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Life events and functional somatic symptoms: A population study in older adolescents

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The purpose of this study was to investigate the effect of negative life events on functional somatic symptoms (FSSs) in adolescents, based on data from 957 participants of the population cohort TRacking Adolescents' Individual Lives Survey. Life events experienced between age 16 and age 19 were assessed with the Kendler's Life Stress interview. FSSs at age 19 and age 16 were measured with the Youth and Adult Self-Report. The hypotheses were tested by the use of a latent change model. Life events predicted FSSs, even when adjusted for pre-event levels of FSSs, symptoms of anxiety and depression, and socio-economic status ($B = 0.006$, 95% CI [0.003, 0.008], $\beta = .32$). Whereas illness-related life events did not predict FSSs independently ($B = -0.003$, 95% CI [−0.005, 0.09], $\beta = .05$), non-illness-related life events did ($B = 0.007$, 95% CI [0.004, 0.010], $\beta = .31$). A past-year diagnosis of anxiety and/or depression had a significant influence on the association between life events and FSSs ($B = 0.37$, 95% CI [0.30, 0.46], $\beta = .71$), while female sex, exposure to childhood adversities, and family malfunctioning had not. In conclusion, our findings show that FSSs are associated with negative life events in older adolescents. We did not find evidence for stronger effects of illness-related events.

Functional somatic symptoms (FSSs), that is bodily symptoms not well explained by an underlying disease, are common in adolescents and can cause substantial impairments (King *et al.*, 2011; Konijnenberg *et al.*, 2005). Around 25% of all adolescents report FSSs during adolescence (Janssens *et al.*, 2011; van Geelen, Rydelius, & Hagquist, 2015). Although the occurrence of functional symptoms declines from childhood up to adulthood, chronic complaints seem to increase with age (King *et al.*, 2011; van Geelen *et al.*, 2015). FSSs include a wide range of symptoms, including fatigue, dizziness, and pain complaints such as headache and abdominal pain. Adolescents with FSSs are frequently seen in health care, but limited knowledge about the aetiology of their symptoms hampers adequate treatment (Starfield *et al.*, 1980). This study aimed to identify the role of negative life events in the development and persistence of FSSs in adolescents.

Early exposure to negative life events is thought to play a major role in the development and course of FSSs in adolescents (Eminson, 2007; Kozlowska, 2013). Suggested mechanisms for the relation between negative life events and FSSs are physiological and emotional stress responses (Kozlowska, 2013). These responses are postulated to increase the generation, awareness, and interpretation of bodily signals,

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thus predisposing individuals for the development of FSSs (Deary, Chalder, & Sharpe, 2007; Kozlowska, 2013). Indeed, some negative life events during adolescence, such as parental death, have been found to be predictive of some FSSs in adolescents (Bonvanie, van Gils, Janssens, & Rosmalen, 2015; Poikolainen, Kanerva, & Lonnqvist, 1995; van Gils, Janssens, & Rosmalen, 2014; Villalonga-Olives *et al.*, 2011; Walker, Garber, & Greene, 1994). Yet, to our knowledge, it remains unknown whether and to what extent a broad range of recently experienced life events predict the level of FSSs in adolescents.

Studies conducted thus far also have some limitations. Life events were measured with questionnaires (Boey & Goh, 2001; Poikolainen *et al.*, 1995; Walker *et al.*, 1994). This approach is prone to bias (Dobson, Smith, & Panchana, 2005; Grant, Compas, Thurm, McMahon, & Gipson, 2004): Individuals suffering from FSSs may over-report life events that caused physical discomfort (Blaney, 1986), or perceive experienced life events as more negative than healthy individuals (Hardt & Rutter, 2004). 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 FSSs before the life event. This is regrettable because FSSs 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 FSSs makes it hard to exclude reverse causality. Likewise, pre-event symptoms of anxiety and depression and socio-economic status (SES) could account for part of the reported associations between life events and FSSs (Janssens, Rosmalen, Ormel, van Oort, & Oldehinkel, 2010; McLeod & Kessler, 1990).

