Chapter 5
life events and functional somatic symptoms: a population study in older adolescents

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Abstract

Background: The purpose of this study was to investigated the effect of negative life events on Functional somatic symptoms (FSS) in adolescents.

Methods: Data from 957 participants of the population cohort TRAILS were used for this study. Life events experienced between age 16 and age 19 were assessed with the Kendler’s Life Stress interview. FSS at age 19 and age 16 were measured with the Youth and Adult Self-Report. The hypotheses were tested by use of a latent change model.

Results: Life events predicted FSS, even when adjusted for pre-event levels of FSS, symptoms of anxiety and depression, and socioeconomic status ($B=0.006$, 95% CI $[0.003, 0.008]$, $\beta=0.32$). Whereas illness-related life events did not predict FSS independently ($B=-0.003$, 95% CI $[-0.005, 0.09]$, $\beta=0.05$), non-illness-related life events did ($B=0.007$, 95% CI $[0.004, 0.010]$, $\beta=0.31$). A past year diagnosis of anxiety and/or depression had a significant influence on the association between life events and FSS ($B = 0.37$, 95% CI $[0.30, 0.46]$, $\beta = 0.71$), while female sex, exposure to childhood adversities, and family malfunctioning had not.

Conclusion: Our findings show that FSS are associated with negative life events in older adolescents. We did not find evidence for stronger effects of illness-related events.
Introduction

Functional somatic symptoms (FSS), that is, bodily symptoms not well explained by an underlying disease, are common in adolescents and can cause substantial impairments (1,2). Around 25% of all adolescents report FSS during adolescence (3,4). Although the occurrence of functional symptoms declines from childhood up to adulthood, chronic complaints seem to increase with age (1,3). FSS includes a wide range of symptoms, among which fatigue, dizziness, and pain complaints such as headache and abdominal pain. Adolescents with FSS are frequently seen in health care, but limited knowledge about the etiology of their symptoms hampers adequate treatment (5). This study aims to identify the role of negative life events in the development and persistence of FSS in adolescents.

Early exposure to negative life events is thought to play a major role in the development and course of FSS in adolescents (6,7). Suggested mechanisms for the relation between negative life events and FSS are physiological and emotional stress-responses (7). These responses are postulated to increase the generation, awareness, and interpretation of bodily signals, thus predisposing individuals for the development of FSS (7,8). Indeed, some negative life events during adolescence, such as parental death, have been found to be predictive of some FSS in adolescents (9-13). Yet, to our knowledge, it remains unknown if and to what extent a broad range of recently experienced life events predicts the level of FSS in adolescents.

Studies conducted thus far also have some limitations. Life events were measured with questionnaires (9,11,14). This approach is prone to bias (15,16): individuals suffering from FSS may over-report life events that caused physical discomfort (17), or perceive experienced life events as more negative than healthy individuals (18). The risk of bias can be diminished by assessing a broad range of negative life events through a systematic interview in which the severity (i.e. the contextual long-term threat) of the event is explored and rated by the interviewer. Another limitation of previous studies is that they were not able to adjust for FSS before the life event. This is regrettable because FSS may not only be the consequence of life events, but also trigger them (e.g. loss of social contacts, financial problems). Not taking into account pre-event FSS makes it hard to exclude reverse causality. Likewise, pre-event symptoms of anxiety and depression and socioeconomic status (SES) could account for part of the reported associations between life events and FSS (19,20).

Symptoms of anxiety and depression are prevalent in people with FSS, predict increased FSS in adolescents, and share genetic and environmental risk factors (20-22). Yet, research has also shown that FSS, anxiety, and depression are separate constructs and that the relative importance of risk factors for the development of anxiety and depression differs from that for the development of FSS (22,23). This raises the question if negative life events are predictive of internalizing symptoms in general, or
have a particular effect on FSS. It has also been suggested that particularly illness-related life events are strong risk factors for FSS (24,25). Illness-related events are likely to increase bodily attention and to induce health anxiety, which might result in higher levels of FSS (26). How family members cope with their own illnesses or react to the illness of their child may also influence the development of FSS (27), possibly through modeling and reinforcement (28). Indeed, children’s own and parental somatic complaints, illnesses, and hospitalizations were found to be associated with FSS (24,25,29). Yet, to our knowledge, there are no studies that actually compared whether illness-related events are stronger related to FSS than non-illness-related events.

