factors). Cox proportional hazards models were fitted.

RESULTS   In total, 43 572 and 51 772 person-years were analyzed. There were 479 and 291 new CVD cases in men and women, respectively. An age-adjusted model showed an increase in CVD risk in men exposed to 3 and 4 psychosocial risk factors by nearly 60% and 125%, respectively ($P < 0.05$). Further adjustment waved the association in individual strata, but a significant linear trend was observed. In women, in a fully adjusted model, the second and subsequent risk factors increased the risk of CVD by nearly 70% up to over 2-fold ($P < 0.001$). The total population attributable risk associated with exposure to psychosocial risk factors in women was 34.1%.

CONCLUSIONS   The accumulation of psychosocial risk factors was associated with increased risk of CVD. In men, the relation was substantially explained by classic risk factors. In women, about one-third of incident CVD cases could be attributed to psychosocial risk factors.

INTRODUCTION   During the last 2 decades, substantial evidence has been collected on the association between cardiovascular disease (CVD) and psychosocial factors such as stress, low socioeconomic position, depression, and low perceived control.[1-3] A recent study of Tillmann et al[4] confirmed the importance of psychosocial characteristics as predictors of cardiovascular mortality in Central and Eastern Europe. The 2016 European guidelines on CVD prevention in clinical practice consider low social position, stress at work or in the family, social isolation, depression, anxiety, hostility, and personality type D as the most important psychosocial factors.[5] It is indicated that this is a group of heterogeneous, but interrelated factors, which cluster in individuals and groups. The guidelines suggest consideration of psychosocial factors assessment and provide a quick tool to do so, but they do not recommend any intervention as a result of this assessment. This is because the effect of a cumulative exposure to psychosocial risk factors, although noticed, has not been thoroughly quantitatively described in terms

WHAT'S NEW?

Psychosocial risk factors for cardiovascular disease (CVD) are known to cluster in individuals. The effect of cumulative exposure to psychosocial risk factors, although noticed, has not been thoroughly quantitatively described in terms of CVD risk. This is the first prospective study assessing a cumulative effect of psychosocial factors on CVD incidence in Central and Eastern Europe. Cumulative exposure to low education, material deprivation, depression, and low perceived control was found to be associated with increased risk of CVD. In men, the relation was substantially explained by classic risk factors. However, this relationship in women was found to be strong and independent of classic risk factors. Moreover, about one-third of incident CVD cases could be attributed to psychosocial risk factors.

of CVD risk. The results of the case-control IN-TERHEART study showed that a cluster of psychosocial risk factors such as social deprivation, stress at work or at home, and depression was associated with an increased prevalence of myocardial infarction.[6] However, the vast majority of prospective evidence on psychosocial CVD risk factors in the general population focuses on the estimation of the health impact of individual factors. There is an extensive body of data for the individual association of education, depression, and deprivation with CVD risk. Perceived control in the Polish population was found to be a very strong predictor of CVD mortality, especially in women[3,7-10]; however, no evidence on the combined effect of these characteristics is available.

The main objective of the present study was to assess the relationship between accumulation of psychosocial risk factors such as low level of education, material deprivation, depressive symptoms, and low perceived control and the risk of incident CVD.

METHODS This prospective cohort study with an 11-year follow-up was conducted within the Polish part of the HAPIEE project (Health, Alcohol and Psychosocial Factors in Eastern Europe). The rationale and methodology of the whole study were described in a previous publication.[11] Methodological information relevant for this study is summarized below.

At baseline, a random sample of 19 865 men and women aged 45 to 69 years was drawn from permanent residents of Kraków, Poland. We examined 10 728 persons, achieving a participation rate of 61%. After excluding participants who did not agree to participate in follow-up (7%), the study sample included 10 012 persons. All participants gave written consent for participation in the study. The study was approved by the Bioethical Committee at Jagiellonian University Medical College. At baseline, trained nurses interviewed participants in their homes, using an extensive structured questionnaire. Then, all participants underwent a physical examination in a clinic where a fasting blood sample was collected.

Educational attainment was determined based on the answer to the question about the highest completed level of education as 1 of 5 possible answers (incomplete primary or no formal education, primary, vocational, secondary, university). Low education was defined as vocational or lower.

