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## Functional somatic symptoms in adolescence and young adulthood

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# Chapter 7| general discussion

## Main findings explained

FSS in young people can be conceptualized as the result of an interaction between personal vulnerabilities for FSS and external factors triggering (further) development of FSS. In this thesis we aimed to reveal if, and to what extent, perfectionism and sleep problems predispose young people for FSS. In addition, the effects of the external stressors childhood sexual abuse and severe negative life events on FSS were investigated. Further, we systematically reviewed the content and analyzed the effectiveness of investigated psychological treatments for FSS in children and adolescents.

### *Personal vulnerability factors or diathesis*

In line with earlier findings in young and middle aged adults with chronic fatigue syndrome (44,45), we found that adolescents who have the feeling they should be perfect are prone to experiencing higher levels of FSS. Maladaptive perfectionism enhances the experience of daily stressors (67,68), possibly because perfectionists appraise environmental demands more often as unpredictable or uncontrollable (69). Moreover, it is thought that young people with this trait easily lapse into non-adaptive stress-responses such as anxious or depressive feelings, rumination, catastrophizing, and endurance behavior when acute stressors are encountered (44). We indeed found that part of the effect of perfectionism on FSS ran through feelings of anxiety and depression in our sample. Non-adaptive psychological stress-responses have also been found to prolong physiological stress-responses such as high cortisol secretion (70). Although exact mechanisms remain unclear, this can eventually result in a not well functioning hypothalamic–pituitary–adrenal axis with ineffective cortisol secretion (70). Recent findings indicate that maladaptive perfectionism is indeed associated with blunted hormonal stress-responses (71). Further, non-adaptive and prolonged stress-responses are thought to increase (the perception of) bodily signals and attention towards these signals (25,28,72,73). Negative feelings and thoughts, persistence of activities despite signals of overburdening, and blunted cortisol responses upon stressors could thus increase further vulnerability for FSS or perpetuate existing symptoms (27,44,74).

Enough and high quality sleep could be a way to recover from the psychological and physiological consequences of external triggers (75-78). We found that problems with sleeping were associated with musculoskeletal pain, headaches, abdominal pain, fatigue, and symptoms of anxiety and depression. Sleep problems increased musculoskeletal pain severity, but not abdominal pain and headache severity, three years later. This was partly mediated by fatigue. Moreover, subgroup analyses revealed that the effect of sleep problems on musculoskeletal pain was actually only present in females. Some potential physiological mechanisms connecting sleep disturbances with

these fibromyalgia-like symptoms are changed cortisol, melatonin and catecholamine responses, and central sensitization (77,79). Sleep deprivation could, like perfectionism discussed earlier (71), lead to overburdening of the cortisol response, eventually resulting in blunted cortisol responses upon stressors such as pain, or decreased responsiveness of receptors for cortisol secretion (77). Cortisol has an important role in pain modulation by suppressing peripheral inflammatory signals and other nociceptive stimuli (70,77). Shortage of cortisol or cortisol responsiveness may thus lead to low-grade inflammation and heightened pain experiences. Indeed, a meta-analysis showed that in patients with chronic fatigue syndrome and females, but not males, with fibromyalgia basal cortisol levels were lower than in controls (80). Next to its influence on the HPA-axis, lack of sleep can cause suppressed or altered melatonin and increased catecholamine secretion. These pathways have also been hypothesized to enhance inflammatory responses and oxidative stress (81). Again, this could be especially important in females (82). Lack of sleep is also thought to contribute to the development of central sensitization resulting in increased sensitivity to somatic sensations including pain (50). Central sensitization is a state of altered pain facilitation and inhibition in the brain which increases signaling of, and responsiveness upon, potential harmful stimuli to promote immobilization and protection of tissues. Some preliminary evidence indicates that through estrogen induced pathways central sensitization is more easily initiated and perpetuated in females (83). Impaired cortisol secretion, altered inflammatory responses and central sensitization, may be specifically important in muscle pains and fibromyalgia-like symptoms, as opposed to other types of pain, by increasing muscle tension, muscle requirements and muscle fatigue (50,74,84,85).