The association between life events and FSS is not deterministic, which raises the question which factors act as effect modifiers. Adolescents who experienced adversities in childhood or grew up in poorly functioning households seem to be more sensitive to the effects of recent life events (30). A postulated mechanisms for this sensitization is that chronic stressors early in life alter automatic physiological, psychological and behavioral responses upon stress (7). Some altered and non-adaptive stress-responses, a blunted cortisol response, low-grade inflammation, or certain coping styles for example, can lead to higher levels of FSS than adaptive stress-responses (7). A possible explanation for the overlap between anxiety, depression and FSS mentioned earlier, is that suffering from a generalized anxiety disorder or major depression could make someone more susceptible for higher levels of FSS in reaction to stressors. Furthermore, recent studies indicate that females are more sensitive and less able to adapt to high levels of neuropeptides involved in physiological and psychological stress responses (31). This sex-difference in reactivity towards stressors has been suggested to make females more vulnerable for the development of internalizing problems. Indeed, several studies have found that stressors are stronger predictors of depressive symptoms in girls than in boys (30). It is conceivable that the same sex difference holds for FSS. Hence, the role of childhood adversities, family functioning, and sex in the effect of life events on FSS call for further research.

The aim of the current study was to investigate the effect of negative life events on the level of FSS in a population cohort of older adolescents. We used interviewer-based contextual severity ratings of a broad range of life events to test the following hypotheses: 1) The severity of recently experienced life events predict FSS, even when adjusted for pre-event levels of FSS, SES and symptoms of anxiety and depression; 2) The severity of illness-related life events is a stronger predictor of FSS than non-illness related life events; 3) Female sex, suffering from a major depressive or generalized anxiety disorder, exposure to childhood adversities, and family malfunctioning increase the effect of life events on FSS. In addition we explored if life events have a particular effect on FSS or influence symptoms of anxiety and depression to the same extent.
Methods

Participants

This study is part of the Tracking Adolescents' Individual Lives Survey (TRAILS), a prospective population study of adolescents from the North of the Netherlands. To date, TRAILS participants have been assessed five times (T1 to T5) from the age of 11.1 (SD:0.6) until the age of 22.3 (SD:0.6). Initially, 3483 adolescents were selected as potential participants from five municipalities (rural and urban) based on their date of birth. For inclusion, the child, guardians and primary school had to be willing and able to participate. Five hundred-forty-eight children were excluded because the primary school refused to participate, because they were incapable of participation (mental retardation, serious physical illness), or because of language problems (no Dutch, Turkish or Moroccan speaking guardian). Of the remaining 2935 children, 2230 children (76%; mean age 11.1 years [SD:0.6]; 50.8% girls) were enrolled in the first measurements (T1), which ran from March 2001 to July 2002 (32). Non-responders did not differ from responders in their prevalence of FSS or other internalizing and externalizing behaviours, but were more often boys and had more often parents with a lower SES (33). Written informed consent was given by parents at T1, by both adolescents and parents at T2 and T3, and by adolescents at T4 and T5. TRAILS was approved by the medical ethical committee.

The present study was based on data from the first four waves. Of the 2230 adolescents enrolled at T1, 94% participated at T2 (mean age: 13.6 years [SD:0.5]; 51% girls), 81% at T3 (mean age: years 16.3 [SD:0.7]; 52% girls), and 84% at T4 (mean age: 19.1 years [SD:0.6]; 52% girls). Attrition over the four waves was associated with being male, low SES, and externalizing problems, but not with internalizing problems including somatic complaints (34). For more details about participant characteristics, recruitment, non-responders and attrition, see (32,33). For an overview of when the questionnaires and interviews used in this study were completed see Figure 1.