Symptoms of anxiety and depression are prevalent in people with FSSs, predict increased FSSs in adolescents, and share genetic and environmental risk factors (Henningsen, Zimmermann, & Sattel, 2003; Janssens *et al.*, 2010; Kato, Sullivan, Evengard, & Pedersen, 2009). Yet, research has also shown that FSSs, 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 FSSs (Kato *et al.*, 2009; Lipsanen, Saarijarvi, & Lauerma, 2004). This raises the question whether negative life events are predictive of internalizing symptoms in general, or have a particular effect on FSSs. It has also been suggested that particularly illness-related life events are strong risk factors for FSSs (Hotopf, 2002; Schulte & Petermann, 2011). Illness-related events are likely to increase bodily attention and to induce health anxiety, which might result in higher levels of FSSs (van Tilburg *et al.*, 2015). How family members cope with their own illnesses or react to the illness of their child may also influence the development of FSSs (Wilson, Moss, Palermo, & Fales, 2014), possibly through modelling and reinforcement (Whitehead *et al.*, 1994). Indeed, children's own and parental somatic complaints, illnesses, and hospitalizations were found to be associated with FSSs (Craig, Cox, & Klein, 2002; Hotopf, 2002; Schulte & Petermann, 2011). Yet, to our knowledge, there are no studies that actually compared whether illness-related events are stronger related to FSSs than non-illness-related events.

The association between life events and FSSs 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 (Grant *et al.*, 2006). A postulated mechanism for this sensitization is that chronic stressors early in life alter automatic physiological, psychological, and behavioural responses upon stress (Kozlowska, 2013). 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 FSSs than adaptive stress responses (Kozlowska, 2013). A possible explanation for the overlap between anxiety, depression, and FSSs mentioned earlier is that suffering from a generalized anxiety disorder or major depression could make someone more susceptible for higher levels of FSSs 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 (Bangasser, 2013). 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 (Grant *et al.*, 2006). It is conceivable that the same sex difference holds for FSSs. Hence, the role of childhood adversities, family functioning, and sex in the effect of life events on FSSs calls for further research.

The aim of this study was to investigate the effect of negative life events on the level of FSSs 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 predicts FSSs, even when adjusted for pre-event levels of FSSs, SES, and symptoms of anxiety and depression; (2) the severity of illness-related life events is a stronger predictor of FSSs 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 FSSs. In addition, we explored whether life events have a particular effect on FSSs 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–T5) from the age of 11.1 (*SD*: 0.6) until the age of 22.3 (*SD*: 0.6). Initially, 3,483 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 and forty-eight children were excluded because the primary school refused to participate or 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 2,935 children, 2,230 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 (Huisman *et al.*, 2008). Non-responders did not differ from responders in their prevalence of FSSs or other internalizing and externalizing behaviours, but were more often boys and had more often parents with a lower SES (de Winter *et al.*, 2005). 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 2,230 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 (Nederhof *et al.*, 2012). For more details about participant characteristics, recruitment, non-responders, and attrition, see de Winter *et al.* (2005) and Huisman *et al.* (2008). 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 administered 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 aetiology and course of psychopathology, one of the main aims of the TRAILS study. In total, 1,584 participants (84.2% of all T4 participants) gave informed consent and participated in a psychiatric diagnostic interview. Hereof, 1,547 participants also gave informed consent for the LSI. Of these 1,547 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.

