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## Age- and sex-specific associations between adverse life events and functional bodily symptoms in the general population



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### ABSTRACT

**Objective:** To test age- and sex-specific associations between adverse life events and functional bodily symptoms (FBS) in the general population.

**Methods:** In a population-based cohort, 964 participants (mean age 55 years SD 11, 48% male) completed two measurements waves of the present study. Lifetime exposure to 12 adverse life events was assessed through a modified version of the List of Threatening Experiences. Stress-sensitive personality was assessed with the 12-item neuroticism scale of the Eysenck Personality Questionnaire–Revised. Socio-economic status was retrieved from questionnaires. Participants completed the somatization section of the Composite International Diagnostic Interview to survey the presence of 42 FBS in the previous year.

**Results:** Regression analyses, adjusted for age, revealed that lifetime scores of adverse life events were significantly associated with FBS in the previous year, an association that was nearly identical for females (beta = 0.18,  $t = 4.07$ ,  $p < 0.01$ ) and males (beta = 0.19,  $t = 4.24$ ,  $p < 0.01$ ). This association remained statistically significant when stress-sensitive personality and socio-economic status were added to the model. Associations between adverse life events during childhood and FBS were statistically significant in females (beta = 0.13,  $t = 2.90$ ,  $p = 0.04$ ) but not in males (beta = 0.06,  $t = 1.24$ ,  $p = 0.22$ ), whereas there was a stronger association with adverse life events during adulthood in males (beta = 0.20,  $t = 4.37$ ,  $p < 0.01$ ) compared to females (beta = 0.15,  $t = 3.38$ ,  $p = 0.01$ ). Life events in the previous year were not associated with FBS in the previous year.

**Conclusion:** Adverse life events during lifetime were associated with FBS in the previous year. This association was dependent on age and sex but largely independent of having a stress-sensitive personality or low socio-economic status. Future studies could adopt a life course perspective to study the role of adverse life events in FBS.

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### Introduction

Functional bodily symptoms (FBS) are symptoms that are not explained by conventional somatic pathology. Functional somatic syndromes are characterized by clusters of FBS, such as chronic fatigue syndrome (CFS), fibromyalgia (FM), and irritable bowel syndrome (IBS). When doctors cannot find an organic explanation for somatic symptoms presented by their patients, psychosocial stress is often assumed to contribute to the etiology. Scientific studies have answered the question whether psychosocial stress precedes the onset of FBS or functional somatic syndromes with a “fairly unequivocal yes” [1].

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However, several methodological problems characterize research towards the role of stress in the etiology of FBS and functional somatic syndromes.

With regard to stress and functional somatic syndromes, the field is characterized by case control studies, which have several problems [2]. The presence of a disease label in cases may increase the amount of reported psychosocial life stress through a negative recall bias or by effort after meaning, the latter describing the phenomenon whereby individuals interpret potentially ambiguous events in accord with their implicit theories regarding the causes of their functional somatic syndromes [3]. In addition, selection bias due to the use of patient samples can be problematic, since clinical patient samples may consist of persons with relatively high psychiatric co-morbidity. Thus, the association that has been found between psychosocial stress and functional somatic syndromes in clinical samples may not apply to the development of functional somatic syndromes in general. For etiological research, the association between stress and FBS may be more informative.

When closely appreciating the relationship between psychosocial stress and FBS, however, one observes that straightforward evidence

for a role of recent stress in the etiology of FBS is scarce and characterized by limited generalizability beyond single symptoms, single psychosocial stress variables, or specific populations. For instance, life events in the previous 6 months did precede new onset of chronic widespread pain, but not independent from other psychological factors such as health anxiety and illness behavior [4, 5]. Life events in previous months preceded somatization in the setting of a psychiatric disorder in primary care [5]. In a population-based study among Chinese Americans [6] and a population-based study of adolescents [7], lifetime events were associated with the number of continuously measured somatic symptoms, whereas recent life events within the past year were not a predictor for FBS in the first study [6]. Thus, data are conflicting about the contribution of life events.

