Stressful Life Events and the Metabolic Syndrome

The Prevalence, Prediction and Prevention of Diabetes (PPP)-Botnia Study

Antti-Jussi Pyykkönen, ma[1]
Katri Räikkönen, phd[1]
Tiinamaija Tuomi, md, phd[2,3]

Johan G. Eriksson, md, phd[2,4,5,6,7]
Leif Groop, md, phd[3,8]
Bo Isomaa, md, phd[2,9]

OBJECTIVE — Stress may play a role in the pathogenesis of the metabolic syndrome. However, the scant evidence available is not population-based, restricting the external validity of the findings. Our aim was to test associations between stressful life events, their accumulation, and the metabolic syndrome in a large population-based cohort. We also tested associations between stress and the individual components related to the metabolic syndrome.

RESEARCH DESIGN AND METHODS — This was a population-based, random sample of 3,407 women and men aged 18–78 years residing in Western Finland. Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III and International Diabetes Federation criteria. The severity of 15 stressful life events pertaining to finance, work, social relationships, health, and housing was self-rated.

RESULTS — In comparison with subjects not reporting any extremely stressful life events, those reporting work- or finance-related events had an increased odds for having the metabolic syndrome. The risk was further increased according to accumulation of stressful finance-related events and to having at least three stressful life events in any of the life domains assessed. Accumulation of stressful life events was associated with insulin resistance, obesity, and triglycerides. The associations were not confounded by sex, age, lifestyle, or family history of diabetes.

CONCLUSIONS — Life events perceived as stressful, particularly those related to finance and work, may be a signal for poor metabolic health.

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Metabolic syndrome refers to a cluster of aberrations of metabolic origin that increases the risk for morbidity and mortality from type 2 diabetes (1,2), cardiovascular disease (3), and all-cause mortality (1). Features of the metabolic syndrome include a combination of impaired glucose and lipid metabolism, obesity, and hypertension (4–6). Along with the worldwide increase in the prevalence of the metabolic syndrome (7), there exists a strong need to identify underlying, causative factors that may render an individual susceptible to the metabolic syndrome.

The metabolic syndrome is thought to be multifactorial in origin, arising from a combination of genetic and environmental factors (4). Among the plausible environmental factors is psychosocial stress (8). However, research on the importance of stress in the etiology of the metabolic syndrome is scanty. Vogelzangs et al. (9) found in their cross-sectional cohort study of 2,917 elderly men and women that for each experienced negative life event the odds for having the metabolic syndrome increased by 13%. In a small sample of elderly women and men (10), caregiver stress predicted metabolic syndrome at follow-up >15 years later. In the Whitehall II study of >10,000 middle-aged civil servants, chronic work stress predicted higher odds for having the metabolic syndrome at a follow-up 14 years later (11). In the Pittsburgh Healthy Women Study, middle-aged women who experienced life events as extremely stressful had an increased risk for developing the metabolic syndrome over an average 15 years of follow-up (12). In the same study marital dissatisfaction, divorce, and widowhood also predicted an increased risk for developing the metabolic syndrome over an average follow-up of 11.5 years (13).

Although important, none of the studies so far have been population-based, restricting the external validity of the findings: the participants have been recruited from health care beneficiaries (9), from Alzheimer's caregivers (10), from employees of civil service departments (11), and from initially healthy premenopausal women holding a driver's license (12,13). Accordingly, the first major aim of this study was to test associations between severity of stressful life events arising from various life domains and the metabolic syndrome defined according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) and International Diabetes Federation (IDF) clinical criteria in a large population-based sample of women and men residing in Western Finland. The second major aim of our study was to test the significance of stressful life events for the individual components of the metabolic syndrome.

