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Major life events increase the risk of stroke but not of myocardial infarction: results from the Copenhagen City Heart Study

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Abstract

Background—More attention has been paid to psychosocial conditions as possible risk factors for cardiovascular disease (CVD) and the impact of accumulated major life events (MLE) on the development of CVD has received little attention.

Design—The aim of this study was to explore the influences of MLE on CVD risk in a large cohort study.

Methods—The study population consisted of 9542 randomly selected adults free of CVD examined in the Copenhagen City Heart Study in 1991–1994 and followed up for CVD defined as myocardial infarction or ischaemic stroke until 2001. MLE were analysed using an 11-item questionnaire and hazard ratios (HR) were calculated using the Cox proportional hazards model.

Results—During follow-up there were 443 myocardial infarctions (MI) and 350 ischaemic strokes. Financial problems in both childhood and adulthood were associated with risk of stroke with an HR of 1.71 (95% CI: 1.29–2.26) and 1.60 (1.12–2.30), respectively. Accumulation of MLE was also associated with risk of stroke with HR reaching a maximum of 1.41 (95% CI: 1.06–1.90) for more than one event in childhood and 1.49 (95% CI: 1.09–2.04) for more than one event in adulthood. MLE accumulated over a life course showed a dose–response relationship with stroke. Associations were somewhat attenuated by adjustment for vital exhaustion suggesting a mediating role, but not by adjustment for behavioural risk factors. There were no associations between MLE and MI.

Conclusion—In this population-based cohort study, we found that MLE conveyed a moderately increased risk of stroke partly mediated through vital exhaustion. We found no association between MLE and the risk of MI.

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There is no conflicts of interest.

Keywords

adulthood; childhood; ischaemic stroke; myocardial infarction; prospective study

Introduction

More attention has been paid to several psychosocial conditions as independent risk factors that may contribute to the development of ischaemic heart disease and stroke.

Depression [1–3] and lack of social contacts [4] are some of the psychosocial factors that have been proposed and several studies find an association independent of traditional risk factors. Major life events (MLE) such as loss of a child and marital dissolution have also been studied as potential risk factors for CVD with different results [5,6]. The Interheart study, a large case–control study, found that accumulation of stressful life events 12 months before acute myocardial infarction (MI) was more frequent in cases than controls [7], whereas a prospective study, which included only men, found no relationship between MLE and MI [8]. There are no previous studies of MLE and stroke.

From a life course perspective it is possible that MLE experienced in childhood and adulthood may be psychosocial stressors that increase the risk of CVD. The potential health effects of psychosocial factors measured over the life course have been described by the cumulative and the sensitive period model, but it has never been applied to studies of the effect of MLE on health outcomes. The model of accumulation states that the number and the intensity of unfavourable exposures adversely affect health in a dose—response-like manner. Applying this model to MLE, number of events should be associated with increased health risks. In contrast, the sensitive period model implies that some periods in life are more sensitive to harmful effects of MLE. Childhood may be regarded as a particularly sensitive period because other important life transitions take place during this time.

The aim of this study was to examine the joint and separate influences of MLE during childhood and adulthood on the development of CVD and explore whether any such associations were mediated by other psychosocial or behavioural factors. Furthermore, the objective was to determine whether there are any sex differences, as men and women can be expected to differ in exposure, reaction to and effects of MLE.

Methods

Population

The study is based on data from the third examination (1991–1994) of the Copenhagen City Heart Study [9], comprising 10 135 individuals (response rate 61%). A total of 593 patients were excluded owing to prior hospital discharge with a diagnosis of stroke or MI obtained from the Danish National Register of Patients. Thus, the study population consisted of 9542 individuals free of diagnosed CVD at baseline: 5454 women and 4088 men.

Variables

Cardiovascular risk factors were assessed using a self-administered questionnaire, a physical examination and paraclinical tests. MLEs were self-reported and for the accumulation analyses categorized into the following two subsets: childhood (five items) and adulthood (six items).

Positive responses were summed for each person within each category and categorized into zero, one or more than one events within the two subsets. Several of the MLE experienced

in adulthood were related to parenthood and participants without children were excluded, but there was insufficient statistical power to analyse participants without children separately. Analyses of effect of MLE in childhood were based on 8916 participants, MLE in adulthood on 6578 participants and MLE accumulated over a life course on 6519 participants.