Furthermore, meta-analyses showed that childhood trauma is associated with FBS and functional somatic syndromes [8]. Health effects, including FBS, of childhood adversities seem larger in females than in males [9]. A pathway linking psychosocial stress and FBS may be its effects on stress-responsive systems, such as the hypothalamic–pituitary–adrenal axis and the autonomic nervous system [10]. Effects of psychosocial stress on stress-responsive systems may be influenced by timing of exposure during lifespan [11, 12] and may be sex specific [13, 14]. Sex- and age-specific pathways on the association between psychosocial stress and FBS should, therefore, be further investigated.

Moreover, objectively measured stressful life events are associated with neuroticism [15, 16]. Yet potential confounding by having a stress-sensitive personality (i.e., trait neuroticism) has usually not been tested in previous studies on the association between psychosocial stress and FBS. When researching the influence of psychosocial stress on physical symptoms, it has been recommended to administer a personality test and examine to what extent and which variance in the stress measure is explained by neuroticism [17]. Likewise, especially in population-based studies, one needs to take into account the distribution of life events according to demographic factors such as socio-economic status. Since it was concluded in a review that adverse life events are more frequent in persons with a low socio-economic status [18] and a low socio-economic status itself is a risk factor for FBS [19], low socio-economic status may act as a confounding factor in the association between life events and FBS. Although life events may also explain part of the increased risk of FBS in low SES populations, SES could act as a confounder given its associations with many other risk factors for FBS such as unhealthy lifestyles and unhealthy living environments [20].

In conclusion, it is unknown to what extent adverse life events are directly associated with FBS, whether there is a critical time frame, whether this association is the same for males and females, and whether this relation exists independently of a stress-sensitive personality or socio-economic status.

This population-based cohort study aims to test whether the generally accepted role of psychosocial stress in the development of FBS is justified and whether there are age- and sex-specific associations. We have the following hypotheses based on previous research. First, the lifetime score of adverse life events increases the risk for FBS in the general population. Second, the effects of adverse life events are stronger in childhood and in females. Third, these associations remain after adjustment for personal (neuroticism) and environmental (socio-economic) factors associated with both psychosocial stress and FBS. Data from a general population of adults, including two measurement waves, were used to examine the hypotheses.

## Methods

### Population

This study has been performed in a cohort derived from PREVENT (Prevention of RENal and Vascular ENd stage Disease), a major Dutch population cohort study investigating risk factors for renal and

cardiovascular disease. The recruitment of participants for PREVENT has been extensively described elsewhere [21]. The PREVENT baseline sample consisted of 8592 subjects randomly selected from the population of the city of Groningen with oversampling for albuminuria (T1). Selection of subjects for the present study was aimed at recruiting a representative sample of the general population of Groningen, while simultaneously rectifying PREVENT's oversampling for albuminuria. Research assistants approached participants in the PREVENT study during their visit to the outpatient clinic during follow-up (2554 participants). Measurements were completed by a total of 1094 participants (43%), forming the present study sample. PREVENT participants who declined to participate in the current study did not significantly differ from those who did participate concerning sex, age, and scores on a 12-item neuroticism scale [22]. Baseline measurements for the present study took place between 2001 and 2002 (T2). Follow-up measurements were made approximately 2 years later, between 2003 and 2004 (T3), and were completed by a total of 976 participants (89%). The study was approved by the University of Groningen medical ethics committee. Written informed consent was obtained from all participants.

### Functional bodily symptoms

FBS were measured by the somatization section of the Composite International Diagnostic Interview (CIDI). The CIDI is a fully structured diagnostic interview developed by the World Health Organization for use in epidemiological studies on mental disorders and provides diagnosis according to *Diagnostic and Statistical Manual, Fourth Edition (DSM-IV)* criteria. A fully computerized version of the CIDI 2.1 was applied, suitable for self-administration. Trained interviewers were present for questions and for participants that needed computer help. In the CIDI somatization section, 43 symptoms are assessed through asking “have you had” this symptom and are considered present when they meet severity criteria, i.e., provoking a health care visit. The symptom sexual indifference was excluded from analysis since it is not surveyed in the CIDI whether this symptom provoked a health care visit. The total number of potential FBS in this study is therefore 42. If the severity criteria are met, the interview assesses in a hierarchical fashion whether a medical doctor diagnosed a symptom as due to physical illness or injury, or whether a symptom was caused by the use of medication, drugs, or alcohol. If these inquiries are negative for medical explanations, the symptom is scored as a FBS. The CIDI has adequate test–retest reliability and validity [23]. Participants first completed the CIDI lifetime version measuring lifetime FBS. A total of 1088 completed CIDs were available at baseline. Two years later, participants were re-interviewed and completed the CIDI 12-months version, in which the occurrence of the 43 symptoms in the previous year is surveyed; 964 completed CIDs were available at follow-up. In the main analyses, we use the sum of all FBS in the previous year, defined as 1-year FBS.