Life events

Negative life events experienced between T3 and T4 were assessed with the Kendler's LSI (Kendler, Karkowski, & Prescott, 1998), 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

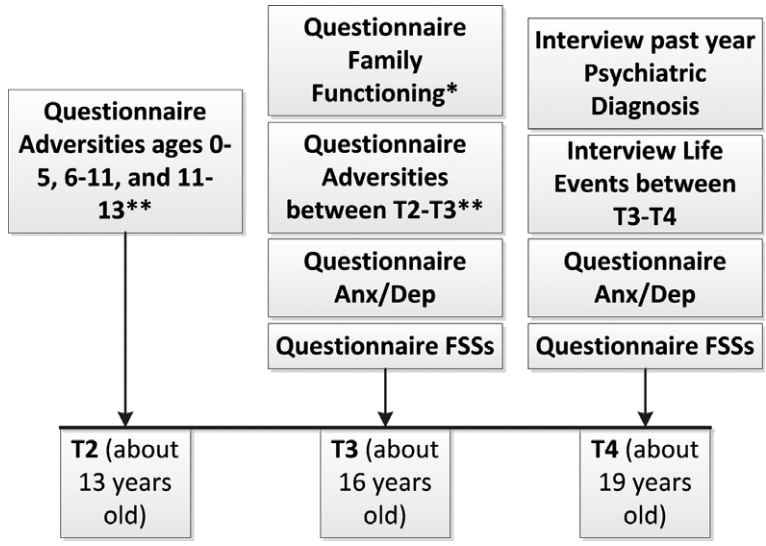

Figure 1. Assessed questionnaires over time. *Note.* *Completed by one parent. **Completed by participant and parent. FSSs, functional somatic symptoms; Anx/Dep, symptoms of anxiety and depression.

Table 1. Sample characteristics

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

Note. The weighted and pooled means of the imputed data sets revealed essentially the same values. LSI, Life Stress interview; FSSs, functional somatic symptoms. T4, wave 4, T3, wave 3; Anx/Dep, symptoms of anxiety and depression.
[a]Based on the weighted values of the original database.

(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 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' judgement. 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, 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, FSSs were measured with seven items of the Somatic Complaints subscale of the Adult Self-Report (ASR; Achenbach & Rescorla, 2003). 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 6 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 (Janssens, Klis, Kingma, Oldehinkel, & Rosmalen, 2014). 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 Youth Self-Report (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 6 months, the response to all five items was set to 'never'. This led to lower mean scores in the online version than in the paper-and-pencil version (Bonvanie *et al.*, 2015). Therefore, type of questionnaire (online vs. paper-and-pencil) was included as a covariate in our analyses.

Potential confounders

FSSs at T3

Functional somatic symptoms at T3 were measured with seven items of the 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

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).

Socio-economic status

Data on the household income, educational levels of both parents, and occupational levels of both parents were assessed at T1. These five indicators of SES were standardized, where after the mean SES score was calculated for each participant.

Potential moderators

Past-year diagnosis of anxiety or depression

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. The CIDI is a structured interview designed for the assessment of mental disorders according to the definitions and criteria of the DSM-IV (World Health Organisation, 1990).

Childhood adversities

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 and 5, the ages 6 and 11, and the ages 11 and 13 at T2, and between the ages 13 and 15 at T3. The mean of these eight items (range 0–10) was calculated.

Family malfunctioning

Family malfunctioning was measured with the General Functioning subscale of the Family Assessment Device (Byles, Byrne, Boyle, & Offord, 1988), 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 whether life events predicted the level of FSSs, a latent change model was built. First, we assessed scalar invariance of the latent construct FSSs across time points. This was performed 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 (van de Schoot, Lugtig, & Hox, 2012). 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 > .95, the CFI > .95, and the RMSEA < .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 FSSs 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 = .98, TLI = .98, RMSEA = .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 = .98, TLI = .97 RMSEA = .032). When intercepts were also specified to be equal across time, model indices were still acceptable but worsened considerably (df = 66, CFI = .93, TLI = .90, RMSEA = .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 = .97, TLI = .96, RMSEA = .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 FSSs are partly due to differences in intercepts of the two unconstrained items. Yet, valid inferences about mean-level differences of the latent factor FSSs can probably still be made when the loadings and intercepts of at least two items are constrained (Byrne, Shavelson, & Muthén, 1989).