Risk factors regarded as confounders/mediators were measured as follows: tobacco consumption was categorized into never-smokers, ex-smokers, current smokers of 1–15 g tobacco per day and current smokers of more than 15 g tobacco per day. Alcohol consumption was categorized according to weekly intake: no alcohol consumption, 1–7, 7–14, 15–21 and more than 21 units per week. One unit was defined as 9–13 g alcohol. Diabetes was self-reported. Physical activity in leisure time was classified as follows: sedentary, moderate activity less than 4 h and moderate activity more than 4 h per week. Medicine use was self-reported and categorized into antihypertensive medication, cholesterol-lowering medication and hormone replacement therapy (women). Systolic blood pressure was measured in a sitting position after 5-min rest using a London School of Hygiene sphygmomanometer and divided into the following four categories: less than 120, 120–140, 140–160 and greater than 160 mmHg. Body mass index (BMI) was categorized into: BMI < 18.5, 18.5 ≤ BMI < 25, 25 ≤ BMI ≤ 30 and BMI > 30. Atrial fibrillation was registered by ECG and classified according to the Minnesota classification [10]. Blood lipids and blood glucose were measured nonfasting. Socioeconomic status: education level was classified as less than 8 years of schooling, 8–11 years of schooling and more than 11 years of schooling. Employment was categorized into self-employed or superior skilled employee, subordinate skilled employee, unskilled employee/unemployed and pensioner/working at home. Household income was classified into four quartiles. Cohabitation was categorized as living alone or not living alone. Vital exhaustion, a measure of depression and fatigue, was estimated by using a 17-item questionnaire modified from Appels [11]. Positive responses were summed for each person and divided into four categories as used earlier [2]: 0, 1–4, 5–9 and 10–17.

Endpoint

Outcomes were first-ever MI (n=443), (International Classification of Diseases, ICD-8 diagnosis codes 410–414 until 1 January 1994, ICD-10 diagnosis codes I21 to I25 from 1994 onwards) or ischaemic stroke (n=350), (ICD-10 diagnosis code I60–I69 and G45), both fatal or nonfatal obtained from the Danish National Register of Patients. Forty-three participants had both MI and stroke. All strokes were validated [12]. Strokes validated as cerebral ischaemic stroke (n=233) or cerebral stroke – unspecified (n=117) were used in the analyses, whereas strokes classified as cerebral haemorrhage (n=43), brainstem stroke (n=2), subarachnoid haemorrhage (n=43), transient ischaemic attack (n=47) or undefined (n=2) were excluded. Inclusion of unspecified stroke was chosen because of the fact that 85% of all strokes are ischaemic. Data were collected from the beginning of the examination until 2001.

Statistical analysis

The Cox proportional hazards model was used to describe MLE as a potential risk factor for CVD. Age was used as the underlying time scale and age at baseline was used as entry time. Each patient contributed with time at risk from baseline to endpoint, death or lost to follow-up (< 1%), whichever came first. Several risk factors are known to have a nonlinear relationship with IHD and stroke (e.g. BMI, alcohol and blood pressure). To assure optimal adjustment, covariates were treated as categorical variables as described. Statistical analyses were performed for MI and stroke separately. Initial analyses were performed for men and women separately. If effects of MLE did not differ by sex (formally tested by tests of

interaction), subsequent analyses were carried out on pooled data controlled for sex. Effect of each of the confounders was tested with respect to interaction with sex. For atrial fibrillation and ischaemic stroke, a significant interaction with sex was found but this had no influence on the MLE estimate. The assumption of proportional hazards was tested formally as described by Grambsch and Thernau [13] and was met. Then, models were performed with four different levels of adjustments using sex and age (in the time axis) in the first model; adding vital exhaustion in the second model; using age, sex, traditional biological and behavioural risk factors (smoking, diabetes, physical activity, blood pressure and cholesterol-lowering drugs, systolic blood pressure, body mass index, atrial fibrillation, blood lipids) in the third model and adding socioeconomic risk factors (cohabitation, education, household income) and vital exhaustion in the fourth model (Tables 3 and 4).

