# Health anxiety and illness behaviour in children of mothers with severe health anxiety

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**THE 3 ORIGINAL PAPERS ARE**

**Paper I**.
Thorgaard MV, Frostholm L, Rask CU. Childhood and family factors in the development of health anxiety – a systematic review. Under review.

**Paper II**.
Thorgaard MV, Frostholm L, Walker L, Stengaard-Pedersen K, Karlsson MM, Jensen JS, Fink P, and Rask CU. Effects of maternal health anxiety on children's health complaints, emotional symptoms, and health related quality of life. European Child & Adoclescent Psychiatry, accepted 2016.

**Paper III**.
Thorgaard MV, Frostholm L, Walker LS, Jensen JS, Morina B, Lindegaard H, Salomonsen L, and Rask CU. Health anxiety by proxy in women with severe health anxiety: a case control study. Under review.

## OUTLINE AND SETTING OF THE THESIS

### Outline

The present dissertation examines health anxiety (HA) and illness behaviours in children of mothers with severe HA. During the initial planning of the PhD study, it became clear that no prior systematic review was published regarding the influence of family and childhood factors associated with the development of HA. The first part of this dissertation therefore deals with a systematic review, whereas the second part is based on original data from a family case-control study.

The dissertation starts with a general introduction to HA and an overview of the current knowledge on HA in children and adolescents. The aims and considerations about study design and methods used are also laid out.
Then three papers are presented: Paper I, which is a systematic review on the influence of family and childhood factors associated with the development of HA followed by paper II and III, which are both based on original data from a family case-control study including 150 families. Paper II describes results on HA symptoms and related constructs in children of mothers with 1) severe HA, 2) rheumatoid arthritis (RA) and 3) healthy mothers and thereby focuses on the potential intergenerational transmission of HA. The writing of Paper III was inspired by our findings in Paper II and examines illness perception, illness behaviour and HA by proxy in mothers with severe HA. HA by proxy is a newly introduced term that describes parental excessive concern and preoccupation with their child's symptoms.
The presentation of the papers is followed by a general discussion of methods and results, perspectives for future research, a summary and a complete reference list.

### Setting

This PhD dissertation origins from the Research Clinic for Functional Disorders and Psychosomatics, Aarhus University Hospital, Denmark. The original data for paper II and III are based on a family case-control study where the case group, i.e. mothers with severe HA, were recruited from three different University Hospitals (Aarhus, Køge and Bispebjerg) in Denmark specialised in somatoform disorders including HA. Control group 1, i.e. mothers with RA, were recruited from 3 University Hospitals (Aarhus, Aalborg and Odense) and one Regional Hospital (Silkeborg) in Denmark specialised in rheumatologic disorders. The planning, conducting, recruitment and assessment for this study and the subsequent evaluation of its data were the primary objectives of the present PhD dissertation.

## INTRODUCTION

The aim of this chapter is to give an introduction to health anxiety (HA) in adults and children. Throughout the dissertation, severe HA will be used synonymously with diagnostic designations such as hypochondriacal disorder used in the ICD-10 [1], hypochondriasis used in the DSM-IV [2] and somatic symptom disorder and illness anxiety disorder used in DSM-5 [3].

### What is health anxiety in adults?

Transient health worries are common in the population and may begin after a newly perceived symptom or following infor-

mation about an illness in the media [4]. If the worries motivate an individual to seek appropriate medical care and thereby reduce his/her risk of morbidity and mortality, it is considered adaptive behaviour [5]. However, if the worries are out of proportion with the actual degree of medical risk, it becomes maladaptive and may be labelled HA.

Severe and persistent HA in adults is estimated to be 3.4% in the general population [6] and 9.5% in primary care consultations [7]. Severe HA is persistent and associated with great personal distress and a high health care use [8,9]. In addition, a recent study found that severe HA is associated with a considerable societal burden in terms of sickness-related benefits [10].

The disorder is characterised by core cognitive, somatic and behavioural features [5], where the cognitive feature includes worries and ruminations about illness [7], which usually occurs due to the (mis)interpresentations of bodily sensations that are interpreted as signs of serious illness [11].

Somatosensory amplification, a tendency to experience normal somatic sensations as unusual intense, noxious or disturbing, is proposed to be involved in the somatic perception of symptoms, and because of the intensity, they may be perceived as pathological [12-14].