### ***External stressors***

Our findings revealed that negative life events are predictive of a broad range of FSS in adolescents. These findings are not entirely novel, since many studies in clinical and general adult populations already confirmed relations between severe childhood stressors and FSS (54,55,86). However, we confirmed this with prospective data from TRAILS, a general adolescent population cohort, which makes it more likely that the associations found are not solely due to selection and recall bias. In addition, we were able to adjust for pre-event levels of FSS, anxiety, and depression, and in this way ruled out that pre-existing internalizing symptoms caused some deteriorating life experiences instead of the other way around. In line with a previous study in adults (86), another relevant finding from this thesis is that the effects of negative life events were independent of the socio-economic status of the parents. This suggests that growing up in poor financial circumstances and being raised by low educated or unemployed parents cannot be held responsible for the found relations between negative life events and FSS. In a sense this is a hopeful message; interfering with the

pathway from severe life events towards FSS development may be effective in the prevention and treatment of FSS in adolescents, independent of their background.

Both psychological and physiological mechanisms have been postulated to mediate the effects of severe stressors on FSS (25,28,72,73,87). Stress-induced psychological reactions are thought to change the awareness, appraisal and behavior towards bodily signals (25,28,72,73). Empirical studies indicate that traumatic stressors enhance memory and attention for all features related to the stressful event, such as bodily signals (88,89). Stressful events like abuse negatively influence self-evaluation and appraisals in young people (90). Non-adaptive cognitions probably play an important perpetuating role in the experience of FSS (28). Further, severe childhood events can lead to changed sleeping habits and sleep problems later in life (91), which we found to be related to FSS in emerging adults.

Prolonged physiological reactions, such as overburdening of the hypothalamic–pituitary–adrenal axis and thus an impaired cortisol response or functioning, changed function of the autonomic nervous system, and the central sensitization discussed earlier, are thought to be another link between severe stressors and FSS (36,87,92). However, it is important to note that prospective and good quality evidence for these pathways remains scarce and conflicting (80,93-95). In line with the overburdening theory, sexually abused young adults show low cortisol levels after initial high cortisol levels in childhood (96). Another study found that the timing of adversities (i.e. adversities in childhood vs adolescence) did also matter: adversities in childhood predicted higher cortisol levels while adversities during adolescence resulted in lower cortisol levels. In the TRAILS sample, sexual abuse had a peak incidence around middle adolescence, and earlier research showed that low cortisol levels were associated with some FSS in adolescents (74). Changes in responsiveness of the autonomic nervous system have also been associated with both stressors and FSS (97-100), although a recent TRAILS study could not confirm an association between stress-induced cardiac autonomic nervous responsiveness and FSS (94). Some preliminary findings indicate features of central sensitization in adults suffering from post-traumatic stress disorder (101), suggesting a potential role for this mechanism too.

FSS were not more strongly related to illness-related events than to other events in the TRAILS sample. This suggests that not particular events but the cumulative stress of all experienced negative events are related to FSS. Yet, this supposed linear relation between external stressors and FSS is not completely in agreement with some other findings in the same TRAILS sample. External stressors in early life (i.e. earlier adversities or poorly functioning households) did not sensitize older adolescents for the effect of recently experienced stressors on FSS. A potential explanation is that early life stressors do not have a linear but a curve-linear relation with negative health outcomes. Both relatively low stress and high stress early in life may predispose people

for poorer health in reaction to stressors later in life, while experiencing moderate levels of stress in childhood may actually confer resilience (102). The latter has been named ‘the steeling effect’ based on the assumption that moderate stressors can create the opportunity to develop cognitive skills, learn to regulate emotions, and explore adaptive and less adaptive responses to stress. In this way a person is better prepared for stressors later in life. This may be especially true when similar stressors are encountered: i.e. a moderate level of poor family functioning may steel adolescents for later family-related stressors but not for personal adversities. It is conceivable that the earlier discussed vulnerability factors also interfere with this postulated process. As mentioned, perfectionists appraise external stressors more often as unpredictable or uncontrollable (69). Perfectionism may thus substantially lower the thresholds for the levels of stressors experienced as moderate and thus steeling, and the levels experienced as extreme and harmful.