RESEARCH DESIGN AND METHODS

— The Prevalence, Prediction and Prevention of Diabetes (PPP)-Botnia Study is a population-based study in the Botnia region of Western Finland. The study was designed to obtain accu-

rate estimates of prevalence and risk factors for diabetes, impaired glucose tolerance (IGT), and the metabolic syndrome in the population aged 18–78 years and to use this information for prediction and prevention of the disease. The current study was initiated in 2004 in five centers (Närpes, Malax-Korsnäs, Korsholm, Vasa, and Jakobstad). Using the population registry we selected a random sample of subjects aged 18–78 years (96,000 subjects) representing on average 9% of the population. The aim was to include altogether 5,000 individuals. This article reports data from the first 3,621 persons (1,712 men and 1,899 women) of the 6,079 invited (60%). Of them, 17 had at least one of the components of the metabolic syndrome missing, and 192 did not fill in the stressful life events questionnaire. Altogether, 3,407 (1,618 men and 1,789 women) participants had complete data available on the components of the metabolic syndrome and life events. They were younger and more educated, reported higher alcohol intake, had a family history for diabetes less often, and met the ATP III/IDF criteria for metabolic syndrome less often compared with the entire group ($P < 0.001$; no differences were found in sex distribution or frequency of smoking and regular exercise, $P > 0.31$). The participants gave their written informed consent. The study protocol was approved by the ethics committee of Helsinki University Hospital.

Metabolic syndrome
The subjects participated in an oral glucose tolerance test (OGTT) by ingesting 75 g of glucose after a 12-h overnight fast. Subjects with known diabetes who were taking antidiabetes medication or with fasting plasma glucose >10 mmol/l did not take part in the OGTT ($n = 19$). During the OGTT, blood samples for plasma glucose and serum insulin were drawn at 0, 30, and 120 min. The diagnosis of diabetes was based on the results from the OGTT or a history of previously known diabetes. The diagnosis of diabetes was based on the World Health Organization criteria (5). Thus, subjects with a fasting plasma glucose ≥7.0 mmol/l and/or 2-h plasma glucose ≥11.0 mmol/l during an OGTT were considered to have diabetes. Subjects with fasting plasma glucose between 6.1 and 6.9 mmol/l were considered to have impaired fasting glucose (IFG) and subjects with fasting plasma glucose <7.0 mmol/l and 2-h plasma glucose between 7.8 and 11.0 mmol/l were considered to have IGT (5).

Waist circumference was measured with a soft tape midway between the lowest rib and the iliac crest when the subject was standing. Fasting blood samples were drawn for the measurement of HDL cholesterol and triglycerides. Two blood pressure recordings were obtained from the right arm of a sitting subject after 10 min of rest, and the mean value was calculated.

We used the ATP III (4) and the IDF criteria (6) to define the metabolic syndrome. According to the ATP III criteria at least three of the following five criteria have to be met: waist circumference ≥102 cm in men and ≥88 cm in women, serum triglycerides ≥1.7 mmol/l and HDL cholesterol <1.0 mmol/l in men and <1.3 mmol/l in women, IFG/IGT or diabetes, and blood pressure ≥130/85 mmHg and/or use of antihypertensive medication. The IDF clinical criteria include waist circumference ≥94 cm in men and ≥80 cm in women and an additional two of the following criteria: serum triglycerides ≥1.7 mmol/l, HDL cholesterol <1.03 mmol/l in men and <1.29 mmol/l in women, blood pressure ≥130/85 mmHg and/or use of antihypertensive medication, or fasting plasma glucose ≥5.6 mmol/l.

In addition to the components defined by the ATP III and the IDF, we extended our analyses to using the homeostasis model assessment of insulin resistance ($HOMA_{IR}$) [(fasting plasma glucose × fasting insulin)/22.5] (14) as an additional index in insulin resistance and BMI (weight in kilograms divided by the square of height in meters, measured with subjects in light indoor clothing and without shoes) as an additional index of general obesity as outcomes.

Assays
Plasma glucose during the OGTT was measured with a glucose dehydrogenase method (HemoCue, Ängelholm, Sweden) and serum insulin by a fluoroimmunoassay (Delphia; Perkin-Elmer Finland, Turku, Finland). Serum HDL cholesterol and triglyceride concentrations were analyzed by an enzymatic method on a Konelab 60i analyzer (Thermo Electron Oy, Vantaa, Finland).