The life stress interview (LSI) used in this study was labour-intensive and therefore administrated to a subgroup (n=957) of all participants attending T4 (see Table 1). Participants with a psychiatric diagnosis were oversampled to increase the power to study the etiology and course of psychopathology, one of the main aims of the TRAILS study. In total, 1584 participants (84.2% of all T4 participants) gave informed consent and participated in a psychiatric diagnostic interview. Hereof, 1547 participants also gave informed consent for the LSI. Of these 1547 participants, 709 had a past year psychiatric diagnosis (according to the DSM-IV criteria) and 838 had not. Of the adolescent with a diagnosis, 698 (98%) participants were selected for the interview whereof 580 (83%) were actually interviewed with the LSI. Of the adolescents without a past year diagnosis 427 (51%) participants were selected whereof 377 (88%) were interviewed. Thus, the sample of 957 adolescents consisted of 580
(61%) adolescents with a past year psychiatric diagnosis, and 377 (39%) adolescents without a past year psychiatric diagnosis.

**Figure 5.1.** Assessed questionnaires over time.

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Interview past year</th>
<th>Questionnaire FSSs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family Adversities ages 0-5, 6-11, and 11-13**</td>
<td>Psychiatric Diagnosis</td>
<td>FSSs</td>
</tr>
<tr>
<td>Questionnaire Adversities between T2-T3**</td>
<td>Life Events between T3-T4</td>
<td>Questionnaire FSSs</td>
</tr>
<tr>
<td>Questionnaire Anx/Dep</td>
<td></td>
<td>Questionnaire FSSs</td>
</tr>
<tr>
<td>Questionnaire FSSs</td>
<td></td>
<td>T2 (about 13 years old)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3 (about 16 years old)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T4 (about 19 years old)</td>
</tr>
</tbody>
</table>

Note. *Completed by one parent. **Completed by participant and parent. FSS = Functional somatic symptoms. Anx/Dep = Symptoms of anxiety and depression.

**Measures**

**Life Events.** Negative life events experienced between T3 and T4 were assessed with the Kendler’s Life Stress interview (LSI) (35), which was based on the Life Events and Difficulties Schedule. This semi-structured interview screens for fourteen negative life events primarily experienced by the participant (e.g. a breakup, illnesses, the experience of assault) and four classes of negative life events primarily happening to someone close (serious personal crises of others, illnesses of others). In addition, participants were asked to disclose experienced life events not already assessed by the interview. See Appendix A for an overview of the life events considered in this study.

Each reported event was dated as precisely as possible using personal calendars to aid memory. The interviewer explored the circumstances in which the event happened and rated the severity of the life events on a 4-point scale based on this information (1 = minor, 4 = severe). This interviewer-based contextual rating reflected how most people would experience that life event given the same biography and circumstances. The rating was explicitly not based on how the participant felt about the event, or retrospectively evaluated the consequences of the event. The severity of the events was additionally rated by a second assessor, based on tape-recordings of the interview. In the rare case of discrepancies in ratings, these were solved through discussion, or when needed by a third assessors’ judgment. The interviewers, research assistants, were all well trained and received booster sessions during the study period of T4. We
calculated the summed severity of all life events. The inter-rater reliability (average absolute agreement) on the sum scales was excellent ($\text{ICC}(1,2) = 0.99$, 95% CI [0.98, 0.99]). Illness-related events consisted of personal illnesses and injuries and illnesses or injuries experienced by someone in the direct network (relatives plus other mentioned important persons). All other events together represented the non-illness-related life events.

**Functional Somatic Symptoms.** At T4, FSS were measured with seven items of the Somatic Complaints subscale of the Adult Self-Report (ASR) (36). The items refer to the experience of somatic complaints (pain, headache, stomachache, nausea, vomiting, dizziness, and fatigue) without a known medical cause or without an obvious reason in the past six months. Originally the ASR Somatic Complaint scale consisted of eleven items instead of seven. Yet, two items (eye problems and skin problems) had low loadings in factor analyses and were therefore excluded (37). Two other items (numbness or tingling sensations in parts of the body and palpitations) were only assessed in the ASR questionnaire at T4 and not in the YSR questionnaire at T3. These items were also excluded to keep the assessed items consistent over time. Participants were asked whether they experienced these complaints ‘never’ (0), ‘sometimes or a bit’ (1) or ‘often or a lot’ (2). The online version of the Somatic Complaints scale differed slightly from the paper-and-pencil version at T4. In the online version five items were preceded by a screening question, which was only followed by the above-mentioned items if participants indicated they had experienced physical complaints without a known medical cause ‘sometimes or a bit’ or ‘often or a lot’. When participants indicated they had never experienced physical complaints without a known medical cause in the past six months, the response to all five items were set to ‘never’. This led to lower mean scores in the online version than in the paper and pencil version (13). Therefore, type of questionnaire (online vs paper-and-pencil) was included as a covariate in our analyses.