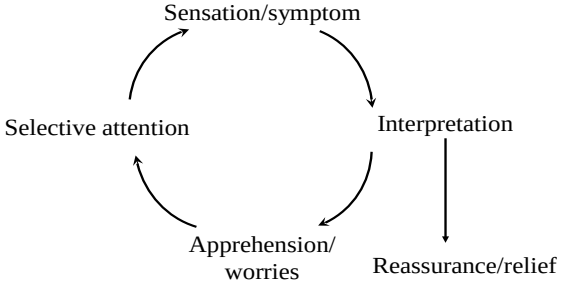
Finally, a characteristic safety-seeking behaviour with a need for reassurance is often seen and may include self-investigations of the body (e.g. lymph nodules or heart rate) and/or frequent doctor visits. This behaviour can lead to a transient reduction in HA symptoms [15], but can in the long run aggravate the symptoms of severe HA [16].

- The prevalence of severe HA in the general population is 3.4 %.
- Severe HA is associated with personal suffering and a high health care use.
- Severe HA is characterised by core cognitive, somatic and behavioural features features.

Catastrophic perceptions of most often transient and benign bodily sensations and symptoms are the defining psychological mechanism involved in the experience and maintenance of severe HA [17]. That is, a person with severe HA often has very maladaptive perceptions of the cause, consequences and the timeline perspective of experienced sensations/symptoms. Believing a benign sensation/symptom is a sign of e.g. cancer increases worries and apprehension, and the individual will as a consequence be aware of any sensations or signs that could be indicative of such a serious disease leading to a selective attention toward the body (Figure 1).

Figure 1 is a simple, frequently used model also in patient psychoeducation that illustrates the vicious circle that is supposed to maintain severe HA.

**Figure 1. The perception model** [18]




**Diagnostic classification of health anxiety**

Thirty years ago, Kellner stated that "the history of hypochondriasis is more about the history of a term rather than that of a disorder or a syndrome" [19], and today the debate is still ongoing regarding the classification of severe HA [20,21]. At present, severe HA is included under the somatoform disorders in the diagnostic classification system ICD 10 and under the group of somatic symptom and related disorders in the new DSM-5.

The hypochondriasis diagnosis in the previous DSM-IV-TR [22] is characterised by preoccupations with fears of having, or the idea that one has, a serious disease based on misinterpretations of bodily signs or symptoms, and that the preoccupation is persistent despite of appropriate medical evaluation and reassurance (Table 1). In the ICD-10 [1], severe HA is known as Hypochondriacal disorder. The criteria used either require a persistent belief that one has a specifically named serious illness or a persistent preoccupation with a presumed deformity. The ICD-10 as well as the DSM-IV criteria have been critised for being too narrow and overlapping with other somatoform disorders, and Fink et al. introduced in 2004 new empirically-based diagnostic criteria for HA [7] (Table 1).

In the new DSM-5 [3], severe HA is classified under two different diagnoses; somatic symptom disorder and illness anxiety disorder. Both disorders share HA as a key symptom, but in somatic symptom disorder, it is the somatic symptoms that are distressing, whereas illness anxiety disorder excludes patients with moderate and severe somatic symptoms (Table 1).

Overall, the lack of expert consensus and empirically validated diagnostic criteria of severe HA [23] has resulted in different diagnostic labels and criteria, which has hampered the research.

- Severe HA is classified as a somatoform disorder in the ICD-10.
- A lack of expert consensus and empirically validated diagnostic criteria of severe HA has resulted in different diagnostic labels.

**Clinical aspects**

Untreated, severe HA has a recovery rate below 50% in adults [24], and the disorder is found difficult to threat [25]. However, newer studies suggest that especially cognitive behavioural therapy (CBT) is an effective treatment in adults [26-28], and CBT is recommended as the gold standard in the treatment of severe HA in the latest Cochrane review [29]. Furthermore, pharmacotherapy with Fluoxetine [30] and Paroxetine [31] is found to be effective.

A potential new focus points in treatment, though still speculative, could be family-oriented such as targeting health-related worries directed towards significant others, i.e. children, in parents with severe HA [32] or child-oriented such as preventive strategies towards children and adolescents with expressions of HA early in life [33,34].

- Untreated severe HA has a recovery rate below 50%.
- Cognitive behavioural therapy is an effective treatment for HA in adults.
- A new focus in severe HA could be family-oriented treatment.