Material deprivation was measured using 3 questions assessing how often participant lacked money for food, clothes, or bills. Responses from "never" to "all the time" were coded from 0 to 4 and summed up. The total score ranged from 0 to 12. Respondents who obtained at least 3 points (1st tertile value) were considered as highly deprived.

Perceived control was assessed using an 11-item questionnaire, initially developed by the MacArthur Foundation Research Network on Successful Midlife Development[12] and subsequently used in the Whitehall II study and in the New Democracy Barometer surveys.[13,14] Participants were asked to indicate to what extent they agree or disagree with 11 statements referring to their perceived control over life events and health. Their responses, ranging from "totally agree" to "totally disagree," were recorded on a 6-point scale (coded from 0 to 5 and summed up). The total perceived control score ranged from 0 (total lack of control) to 55 (maximum perceived control). The algorithm allowed 2 missing answers at most, which were replaced by the arithmetic mean of valid responses. Low perceived control was considered if the total score was 34 or lower (1st tertile value).

Depressive symptoms were assessed using the Centre for Epidemiologic Studies Depression Scale.[13,15] The questionnaire consisted of 20 items referring to symptoms experienced during the past week. Severity of each item was scored from 0 to 3, thus the total score range was 0 to 60. Calculation of the final score allowed no more than 4 missing answers, which were replaced by the average score from valid responses. The cutoff value of 16 points was accepted.[15]

Accumulation of psychosocial risk factors was determined by summing up the number of the 4 above factors (depression, low perceived control, high deprivation, and low education), to which an individual was exposed.

Ten-year risk of fatal CVD was calculated for each participant using the Systematic Coronary Risk Evaluation (SCORE) algorithm, which includes age, sex, smoking status, systolic blood pressure, and total cholesterol levels, according to Conroy et al.[16] Body mass index (BMI) was calculated as kg/m². Diabetes was defined as fasting plasma glucose levels of 7 mmol/l or higher or as having diabetes diagnosed by a doctor. Marital status was dichotomized as married/cohabiting vs single/divorced/widowed.

Follow-up Data on deaths and their causes were obtained from the death register of the city of Kraków, Central Statistical Office, and by contacting the respondents' families. The causes of deaths were coded according to the 10th revision of the *International Statistical Classification of Diseases and Health Problems* (*ICD-10*). Deaths due to CVD were accepted for *ICD-10* codes from I.00 to I.99.

New CVD cases (ie, myocardial infarction, stroke, coronary artery bypass grafting, percutaneous coronary interventions, and unstable coronary disease confirmed by coronary angiography) were identified on the basis of information obtained from respondents through 3 postal questionnaires and the second interview and verified by the review of medical documentation. Postal questionnaires were sent to the respondents together with addressed return envelopes, with a request for information whether the respondent had experienced myocardial infarction, stroke, coronary angiography, coronary artery bypass grafting, or percutaneous coronary intervention in the period from the last contact with the HAPIEE research team. The information from the first postal questionnaires was obtained between 2005 and 2006; second, between 2008 and 2010; and third, between 2012 and 2013. The second screening was carried out in the respondents' homes in the years 2006 to 2008, and the questions regarding new cases were formulated identically to those asked in postal questionnaires. For each respondent, the status at the end of the follow-up was determined and the exact survival time was calculated. The follow-up was completed on December 31, 2014. For participants who were lost to follow-up, the censorship date was the date of the last contact.

Statistical analysis The distribution of education categories was presented as number (percentage), and of material deprivation, depressive symptoms, and perceived control, both as continuous and categorical variables indicating the number and percentage or as mean (SD) or median (interquartile range), as appropriate. The associations between perceived control, depressive symptoms, deprivation, and education were assessed using the Spearman correlation. The main statistical method was the Cox proportional hazards model. The associations between psychosocial risk factors and CVD incidence and then between the accumulation of psychosocial risk factors and CVD incidence were assessed, using time-on-study as the time scale. Hazard ratios (HRs) with 95% confidence intervals (CIs) were presented. Three models were fitted: 1) adjusted only for age; 2) adjusted for SCORE risk; and 3) adjusted for marital status SCORE risk, diabetes, and BMI. Population attributable risks (PARs, ie, the proportion of all cases which could

be attributed to the risk factor if causality was proved) were calculated according to the formula appropriate for HRs estimated in multidimensional models.[17] All statistical analyses were conducted using STATA version 14 (StataCorp LP, College Station, Texas, United States).