The first model tested whether life events that happened after T3 (time-variant predictor) predicted FSSs at T4 when adjusted for the effect of sex (time-invariant predictor) on the initial level of FSSs at T3 (the intercept FSSs) and the increase of FSSs (the slope FSSs). 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 whether pre-event levels of FSSs, Anx/Dep, and SES were, in

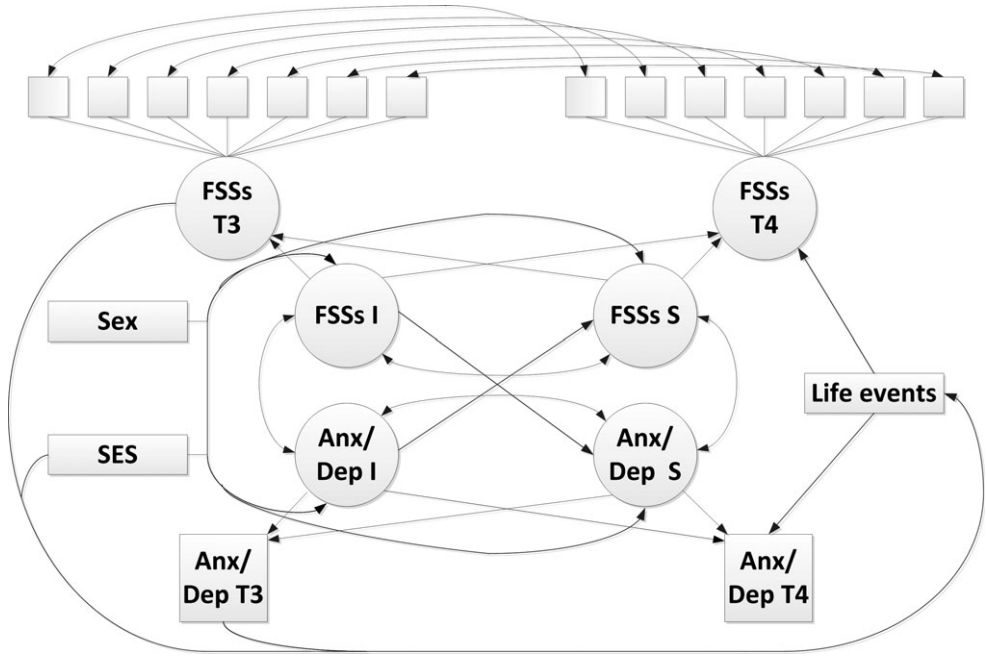

Figure 2. A parallel latent change model of FSSs and symptoms of anxiety and depression. *Note.* FSSs, functional somatic symptoms; Anx/Dep, symptoms of anxiety and depression; SES, socio-economic status; I, intercept; S, slope. FSSs T4 is also regressed on 'type of questionnaire' (not displayed).

their turn, predictive of life events, as postulated, we also regressed life events on these variables (Figure 2). To investigate whether illness-related life events predicted FSSs at T4 to a greater extent than other life events, FSSs 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 FSSs were considered different when the probability that the two confidence intervals showed overlap in their 95% CIs was less than 5% (Knol, Pestman, & Grobbee, 2011). The same approach was used to compare the effects of life events on FSSs with the effects on symptoms of anxiety and depression. Finally, we tested whether sex, a past-year diagnosis of anxiety or depression, childhood adversity, and family malfunctioning increased the effect of life events on FSSs, by entering the interactions (time-variant predictors) of the mean-centred life events variables with each of these potential moderators (also mean-centred) 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 = 1,584; see: Method, Participants). The amount of missing values on variables ranged from 2% to 15%. FSSs 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%) and 612 (64%) participants, respectively. The mean level of FSSs experienced by participants declined from T3 to T4, which was partly attributable to the screening question used for the assessment of FSSs at T4 (see Methods section).