**Table 1. Different diagnostic classification for health anxiety**

**DSM-IV-TR: Hypochondriasis** [22]

**Criterion A**
Preoccupation with fears of having, or the idea that one has, a serious disease, based on a misinterpretation of one or more bodily signs or symptoms.

**Criterion B**
The preoccupation persists despite appropriate medical evaluation and reassurance.

**Criterion C**
The belief is not of delusional intensity and is not restricted to circumscribed concern about appearance (as in Body Dysmorphic Disorder).

**Criterion D**
The preoccupation causes clinically significant distress or impairment.

**Criterion E**
Duration at least 6 months.

**Criterion F**
The symptoms is not better accounted for by Generalized Anxiety Disorder, Obsessive-Compulsive Disorder, Panic Disorder, a Major Depressive Episode, Separation Anxiety, or another Somatoform Disorder.

**DSM-5: Illness Anxiety Disorder** [3]

**Criterion A**
Preoccupation with having or acquiring a serious illness.

**Criterion B**
Somatic symptoms are not present or, if present, are only mild in intensity. If another medical condition is present or there is a high risk for developing a medical condition (e.g. strong family history is present), the preoccupation is clearly excessive or disproportionate.

**Criterion C**
High level of anxiety about health, and the individual is easily alarmed about personal health status.

**Criterion D**
Excessive health-related behavior or exhibiting maladaptive avoidance.

**Criterion E**
Duration at least 6 months.

**Criterion F**
The illness-related preoccupation is not better explained by another mental disorder.

**DSM-5: Somatic symptom disorder** [3]

**Criterion A**
One or more somatic symptoms that are distressing or result in significant disruption of daily life.

**Criterion B**
Excessive thoughts, feelings, or behaviors related to the somatic symptoms or associated health concerns as manifested by at least one of the following:
1. Disproportionate and persistent thoughts about the seriousness of one's symptoms.
2. Persistently high level of anxiety about health or symptoms.
3. Excessive time and energy devoted to these symptoms or health concerns.

**Criterion C**
Duration at least 6 months.

Severity:
Mild, moderate, severe.

**ICD-10: Hypochondriacal disorder** [1]

**Criterion A**
Either of the following must be present:
1) a persistent belief, of at least 6 months' duration, of the presence of a maximum of two serious physical diseases (of which at least one must be specifically named by the patient);
2) a persistent preoccupation with a presumed deformity or disfigurement (body dysmorphic disorder).

**Criterion B**
Preoccupation with the belief and the symptoms causes persistent distress or interference with personal functioning in daily living and leads the patient to seek medical treatment or investigations.

**Criterion C**
Persistent refusal to accept medical reassurance that there is no physical cause for the symptoms or physical abnormality. (Short-term acceptance of such reassurance, i.e. for a few weeks during or immediately after investigations, does not exclude this diagnosis).

**Criterion D**
The symptoms is not due to another mental disorder.

**Severe health anxiety (according to Fink et al.)** [7]

**Criterion A**
Obsessive rumination with intrusive thoughts, ideas, or fears of harbouring an illness that cannot be stopped or can be stopped only with great difficulty.

**Criterion B**
One (or more) of the following five symptoms
1. Presence of a, b or both
   a. Worrying about or preoccupation with fears of harbouring a severe physical disease or the idea that disease will be contracted in the future or preoccupation with other health concerns.
   b. Attention to and intense awareness of bodily functions, physical sensations, physiological reactions, or minor bodily problems that are misinterpreted as serious disease.
2. Suggestibility or autosuggestibility; if the patient hears or Reads about an illness, he or she is inclined to fear that he or she has the same disease.
3. Excessive fascination with medical information.
4. Unrealistic fear of being infected or contaminated by something touched or eaten or by a person met.
5. Fear of taking prescribed medication.

**Criterion C**
If a medical condition is present, the patient's reaction clearly exceeds what would be expected from the medical condition alone.

**Criterion D**
The symptoms are not better explained by another psychiatric disorder.

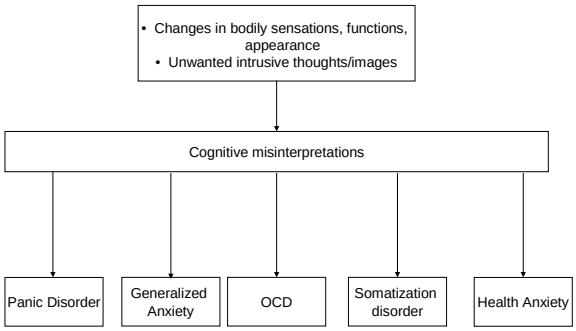
**Criterion E**
Duration at least 2 weeks.