Stressful life events
The subjects completed a questionnaire consisting of 15 stressful life events (Table 2). All questions concerned life events known to be major stressors (12,15–17).

The subjects were asked to evaluate the occurrence and stressfulness of these events (0, not occurred; 1, not at all stressful; 2, mildly stressful; 3, moderately stressful; and 4, extremely stressful) during the past 12 months. For the analyses, the measurement scale was dichotomized by contrasting moderately and extremely stressful events (hereafter called "extremely stressful life events") with events that were not at all or mildly stressful or had not occurred at all (hereafter called "no stressful life events") (12).

Mediating and confounding factors
The subjects self-reported their weekly alcohol consumption (grams per week), current smoking (yes vs. no or former smoker), regular exercise (yes vs. no), level of education (less than high school, high school or college graduate, or degree beyond college), and family history of known diabetes (yes vs. no) in at least one first-degree relative (father, mother, or sibling).

Statistical analyses
Logistic regression analyses, odds ratios (OR), and 95% CIs were computed to examine associations between stressful life events and the metabolic syndrome. Multiple linear regression analyses, unstandardized regression coefficients, and 95% CIs were computed to examine associations between stressful life events and $HOMA_{IR}$, waist circumference, BMI, triglycerides, HDL cholesterol, systolic blood pressure and diastolic blood pressure, and logistic regression analyses to examine associations with IFG and IGT. The associations were adjusted for the mediating and confounding factors. Because the unadjusted and fully adjusted models resulted in essentially similar results, we present the fully adjusted associations only. Finally, because associations between psychosocial factors and the metabolic syndrome may be moderated by sex (9,10), we tested whether any of the associations varied for men and women by including an interaction term, "sex × extremely stressful life event" in the models. Tests of moderation by sex were also supported by our own data demonstrating a preponderance for women to report more life events as extremely stressful in all of the measured life domains (supplementary Tables A1 and A2, available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc09-1027/DC1). In no instance was there a significant sex interaction term ($P > 0.07$) (data not shown).

Table 1—Characteristics of the sample according to the NCEP ATP III clinical criteria of the metabolic syndrome

Characteristic	ATP III		$P_{\text{difference}}$ between groups
	No ($n = 2,693$)	Yes ($n = 714$)	
IDF clinical criteria, yes	391 (14.5)	675 (94.5)	0.001
Male sex	1,260 (46.8)	358 (50.1)	0.111
Age (years)	46.5 ± 15.9	56.5 ± 12.8	0.001
Fasting glucose (mmol/l)	5.2 ± 0.8	5.8 ± 1.3	0.001
Glucose 30 min (mmol/l)	8.1 ± 1.6	9.4 ± 2.0	0.001
Glucose 120 min (mmol/l)	5.0 ± 1.6	6.8 ± 3.0	0.001
HOMA$_{\text{IR}}$ index*	1.35 ± 1.39	3.19 ± 4.76	0.001
Waist circumference (cm)	85.3 ± 11.1	102.0 ± 11.2	0.001
BMI (kg/m^2)	25.2 ± 3.5	30.7 ± 4.5	0.001
Triglycerides (mmol/l)	1.1 ± 0.5	2.1 ± 1.1	0.001
HDL cholesterol (mmol/l)	1.44 ± 0.36	1.10 ± 0.27	0.001
Systolic blood pressure (mmHg)	131 ± 19	146 ± 19	0.001
Diastolic blood pressure (mmHg)	79 ± 10	86 ± 9	0.001
Current smoker, yes	393 (14.7)	123 (17.7)	0.056
Regular exercise, yes	1,492 (55.9)	332 (47.1)	0.001
Alcohol consumption			
None	664 (25.6)	232 (34.2)	0.001
12–48 g/week	1,233 (47.5)	282 (41.6)	
≥60 g/week	701 (27.0)	164 (24.2)	
Level of education			
Less than high school	1,821 (67.7)	605 (84.7)	0.001
High school or college degree	439 (16.3)	50 (7.0)	
Degree beyond college	430 (16.0)	59 (8.3)	
Family history for diabetes, yes	733 (29.1)	292 (45.0)	0.001

Data are n (%) or means ± SD. *Fasting plasma insulin (microunits per milliliter) × fasting plasma glucose level (millimoles per liter)/22.5.