### **Colouring the hypothesised stress-diathesis picture: targets for treatment**

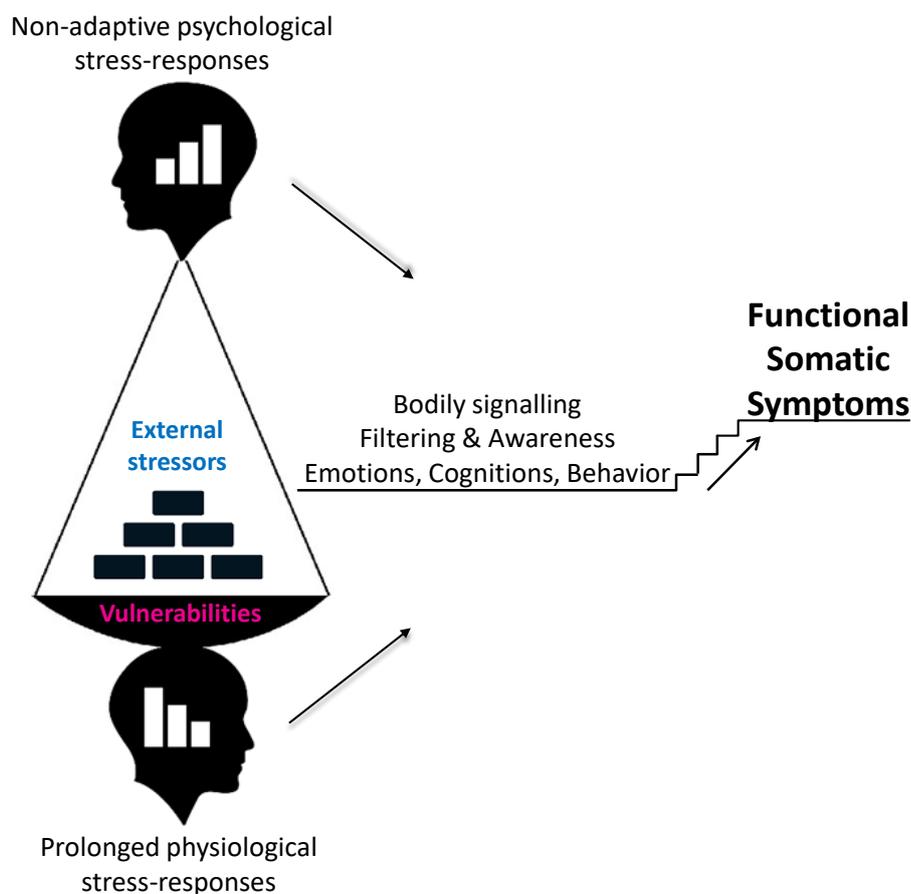
The above discussed findings, and explanatory mechanisms for these findings, are summarized in the stress-diathesis model as displayed in Figure 1. FSS can be seen as the result of a continuous interaction between personal vulnerabilities to develop FSS and external factors, including psychosocial stressors, triggering FSS. Both vulnerabilities and triggers may induce non-adaptive or prolonged psychological and physiological stress-responses. These responses are thought to cause and perpetuate FSS by increasing bodily signals, decreasing filtering of signals and/or changing cognitions, emotions and behavior towards signals.

Psychological treatments can interfere on different levels with the development and persistence of FSS. In chapter six we found that most treatments for FSS in children are based on cognitive behavioral principles. In this type of therapy potentially perpetuating factors such as non-adaptive cognitions and behaviors with regard to the FSS are targeted. Some other types of psychological therapies such as relaxation or coping skills training aimed to interfere with the effect of external triggers. Biofeedback and hypnotherapy were therapies in which physiological processes were addressed.

Most studies that investigated the effectiveness of psychological treatments for FSS in childhood did not take the potential influence of vulnerability factors into account. This is regrettable because maladaptive perfectionism negatively influences treatment effects, at least in adults with chronic pain (103). A recent intervention study has shown that treating perfectionism can also decrease experienced stress and related symptoms of anxiety and depression (104). Previous research already showed that symptoms of anxiety and depression are prevalent in adolescents with FSS and can predict the course of these symptoms (105,106). Moreover, symptoms of anxiety and

depression mediated the effect of perfectionism on FSS, and were also identified as a vulnerability factor for further development of FSS in reaction to stressful events. Treatment of comorbid symptoms of anxiety and depression did indeed improve outcomes in adult patients with chronic pain (107). However, in our review we found that most intervention studies in pediatric populations excluded participants with comorbid anxiety and depression disorders. Moreover, in none of the studies symptoms of anxiety and depression were specifically addressed in treatment. It therefore remains unknown if treatment of comorbidities would be effective for symptom reduction in adolescents with FSS. Sleep problems can be another potential lead for prevention and treatment of chronic FSS in adolescents and young adults, especially in females with chronic pain or musculoskeletal pain. Some studies assessed sleep as an outcome to investigate the effects of psychological treatment in pediatric pain populations (108,109). None of these studies incorporated specific elements to treat sleep problems or studied if improvement in sleep problems was responsible for improvements in pain parameters.