Results

Study cohort at baseline

Table 1 presents the baseline characteristics of the study cohort by sex. The mean age of women was higher than that of men; fewer women had CVD and CVD in women occurred at a higher age. Both men and women had approximately two-and-a-half MLE seen from a life course perspective. Approximately half of the cohort was a smoker and 12–13% had a sedentary lifestyle. Men had a more adverse risk factor profile regarding lifestyle; more men smoked and their alcohol consumption and proportion of diabetics were almost twice as high as in women. A higher proportion of the women was living alone and had lower household income.

Accumulation of MLE (no MLE vs. having one or more MLE) in childhood and adulthood, respectively, was associated with increased smoking and alcohol consumption, although differences were not large. Notably, systolic blood pressure was significantly lower in patients with accumulation of MLE. There was no consistent association between accumulated MLE and other CVD risk factors.

Single major life events

Table 2 shows hazard ratios (HR) for each MLE item and the risk of MI and stroke, respectively. There were no associations between the MLE items and MI in childhood or in adulthood. Financial problems in childhood were associated with risk of stroke with an HR of 1.71 (95% CI: 1.29–2.26). However, on analysing for sex differences, the association was found in women but not in men: HRs were 2.28 (95% CI: 1.58–3.28) and 1.19 (95% CI: 0.76–1.86), respectively (test for interaction between sex P=0.03)(not shown). In adulthood, financial problems were associated with stroke with an HR of 1.60 (95% CI: 1.12–2.30), but no sex differences were found. No other single MLE were associated with risk of stroke.

Accumulated major life events

Neither accumulated MLE in childhood nor adulthood was associated with increased risk of MI (Table 3). An association between MLE in childhood and stroke was found with an HR of 1.41 (95% CI: 1.06–1.90) for more than one event. HR was not attenuated much by adjustment for traditional and socioeconomic risk factors, whereas vital exhaustion, a measure of depression and fatigue, attenuated HR with approximately 33%. A relationship between accumulated MLE in adulthood and ischaemic stroke was found reaching a maximum HR of 1.48 (95% CI: 1.08–2.02), also with a 33% reduction of the excess risk by adjustment for vital exhaustion. No sex differences for accumulated MLE in childhood or adulthood were found. Finally, Table 4 presents MLE from a life course perspective, defined as accumulated MLE in childhood and adulthood, and the association with the risk of ischaemic stroke and MI. As with childhood and adulthood as separate categories, no

association between MLE over a life course and MI was found. Risk of stroke increased with numbers of MLE over a life course, but the trend did not reach statistical significance (P=0.07). The excess risk was reduced approximately 40% by adjustment for vital exhaustion suggesting a mediating role, whereas adjusting for traditional CVD risk factors did not alter the excess risk.

Discussion

This first prospective cohort study on the influence of MLEs during the life course on the risk of MI and stroke showed that accumulation of MLE in childhood and adulthood are associated with a modest increase in the risk of stroke in both women and men, whereas there were no associations with MI. Associations were somewhat attenuated by adjustment for vital exhaustion suggesting that psychosocial factors may have a mediating role.

Few studies have studied the effect of MLE on MI with different results. The Interheart Study [7], a case– control study, investigated the associations of several psychosocial stressors, including occurrence of major adverse life events, with the risk of acute MI in different populations. The study found that stressful life events in the 12 months before MI (business failure, major intrafamily conflict, job loss, death of spouse and violence) were more frequent in cases than in controls (1 event OR=1.21, >1 events OR=1.48). This study explores MLE accumulated over a long period of time and has extended follow-up. If MLE increased the risk of MI for a limited time period after the life event, this may explain the discrepancy between the two studies. Rafanelli *et al.* [14] also found relationship between life events and MI in a case–control study. Life events were found to be significantly more frequent in patients suffering from MI than in controls. However, the events reported were heterogeneous in quality, involving both positive desirable changes and negative undesirable changes. This raises the question whether patients actually experience more events before illness, or whether associations in case–control studies are spurious because of systematic differences between cases and controls in recall of MLE. In a prospective study of 12 866 men with high risk of coronary heart disease, Hollis *et al.* [8] found that MLE were associated with angina but not with hard endpoints such as MI, coronary heart disease and total mortality. This could indicate that individuals who report more MLE also report more symptoms even without having cardiovascular disease. However, one register-based prospective study with 17 years of follow-up [5] has reported an association between loss of a child and MI (relative risk=1.31–1.58). The study adjusted for potential confounders such as education and residence, but not for other cardiovascular risk factors. There are no previous studies of MLE and stroke.