For this reason, we report the results in both sexes combined.

RESULTS — Table 1 shows that the agreement rate between the ATP III and the IDF criteria was high. Consequently, the ATP III and the IDF criteria resulted in similar differences between the groups meeting and not meeting the metabolic syndrome in biological, sociodemographic, and lifestyle characteristics and in family history of diabetes. Therefore, characteristics of the sample are presented according to the ATP III criteria only (Table 1).

Stressful life events and the metabolic syndrome
Table 2 shows that the odds for having the metabolic syndrome according to the ATP III, the IDF, or both criteria were significantly higher among participants who had experienced extremely stressful life events in finance-related (ongoing financial strain, severe financial strain, threat of unemployment, or personal bankruptcy), work-related (troubles with coworkers or beginning a new job), and health-related domains (concern over own or child's ability to cope with stress). Further, the odds for having the metabolic syndrome according to the ATP III and the IDF cri-

Table 2—Fully adjusted (sex, age, alcohol consumption, current smoking status, regular exercise, level of education, and family history of diabetes) associations between stressful life events during the past 12 months and the metabolic syndrome according to the NCEP ATP III and the IDF criteria

No ($n = 2,296$) vs. extremely stressful life events	ATP III	P	IDF	P
Finance				
1. Ongoing financial strain ($n = 213$)	1.60 (1.07–2.39)	0.023	1.24 (0.85–1.81)	0.267
2. Severe financial strain, laid-off business ($n = 100$)	2.80 (1.69–4.63)	0.001	2.10 (1.29–3.42)	0.003
3. Threat of unemployment or personal bankruptcy ($n = 89$)	2.90 (1.70–4.94)	0.001	1.95 (1.16–3.27)	0.012
Work				
4. Continuous work overload ($n = 318$)	1.17 (0.83–1.65)	0.381	1.15 (0.85–1.56)	0.361
5. Troubles with coworkers ($n = 167$)	1.79 (1.17–2.75)	0.007	1.75 (1.18–2.59)	0.005
6. Began a new job ($n = 42$)	2.29 (1.05–4.98)	0.037	1.93 (0.92–4.02)	0.081
Social relationships				
7. Ongoing difficulties in close relationships ($n = 160$)	0.95 (0.56–1.62)	0.856	0.86 (0.54–1.37)	0.521
8. Divorced or separated from husband/wife/partner ($n = 153$)	1.44 (0.90–2.31)	0.127	1.31 (0.85–2.01)	0.220
9. Death of spouse/partner/close friend ($n = 224$)	1.17 (0.79–1.72)	0.431	1.07 (0.75–1.53)	0.692
Health				
10. Serious injury or illness ($n = 194$)	1.29 (0.87–1.91)	0.210	1.15 (0.80–1.66)	0.454
11. Concern over health of a family member or a close friend ($n = 376$)	1.20 (0.88–1.62)	0.246	1.07 (0.81–1.42)	0.609
12. Concern over own or child's ability to cope with stress ($n = 210$)	1.59 (1.11–2.28)	0.012	1.26 (0.89–1.79)	0.186
Housing				
13. Loss of home ($n = 26$)	1.67 (0.61–4.55)	0.314	1.84 (0.68–4.97)	0.232
14. Change of residence ($n = 58$)	1.22 (0.53–2.82)	0.643	1.13 (0.53–2.42)	0.758
15. Difficulties in housing ($n = 22$)	2.51 (0.89–7.05)	0.081	1.80 (0.65–5.03)	0.261

Data are ORs (95% CI). No stressful life events refer to a category combining individuals who report no stressful life events or life events that are not at all or mildly stressful; extremely stressful life events refer to a category combining individuals who report moderately or extremely stressful life events. Numbers of individuals reporting extremely stressful life events are in parentheses.

