Chapter 1
General introduction
CHAPTER 1

Functional somatic symptoms in adolescents

Functional somatic symptoms (FSS) are somatic symptoms which cannot be fully explained by underlying pathology. Other commonly used terms for these symptoms are: medically unexplained (physical) symptoms, somatoform symptoms, psychosomatic symptoms, and subjective health complaints. Because patients suffering from such symptoms feel least offended by the term functional somatic symptoms (Stone et al., 2002), this term will be used in this thesis. FSS are very common during adolescence, especially chronic or recurrent pain, which is experienced by about 25 per cent of all adolescents (Perquin et al., 2000), and chronic fatigue, which is experienced by about 10 per cent (ter Wolbeek et al., 2006). One may doubt whether FSS are truly problematic or just harmless ailments that children will grow out of. Studies have shown that FSS are actually problematic. They are a burden for the child and the family (Hunfeld et al., 2002); adolescents experiencing FSS frequently miss school (Wiendels et al., 2005), and the symptoms ultimately contribute to high health care costs (Sleed et al., 2005). Furthermore, FSS may persist until adulthood and remain a major health problem (Hotopf et al., 2000; Steinhausen, 2006). More insight into the etiology of this important health problem might aid the development of effective prevention and intervention strategies. Therefore, this thesis will focus on the etiology of FSS in adolescents.

The etiology of FSS in adolescents

The etiology of FSS in adolescents is not well understood, but it is generally assumed that FSS are the result of interacting biological, psychological and environmental factors. The most recent overview of the etiology of FSS in adolescents is provided in a review by Beck (Beck, 2008). She proposed that FSS are the result of a complex interplay between child factors (e.g. age, gender, puberty, and stress reactivity), environmental factors (e.g. family characteristics, stressors, rewards, and social economic status), and moderating factors (e.g. coping, pain severity, depression, and social or academic competence). We believe that better insight into the complex etiology of FSS in adolescents requires an approach that takes into account bodily processes. Such an approach is provided by the filter model developed by Barsky and Rief (Rief and Barsky, 2005; Rief and Broadbent, 2007). In this model two bodily processes are assumed to play a role in the development of FSS: bodily signal generation and bodily attention. Bodily signal generation, i.e. the development of bodily signals, is presumably the first step in the generation of FSS. Although the generation of bodily signals is a constant process, most signals that are generated by the body will remain unnoticed due to filter activity in the brain (Rief and Barsky, 2005; Rief
and Broadbent, 2007). This filter activity will probably be influenced by the amount of attention that adolescents pay to bodily signals. Bodily attention will therefore determine to which extent bodily signals are noticed. Both an increased generation of bodily signals and an increased amount of attention paid to bodily signals have indeed been found to play a role in the development of FSS (Rief and Barsky, 2005; Rief and Broadbent, 2007). An increase in bodily signals may, for example, arise from dysfunctional stress-axes or hormonal disturbances (LeResche et al., 2005; Tak and Rosmalen, 2010). Examples of factors that may increase attention to bodily signals are a lack of distraction from the body, mood disturbances, and the attention others pay to adolescents’ bodily symptoms (Rief and Barsky, 2005). Thus, bodily signal generation and bodily attention can be influenced by many different factors, which presumably explains the wide diversity of factors involved in the etiology of FSS. Finally, it is important to note that FSS tend to occur together and result in functional somatic disorders (FSD), that is, syndromes of related complaints with unknown organic pathology. The three most well-known FSD are irritable bowel syndrome, primarily characterized by gastrointestinal problems, chronic fatigue syndrome, primarily characterized by overtiredness and fibromyalgia, primarily characterized by musculoskeletal pain. FSD will not be addressed in this thesis, since they are rare during adolescence (Price et al., 1992; Sohrabi et al., 2010).

Not lumping or splitting, but lumping and splitting
Researchers on the etiology of FSS and FSD can be roughly divided into two groups. On the one hand, there are “lumpers”, who take the approach that all FSS and FSD result from the same etiology and thus can be studied together (Wessely et al., 1999). On the other hand, there are “splitters”, who believe that every particular FSS or FSD has its own specific background and should therefore be studied separately (Moss-Morris and Spence, 2006). In this thesis, a combination of the lumper and splitter approach will be taken, based on the hypothesis that FSS partially result from a shared background, and partially from their own specific background. As mentioned, biological, psychological, and environmental risk factors have been found to play a role in the etiology of FSS (Beck, 2008). Biological factors have been found to be involved in the specific background of particular symptoms, whereas psychological and environmental factors have been found to reflect generic risk (Hamilton et al., 2009; Moss-Morris and Spence, 2006). This might be related to the fact that the symptom-specific process of bodily symptom generation directly results from biological factors, while the more generic process of bodily attention is more likely to be influenced by psychosocial factors (Rief and Broadbent, 2007). Thus, the splitter approach will be followed when
studying biological factors, whereas the lumper approach will be taken when studying psychological and environmental risk factors (Figure 1). One advantage of this combined approach is that studying biological risk factors for separate symptoms allows examination of which symptoms share the same biological background. Another advantage is that lumping FSS into a sum score when studying psychological and social factors increases the power to detect associations.