The major finding of the study is the moderate association between both childhood and particularly adulthood MLE and risk of stroke. Associations were similar in both men and women. The relationship was actually strengthened by adjustment for other cardiovascular risk factors. This reflects the inverse association between systolic blood pressure and some socioeconomic factors and MLE, which in itself is a surprising finding. Interestingly, Theorell *et al.* [15] reported in a study of young men that asymptomatic hypertensive men report fewer MLE than nonhypertensive men. The study also showed that hypertensive men had fewer social contacts, which could result in fewer possible MLE. In both MLE in childhood and adulthood adjustment for vital exhaustion attenuated, the HRs by approximately 33%. Vital exhaustion is a measure of depression and fatigue and it would seem plausible that part of the increased risk associated with MLE is mediated through psychosocial factors.

From a life course perspective the study partly supports the model of accumulation, but the results are not convincing. The findings also fail to support the sensitive period model, as the estimates for childhood and adulthood are similar.

The finding that there was an association with stroke but not with MI puzzles us. If these findings can be confirmed they would imply that the mechanisms through which MLE and possibly other psychosocial factors exert their effect should be sought for in the pathways where MI and stroke differ.

The strengths of this study are several. By using a prospective design with data collected before the onset of CVD reporting bias is prevented. The large sample size of 9542 participants, the participants' wide range of age and the 750 cardiovascular events during the 6–9 years follow-up period are also to be considered strengths, as well as the wide range of confounders included in the analysis. In contrast to a number of studies, we used register-based strokes that have been validated. Krarup *et al.* [12] investigated the validity of the register-based stroke diagnosis and found that one in six strokes in the Danish National Register of Patients did not meet the criteria of the World Health Organization stroke definition, and 66% of strokes classified as 'unspecified' were found to be ischaemic. Thus, endpoints based on registers that have not been validated may tend to overestimate the number of cerebrovascular events and underestimate the number of ischaemic strokes.

The study also has limitations. MLE are self-reported. Studies have shown that self-reported childhood disadvantage does not have high validity when compared with school records [16]. However, only if the bias in self-report is differential, that is, associated with both MLE and outcomes, then it affect the results. There is no reason to suspect this. In addition, as the effect of MLE is exerted through the individuals' reaction to these events, perceived MLE may more accurately reflect exposure.

Conclusion

This large population-based cohort study questions the previously reported associations between MLE and MI. The results suggest that MLE convey a moderately increased risk of stroke, which is partly explained by vital exhaustion, a measure of depression and fatigue. To our knowledge, this is the first study of MLE as risk factor for stroke. Further studies are needed to confirm these findings.

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References

1. Barefoot JC, Schroll M. Symptoms of depression, acute myocardial infarction, and total mortality in a community sample. Circulation. 1996; 93:1976–1980. [PubMed: 8640971]
2. Prescott E, Holst C, Grønbaek M, Schnohr P, Jensen G, John B. Vital exhaustion as a risk factor for ischemic heart disease and all-cause mortality in a community sample. A prospective study of 4084 men and 5479 women in the Copenhagen City Heart Study. Int J Epidemiol. 2003; 32:990–997. [PubMed: 14681262]
3. Kamphuis MH, Kalmijn S, Tijhuis MA, Geerlings MI, Ciampaoli S, Nissinen A, et al. Depressive symptoms as risk factor of cardiovascular mortality in older European men: the Finland, Italy and Netherlands Elderly (FINE) study. Eur J Cardiovasc Prev Rehabil. 2006; 13:199–206. [PubMed: 16575273]