Table 3—_Fully adjusted (sex, age, alcohol consumption, current smoking status, regular exercise, level of education, and family history of diabetes) associations between accumulation of stressful life events during the past 12 months and the metabolic syndrome according to the NCEP ATP III and the IDF criteria_

No ($n = 2,296$) vs. accumulation of extremely stressful life events	ATP III	P	IDF	P
Finance				
At least 1 event ($n = 273$)	1.78 (1.25–2.53)	0.001	1.42 (1.03–1.98)	0.036
At least 2 events ($n = 98$)	2.91 (1.75–4.89)	0.001	1.85 (1.12–3.05)	0.016
At least 3 events ($n = 31$)	4.08 (1.66–10.06)	0.002	2.82 (1.15–6.92)	0.023
Work				
At least 1 event ($n = 421$)	1.34 (0.99–1.81)	0.061	1.30 (0.99–1.70)	0.058
At least 2 events ($n = 97$)*	1.70 (0.99–2.92)	0.055	1.63 (0.99–2.66)	0.053
Social relationships				
At least 1 event ($n = 425$)	1.13 (0.83–1.53)	0.447	1.06 (0.81–1.40)	0.666
At least 2 events ($n = 98$)†	1.56 (0.88–2.75)	0.125	1.25 (0.73–2.14)	0.419
Health				
At least 1 event ($n = 592$)	1.23 (0.96–1.59)	0.101	1.12 (0.89–1.41)	0.347
At least 2 events ($n = 155$)	1.65 (1.10–2.50)	0.016	1.27 (0.85–1.88)	0.240
At least 3 events ($n = 33$)	1.45 (0.63–3.34)	0.378	1.06 (0.47–2.40)	0.888
Housing				
At least 1 event ($n = 86$)‡	1.56 (0.84–2.91)	0.163	1.36 (0.76–2.45)	0.304
Across all life domains				
At least 1 event ($n = 1,111$)	1.21 (0.98–1.49)	0.075	1.09 (0.90–1.31)	0.395
At least 2 events ($n = 583$)	1.42 (1.10–1.84)	0.008	1.16 (0.91–1.47)	0.225
At least 3 events ($n = 300$)	1.64 (1.18–2.28)	0.003	1.47 (1.08–1.99)	0.013
At least 4 events ($n = 174$)	1.91 (1.28–2.86)	0.002	1.81 (1.24–2.64)	0.002
At least 5 events ($n = 88$)	2.23 (1.31–3.81)	0.003	1.78 (1.06–2.98)	0.028
At least 6 events ($n = 45$)§	2.95 (1.43–6.11)	0.004	2.70 (1.32–5.52)	0.007

Data are ORs (95% CI). No stressful life events refer to a category combining individuals who report no stressful life events or life events that are not at all or mildly stressful; extremely stressful life events refer to a category combining individuals who report moderately or extremely stressful life events. Numbers of individuals reporting extremely stressful life events are in parentheses. *Number of participants reporting at least 3 events was 9; therefore, this category was not analyzed separately. †Number of participants reporting at least 3 events was 14; therefore, this category is not analyzed separately. ‡Number of participants reporting at least 2 events was 20; therefore, this category was not analyzed separately. §Number of participants reporting at least 7 events was 25; therefore, this category was not analyzed separately.

teria were significantly higher among participants who had experienced at least one stressful life event in the finance-related domain and at least three events in any of the life domains (Table 3).