Life events and FSSs

The overall severity of negative life events experienced in the past 2–3 years significantly predicted FSSs at T4 (B = 0.006, 95% CI [0.003, 0.008], β = .32, R^2 FSSs at T4 = 0.76). The intercept and slope were negatively correlated with each other (B = −0.01, 95% CI [−0.025, −.0.004], β = −.48), indicating that a higher level of FSSs at T3 was related to a steeper decline of FSSs over the next 2 years' time. When we additionally adjusted our model for SES and symptoms of anxiety and depression, the effect size of life events on FSSs at T4 was not changed (Table 2). Post-hoc explorative analyses showed that pre-event levels of FSSs at T3 (B = 4.17, 95% CI [1.96, 6.21], β = .19) and SES (B = −0.89, 95% CI [−1.37, −.0.34], β = −.09) predicted the severity of life events, but symptoms of anxiety and depression did not (B = 0.65, 95% CI [−1.04, 2.75], β = .03). Life events predicted FSSs and symptoms of anxiety and depression to a similar extent (Table 2).

Table 2. Effects of life events on FSSs

	B	95% CI	β
Intercept FSSs			
Sex: Female	**0.26**	[0.22, 0.29]	.96[a]
SES	**−0.05**	[−0.07, −0.03]	−.14
Intercept Anx/Dep[b]	**0.05**	[0.04, 0.06]	.78
Slope FSSs			
Life events[c]	**0.006**	[0.003, 0.008]	.32
Sex: Female	**0.09**	[0.05, 0.12]	.64[a]
SES	**0.03**	[0.01, 0.05]	.18
Intercept FSSs	**−0.01**	[−0.016, −0.011]	−.42
Intercept Anx/Dep	**−0.02**	[−0.023, −0.012]	−.59
Slope Anx/Dep[b]	**0.03**	[0.023, 0.035]	.84
Slope Anx/Dep			
Life events[c]	**0.006**	[0.003, 0.009]	.20

Note. R^2 FSSs at T4 = 0.81. Bold = significant. Estimates of predictors of FSSs slope adjusted for type of questionnaire. FSSs, functional somatic symptoms; Anx/Dep, symptoms of anxiety and depression; SES, socio-economic status.

[a]Standardized change in FSSs scale for female versus male.

[b]Cross-sectional estimate.

[c]Modelled as a time-variant predictor of FSSs at T4.

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 FSSs (B = 0.007, 95% CI [0.004, 0.010], β = .31). Illness-related events were not significantly predictive of FSSs (B = 0.003, 95% CI [−0.005, 0.009], β = .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 FSSs either (B = 0.006, 95% CI [−0.004, 0.018], β = .09). Only when the effect of illnesses in the household on FSSs were not adjusted for other life events this variable did predict FSSs (B = 0.010, 95% CI [0.002, 0.026], β = .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 FSSs at T4. Thus, the effect of life events on FSSs 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], β = −.05; Adversity × Life events: B = 0.002, 95% CI [−0.001, 0.004], β = .12; Family × Life events: B = 0.001, 95% CI [−0.008, 0.008], β = .13).

A past-year diagnosis of anxiety and/or depression had no effect on FSSs at T4 (B = 0.002, 95% CI [−0.005, 0.009], β = .009), but increased the effect of life events on FSSs at T4 (Diagnosis × Life events: B = 0.37, 95% CI [0.30, 0.46], β = .71).