RESULTS The observation included 43 572 person-years in men and 51 772 person-years in women. There were 479 and 291 new CVD cases observed in men and women, respectively. The mean age of the studied sample was 57 years and did not differ significantly between sexes. Small but significant differences in education in favor of women with higher education were found. The prevalence of deprivation, depressive symptoms, and low perceived control at baseline was more frequent in women than in men (P <0.001). The mean BMI in both sexes was quite high (about 28 kg/m^2). The SCORE risk and the prevalence of diabetes were higher in men than in women (P <0.001) (TABLE 1).

Depressive symptoms, perceived control, deprivation, and education were strongly correlated with each other (TABLE 2). The associations between individual psychosocial factors and CVD incidence for the whole sample and according to sex are presented in TABLE 3. In the whole sample, in the fully adjusted model, depressive symptoms, low perceived control, and high deprivation were independent predictors of incident CVD, increasing the risk by 30% (HR, 1.30; 95% CI, 1.08–1.55), 28% (HR, 1.28; 95% CI, 1.09–1.51), and 21% (HR, 1.21; 95% CI, 1.02–1.44), respectively. The analysis by sex showed that the associations observed in the whole sample were the consequence of strong relations found mostly in women. Each of the analyzed psychosocial risk factors increased the risk of incident CVD in women from 34% (low perceived control) to 50% (depression). In men, only depression and low perceived control were significant predictors of CVD in the fully adjusted model, increasing the risk by 31% and 30%, respectively.

The risk of incident CVD and PARs according to the number of psychosocial risk factors and sex are presented in TABLE 4. The age-adjusted model showed an increase in CVD risk in men exposed to 3 and 4 psychosocial risk factors by nearly 60% and 125%, respectively (P <0.05). Further adjustment for covariates attenuated the association, and eventually the relation between the accumulation of psychosocial risk factors and CVD risk in men was largely explained by the influence of the main CVD risk factors. In the fully adjusted model, the total PAR was 7.1%. Nevertheless, a significant linear trend was found. In women, a positive association independent of classic CVD risk factors between cumulative exposure to psychosocial risk factors and incident CVD was observed. In women, in

TABLE 1 Distribution of study variables by sex

Parameter		Men (n = 4107)	Women (n = 4726)	P value
Person-years		43 572.0	51 772.9	–
Follow-up duration, y, mean (SD)		10.6 (2.13)	11.0 (1.53)	–
CVD cases, n (%)		479 (11.7)	291 (6.2)	<0.001
Age, y, mean (SD)		57.3 (6.93)	57.1 (6.92)	0.052
Marital status, n (%)	Married / cohabiting	3579 (87.3)	3177 (67.4)	<0.001
	Single / widowed / divorced	520 (12.7)	1540 (32.7)	
Education, n (%)	Incomplete primary or no formal education	9 (0.2)	13 (0.3)	<0.001
	Primary	353 (8.6)	572 (12.1)	
	Vocational (apprenticeship)	1095 (26.7)	707 (15.0)	
	Secondary	1358 (33.1)	2092 (44.3)	
	University (degree)	1290 (31.4)	1337 (28.3)	
Depressive symptoms, CES-D score, median (Q1; Q3)		8 (4; 13)	11 (6; 18)	<0.001
Depression, CES-D score ≥16, n (%)		752 (18.7)	1486 (32.1)	<0.001
Perceived control, points, mean (SD)		37.4 (7.41)	36.4 (7.53)	<0.001
Low perceived control, n (%)		1316 (32.6)	1761 (37.8)	<0.001
Deprivation score, points, median (Q1; Q3)		0 (0; 3)	1 (0; 5)	<0.001
High deprivation, n (%)		992 (24.4)	1547 (33.0)	<0.001
Number of psychosocial factors, n (%)	None	1425 (36.2)	1439 (31.6)	<0.001
	1	1247 (31.7)	1324 (29.1)	
	2	777 (19.7)	993 (21.8)	
	3	382 (9.70)	586 (12.9)	
	4	108 (2.74)	211 (4.6)	
SCORE risk, %, median (Q1; Q3)		6.01 (3.16; 10.54)	1.56 (0.65; 3.47)	<0.001
Smoking, n (%)		2911 (71.1)	2337 (49.6)	<0.001
BMI, kg/m², mean (SD)		27.9 (3.99)	28.3 (5.05)	<0.001
Diabetes, n (%)		579 (15.7)	498 (11.8)	<0.001

Abbreviations: BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; CVD, cardiovascular disease; SCORE, Systematic Coronary Risk Evaluation

the fully adjusted model, the second and subsequent risk factors increased the risk of CVD by nearly 70% if exposed to 2 psychosocial factors, and by over 2-fold if exposed to 3 or 4 psychosocial factors, independently of the main CVD risk factors. The total PAR associated with exposure to psychosocial risk factors in women was 34.1%.