**Criterion F**
Severity: Mild or severe.

**Differential diagnosis and boundaries of health anxiety**
Psychiatric comorbidity is common in severe HA [31], the most prevalent being depression or anxiety disorders [35]. According to a population-based study, 11.8% of those with current HA had a comorbid major depression and 31.8% had an anxiety disorder [6].

As seen in Figure 2, misinterpretation of bodily symtoms / sensations is also seen in other psychiatric disorders, and the following section gives a short overview of important differential diagnoses and diagnostic boundaries of severe HA.

**Figure 2. The relation of HA to other types of anxiety disorders and somatisation disorder (modified after Rachman [36])**




**Panic Disorder**
Individuals with panic disorder misinterpret their symptoms [37], which is also a central feature in severe HA [11]. However, the misinterpretations in panic disorder are related to an acute anxiety response (i.e. symptoms from the autonomic nervous system), whereas symptoms involved in severe HA include autonomic symptoms as well as other physical sensations and signs [38]. Moreover, it is characteristic that individuals with panic disorder fear dying, whereas individuals with HA fear death [39]. Finally, where reassurance is a common behaviour seen in severe HA, escape/avoidance behaviour more often occurs in panic disorder [38].

**Generalised Anxiety Disorder**
Generalised anxiety disorder (GAD) is characterised by excessive worries about several domains of life [40,41] that may include persistent health-related worries. The prevalence of health-related worries in GAD has been fund to vary considerably in different studies ranging from 3% [41] to 76% [40]. In addition, the catastrophic misinterpretations of bodily sensations seen in severe HA, which may lead to autonomic hyperactivity, is generally lacking in individuals with GAD [42].

**Obsessive Compulsive Disorder**
Somatic obsessions seen in Obsessive Compulsive Disorder (OCD) can be indistinguishable from the intrusive fears of illness in severe HA [43], and moreover reassurance performed to reduce stress [44] only has a transient effect in both disorders [45,46]. However, individuals with OCD experience their illness worries as unrealistic trying to resist them and moreover, they do not necessarily have accompanying bodily sensations [45]. In addition, individuals with OCD have obsessions and compulsions beyond health- and illness-related areas [43], and their symptom insight and control over obsessions and/or compulsions are different from that seen in severe HA, where less symptom insight and a lower degree of resistance and control have been described [36,44,45]

**Medically unexplained symptoms/other somatoform disorders**
Medically unexplained symptoms are symptoms that after appropriate medical assessment cannot be explained by conventionally defined medical disease [47]. Individuals with medically unexplained symptoms are encountered in psychiatric settings (e.g. patients diagnosed with somatisation disorder), but mainly in medical departments where they often get diagnoses of functional somatic syndromes (e.g. fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome). The new diagnostic term, currently only used as a research diagnosis, Bodily Distress Syndrome (BDS), is suggested to cover most of the various functional syndromes as well as somatoform disorders except for HA [48]. Patients with severe HA may as patients with other somatoform disorders/functional somatic syndromes or BDS present physical symptoms for which no organ-pathology can be found. However, for individuals with the latter diagnosis, the physical symptoms are the primary problem, whereas in severe HA, the illness worries themselves, suggested to arise from bodily sensations or minor symptoms, are dominant and the most distressing feature [49].
All in all, severe HA shares phenomenological and functional similarities with various anxiety disorders and other somatoform disorders, and hence a shared aetiology between these disorders has been suggested [50].

- Severe HA shares phenomenological and functional similarities with especially anxiety disorders and other somatoform disorders.
- Comorbidity is common, the most prevalent being depression and anxiety disorders.

**The aetiology of health anxiety**
The DSM-5 [3] highlights that early risk factors are suggested to contribute to the development of severe HA also described in two separate theoretical models, namely the cognitive behavioural model [16,51] and the interpersonal model [52,53]. Both models conceptualise how early environmental factors may be associated with severe HA. This section will focus on the aetiology of severe HA as described in the two models.