Discussion

We found that the combined severity of a broad range of negative life events predicted FSSs in older adolescents (aged 18 years), also when adjusted for sex, pre-event levels of FSSs, symptoms of anxiety and depression, and SES. Contrary to our hypothesis, non-illness-related events predicted FSSs, while illness-related events did not when controlled for other life events. In other words, illness-related life events had no independent effect on FSSs in this study sample. Furthermore, the effect of life events on FSSs 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 FSSs for pre-event levels of FSSs, anxiety and depressive symptoms, and SES. This approach decreased the probability that findings were influenced by report bias, an important limitation of previous studies (Boey & Goh, 2001; Poikolainen *et al.*, 1995; Villalonga-Olives *et al.*, 2011; Walker *et al.*, 1994). 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 FSSs. 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 FSSs will be diagnosed with a medical condition explaining these symptoms (Drossman, 1982; Kroenke, Wood, Mangelsdorff, Meier, & Powell, 1988; Skovenborg & Schroder, 2014). 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 FSSs as an illness-related life event. However, this potential overlap between illness-related life events and FSSs was probably minor because illness-related events were not significantly related to FSSs 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 FSSs (Poikolainen *et al.*, 1995; Walker *et al.*, 1994). Adjustment for pre-event FSSs and pre-event symptoms of anxiety and depression reduced the effect of life events on FSSs, but it remained significant. These findings suggest that the effect of negative life events on the level of FSSs 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 FSSs in our sample. Earlier studies found that parental pain and parental hospitalization were associated with pain symptoms in children (Boey & Goh, 2001; Devanarayana, de Silva, & de Silva, 2008; Saunders, Von Korff, Leresche, & Mancl, 2007; Schulte & Petermann, 2011). Furthermore, adults suffering from FSSs mentioned more self-experienced and familial illnesses than healthy adults (Craig *et al.*, 2002; Hotopf, 2002; Schulte & Petermann, 2011). 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 FSSs might have been overstated in earlier studies due to report bias (Schulte & Petermann, 2011): People suffering from FSSs may remember and report more childhood illnesses. Indeed, one study found that while retrospectively reported illnesses were related to FSSs in children, prospectively assessed illnesses were not (Mechanic, 1980). Second, prior findings indicate that chronic rather than short-term illnesses are related to the development of FSSs (Hotopf, 2002), possibly because the postulated mechanisms through which illnesses are related to FSSs in young people, such as observational learning and rewarding models, are more likely in case of chronic illnesses (Levy, Langer, & Whitehead, 2007). 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 FSSs. Third, previous studies did not adjust the effect of illness-related events on FSSs for the concurrent experiences of non-illness-related life events. In our study, the effect of illness-related events on FSSs was significant when not controlling for other negative life events. This indicates that the effect of illness-related life events on FSSs 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 FSSs raises the question how life events influence FSSs. A potential pathway runs from negative life events through chronic stress to altered hypothalamic–pituitary–adrenal axis functioning (Heim *et al.*, 2009) and reduced cortisol levels (Bosch *et al.*, 2012). Low cortisol levels are associated with higher levels of FSSs (Janssens *et al.*, 2012). Other potential mechanisms are emotional, cognitive or behavioural reactions to stress, which eventually perpetuate the generation of bodily symptoms or influence the awareness and interpretation of these symptoms (Deary *et al.*, 2007). For example, emotional arousal, selective attention, and problems with sleeping

can be triggered by stress and may also influence the level of FSSs (Deary *et al.*, 2007). Surprisingly, we did not find that childhood adversities or living in a poorly functioning household sensitized adolescents for the effect of life events on FSSs. This indicates that chronic stressors early in life do not permanently alter the long-term physiological and psychological stress responses which may predispose to FSSs later in life.

Our findings indicate that recently experienced negative life events predict the level of FSSs over time, especially in participants who also experienced depression or anxiety during this period. The effect of life events on FSSs 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 aetiology of FSSs, and underlines the need for practitioners working with adolescents suffering from FSSs 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 FSSs. In future research, it would be interesting to investigate whether the level of FSSs 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.

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Appendix: 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
16.	Child died
17.	Mother or father died
18.	Brother or sister died
19.	Other family member died
20.	Someone else close died
21.	Husband/wife/partner serious/life-threatening illness/injury
22.	Child serious/life-threatening illness/injury
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
26.	Someone else close 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
37.	Child serious personal crisis
38.	Brother or sister serious personal crisis
39.	Someone else close serious personal crisis
c.	**Other problems or events**
40.	Other serious personal problems or events
41.	Other serious problems or events in network