**Potential Confounders.** FSS at T3 were measured with seven items of the Youth Self-Report (YSR), covering the same symptoms as measured by the ASR at T4. The YSR and ASR items were also phrased in exactly the same way. The only difference between the YSR and ASR is that in the ASR five items were preceded by a screening question. Symptoms of anxiety and depression were assessed at T3 and T4 with 13 items of the Anxious/Depression (Anx/Dep) subscale of the YSR/ASR. The scale score represents the mean score on these items (range 0–2). Socioeconomic status was assessed at T1. Data on the household income, educational levels of both parents, and occupational levels of both parents were standardized (five indicators), where after the mean SES score was calculated for each participant.

**Potential Moderators.** Suffering from a generalized anxiety disorder or a major depressive disorder in the past 12 months was assessed with the Composite International Diagnostic Interview (CIDI) developed by the World Health Organisation (WHO).
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The CIDI is a structured interview designed for the assessment of mental disorders according to the definitions and criteria of the DSM-IV (38). Exposure to *childhood adversities* between the ages 0-15 was assessed at T2 and T3. Participants were asked to rate how many bad things happened to them and parents were asked to rate how stressful their child’s life was (0=none, 10=very much) between the ages 0-5, the ages 6-11, and the ages 11-13 at T2, and between the ages 13-15 at T3. The mean of these eight items (range 0-10) was calculated. *Family malfunctioning* was measured with the General Functioning subscale of the Family Assessment Device (39), consisting of 12 statements about the functioning of the household. One of the parents, the biological mother in 83% of the cases, was asked to indicate to what extent they agreed with the statements (e.g. 0 = totally disagree, 3 = totally agree). The mean of these 12 items was calculated.

**Statistical Analyses**

To investigate if life events predicted the level of FSS, a latent change model was built. First, we assessed scalar invariance of the latent construct FSS across time points. This was done in a step by step approach in which first configural (i.e baseline model) and metric invariance (i.e. factor loadings equal across time) were established (40). The Tucker-Lewis Index (TLI), the Comparative Fit Index (CFI), and the Root Mean Square Error of Approximation (RMSEA) were used to compare models. We considered the model well fitted when the TLI > 0.95, the CFI > 0.95, and the RMSEA < 0.05. Because of our large sample size and thus the high chance of rejecting acceptable models by chi-square difference testing, we did not rely on this indicator. In the configural model the loadings and intercepts of the seven items of FSS at T3 and T4 were allowed to differ over time, and the residuals of the items were allowed to correlate over time. In addition, the errors of five out of seven items that appeared after each other in the questionnaire and for which the same phrasing was used were allowed to correlate with each other cross-sectionally. After these specifications the model fit of the configural model was good (df=49, CFI=0.98, TLI=0.98, RMSEA=0.028). After that, the factor loadings of all items were constrained to be equal over time, which resulted in similar and overall good model indices (df=55, CFI = 0.98, TLI=0.97 RMSEA = 0.032). When intercepts were also specified to be equal across time, model indices were still acceptable but worsened considerably (df=66, CFI=0.93, TLI=0.90, RMSEA=0.066). The modification indices showed that two items (fatigue and headache) were potential sources of misfit. After freeing the intercepts of these two items model fit improved again (df=62, CFI=0.97, TLI=0.96, RMSEA=0.041). Based on these results we considered partial scalar invariance established. Partial invariance instead of full invariance introduces the risk that estimated mean differences of the latent variable FSS are partly due to differences in intercepts of the two unconstrained items. Yet, valid inferences about mean-level
differences of the latent factor FSS can probably still be made when the loadings and intercepts of at least two items are constrained (41).