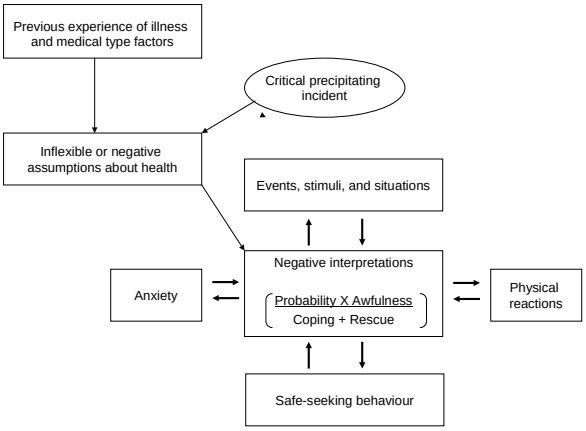
**The cognitive-behavioural model**
The most well-established and empirically supported model [54] is the cognitive-behavioural model. This model describes the origins and maintenance of misinterpretations and health-related assumptions in individuals with HA as being a product of environmental factors [51] that may include illness in self or significant others, illness-focused information in the media and unsatisfactory medical management. This can result in negative illness beliefs, physical reactions and maladaptive illness behaviours and thereby predispose an individual to develop severe HA (Figure 3). Empirical data that have supported the model with regard to past illness-related experiences are based on retrospective studies on adults with severe HA which have investigated 1) illness experiences in self during childhood [55,56] and 2) the experience of illness in a family member or close friend [56-59]. The model furthermore suggests that an important maintenance of HA is safety-seeking behaviour.

The model has been criticised for not taking genetic factors into account [54].

**The interpersonal model**

The interpersonal model like the cognitive-behavioural model conceptualises how environmental factors may be associated with severe HA. The focus is negative parental style and exposure to early aversive experiences that leads to an insecure

**Figure 3. Cognitive model of how assumptions, critical incidents, and misinterpretations interact in health anxiety** [51]



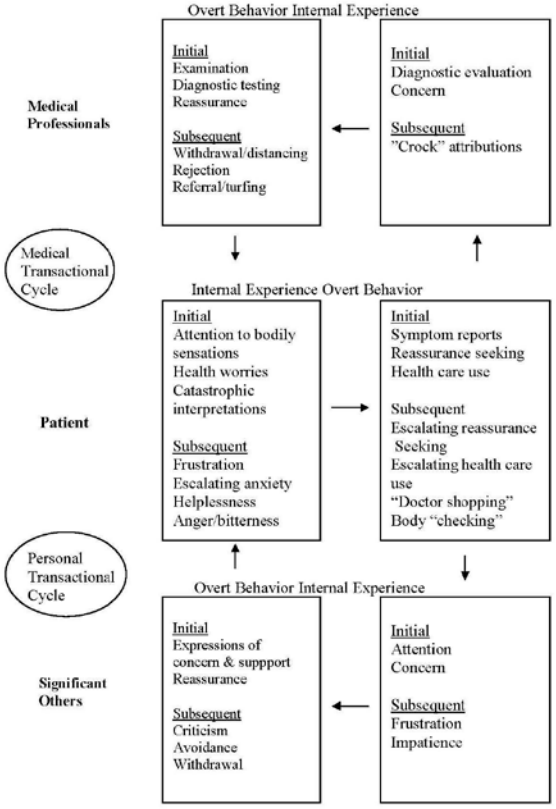

attachment style. Inadequate parental care or adverse childhood experiences (e.g. illness in a parent who is hospitalised for a longer period or physical or sexual abuse) may cause an inadequate relation with caregivers that result in insecure attachment. Furthermore, the experience of illness in childhood can heighten the fear of separation and reinforce reassurance-seeking behaviour. The insecurely attached individual can later in life express strong need for reassurance by family members or a doctor in an attempt to seek emotional and interpersonal support as may be done through physical complaints [52]. This communication of attachment needs often evokes rejecting responses from others if it is performed over a longer period [52].

William et al. have elaborated on the interpersonal model and suggested a model (Figure 4) that focuses on transactional cycles in relation to family members and health care providers [60]. When an individual expresses bodily symptoms or worries to family members, it will initially lead to reassurance and reinforcement, but over time, the repeated complaints will tire the family members, which in an insecurely attached individual can be perceived as rejection and criticism. In the meeting with the health care system, the same pattern is seen in that reassurance is initially obtained when the doctor fails to find a medical cause of the bodily sensations. However, over time the doctor recognises the individual as having medically unexplained symptoms, and the insecurely attached individual will feel criticised instead of being supported [60] (Figure 4).