Stressful life events and components of the metabolic syndrome

Analyses of the components of the metabolic syndrome indicated that participants who had experienced stressful life events in the finance-, work-, and health-related domains or had experienced at least three events in any of the life domains displayed higher levels of HOMA$_{IR}$, waist circumference, BMI, and triglycerides and had a higher odds for having IGT (Table 4). Stress did not associate significantly with IFG, HDL cholesterol, or blood pressure (data not shown).

CONCLUSIONS — The key finding in the present study is that individuals who reported extremely stressful life events within finance- and work-related life domains had significantly higher odds for having the metabolic syndrome. The risk was further increased according to accumulation of stressful finance-related events and according to having at least three events in any of the life domains we measured, namely finance, work, social relationships, health, and housing. Accumulation of stressful finance- and work-related life events and having at least three stressful events in any of the life domains also associated significantly with insulin resistance, obesity, and triglycerides. The associations were not confounded by sex, age, lifestyle, or family history of diabetes.

Our findings are in agreement with previous studies (9–13) by showing that major stress-related events associate with an increased risk of having the metabolic syndrome. However, our findings further suggest that of the life events we measured, those relating more specifically to finance and work seemed the most harmful. Although chronic work stress has been associated with an increased risk of having the metabolic syndrome in the Whitehall II study (11), the other existing studies have not specifically focused on work-related stress, and none of the studies focused on finance-related stress, precluding direct comparisons among the studies.

Our findings with the different components of the metabolic syndrome agree well with the work and hypothesis put forward by Björntorp (8). According to Björntorp, an hypothalamic-pituitary-adrenocortical axis abnormality may contribute to both insulin resistance and abdominal obesity with lipids and blood pressure being the secondary complications. In addition to alcohol and smoking, among the major triggers of this chain of events is psychosocial stress of a "defeat," "helpless" type (8). Although the cross-sectional nature of our study precludes any inferences about causality, our finding that major stressful life events associated most closely with indexes of insulin resistance, obesity, and triglycerides is interesting. To our knowledge, one previous study has shown that accumulation of non–work-related stressful life events was associated with increased risk of obesity in men and with higher waist-to-hip ratio in women and men but not with fasting insulin concentrations (17), findings that are at least partly in line with the current ones.

Apart from the hypothalamic-pituitary-adrenocortical axis abnormality, other mechanisms that may underlie these associations include autonomic nervous system changes and inflammatory activity (4,8,18). Alterations in these physiological systems are linked with the metabolic syndrome, insulin resistance, and obesity (19). By inducing changes in lifestyle, stress may associate with metabolic changes through smoking, alcohol use, and physical inactivity. Our associations were not, however, affected by controls of lifestyle and neither were the associations affected by educational attainment or by a family history of diabetes. Finally, stress may induce changes in other psychosocial risk factors, such as sleep pattern (20) and depression (21). Because poor sleep and depression are as-

Table 4—Fully adjusted (sex, age, alcohol consumption, current smoking status, regular exercise, level of education, and family history of diabetes) associations between accumulation of stressful life events during the past 12 months and insulin resistance, obesity, and triglycerides