The first model tested whether life events that happened after T3 (time-variant predictor) predicted FSS at T4 when adjusted for the effect of sex (time-invariant predictor) on the initial level of FSS at T3 (the intercept FSS) and the increase of FSS (the slope FSS). In the second model we additionally adjusted for SES and Anx/Dep at T3 and simultaneously modelled Anx/Dep at T4 as a dependent variable. The intercepts and slopes of both models were allowed to correlate in a cross-lagged panel design (Figure 2). To explore if pre-event levels of FSS, Anx/Dep, and SES were, in their turn, predictive of life events, as postulated, we also regressed life events on these variables (Figure 2). To investigate if illness-related life events predicted FSS at T4 to a greater extent than other life events, FSS at T4 were regressed on both illness-related events and non-illness-related events simultaneously in the first model. The regression coefficients of illness-related life events versus other life events on FSS were considered different when the probability that the two confidence intervals showed overlap in their 95% CIs was less than 5% (42). The same approach was used to compare the effects of life events on FSS with the effects on symptoms of anxiety and depression. Finally, we tested if sex, a past year diagnosis of anxiety or depression, childhood adversity and family malfunctioning increased the effect of life events on FSS, by entering the interactions (time-variant predictors) of the mean-centered life events variables with each of these potential moderators (also mean-centered) in the first model. The variables childhood adversity and family malfunctioning were, in line with the sex variable, modelled as predictors of intercept and slope FSS (time-invariant predictors). A past year diagnosis of anxiety or depression was modelled as a predictor of FSS at T4 (time-variant predictor). The descriptive statistics and all analyses are based on the weighted values of the original database. Specification of sampling weights was based on the inverse sampling probability because participants with a psychiatric diagnosis were overrepresented in this sample (reference sample: N=1584, see: Method, Participants). The amount of missing values on variables ranged from 2% to 15%. FSS were not normally distributed and therefore bias corrected bootstrapping was performed. Statistical significance was defined as estimates with a 95% CI not crossing zero.

**Results**

**Sample characteristics**

The characteristics of the study sample are shown in Table 1. Of the 957 participants (55% females) who completed the LSI, 932 (97%) participants experienced one or more life events of at least minor severity. Non-illness-related and illness-related life events with a severity of at least one were experienced by 901 (94%)
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and 612 (64%) participants, respectively. The mean level of FSS experienced by participants declined from T3 to T4, which was partly attributable to the screening question used for the assessment of FSS at T4 (see method section).

Figure 5.2. A parallel latent change models of FSS and symptoms of anxiety and depression.

Table 5.1. Sample characteristics

<table>
<thead>
<tr>
<th></th>
<th>Valid N</th>
<th>M (SD)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age T3 years</td>
<td>915</td>
<td>16.2 (0.7)</td>
</tr>
<tr>
<td>Age T4 years</td>
<td>957</td>
<td>19.0 (0.6)</td>
</tr>
<tr>
<td>Life events (range 0-45)</td>
<td>957</td>
<td>9.2 (7.0)</td>
</tr>
<tr>
<td>Illness-related life events (range 0-16)</td>
<td>957</td>
<td>2.1 (2.4)</td>
</tr>
<tr>
<td>Non-illness-related life events range (0-40)</td>
<td>957</td>
<td>7.1 (6.1)</td>
</tr>
<tr>
<td>FSS T3 (range 0-2)</td>
<td>874</td>
<td>0.35 (0.35)</td>
</tr>
<tr>
<td>FSS T4 (range 0-2)</td>
<td>942</td>
<td>0.19 (0.28)</td>
</tr>
<tr>
<td>Anx/Dep T3 (range 0-2)</td>
<td>873</td>
<td>0.30 (0.30)</td>
</tr>
<tr>
<td>Childhood adversities (range 1-10)</td>
<td>889</td>
<td>2.9 (1.4)</td>
</tr>
<tr>
<td>Family malfunctioning (range 0-2)</td>
<td>810</td>
<td>0.6 (0.4)</td>
</tr>
</tbody>
</table>

Note. *Based on the weighted values of the original database. The weighted and pooled means of the imputed datasets revealed essentially the same values. LSI = Life stress interview. FSS = Functional somatic symptoms. T4 = wave 4, T3 = wave 3. Anx/Dep = Symptoms of anxiety and depression.