### Adverse life events

The original List of Threatening Experiences (LTE) assesses 12 life events with long-term health consequences [24]. The choice of events on the list was based on earlier work on the social origins of depression [25]. The original LTE was translated in Dutch and applied in a modified version with age categories. Construct reliability was considered acceptable [26]. Participants completed the LTE at home prior to their visit to our research facilities, where a researcher checked with the participant whether the list had been filled out correctly. The original LTE comprises 12 items that were selected for their established long-term consequences [24, 27]. The original LTE asked whether or not these events took place in the previous year. For the purpose of this study, the LTE was extended with the addition of age categories. In addition to the question about the occurrence of adverse life events in the previous

year, the altered questionnaires comprise questions about the occurrence of adverse life events in the following age categories: 0–18 years (childhood) and 19 years or older (adulthood). A lifetime sum score of adverse life events (lifetime SUM-LTE) for each participant was calculated by adding the scores for the life events for those two categories (with two age categories and 12 life events the maximum score is 24). Also, sum scores of the LTE for the previous year and for the two specific age categories were used, with a maximum of 12 life events per age category. All participants filled in the LTE again approximately 2 years after the first assessment of these questionnaires. The test-retest reliability of the lifetime SUM-LTE with a 2-year interval was Pearson's  $r = 0.606$ ,  $p < 0.001$ . More details about this modified version of the LTE are described elsewhere [26].

### Neuroticism

Participants completed the Dutch translation of the neuroticism scale of the Eysenck Personality Questionnaire–Revised (EPQ-RSS-N) [22], comprising 12 questions representing nervousness, emotional instability, feelings of guilt, and low self-esteem. The respondent is asked whether he or she has recently experienced a particular symptom or item of behavior on a scale ranging from “less than usual” to “much more than usual.” For the EPQ-RSS-N, we constructed a sum score that represents the total number of neuroticism symptoms reported. Missing data were imputed according to the method of corrected item mean substitution, if at least half of the items were completed.

### Socio-economic status

For the assessment of socio-economic status, information on educational level, work situation, and income was retrieved from questionnaires. Educational level consisted of the following categories: not applicable, low, middle, or high educational level. Low educational level was defined as lower secondary education or less, middle educational level was defined as higher secondary education, and high educational level was defined as tertiary education. Working situation was categorized in the following categories: employed (i.e., currently having a job), willingly unemployed (i.e., housekeeping or retired), or unwillingly unemployed (i.e., job seeker or unable to work). Income was measured through the gross monthly household income divided by the square root of the number of people living in the household [28]. In addition, we performed a sensitivity analysis using the absolute income (instead of the equivalence scale of the monthly household income divided by the square root of the number of people living in the household) and the results remained essentially the same.

### Statistical analyses

We performed all analyses using the Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Armonk, NY, USA). The differences between males and females were measured with t-tests for parametric continuous variables (age, income, neuroticism score, SUM-LTE in childhood), Mann–Whitney  $U$  tests for nonparametric continuous variables (lifetime SUM-LTE, SUM-LTE in previous year, SUM-LTE in adulthood, 1-year FBS), and chi-squares for categorical variables (educational level, work situation). Multivariable linear regression analyses were performed. Predictor variables were numbers of adverse life events (operationalized as SUM-LTE during lifetime, SUM-LTE during childhood, SUM-LTE during adulthood and SUM-LTE in the previous year) and the outcome variable was the number of FBS in the previous year. The analyses were repeated, including socio-economic status and neuroticism as covariates. All analyses were adjusted for age. With a small anticipated effect size of 0.1, a power of 0.8, and an alpha of 0.05, a sample of 99 participants would be enough to reject the null hypothesis.