**Figure 7.1.** Vulnerabilities and triggers may cause FSS through psychological and physiological stress-responses.



Note. Both vulnerability factors and external stressors can cause non-adaptive or prolonged stress-responses. These altered stress-responses could be responsible for the development of FSS.

## Strengths and limitations

When interpreting the findings of this thesis some limitations of our studies should be kept in mind. In three of our four empirical studies we used the Somatic Complaints subscale of the Youth Self-Report (YSR) and/or the Adult Self-Report (ASR) to assess FSS. This subscale asks participants for the qualitative frequency (never vs sometimes vs often) of nine symptoms not well explained by a medical diagnosis or an obvious reason over a period of six months. After exclusion of two items, the Somatic Complaint scale showed good internal consistency on all assessment waves of the TRAILS study in both females and males. In addition, mean scores on this 7-item scale have been correlated with various hypothesized risk factors within our sample, which could be interpreted as a sign of validity (3,13,56,74,106,110-112). However, formal validity (i.e. a medical diagnostic work-up to confirm the somatic symptoms are functional), repeatability and responsiveness of the instrument remain unknown. More important, clinically relevant scores or relations with impairments, apart from school absenteeism, are not well known. These unknown psychometric properties of the Somatic Complaint scale hamper the interpretation of mean scores and found effect-sizes in our studies. Unfortunately, alternative questionnaires for large-scale epidemiological research in children are scarce and generally also not well validated (113). Another limitation is that we had no detailed information about the potential risk factors we studied. Perfectionism was assessed with one item, we only assessed how many sleep problems out of five were generally experienced by young adults, and important details of the sexual abuse experienced by adolescents were not assessed. Although the use of these broad measures could be seen as inevitable in large scale cohort studies, they hinder straightforward interpretations of findings. For example, in the analyses performed in chapter three we were not able to adjust for other forms of childhood abuse or take the duration and frequency of the abuse into account. Next to these limitations of our instruments, the sample we used also has its drawback. Because we used data from a general population cohort, overall scores on FSS and pain severity were low. In addition, it seems reasonable to assume that despite extensive recruitment efforts young people exposed to sexual abuse did less frequently enroll in the TRAILS study. Low overall scores and underrepresentation of potentially high scoring participants could be partly responsible for the overall low effect-sizes of investigated risk factors we found.

Our studies also have several methodological strengths. We investigated risk factors for FSS in the large general population cohort TRAILS. Extensive recruitment efforts ensured high initial response rates of participants at baseline measurements and low attrition rates at subsequent waves (114-116). Although there were differences in characteristics between responders and initial non-responders/drop-outs, these groups did not differ with respect to internalizing mental health outcomes or scores on the

Somatic Complaint scale. Moreover, no differences were found in the associations between differences in characteristics (e.g. sex, SES, school performance) and mental health outcomes (114). The high representativeness of the TRAILS sample makes it likely that findings from this sample can be translated to the general population. Our long follow-up period also enabled us to investigate the long-term effects of vulnerabilities and external stressors on the course of FSS, a relatively unexplored territory. We were also able to investigate risk factors in specific developmental periods, such as emerging adulthood. Further, we assessed almost all predictors and outcomes in our studies at more than one time-point. Therefore we could adjust the effect of potential risk factors on FSS for previous levels of FSS, and investigate bidirectional relations. Because we assessed several FSS we could explore specificity of risk factors for certain FSS such as gastrointestinal symptoms or musculoskeletal pain. In addition, we were the first to provide a systematic review and meta-analysis of the content and efficacy of psychological treatments for various FSS in children. This review provides useful information for clinicians working with children who suffer from FSS, and starting points for further research.