4. Barefoot JC, Grønbaek M, Jensen G, Schnohr P, Prescott E. Social network diversity and risks of ischemic heart disease and total mortality: findings from the Copenhagen City Heart Study. Am J Epidemiol. 2005; 161:960–967. [PubMed: 15870160]
5. Li J, Hansen D, Mortensen PB, Olsen J. Myocardial infarction in parents who lost a child: a nationwide prospective cohort study in Denmark. Circulation. 2002; 106:1634–1639. [PubMed: 12270855]
6. Mathews KA, Gump BB. Chronic work stress and marital dissolution increase risk of posttrial mortality in men from the multiple risk factor intervention trial. Arch Intern Med. 2002; 162:309–315. [PubMed: 11822923]
7. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M. Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study. Lancet. 2004; 364:953–962. [PubMed: 15364186]
8. Hollis JF, Connett JE, Stevens VJ, Greenlick MR. Stressful life events, Type A behavior, and the prediction of cardiovascular and total mortality over six years. MRFIT Group. J Behav Med. 1990; 13:263–280. [PubMed: 2213869]
9. Schnohr P, Jensen G, Lange P, Scharling H, Appleyard M. The Copenhagen City heart study – Introduction. Eur Heart J Suppl. 2001; 3:H1–H83.
10. Blackburn H. Electrocardiographic classification for population comparisons. The Minnesota code. J Electrocardiol. 1969; 2:5–9. [PubMed: 5780211]
11. Appels A. Mental precursors of myocardial infarction. Br J Psychiatry. 1990; 156:465–471. [PubMed: 1974819]
12. Krarup L, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a national register of patients. Neuroepidemilogy. 2007; 28:150–154.
13. Grambsch PM, Thernau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 2000; 81:515–526.
14. Rafanelli C, Roncuzzi R, Milaneschi Y, Tomba E, Colistro MC. Stressful life events, depression and demoralization as risk factors for acute coronary heart disease. Psychother Psychosom. 2005; 74:179–184. [PubMed: 15832069]
15. Theorell T, Svensson J, Knox S, Waller D, Alvarez M. Young men with high blood pressure report few recent life events. J Psychosom Res. 1986; 30:243–249. [PubMed: 3723455]
16. Kauhanen L, Lakka HM, Lynch JW, Kauhanen J. Social disadvantages in childhood and risk of all-cause death and cardiovascular disease in later life: a comparison of historical and retrospective childhood information. Int J Epidemiol. 2006; 35:962–968. [PubMed: 16556645]

Table 1

Baseline characteristics of the study population by sex

	Women 5454 (57)	Men 4088 (43)
Age at baseline (years)	59.1 (15.4)	56.6 (15.5)
CVD	362 (6.6)	388 (9.5)
Age at CVD (years)	75.2 (9.5)	71.2 (10.5)
Major life event, sum score	2.6 (2.2)	2.4 (2.2)
Current smokers	2451 (45.4)	2135 (52.9)
Alcohol consumption/week	5.6 (7.5)	14.0 (15.5)
Physical active: sedentary	685 (12.8)	520 (12.9)
Self-reported diabetes	131 (2.4)	170 (4.2)
Body mass index (kg/m^2)	25.2 (4.7)	26.0 (3.9)
Systolic blood pressure (mmHg)	137.4 (23.8)	140.0 (21.1)
Antihypertensive medication	643 (11.9)	364 (9.0)
Atrial fibrillation	48 (0.9)	84 (2.1)
School education < 8 years	1864 (34.6)	1326 (32.8)
Low household income	1350 (25.7)	658 (16.4)
Cohabitation/live alone	2391 (44.2)	1235 (30.4)

Values are mean (SD) or number (%) as indicated. CVD, cardiovascular disease.

Table 2

Major life events and risk of myocardial infarction and stroke

	Myocardial infarction	Stroke
Major life events	**HR[a] (95% CI)**	**HR[a] (95% CI)**
Childhood		
Parents with critical illness	1.12 (0.91–1.38)	1.00 (0.78–1.30)
Unemployed parents	1.22 (0.88–1.68)	1.36 (0.95–1.95)
Financial problems	0.95 (0.72–1.30)	1.71 (1.29–2.26)[b]
Prolonged family conflicts	0.87 (0.63–1.21)	1.32 (0.94–1.87)
Placed away from home	1.09 (0.81–1.46)[b]	1.22 (0.87–1.73)
Adulthood		
Children with critical illness	1.08 (0.79–1.46)	0.89 (0.62–1.28)
Critical illness in close family	1.07 (0.88–1.30)	1.20 (0.96–1.51)
Children with educational problems	1.14 (0.73–1.78)	1.00 (0.57–1.76)
Conflicts with adult children	1.11 (0.75–1.65)	0.80 (0.47–1.35)
Financial problems	0.97 (0.68–1.38)	1.60 (1.12–2.30)
Marital problems	0.93 (0.72–1.22)	1.28 (0.96–1.70)

CI, confidence interval; HR, hazard ratio.

[a]Adjusted for age and sex.

[b]Significant interaction between sexes.