## Results

### Study population

In total, 964 participants completed all measurements for this study. General characteristics of this study population, including statistics for sex differences, can be found in Table 1. These results show that males were more employed and had higher income than females. Neuroticism scores were significantly higher in females than in males. Lifetime SUM-LTE was significantly higher in females than in males. Adverse life events were most prevalent in adulthood, both in males and females. In addition, the total number of FBS was slightly higher in females compared to males.

### Adverse life events and FBS

Associations between adverse life events and FBS can be found in Table 2. Multivariable regression analyses, adjusted for age, revealed that lifetime SUM-LTE was significantly positively associated with FBS. This association was nearly identical for females and males. Sex and age differences emerged for the associations between the specific age categories and FBS. The SUM-LTE in childhood (0–18 years) was significantly positively associated with FBS in females, but not in males. The SUM-LTE in adulthood ( $\geq 19$  years) was significantly positively associated with FBS in females, but stronger in males. No association was found between SUM-LTE in the previous year (263 participants reported that they had experienced one or more adverse life event(s) in the past year) and FBS.

### Role of stress-sensitive personality and socio-economic status

When neuroticism was added to the model, the association between lifetime SUM-LTE and FBS slightly attenuated for males ( $\beta = 0.15$ ,  $t = 3.20$ ,  $p < 0.01$ ) and females ( $\beta = 0.12$ ,  $t = 2.69$ ,  $p < 0.01$ ), but remained statistically significant. When socio-economic status was added to the model, the association between SUM-LTE and FBS also slightly attenuated for males ( $\beta = 0.23$ ,  $t = 4.33$ ,  $p < 0.01$ ) and females ( $\beta = 0.11$ ,  $t = 2.02$ ,  $p < 0.05$ ), but remained statistically significant. For life events in the previous year, the association with FBS did not remain statistically significant after adjusting for neuroticism (males,  $\beta = 0.07$ ,  $t = 1.55$ ,  $p = 0.12$ ; females,  $\beta = -0.03$ ,  $t = -0.78$ ,  $p = 0.44$ ), or socio-economic status (males,  $\beta = 0.05$ ,  $t = 0.88$ ,  $p = 0.38$ ; females,  $\beta = -0.08$ ,  $t = -1.50$ ,  $p = 0.14$ ).

## Discussion

This is the first study that showed age- and sex-specific associations between adverse life events and FBS in the general population. The association between lifetime sum score of adverse life events and FBS was largely independent of having a stress-sensitive personality and low socio-economic status. Sex differences were observed for specific age categories. In childhood, an association of adverse life events with FBS was only found in females. In adulthood, the association of adverse life events in adulthood with FBS was stronger in males compared to females.

**Table 1**  
General characteristics of the study population.

	Males	Females	Test statistic
Number of participants	461	503	
Mean age in years (SD)	56.0 (11.4)	54.1 (11.0)	$t = 2.7^*$
Educational level			$\chi^2 = 2.8$
No (%)	3.7	4.8	
Low (%)	23.6	27.2	
Middle (%)	28.9	25.5	
High (%)	43.8	42.5	
Work situation			$\chi^2 = 11.7^*$
Unwillingly unemployed (%)	10.6	9.5	
Willingly unemployed (%)	21.9	32.1	
Employed (%)	67.5	58.4	
Mean income in guilders (SD)	2644 (977)	2375 (936)	$t = 4.0^*$
Neuroticism score, mean (SD)	2.1 (2.8)	3.2 (3.2)	$t = -5.7^*$
Lifetime SUM-LTE	4.9 (3.2)	5.7 (3.2)	$z = -4.9^*$
SUM-LTE in the previous year	0.4 (0.8)	0.4 (0.9)	$z = -1.0$
SUM-LTE in childhood (0–18 years)	0.8 (1.3)	0.9 (1.3)	$t = -1.8$
SUM-LTE in adulthood ( $\geq 19$ years)	4.1 (2.8)	4.8 (2.8)	$z = -4.8^*$
Median number of 1-year FBS (IQ)	0 (0–1)	1 (0–2)	$z = -5.6^*$

FBS = functional bodily symptoms, IQ = interquartile range, SD = standard deviation. SUM-LTE = sumscore of adverse life events.