### **Future research in the field of pediatric FSS: Towards an individual approach**

Today, many factors of potential influence on the development and course of FSS have been identified in large child and adolescent population cohorts (2,3,5,13,21,30,31,33,56,74,106,110-112,117). The effect-sizes found for these risk factors are generally small. This could lead to the conclusion that most of these factors are not that important on their own and that only the accumulation of many of these factors leads to FSS. Yet, this is not supported by the fact that FSS are not rare, but in fact common in the general population (2). Accumulation of multiple risk factors in such many young people seems unrealistic as an exclusive cause of FSS. Another, more convincing, explanation for overall small effect-sizes on group levels is that the development of FSS in young people is a heterogeneous process. Young people with FSS probably differ in their personal vulnerabilities. Particular stressors could be very relevant for some individuals, but irrelevant for others. We found that sleep problems, for example, were only predictive of musculoskeletal pain severity in females and not in males. Another indication that FSS are probably very heterogeneous in nature, is that even opposing behavior can lead to FSS. Not only lack of sleep or limited activities but also prolonged sleeping and high levels of physical activity increase pain levels in children (118,119). As mentioned earlier, the severity of early life stressors may also have a curve-linear relation with FSS (102). It is thus conceivable that in different people, different combinations of personal vulnerabilities and external stressors lead to FSS.

The identification of risk factors for FSS in cohort studies can provide important and reliable leads for future research and treatments. Yet, findings from our studies cannot be directly translated into evidence based treatment decisions about individuals because they are bound to broadly defined subgroups of people (e.g. young adults, females, individuals with sleep problems). A complementary approach, building on to these epidemiological findings, is diary research in which the associations between the identified risk factors for FSS can be studied within persons. We found that life events predicted higher levels of FSS on a group level, but quite surprising individual patterns emerged from recent diary research in adults (120). In line with our findings, data of the individual relations between stress and FSS showed that in some adults stress preceded FSS. However, there were also individuals in which stress was actually the consequence of FSS, had no relation with FSS at all, or even improved FSS the next day (120). These diary data reveal existing subgroups the other way around; not by identification of moderators or curve-linear relations in large population research, but by grouping similar individual patterns. One can imagine that, based on their relation of stress with FSS, quite different treatment approaches could be effective in these subgroups of patients. A next step would be to provide young patients with FSS with treatments tailored to personal risk factors for FSS, and to investigate if personalized treatment actually diminished the effects of personal risk factors on FSS. Another line of approach could be to study if a treatment with one or more patient-tailored components is more effective than treatments based on general principles.

Unfortunately, young patients with FSS in need for treatment are currently only divided into subgroups based on their type of symptoms and not on their etiologic profile. It is an ongoing debate if this symptom-based division is meaningful, or just the result of medical sub-specialization (121-124). A common hypothesis is that risk factors which can be labelled as physiological (e.g. a dysregulated HPA-axis or autonomic nervous system, sensitization, inflammation) may more often cause a specific type of symptoms, while psychological and social or external risk factors are probably shared among different types of FSS (73,74). We found a specific relation between sleep problems, fatigue and muscle pain in females, probably driven by physiological pathways. Sexual abuse, on the other hand, was not specifically associated with later gastrointestinal symptoms but with a broad range of FSS. The assumption that psychological risk factors are probably related to various FSS, and not only to specific FSS, is further supported by our systematic review. In our review we found that psychological interventions are beneficial for children with various types of FSS, independent of the main symptom of the child (i.e. fatigue, abdominal symptoms, headaches and musculoskeletal pain). Interestingly, our review also showed that young people are generally not grouped and treated differently based on personal vulnerabilities or stressors that may have induced or perpetuate FSS. In most studies identified in the review all participants received the same treatment based on

commonly recognized risk factors for FSS such as catastrophizing thoughts and all or nothing behavior. An exception is the treatment in the study of Stulemeijer et al. in which adolescents received a slightly different psychological intervention based on their measured physical activity level (i.e. inactive vs. relatively active participants) (125,126). Yet, it remains unknown if this difference in treatment strategy resulted in better outcomes for both groups of participants. Comparing the effectiveness of this somewhat patient-tailored approach with other treatments in which participants received a non-personalized approach is not very useful. There is too much heterogeneity between studies on many other factors (e.g. patient population, duration of the treatment etc.), to interpret any found differences in effectiveness. In future research the influence of potential moderators of treatment effects identified in cohort studies, such as level of physical activity or sleep problems, should be investigated.