Most of the empirical evidence supporting the interpersonal model is found in the literature on somatisation in general. However, a handful of studies on HA have found an association with insecure attachment [52,61-65] as well as adverse childhood experiences [66-68].

- Two models - the cognitive behavioural and the interpersonal models - suggest that early childhood and family factors are important in the development of HA.
- The cognitive behavioural model focuses on the origins and development of HA as a product of environmental factors that include illness in self or significant others.
- The interpersonal model focuses on negative parental style or exposure to aversive experiences, including early illness experiences, that leads to an insecure attachment style.

**Figure 4. The medical and personal transactional cycles in health anxiety** [60]



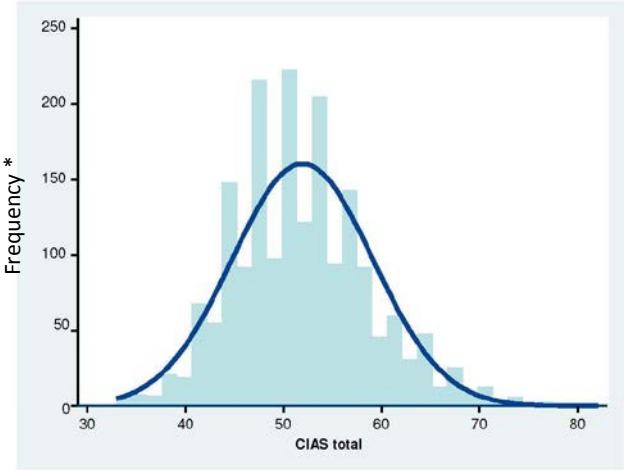

**Can children suffer from health anxiety?**

Severe HA is believed to be fairly uncommon in children and adolescents [69], and even though it may arise at any age, the most common age is proposed to be in early adulthood [3]. However, preliminary results from a recent study, based on a medical record review, on the onset of HA symptoms in 121 patients diagnosed with severe HA and treated at the Research Clinic for Functional Disorders, Denmark [70] support that HA can present early as 17.4% of the patients reported their first HA symptoms to have emerged in childhood (age 2-12 years), 16.5% in adolescence (age 13-18 years), while 66.1% reported onset in adulthood (age > 18 years) [71].

Few studies have investigated the prevalence of severe HA in children and adolescents using diagnostic criteria, but those that have found that none or only very few meet the full diagnostic criteria [72-74]. This may reflect the inadequacy of the criteria used for children and adolescents [75] rather than the disorder being uncommon in this age group. However, based on children's self-reports [34,76-80] and parental proxy reports

[81], there is now growing support for potential clinical expressions of HA symptoms in children and adolescents.
Figure 5 shows the distribution of HA symptoms in a Danish population-based sample of 1886 children in the age group 11-12 years [34] measured by self-reports using the Childhood Illness Attitude Scales (CIAS) questionnaire [80]. As seen, HA symptoms frequently occur in this group of children. The children with the highest CIAS scores also presented significantly more emotional symptoms and a higher health care use than children with lower scores [34]. Thus, these results in combination with other studies suggest that HA in children shares the same cognitive and behavioural features as seen in adults [79,82].

**Figure 5. Distribution of CIAS total scores among 11-12-year-old Danish children. N= 1886** [83].




* Frequency of children

- There is growing support for the presence of HA symptoms in children and adolescents.
- HA in youth shares the same cognitive and behavioural features as seen in adults.
- Only few children meet the diagnostic criteria for severe HA.