Table 3

Major life events and risk of myocardial infarction and ischaemic stroke

	Childhood			Adulthood		
Major life events, sum (with 0 as reference)	**1**	**> 1**	***P* value***	**1**	**> 1**	***P* value***
Myocardial infarction						
HR (95%)	1.13 (0.90–1.41)[a]	1.13 (0.87–1.47)	0.29	1.03 (0.79–1.33)	1.05 (0.79–1.39)	0.73
	1.07 (0.85–1.34)[b]	1.02 (0.78–1.34)	0.77	1.01 (0.78–1.31)	0.95 (0.71–1.27)	0.74
	1.12 (0.89–1.41)[c]	1.06 (0.80–1.41)	0.54	0.99 (0.75–1.30)	1.07 (0.80–1.44)	0.68
	1.05 (0.83–1.33)[d]	0.97 (0.73–1.29)	0.97	1.03 (0.77–1.36)	1.08 (0.79–1.48)	0.63
Ischaemic stroke						
HR (95%)	0.96 (0.73–1.26)[a]	1.41 (1.06–1.90)	0.06	1.09 (0.80–1.48)	1.48 (1.08–2.02)	0.02
	0.88 (0.67–1.17)[b]	1.28 (0.94–1.73)	0.25	1.06 (0.78–1.44)	1.32 (0.95–1.83)	0.10
	0.94 (0.71–1.24)[c]	1.36 (1.01–1.83)	0.11	1.10 (0.80–1.50)	1.53 (1.11–2.10)	0.01
	0.86 (0.64–1.16)[d]	1.23 (0.90–1.68)	0.38	1.05 (0.76–1.45)	1.39 (0.99–1.96)	0.06

HR, hazard ratio.

[a] Adjusted for age and sex.

[b] Adjusted for age, sex and vital exhaustion.

[c] Adjusted for age, sex and traditional risk factors: smoking, diabetes, physical activity, blood pressure and cholesterol-lowering drugs, systolic blood pressure, body mass index, atrial fibrillation and blood lipids. Alcohol consumption, hormone replacement therapy, familiar disposition and blood glucose were not associated with stroke or myocardial infarction in this study sample.

[d] Adjusted for age, sex, vital exhaustion, traditional and socioeconomic risk factors: cohabitation, education and household income. Employment was not associated with stroke or myocardial infarction in this study sample.

* *P* value for test for trend.

Table 4

MLEs in a life course and risk of myocardial infarction and ischaemic stroke

	MLE in a life course			
MLEs, sum (with 0 as reference)	**1–2**	**3–4**	**> 4**	***P* value***
Myocardial infarction				
HR (95%)	1.31 (0.98–1.73)[a]	1.45 (1.04–2.03)	0.72 (0.40–1.28)	0.65
	1.23 (0.92–1.64)[b]	1.27 (0.90–1.80)	0.61 (0.34–1.09)	0.64
	1.36 (1.01–1.85)[c]	1.43 (1.00–2.05)	0.81 (0.44–1.50)	0.54
	1.34 (0.98–1.82)[d]	1.38 (0.95–2.01)	0.76 (0.41–1.41)	0.74
Ischaemic stroke				
HR (95%)	1.06 (0.77–1.46)[a]	1.26 (0.86–1.86)	1.53 (0.93–2.52)	0.07
	1.00 (0.72–1.39)[b]	1.14 (0.76–1.69)	1.31 (0.79–2.20)	0.27
	1.07 (0.77–1.48)[c]	1.25 (0.84–1.85)	1.57 (0.94–2.61)	0.07
	0.99 (0.71–1.39)[d]	1.17 (0.78–1.76)	1.32 (0.77–2.25)	0.24

HR, hazard ratio; MLE, major life event.

[a] Adjusted for age and sex.

[b] Adjusted for age, sex and vital exhaustion.

[c] Adjusted for age, sex and traditional risk factors such as smoking, diabetes, physical activity, blood pressure and cholesterol lowering drugs, systolic blood pressure, body mass index, atrial fibrillation, blood lipids and familiar dispostion. Alcohol consumption, hormone replacement therapy and blood glucose were not associated with stroke or myocardial infarction in this study sample.

[d] Adjusted for age, sex, vital exhaustion, traditional and socioeconomic risk factors such as cohabitation, education and household income. Employment was not associated with stroke or myocardial infarction in this study sample.

* *P* value for test for trend.