**Aim of this thesis**

Most research on the etiology of FSS so far has been performed in adults. However, research in adolescents might shed more light on the etiology of FSS. Most FSS start to develop during adolescence (Fritz et al., 1997), and therefore results of research in adolescents are less likely to be confounded by the chronicity of the symptoms than results of research in adults. Moreover, different factors might be important in the development of FSS during adolescence than during adulthood, such as parents, peers, school performance, and pubertal development (Beck, 2008). Studies on the etiology of FSS in adolescents conducted so far are characterized by four methodological problems. First, most research was cross-sectional, which precludes conclusions about causality (Beck, 2008). Second, most research followed the splitter approach and studied a single symptom. Studying only one symptom makes it impossible to determine whether a risk factor is specific for that particular symptom or is a risk factor for other FSS as well. Third, most studies compared adolescents suffering from a particular symptom with healthy controls, which makes it difficult to translate findings to the general population. Finally, some of the previous studies were small, especially the ones that examined biological risk factors. This increases the risk of chance findings and false null findings, and might explain the conflicting results from research on biological factors (Tak and Rosmalen, 2010). This thesis aims to overcome these methodological problems by studying the etiology of various FSS in a large prospective population-based cohort study of adolescents.
Figure 1. Working model for the etiology of FSS in adolescents, including both a splitting and a lumping approach.

HPA-axis = hypothalamus pituitary adrenal-axis; ANS = autonomic nervous system.

The TRAILS sample
This thesis consists of seven empirical studies, which were part of the Dutch Tracking Adolescents’ Individual Lives Survey (TRAILS). TRAILS is a prospective population-based cohort study of adolescents, which started in 2001 in order to learn more about the etiology and course of (mental) health problems in the Dutch population. For this thesis, data have been used from the first three data assessment waves, which ran from March 2001 to July 2002, from September 2003 to December 2004, and September 2005 to August 2008, respectively. During the first assessment wave 2230 adolescents participated (mean age = 11.1 years, SD = 0.56; 50.8 % girls); during the second wave the response rate was 96.4% (n=2149, mean age = 13.6 years, SD = 0.53; 51.0 % girls); and during the third wave the response rate was 81.4% (n=1816, mean age = 16.3 years, SD = 0.71; 52.3 % girls). The profile of the TRAILS study is described in more detail elsewhere (de Winter et al., 2005; Huisman et al., 2008). During the assessment waves, information about the adolescents was not only obtained by self-reported
questionnaires, but parents, teachers and classmates were also used as informants. Moreover, adolescents performed neuropsychological tests to obtain information about cognitive functions, and a subsample of 715 adolescents underwent a social stress test to assess physiological and psychological stress responses. All these approaches resulted in a very rich database. An overview of the time line of TRAILS with the assessment waves on which the various chapters in this thesis are based is provided in Figure 2.

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<th>Year</th>
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Figure 2. Time line of the TRAILS assessments waves with corresponding chapters.

*HPA-axis = hypothalamus pituitary adrenal axis; ANS = autonomic nervous system; *This chapter was also based on two assessment waves of the Longitudinal Study of Pain in Adolescents in Seattle.*

**Thesis outline**

The goal of this thesis was to examine the etiology of FSS in adolescents by studying the roles of biological (i.e. pubertal development and functioning of the stress-axes), psychological (i.e. anxiety, depression and intelligence) and environmental (i.e. parental overprotection and school absenteeism) factors. In part I, the roles of psychological and environmental factors in the development of FSS were studied by taking a lumping approach (Figure 1). Chapter 2 dealt with the questions whether anxiety and depression play a role in the development of FSS and whether anxiety is a risk factor, whereas depression is a consequence of FSS. Chapter 3 concerned the association between low intelligence scores and FSS and the question whether this association was influenced by parental expectations. In Chapter 4, the perpetuating effect of parental overprotection was...
investigated and whether this association was mediated by parenting stress was assessed. Chapter 5 dealt with the question whether school absenteeism perpetuated FSS in adolescents and whether this did not hold for adolescents who are being bullied. In part II, the associations between biological factors and FSS were investigated by following a splitting approach (Figure 1). The first chapter of this part, Chapter 6, concerned pubertal development. It answered the question whether pubertal stage predicted the amount of FSS adolescents experience at follow-up and whether these associations differ for Dutch and American adolescents. Then, the two most important stress-axes of the body were studied. Chapter 7 investigated the hypothalamus pituitary adrenal-axis, by examining whether cortisol levels after awakening or during stress were differentially related to FSS. Chapter 8 studied the autonomic nervous system (ANS), and examined whether activity of the ANS, before, during or after a stressful situation is differently related to specific FSS. This chapter also investigated whether psychological arousal before, during and after a stressful situation was differentially related to specific FSS. Finally, in Chapter 9 all findings have been discussed in the light of our lumping and splitting approach.
Part I

The role of psychological and environmental factors in the etiology of functional somatic symptoms studied by the lumping approach