**Measuring health anxiety in children and adolescents**
Health anxiety is a neglected area in child and adolescent psychiatry, which can be a reflection of lack of available and appropriate assessment tools for use in children and adolescents. Some frequently used diagnostic interviews assessing psychopathology in children and adolescents do for instance not include a diagnostic section for the assessment of HA (e.g. the Schedule for Affective Disorders and Schizophrenia (K-SADS) [84], the Development and Well-Being Assessment (DAWBA) [85] and the Anxiety Disorders Interview Schedule (ADIS) [86].
In 2003, Wright and Asmundson developed the first self-report measure of HA symptoms in children and adolescents, namely the Childhood Illness Attitude Scales (CIAS) [80]. It was developed to evaluate beliefs, fears and attitudes associated with HA as well as abnormal illness behaviour in children aged 8-15 years. It was adapted from the Illness Attitude Scales (IAS) [87], a frequently used questionnaire assessing HA in adults, and the IAS has been suggested to be the gold standard for dimensional assessment of HA symptoms in adults [88].
The development of CIAS was done by simplifying the language and rating scale as well as adding 7 items to evaluate child help-seeking behaviour. The questionnaire has been found to posses a high test-retest (10-14 days), reliability (r=0.86) and concurrent validity with a similar construct, i.e. the Childhood Anxiety Sensitivity Index [80]. The Danish version of the CIAS has been tested in a Danish normal population and showed good internal consistency (α=0.80) [34].

- There is a lack of available and validated tools to assess HA in children and adolescents.
- The CIAS is currently the only questionnaire to specifically assess HA symptoms in youngsters (aged 8-15 years).

**Health anxiety by proxy**
Recently, the term HA by proxy has been introduced in the literature and refers to parents who have excessive concerns and preoccupations with their child's health and symptoms [32]. It should not be confused with Münchhausen by Proxy, where a parent seeks personal attention by causing or fabricating symptoms in their child to attract medical attention. However, both conditions can lead to a high health care use on behalf of the child, and the child can therefore be at risk for iatrogenic harm as a result of repeated unnecessary and inappropriate medical investigations [89]. The very sparse knowledge about HA by proxy comes from clinical observations, and the condition has to date not been well researched. To the best of my knowledge, intergenerational transmission of illness beliefs from a parent to a child has only been investigated in three studies, which all found a positive association with parental HA symptoms and child HA symptoms/negative illness beliefs [76,77,79]. The mechanisms for the transmission are not well examined, but are suggested to include genes and environmental factors [90]. It is possible - although still speculative - that HA by proxy can be a risk factor in this transmission. Parental worries regarding the child's health and bodily sensations can due to modelling (vicarious learning) learn the child that bodily sensations need to be taken seriously. Furthermore, bodily sensations can be reinforced (instrumental learning) if the child receives something desirable as a consequence of these (such as special attention) or that something undesirable is removed (for instance performing duties) which can result in extra attention towards body functions.

- HA by proxy is a term describing parental excessive concern and preoccupation with their child's health and symptoms
- HA by proxy must not be mistaken for Münchhausen by proxy
- HA by proxy can be a mechanism involved in the possible intergenerational transmission of health worries.

**Summary**
Severe HA in adults is persistent and associated with great personal distress and a high health care use [8,9], and there is now growing evidence for an early onset of HA with the presence of HA symptoms in children and adolescents [34,76-80]. The literature on early childhood and family factors that may be involved in the later development of HA is scarce and has not been reviewed systematically previously. One of the prevailing suggested factors is the intergenerational transmission of HA symptoms from a parent to a child [76,77,79]. However, only three studies have investigated this phenomenon, and more research is needed, including potential mechanisms involved in the suggested transmission.

HA by proxy refers to parents who have excessive concerns and preoccupations with their child's health and symptoms [32], and these worries could be associated with the transmission of HA symptoms. However, HA by proxy has, to the best of my knowledge, not been addressed empirically in the current research literature. This PhD dissertation aims to expand the limited knowledge on early childhood and family factors involved in the development of HA.

**Aims**

To investigate early risk factors associated with the development of HA by exploring the empirical evidence for the potential role of childhood and family factors associated with the development of HA (part I) by:

1. Performing a systematic review identifying studies which have investigated childhood and family variables as potential aetiological factors for HA (Paper 1).

Next, based on a family case-control study (part II) to:

2. Investigate the possible intergenerational transmission of HA by examining occurrence of HA symptoms and related constructs in three groups of children with different exposure to maternal health status (HA, RA and healthy) (Paper 2).
3. Investigate the level of HA by proxy, illness perceptions and illness behaviour in mothers with severe HA compared to mothers with RA and healthy mothers (Paper 3).

A priori, it was hypothesised that children of mothers with severe HA compared to children of both mothers with RA and healthy mothers 1) have more HA symptoms and more negative illness behaviours and 2) a higher level of physical, emotional and anxiety symptoms. Finally, it is hypothesised that mothers with severe HA expressed a higher level of HA by proxy, a more negative illness perception and illness behaviour compared to mothers with RA and healthy mothers.