\*  $p < 0.05$ .

**Table 2**  
Associations between adverse life events and FBS.

	Males Beta	Females Beta
Lifetime SUM-LTE	0.19** ( <i>t</i> = 4.24, <i>p</i> < 0.01)	0.18** ( <i>t</i> = 4.07, <i>p</i> < 0.01)
SUM-LTE in previous year	0.05 ( <i>t</i> = 1.14, <i>p</i> = 0.25)	−0.01 ( <i>t</i> = −0.30, <i>p</i> = 0.77)
SUM-LTE in childhood (0–18 years)	0.06 ( <i>t</i> = 1.24, <i>p</i> = 0.22)	0.13* ( <i>t</i> = 2.90, <i>p</i> = 0.04)
SUM-LTE in adulthood (≥19 years)	0.20** ( <i>t</i> = 4.37, <i>p</i> = <0.01)	0.15* ( <i>t</i> = 3.38, <i>p</i> = 0.01)

FBS = functional bodily symptoms. SUM-LTE = sum score of adverse life events. All analyses are adjusted for age.

\* *p* < 0.05.

\*\* *p* < 0.01.

Among the strengths of this study is the large population cohort, including about equal percentages of males and females, while covering a wide age range. In addition, adverse life events were measured with a well-validated scale, which consisted of life events selected based on their long-term effects [24, 26]. Furthermore, FBS were measured with an extensive interview, in which complaints were further probed for medical explanations. This interview made it possible to make some statement on symptom severity, since the FBS should at least have provoked a health care visit. Although FBS in the population are in general short lasting and not very disabling, looking at FBS that provoked a health care visit, increases the clinical relevance. The dependent variable was conceptualized as a continuous variable; as criteria for caseness applied to FBS measures in studies of community samples represent arbitrary cutoff points [29].

The following limitations should be acknowledged. First, adverse life events were assessed retrospectively. Nonetheless, retrospective recall in adult life of serious, readily operationalized, stressful experiences in childhood is sufficiently valid to warrant its use even though there is significant under-reporting and probably some bias [30]. Second, the presence or absence of adverse life events was measured for childhood and adulthood separately, with no distinction between one or multiple events of the same type. It is plausible that repeated adverse life events of the same type further increase the risk of developing FBS, indicating that the results are most likely to be underestimations. We did not include multiple events of the same type, because a pilot study we conducted showed that it was too complicated for participants to indicate the exact number of specific life events for each age category [26]. Third, anxiety and depression are possible confounders, given their association with both life events [31] and FBS [32]. Our analyses were not adjusted for anxiety and depression, because this could be regarded as over adjustment, given their overlap with neuroticism [33]. Neuroticism did not significantly alter the association between adverse life events and FBS, suggesting that the effect of anxiety and depression on that association would be small.

The results are in agreement with previous studies in specific populations or towards specific stressors or specific symptoms [8], suggesting that adverse life events may play a generic role in the etiology of FBS. One previous population-based study also found that the association was particularly found for life events more than 1 year ago as opposed to recent life events [6]. In contrast, other studies found an association between relatively recent life events and FBS [5, 34]. One study found that life events in previous months preceded somatization [5]. It was, however, performed in the setting of a psychiatric disorder in primary care, which might possibly explain the discrepancy in results [5]. Another study on predictors of the course of FBS found an association between adverse life events between baseline and 12 months follow-up in primary care patients [34]. However, opposed to our sample, that sample was smaller (*n* = 277) and had an overrepresentation of females (72%). Besides this, the

overrepresentation of patients with functional somatic syndromes in the former sample could render the generalization of their results more difficult [34].