No ($n = 2,296$) vs. accumulation of extremely stressful life events	IGT (no vs. yes)		Log of HOMA$_{IR}$*		Waist circumference		BMI		Log of triglycerides	
	ORs (95% CI)	P	% change (95% CI)	P	Change in cm (95% CI)	P	Change in kg/m^2 (95% CI)	P	% change (95% CI)	P
Finance										
At least 1 event ($n = 273$)	1.71 (0.93–3.16)	0.085	10.03 (0.40–19.65)	0.041	2.30 (0.86–3.74)	0.002	0.95 (0.40–1.51)	0.001	7.65 (1.18–14.11)	0.020
At least 2 events ($n = 98$)	3.27 (1.45–7.33)	0.004	24.20 (8.67–39.72)	0.002	3.82 (1.49–6.14)	0.001	1.23 (0.34–2.11)	0.007	12.07 (1.80–22.34)	0.021
At least 3 events ($n = 31$)	5.65 (1.51–21.19)	0.010	35.61 (5.99–65.22)	0.018	8.64 (4.32–12.96)	0.001	3.91 (2.26–5.55)	0.001	25.75 (6.62–44.88)	0.008
Work										
At least 1 event ($n = 421$)	1.54 (0.91–2.60)	0.106	3.89 (−3.97 to 11.76)	0.332	1.60 (0.44–2.76)	0.007	0.63 (0.20–1.07)	0.005	6.33 (1.14–11.53)	0.017
At least 2 events ($n = 97$)†	2.78 (1.20–6.48)	0.018	12.15 (−3.01 to 27.30)	0.116	3.15 (0.92–5.37)	0.006	1.26 (0.41–2.10)	0.004	13.38 (3.43–23.34)	0.008
Social relationships										
At least 1 event ($n = 425$)	1.41 (0.87–2.27)	0.162	2.21 (−5.71 to 10.13)	0.584	0.73 (−0.46 to 1.92)	0.228	0.39 (−0.06 to 0.84)	0.091	1.52 (−3.75 to 6.80)	0.571
At least 2 events ($n = 98$)‡	2.47 (1.09–5.60)	0.031	17.04 (1.48–32.60)	0.032	0.24 (−2.07 to 2.55)	0.837	0.11 (−0.77 to 0.99)	0.809	10.10 (−0.17 to 20.37)	0.054
Health										
At least 1 event ($n = 592$)	1.56 (1.07–2.28)	0.022	4.91 (−1.92 to 11.73)	0.159	0.80 (−0.24 to 1.84)	0.133	0.47 (0.07–0.86)	0.021	−1.88 (−6.51 to 2.74)	0.425
At least 2 events ($n = 155$)	1.81 (0.99–3.30)	0.054	15.37 (2.87–27.88)	0.016	1.87 (0.01–3.73)	0.048	1.12 (0.42–1.83)	0.002	4.36 (−3.85 to 12.57)	0.297
At least 3 events ($n = 33$)	1.07 (0.30–3.83)	0.923	32.13 (6.39–57.87)	0.014	1.84 (−1.96 to 5.65)	0.342	1.20 (−0.24 to 2.63)	0.102	10.12 (−6.84 to 27.08)	0.242
Housing										
At least 1 event ($n = 86$)§	4.06 (1.88–8.74)	0.001	27.25 (10.39–44.11)	0.002	3.48 (0.97–5.99)	0.007	1.66 (0.70–2.61)	0.001	10.57 (−0.52 to 21.66)	0.062
Across all life domains										
At least 1 event ($n = 1,111$)	1.43 (1.03–1.98)	0.033	3.17 (−2.28 to 8.62)	0.254	1.12 (0.29–1.95)	0.008	0.59 (0.27–0.91)	0.001	0.46 (−3.23 to 4.15)	0.805
At least 2 events ($n = 583$)	1.72 (1.15–2.57)	0.008	6.06 (−0.88 to 12.99)	0.087	1.22 (0.16–2.27)	0.024	0.59 (0.19–1.00)	0.004	3.25 (−1.44 to 7.93)	0.175
At least 3 events ($n = 300$)	1.94 (1.17–3.22)	0.010	13.72 (4.55–22.88)	0.003	2.50 (1.11–3.88)	0.001	1.18 (0.65–1.71)	0.001	6.88 (0.80–12.97)	0.027
At least 4 events ($n = 174$)	2.70 (1.51–4.85)	0.001	21.79 (10.09–33.48)	0.001	2.72 (0.96–4.48)	0.002	1.18 (0.51–1.85)	0.001	13.14 (5.35–20.92)	0.001
At least 5 events ($n = 88$)	2.66 (1.18–6.00)	0.018	25.85 (9.82–41.87)	0.002	3.07 (0.69–5.45)	0.011	1.09 (0.19–1.98)	0.018	16.79 (6.20–27.37)	0.002
At least 6 events ($n = 45$)‖	2.77 (0.88–8.68)	0.081	36.09 (13.29–58.88)	0.002	4.19 (0.83–7.54)	0.014	1.22 (−0.04 to 2.48)	0.058	22.04 (7.14–36.94)	0.004