DISCUSSION Our results indicate that the associations between psychosocial risk factors and CVD incidence are stronger in women than in men. The clustering of psychosocial risk factors in women substantially increased CVD risk. No significant effect of the accumulation of psychosocial factors on CVD incidence in men was found, although the average estimates showed the same direction of the association. The higher prevalence of psychosocial factors as well as stronger associations with CVD risk in women contributed to high estimates of the PAR related to psychosocial factors in women.

It is generally assumed that the effects of the main CVD risk factors are the same in women as in men. Several meta-analyses showed that the exposure to hypertension, smoking, overweight and obesity, as well as hypercholesterolemia impacts CVD to a similar extent in both sexes.[12,18-21] A sex disparity in the risk of coronary heart disease and stroke in patients with diabetes was found.[12] At present, the limited knowledge about the mechanisms underlying the direct effect of psychosocial risk factors on the development of CVD does not allow to clearly address the possibility of a stronger impact of psychosocial risk factors in women. In general, chronic psychosocial stress, metabolic changes, and imbalance between the sympathetic and parasympathetic system as a consequence of exposure to psychosocial factors remain the most probable pathway.[14,22] However, latest evidence both from animal models and human studies suggests sex differences in stress responses.[23] Compared with men, women are more vulnerable to stress-induced hyperarousal and are more resilient to stress-induced attention deficits.[24] To some extent, this may explain more pronounced health effects of chronic

TABLE 2 Correlation between psychosocial characteristics in men and women (Rho coefficient)

Characteristic	Men			Women		
	Perceived control score	Depressive symptoms score	Deprivation score	Perceived control score	Depressive symptoms score	Deprivation score
Depressive symptoms score	−0.47[a]	1.00	–	−0.49[a]	1.00	–
Deprivation score	−0.30[a]	0.30a[a]	1.00	−0.30[a]	0.33[a]	1.00
Education	0.18[a]	-0.10[a]	-0.19[a]	0.18[a]	−0.13[a]	−0.20[a]

[a] *P* <0.001

TABLE 3 Association between depression, low perceived control, high deprivation, and low education with cardiovascular disease risk in the total sample and by sex (reference: no exposure to risk factor)

	HR[a] (95% CI)	HR[b] (95% CI)	HR[c] (95% CI)
Depression			
Total	1.24 (1.06–1.45)	1.34 (1.12–1.60)	1.30 (1.08–1.55)
Men	1.27 (1.02–1.59)	1.28 (1.00–1.63)	1.31 (1.02–1.67)
Women	1.54 (1.22–1.95)	1.53 (1.18–1.99)	1.50 (1.15–1.95)
Low perceived control			
Total	1.30 (1.13–1.50)	1.29 (1.10–1.50)	1.28 (1.09–1.51)
Men	1.36 (1.13–1.64)	1.29 (1.05–1.58)	1.30 (1.04–1.59)
Women	1.33 (1.06–1.69)	1.35 (1.04–1.75)	1.34 (1.03–1.73)
High deprivation			
Total	1.31 (1.13–1.53)	1.22 (1.02–1.44)	1.21 (1.02–1.44)
Men	1.34 (1.09–1.64)	1.17 (0.93–1.47)	1.17 (0.93–1.46)
Women	1.52 (1.20–1.92)	1.36 (1.04–1.78)	1.37 (1.05–1.79)
Low education			
Total	1.36 (1.18–1.57)	1.20 (1.02–1.41)	1.12 (0.95–1.32)
Men	1.16 (0.97–1.39)	1.01 (0.82–1.24)	0.98 (0.80–1.21)
Women	1.53 (1.20–1.93)	1.55 (1.19–2.02)	1.37 (1.04–1.80)

a Adjusted for age; **b** Adjusted for SCORE risk; **c** Adjusted for marital status, SCORE risk, BMI, and diabetes