Life events and FSS

The overall severity of negative life events experienced in the past two to three years significantly predicted FSS at T4 ($B = 0.006$, 95% CI [0.003, 0.008], $\beta = 0.32$, $R^2$
FSS at T4 = 0.76). The intercept and slope were negatively correlated with each other (\(B = -0.01, 95\% \text{ CI } [-0.025, -0.004], \beta = -0.48\)), indicating that a higher level of FSS at T3 was related to a steeper decline of FSS over the next two years’ time. When we additionally adjusted our model for SES and symptoms of anxiety and depression the effect size of life events on FSS at T4 was not changed (Table 2). Posthoc explorative analyses showed that pre-event levels of FSS at T3 (\(B = 4.17, 95\% \text{ CI } [1.96, 6.21], \beta = 0.19\)) and SES (\(B = -0.89, 95\% \text{ CI } [-1.37, -0.34], \beta = -0.09\)) predicted the severity of life events, but symptoms of anxiety and depression did not (\(B = 0.65, 95\% \text{ CI } [-1.04, 2.75], \beta = 0.03\)). Life events predicted FSS and symptoms of anxiety and depression to a similar extent (Table 2).

### Table 5.2: Effects of life events on FSS.

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>95% CI</th>
<th>(\beta)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intercept FSS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex: Female</td>
<td>0.26</td>
<td>[0.22, 0.29]</td>
<td>0.96(^c)</td>
</tr>
<tr>
<td>SES</td>
<td>-0.05</td>
<td>[-0.07, -0.03]</td>
<td>-0.14</td>
</tr>
<tr>
<td>Intercept Anx/Dep</td>
<td>0.05</td>
<td>[0.04, 0.06]</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Slope FSS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life events(^b)</td>
<td>0.006</td>
<td>[0.003, 0.008]</td>
<td>0.32</td>
</tr>
<tr>
<td>Sex: Female</td>
<td>0.09</td>
<td>[0.05, 0.12]</td>
<td>0.64(^c)</td>
</tr>
<tr>
<td>SES</td>
<td>0.03</td>
<td>[0.01, 0.05]</td>
<td>0.18</td>
</tr>
<tr>
<td>Intercept FSS</td>
<td>-0.01</td>
<td>[-0.016, -0.011]</td>
<td>-0.42</td>
</tr>
<tr>
<td>Intercept Anx/Dep</td>
<td>-0.02</td>
<td>[-0.023, -0.012]</td>
<td>-0.59</td>
</tr>
<tr>
<td>Slope Anx/Dep</td>
<td>0.03</td>
<td>[0.023, 0.035]</td>
<td>0.84</td>
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<tr>
<td><strong>Slope Anx/Dep</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Life events(^b)</td>
<td>0.006</td>
<td>[0.003, 0.009]</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Note. \(R^2\) FSS at T4 = 0.81. \(^a\)Cross-sectional estimate. \(^b\)Modelled as an time-variant predictor of FSS at T4. \(^c\)Standardized change in FSS scale for Female vs Male. Bold = significant. Estimates of predictors FSS slope adjusted for type of questionnaire. FSS = Functional somatic symptoms. Anx/Dep = Symptoms of anxiety and depression. SES = socioeconomic status.