Next to the issue of what treatment approach is most beneficial for whom, the question arises when young people with FSS should be treated. We found that, overall, psychological treatments are effective in reducing symptoms load, disability and school absence in children with FSS. Yet, the only trial that investigated the effectiveness of a video-intervention in a pediatric population with non-chronic instead of chronic complaints found an adverse effect of this intervention. After watching the educative video about chronic fatigue, more children suffered from persistence of fatigue with significant school absence compared to the control group (127). This could indicate that acknowledging chronicity of FSS is important for treatment decisions; starting treatment too early could have iatrogenic effects through, for example, reinforcement of illness behavior. Another explanation could be that, similar to the earlier mentioned ‘stealing effect’ of moderate stressors, mild and transient FSS are a learning opportunity to develop adaptive responses to bodily signals. Early treatments may interfere and disturb this learning opportunity. In contrast; our findings suggest that some risk factors such as sleep problems can predict chronic pain levels, which pleads for early intervention and not for a watchful waiting. To solve this dilemma of when to start what kind of treatment, it could be useful to cluster risk factors into factors that more often result in chronic, severe or impairing FSS and risk factors that are predominantly related to transient or benign FSS. Risk factors such as depression or poor self-rated health are known to be associated not only with increased FSS but with persistence of high levels of FSS over many years (3). Children with these characteristics may benefit from early interventions, while others without these characteristics probably have a higher chance of spontaneous recovery.

Patient-tailored timing and content of treatments can be achieved by subgrouping young patients based on their etiological factors and expected course of FSS. However, this approach also implicitly assumes the availability of specific treatment elements and forms. Clinicians probably already work with *expert based* patient-tailoring; based on their background, experience and training they choose for

specific strategies for specific persons. However, this makes successful treatments very therapist-dependent and not easy to adapt for research purposes or by other clinicians. Standardized treatments, as opposed to clinician-dependent treatments, were logically preferred in RCTs. Unfortunately, we found in our review that the rationales for incorporated elements (i.e. what is exactly treated and how) were not elaborated upon in these studies. An important next step for interventional research would be to work with clear descriptions of the distinct treatment aims of separate treatment elements. This would make it easier to investigate and compare the effectiveness of separate treatment elements in various subgroups of patients. Not only choices for treatment elements should be described, but also rationales for formats, timing and dose of treatments should be explained. One can imagine that patient characteristics such as age of participants, severity of symptoms, impairments and comorbidities can and should influence these choices. Yet, we found that interventional studies seldom clearly connected the reasoning behind the choice of treatment dose (i.e. duration, frequency, intensity) with the characteristics of their included population. More studies should focus on finding the optimal dose of treatment, ideally for well described subgroups of patients. Clarity about treatment elements, their main targets, and insight into rationales for timing, implementation and duration are essential in the development of standardized but patient-tailored treatments.

### **Concluding remarks**

This thesis focused on the role of perfectionism, sleep problems and severe external stressors in the development of FSS in adolescents and young adults and found that all these factors predicted an increase in FSS. These findings can be summarized in a stress-diathesis model in which FSS are explained as the result of both vulnerabilities to develop FSS and external stressors triggering further development of FSS. Vulnerabilities and external stressors may both trigger non-adaptive or prolonged psychological and physiological responses. These responses are thought to cause increased bodily signals, decreased filtering of signals and/or changed cognitions, emotions and behavior towards signals. Psychological treatments can interfere on different levels in this process. Treating the non-adaptive cognitive and behavioral responses, for example, is now the common ‘one size fits all’ approach. We found in our systematic review that this uniform approach is effective for improving symptom load, disabilities and school attendance in children. Treatments would probably be even more effective when they would be more patient-tailored. To accomplish this, future research should focus on the identification of relevant subgroups of young people with FSS. These subgroups could be based on the most important personal vulnerabilities and stressors, and/or expected course of the symptoms. To provide subgroup-tailored or even patient-tailored treatments,

interventional studies should aim to be transparent and specific about exact treatment elements and their supposed targets. In addition, the effectiveness of separate treatment elements should be compared. Only by including clearly described subgroups of young people with FSS and providing well rationalized treatments in intervention studies, treatments can be refined and eventually may become more successful.

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