No stressful life events refer to a category combining individuals who report no stressful life events or life events that are not at all or mildly stressful; extremely stressful life events refer to a category combining individuals who report moderately or extremely stressful life events. Numbers of individuals in the extremely stressful life events category are in parentheses. Associations between stressful life events and IGT (no vs. yes) were tested using logistic regression analyses and therefore ORs are presented. All the other associations were tested using linear regression analyses. The scales of HOMA$_{IR}$ and triglycerides were skewed. Therefore, they were log-transformed for the analyses and their units are presented as percentages. *Fasting plasma insulin (microunits per milliliter) × fasting plasma glucose level (millimoles per liter)/22.5. †Number of participants reporting at least 3 events was 9; therefore, this category was not analyzed separately. ‡Number of participants reporting at least 3 events was 14; therefore, this category was not analyzed separately. §Number of participants reporting at least 2 events was 20; therefore, this category was not analyzed separately. ‖Number of participants reporting at least 7 events was 25; therefore, this category was not analyzed separately.

sociated with the metabolic syndrome (12,22), insulin resistance (23,24), and diabetes (24,25), these may provide additional pathways through which stress is related to the metabolic syndrome. Furthermore, we cannot rule out genetic pathways. Although specific genetic markers cannot be designated, these may relate to glucocorticoids, catecholamines, and inflammatory markers or an as yet unknown novel genetic marker.

The strengths of this study lie in the population-based study design and detailed clinical examination and measurement of stressful life events and their severity across various life domains. All of these strengths contribute significantly to the existing literature. None of the prior studies testing associations between stress and the metabolic syndrome have been population-based, restricting the external validity of the findings. None of the prior studies has measured insulin and glucose after an oral glucose challenge, precluding more precise definitions of the metabolic syndrome and focus on glucose tolerance. Except for one study (12), none of the studies has measured the perceived severity of the stressful life events. Different events may pose different experiences in different individuals, thus sorting out the perceived severity of different events (not equating events per se, such as death of a spouse or death of a pet) is important. In addition, our study offered sufficient power to test the sex specificity of the associations. Although the association between some psychosocial factors and metabolic syndrome has been reported to be different in men than in women (9,10), our data did not reveal any such differences.

Apart from a cross-sectional study design, another limitation of the study is that the sample is composed of whites only. Thus, the findings may not generalize to groups with other ethnic backgrounds. Furthermore, 5.9% of our study population were excluded because of missing information, the major reason being missing data in the life events questionnaire (5.3%). Those with full information, compared to those without, were younger, were more educated, consumed more alcohol, had a family history of diabetes less frequently, and met the criteria for metabolic syndrome less frequently. However, a bias toward inclusion of younger, more educated, and healthier participants might diminish rather than increase our ability to detect significant associations. We measured oc-

currence and severity of stressful life events the past 12 months. Yet, we cannot determine the precise timing and duration of the life events and hence cannot address the temporal relationships between stress and health in any further detail. Stressful life events and psychiatric disorders, such as major depression, are associated (21). Because we did not have data available on psychiatric disorders, we cannot rule out the possibility that these may explain the associations. Finally, although all the associations were adjusted for level of education as a proxy of social position, a possibility remains that for a specific subgroup adjustment for level of education may not have been sufficient to capture the overlap that may exist in social position and some of the stressful events.

To summarize, our study shows that extremely stressful life events, particularly those related to finance and work, are associated with increasing odds of having the metabolic syndrome and with having higher degrees of insulin resistance, obesity, and triglycerides. Our study was conducted before the global economic crisis. Thus, if finance- and work-related troubles play a role in the pathogenesis increasing the risk for the metabolic syndrome, we can only speculate that over the next decade we may see an increase in the prevalence of the metabolic syndrome and associated disease.

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