**Illness-related life events**

When life events were divided into illness-related life events and non-illness-related life events, only non-illness-related life events significantly predicted FSS (\(B = 0.007, 95\% \text{ CI } [0.004, 0.010], \beta = 0.31\)). Illness-related events were not significantly predictive of FSS (\(B = 0.003, 95\% \text{ CI } [-0.005, 0.009], \beta = 0.05\)). The probability that the 95% CI of these estimates overlapped was 0.014, and therefore these estimates were considered significantly different. Post-hoc analyses revealed that illness-related events, when illnesses of grandparents and others not living in the household were excluded, did not predict FSS either (\(B = 0.006, 95\% \text{ CI } [-0.004, 0.018], \beta = 0.09\)). Only when the effect of illnesses in the household on FSS were not adjusted for other life events this variable did predict FSS (\(B = 0.010, 95\% \text{ CI } [0.002, 0.026], \beta = 0.16\)).
Moderating effects of sex, childhood adversities and family malfunctioning

Sex, childhood adversity and family malfunctioning did not significantly modify the effect of life events on FSS at T4. Thus, the effect of life events on FSS was comparable for males and females, and was not influenced by reported adversities or family malfunctioning (Sex*Life events: $B = -0.002$, 95% CI [-0.007, -0.003], $\beta = -0.05$; Adversity*Life events: $B = 0.002$, 95% CI [-0.001, 0.004], $\beta = 0.12$; Family*Life events: $B = 0.001$, 95% CI [-0.008, 0.008], $\beta = 0.13$).

A past year diagnosis of anxiety and/or depression had no effect on FSS at T4 ($B = 0.002$, 95% CI [-0.005, 0.009], $\beta = 0.009$), but increased the effect of life events on FSS at T4 (Diagnosis*Life events: $B = 0.37$, 95% CI [0.30, 0.46], $\beta = 0.71$).

Discussion

We found that the combined severity of a broad range of negative life events predicted FSS in older adolescents (aged 18 years), also when adjusted for sex, pre-event levels of FSS, symptoms of anxiety and depression, and SES. Contrary to our hypothesis, non-illness-related events predicted FSS, while illness-related events did not when controlled for other life events. In other words, illness-related life events had no independent effect on FSS in this study sample. Furthermore, the effect of life events on FSS was significantly affected by a past year diagnosis of anxiety and depression, but not by sex, childhood adversities or family malfunctioning.

The main strength of this study is that negative life events were assessed by well-trained interviewers who based their severity ratings on the context wherein the event happened, independently of the emotional state of the participant or consequences of the event. In addition, we were able to adjust the association between life events and FSS for pre-event levels of FSS, anxiety and depressive symptoms, and SES. This approach decreased the probability that findings were influenced by report bias, an important limitation of previous studies (9-11,14). Yet, it should be emphasized that an interview, even when independently rated, still relies on subjective information provided by participants. Therefore, it should be kept in mind that our findings can still be biased to some extent.

When interpreting our results some limitations should be kept in mind. First, we used a self-report questionnaire to assess FSS. Although it was explicitly stated that this questionnaire referred to symptoms without an obvious reason or medical cause, it is possible that some reported symptoms were in fact explained by an underlying medical disease. Follow-up studies in adult populations indicate that over the course of years around 2% of all participants suffering from FSS will be diagnosed with a medical condition explaining these symptoms (43-45). Second, the life events interview did not differ between stress-related illnesses that were medically well-explained and not well-explained, and therefore some participants may have
mentioned their FSS as an illness-related life event. However, this potential overlap between illness-related life events and FSS was probably minor because illness-related events were not significantly related to FSS in our sample. A third limitation of this study is that we assessed poor family functioning by a questionnaire which was completed by the parents, not by adolescents themselves.

In line with earlier findings, we found that negative life events predicted FSS (9,11). Adjustment for pre-event FSS and pre-event symptoms of anxiety and depression reduced the effect of life events on FSS, but it remained significant. These findings suggest that the effect of negative life events on the level of FSS is not completely explained by reverse causality or emotional disturbances.