Abbreviations: HR, hazard ratio; others, see TABLE 1

exposure to psychosocial factors. Our results are consistent with the results of the population--based case-control INTERHEART study, in which the strength of the association between the cluster of psychosocial risk factors (ie, material deprivation, stress at work or in private life, and depression) was substantially higher in women compared with men.[6] Several earlier studies investigating the role of socioeconomic characteristics in CVD risk also found that in women, the social gradient in CVD was stronger than in men.[25-27] Similar to the other studies in both sexes, we found interrelations and clustering of psychosocial risk factors in the same individuals.[28,29]

Two main limitations in the interpretation of our results should be considered. First, by summing up the number of experienced psychosocial risk factors, the same weight was assumed for each of them, while their impact on CVD may be different. However, in the analysis of individual factors, the effect of each of them was roughly the same, especially in women. If so, it seems that the unequal effect of particular factors would not significantly influence the results. Second, the participation rate was modest and further reduction of the study sample was due to the fact that only participants without missing data on any of the covariates were included in the final analysis. However, the participation rate was similar in men and women, so it seems

TABLE 4 Risk of incident cardiovascular disease and population attributable risks by the number of psychosocial risk factors experienced

Number of psychosocial risk factors experienced	HR[a] (95% CI)	PAR, %	HR[b] (95% CI)	PAR, %	HR[c] (95% CI)	PAR, %
Men						
None	1.00	–	1.00	–	1.00	–
1	1.06 (0.80–1.34)	1.7	1.00 (0.77–1.29)	0	0.96 (0.74–1.24)	0
2	1.25 (0.96–1.62)	4.3	1.19 (0.89–1.58)	3.4	1.16 (0.87–1.54)	2.9
3	1.57 (1.15–2.14)	4.6	1.37 (0.97–1.93)	3.4	1.41 (1.00–1.99)	3.7
4	2.24 (1.43–3.52)	2.7	1.62 (0.91–2.87)	1.9	1.53 (0.87–2.73)	1.7
P value for trend	<0.001	–	0.018	–	0.018	–
Total PAR, %		13.2		8.7		7.1
Women						
None	1.00	–	1.00	–	1.00	–
1	1.41 (0.99–2.0)	7.9	1.48 (1.01–2.17)	8.8	1.41 (0.96–2.08)	7.9
2	1.71 (0.20–2.43)	10.1	1.78 (1.20–2.65)	10.7	1.70 (1.14–2.54)	10.0
3	2.49 (1.72–3.60)	12.4	2.60 (1.72–3.92)	12.8	2.39 (1.57–3.63)	12.1
4	2.48 (1.51–4.07)	4.7	2.25 (1.23–4.10)	4.4	2.08 (1.14–3.81)	4.1
P value for trend	<0.001	–	<0.001	–	<0.001	–
Total PAR, %	–	35.2	–	36.7	–	34.1

a Adjusted for age; **b** Adjusted for SCORE risk; **c** Adjusted for marital status, SCORE risk, BMI, and diabetes

Abbreviations: PAR, population attributable risk; others, see TABLES 1 and 3

unlikely that sex differences in the results obtained could be the consequence of such bias. Nevertheless, the response rate could have influenced the representativeness of the sample. In our cohort, nonrespondents were found to have higher mortality rates than study participants.[30] Thus, the studied relationships were investigated in a healthier part of the original population sample. If so, it can be suspected that our results might be underestimated. However, available evidence suggests that a decline in participation rates in epidemiological studies in the last decades does not necessarily affect the estimates of examined associations.[31,32]

On the other hand, the study has important strengths. To our best knowledge, this is the first prospective study assessing the cumulative effect of psychosocial factors on CVD incidence in Poland and the first one analyzing the total effect of the coexistence of these specific factors. The study targeted a random and culturally homogenous sample, which was examined and followed for a long time. We evaluated psychosocial characteristics stable in time, so baseline assessment seems unlikely to change substantially over time. Standardized tools for the assessment of psychosocial factors were previously shown to predict CVD events in longitudinal studies. Strict adherence to standard research methods was provided to ensure data quality.

In conclusion, the accumulation of psychosocial risk factors was associated with increased risk of CVD. In men, the relation was substantially explained by classic risk factors. In women, about one-third of incident CVD cases could be attributed to psychosocial risk factors.

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