There are several explanations for the association between adverse life events and FBS. Adverse life events may be precipitating factors that trigger the onset of FBS. Our results are not consistent with this explanation, since life events in the previous year were not associated with number of FBS. It is possible that the FBS were already present before the previous year. Still, this may suggest a latency time between the occurrence of life events and FBS and may imply that life events could also be regarded as predisposing factors. Perhaps recent life events do not directly lead to FBS; the association may be mediated by physiological and psychological alterations that make vulnerable for somatization. Second, not all types of events have equal effects on the development of FBS. Events such as divorce or separation are less likely to occur frequently than problems with a neighbor, which in turn might not be strong enough to directly result in FBS. Indeed, a small exploratory study in first year students found that especially “loss events,” such as a broken relationship were associated with somatization, opposed to “ordinary stresses,” experienced by every first year student [35]. In addition, this study found no immediate effect from those “loss events” on the presentation of symptoms to doctors. It was suggested that students’ symptoms were caused by an interaction between former loss of support and increased difficulty in coping with the stresses of college life [35]. Although our study sample differs from the former, these findings might help understanding why previous year events are not associated with FBS. A third explanation for the observed association between adverse life events and FBS is confounding, meaning that a third variable related to both stress and FBS is responsible for the observed association. Analyses were adjusted for possible confounders such as personal (neuroticism) and environmental (socio-economic status) factors associated with both stress [15, 16, 18] and FBS [19,36,37]. Although neuroticism and socio-economic status were approached as potential confounders in the analyses, one could question what the role of these factors is in the pathway. Neuroticism [15, 16] or low socio-economic status [18] might provoke more life events, and thereby also be associated with more FBS. Nevertheless, including them in the models revealed that the association between sum scores of adverse life events and FBS was independent of a stress-sensitive personality and socio-economic status. This does not exclude the possibility of unmeasured confounding responsible for a spurious association. For example, one study showed that the association between life events in the previous 6 months and new onset of chronic widespread pain was dependent on psychological factors such as health anxiety and illness behavior [4].

The association between adverse life events and FBS was statistically significant in females across the life span. Intriguingly, adverse life events in childhood were associated with FBS in females but not in males. Recent meta-analyses have also suggested that the health effects of childhood adversities seem larger in females than in males [9]. Potentially, the type of events might explain the sex difference. Childhood adverse life events, specifically sexual abuse, emotional abuse, and emotional neglect, are associated with adult chronic fatigue syndrome [38]. Females are more at risk for these kinds of adverse life events, although that might be because studies in males are scarce [39]. In addition, females that experienced childhood adverse life events may be more vulnerable of long-lasting effects and therefore develop later-life FBS. Not until adulthood does the association between lifetime scores of adverse life events and FBS become statistically significant in males. Perhaps males in this age category might be more vulnerable for specific types of adverse life events. Indeed, among the most frequently reported events in this age category are death of close family, friend, or second-degree relative; events that are slightly more often reported by males in our cohort [26]. Another possible explanation for the association between adverse life events and FBS is dysregulation of the stress-responsive systems in the body, such as the hypothalamus–

pituitary–adrenal (HPA) axis. Stressful experiences have been shown to alter the function of this system. For instance, exposure to life events has been suggested to reduce function of the HPA-axis in the long term [40]. Alterations in cortisol levels have been associated with FBS and functional somatic syndromes [10]. Such a mechanism would fit well with the observation of a sex-specific effect of adverse life events on FBS. Indeed, previous research found an association between adverse life events in early life and increased pituitary reactivity in adult women with chronic fatigue syndrome [41] and of basal hypocortisolism in women with fibromyalgia but not in men [42]. Moreover, psychological factors could be responsible for the association between life events and FBS. In this case, for instance, adverse life events could lead to dysfunctional coping [43], a known perpetuating factor for FBS.

In conclusion, lifetime adverse life events are positively associated with FBS in the previous year. Future studies should adopt a life course perspective to study the role of adverse life events in FBS and functional somatic syndromes, taking age and sex differences into account. Such an approach avoids the problems associated with retrospective reports of life events and permits the study of possible latent effects.

### Conflict of interest

All authors wish to state that they have no conflicts of interest to declare.

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