Experiencing a severe illness or injury was, in contrast to previous findings, not independently associated with FSS in our sample. Earlier studies found that parental pain and parental hospitalization were associated with pain symptoms in children (14,25,46,47). Furthermore, adults suffering from FSS mentioned more self-experienced and familial illnesses than healthy adults (24,25,29). Some methodological differences might explain the discrepancy in findings between these studies and ours. First, the role of illness-related events in the development of FSS might have been overstated in earlier studies due to report bias (25): people suffering from FSS may remember and report more childhood illnesses. Indeed, one study found that while retrospectively reported illnesses were related to FSS in children, prospectively assessed illnesses were not (48). Second, prior findings indicate that chronic rather than short-term illnesses are related to the development of FSS (24). Possibly because the postulated mechanisms through which illnesses are related to FSS in young people, such as observational learning and rewarding models, are more likely in case of chronic illnesses (49). Our measure of illness-related events, which was based only on the severity of the life events, may have been too heterogenic with regard to the duration of the illnesses to show an independent effect on FSS. Third, previous studies did not adjust the effect of illness-related events on FSS for the concurrent experiences of non-illness-related life events. In our study, the effect of illness-related events on FSS was significant when not controlling for other negative life events. This indicates that the effect of illness-related life events on FSS is partly explained by co-occurrence of other life events such as death of a loved one, personal crises, emotional disturbances of family members, or social consequences of being ill.

The finding that negative life events have an effect on FSS raises the question how life events influence FSS. A potential pathway runs from negative life events through chronic stress to altered hypothalamic-pituitary-adrenal axis functioning (50) and reduced cortisol levels (51). Low cortisol levels are associated with higher levels of FSS (52). Other potential mechanisms are emotional, cognitive or behavioral reactions to stress, which eventually perpetuate the generation of bodily symptoms or influence the awareness and interpretation of these symptoms (8). For example; emotional
arousal, selective attention, and problems with sleeping can be triggered by stress and may also influence the level of FSS (8). Surprisingly, we did not find that childhood adversities or living in a poorly functioning household sensitized adolescents for the effect of life events on FSS. This indicates that chronic stressors early in life do not permanently alter the long-term physiological and psychological stress-responses which may predispose to FSS later in life.

Our findings indicate that recently experienced negative life events predict the level of FSS over time, especially in participants who also experienced depression or anxiety during this period. The effect of life events on FSS was only modest in the whole sample, when compared to, for example, the effect of sex, but had a much stronger influence on this subgroup of participants. This emphasizes the multifactorial etiology of FSS, and underlines the need for practitioners working with adolescents suffering from FSS to consider vulnerability factors and other potential risk factors. Interestingly, illness-related events had no independent effect on life events indicating that not the type of life events but the cumulative impact of all types of adverse experiences influences FSS. In future research it would be interesting to investigate if the level of FSS experienced by adolescents who suffer from depression or anxiety could be improved by learning these adolescents techniques to communicate about or cope with negative life events.
References

Appendix A: Overview of events assessed with Kendler's Life Stress interview

**a. Personal events**
1. Divorce or broken relationship after cohabitating.
2. Other serious relationship problems (during marriage or cohabiting).
3. Broken engagement or the end of another romantic relationship.
4. Broken contact with a loved one of dear friend.
5. Serious disease or injury.
6. Serious accident (without (serious) personal injuries).
7. Victim of a burglary or robbery.
8. Sexually assaulted, raped or assailed.
9. In trouble with police or the law.
10. Dismissed from work or expelled from school.
11. Other serious problems at work or at school.
12. Big financial problems.
13. Living in a bad neighbourhood.
14. Other serious housing problems.

**b. Network events**
15. Husband/wife/partner died.
17. Mother or father died.
18. Brother or sister died.
19. Other family member died.
20. Someone else close died.
23. Father or mother serious/life threatening illness/injury.
24. Brother or sister serious/life threatening illness/injury.
25. Other family member serious/life threatening illness/injury.
27. Problematic contact with child.
28. Problematic contact with mother or father.
29. Problematic contact with brother or sister.
30. Problematic contact with in-laws.
31. Problematic contact with other family members.
32. Problematic contact with a good friend.
33. Problematic contact with a neighbour.
34. Problematic contact with a boss, colleague, teacher or fellow student.
35. Husband/wife/partner serious personal crisis.
36. Mother or father serious personal crisis.
38. Brother or sister serious personal crisis.

**c. Other problems or events.**
40. Other serious personal problems or events.
41. Other serious problems or events in network.