## CONSIDERATIONS FOR STUDY DESIGN AND METHODS OF THE DISSERTATION

**Data for the present study were obtained from four sources**

1) Systematic search in three research literature databases as part of a systematic review.
2) Self-reported questionnaires filled in by children, mothers and fathers.
3) Data obtained from schools and school nurses.

### Part I

**Rationale for chosen methods**

The review followed a predefined protocol (registered in PROSPERO) and was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, the PRISMA statement [91,92] to minimise bias and to ensure the reproducibility of the findings. The PRISMA statement consists of a 27-item check list and a four-phase flow diagram. As not enough studies with comparable designs were available to perform a meta-analysis, a narrative synthesis of the data finally included in the review was preformed.

### Part II

**Rationale for chosen study design**

We used a family case-control design to explore degree of HA and related concepts in children and adolescents. A case-control design has several advantages such as being good for examining rare outcomes, relatively quick to conduct, relatively inexpensive, it requires comparatively few subjects and multiple exposures or risk factors can be examined [93].

In the present PhD study, a family case-control design gave the opportunity to include children based on their mothers' health status (HA, RA and healthy mothers). The fact that mothers were recruited from hospital departments ensured that they had a diagnosis of either severe HA or RA and that the diagnoses were given based on a relevant medical examination. Families with a mother having severe HA were defined as the case group since the children a priori were regarded as being at higher risk of developing HA symptoms themselves due to potential genetic and environmental risk factors [90]. Mothers with RA were chosen to represent a control group with a chronic disorder characterised by functional impairment and chronicity similar to severe HA. Because the children were exposed to a maternal physical disorder, they might have a moderate risk of developing HA as mentioned previously. Healthy mothers were chosen as a second control group as they did not expose their child to either a physical or mental disorder.

**Rationale for included participants**

In this study, the inclusion was based on the mothers' health status, not the fathers', since the vast majority of referred patients to the Research Clinic for Functional Disorders, Denmark with HA were women when the study was planned and since RA is a disorder predominantly affecting women. Further, we wanted a homogeneous group of parents to avoid gender bias in the proxy report of the child's symptoms and well-being [94,95], and finally, as some studies have suggested that there is a stronger familiality between maternal anxiety than paternal anxiety [96,97], it seemed sensible.

**Rationale for chosen measures**

Very few children and adolescents fulfil the present diagnostic criteria for HA in the ICD and DSM, and therefore a dimensional approach to measure HA symptoms in the children was used. The CIAS, the only validated self-reported measurement developed for children, was chosen as a main measure to assess HA symptoms and already existed in a Danish version used in the Copenhagen Child Cohort [34]. This in addition gave the opportunity to compare the results from the two studies.

Because HA shares similarities with anxiety disorders and other somatoform disorders, standardised questionnaires measuring symptoms of these (separation anxiety, social anxiety, OCD, panic disorder, GAD, and physical symptoms) were included. Tools measuring life quality and emotional symptoms were included to investigate if children raised by a mother with severe HA were more broadly affected .

**Additional projects**

As part of the data collection, mobile phone-based data were collected. These data were part of a one-week experience sampling, where the children received text messages on a mobile phone 4 times a day regarding their physical and emotional symptoms. This design gave the opportunity to examine the children's real-time physical and emotional symptoms. However, this sub-study is not part of the PhD dissertation and will not be discussed further.

The development of a vignette - as an alternative way to assess the children's illness perceptions - was also carried out during the current PhD study¨. However, the data analyses based on this measure are planned for a future paper and therefore not further described in this dissertation.

**GENERAL DISCUSSION OF METHODS**

This chapter aims to discuss general methodological issues related to the systematic review and the family case-control study. The discussion of the family case-control study has a special focus on selection and information bias in relation to the design and data sources of the study. In the individual papers, some of the strengths and limitations of the studies have already been stated, and therefore not all of these will be presented in this section.

**Part I**

**A systematic review (Paper I)**

*Identification of studies*

The search terms were constructed to include studies with an exclusive focus on HA rather than somatoform disorders in general, and although we included several search terms for HA (i.e. hypochondriasis, hypochondria, health anxiety, illness anxiety disorder, illness phobia, disease phobia and somatic symptom disorder), some studies may have been left out by this procedure. To identify potential missed studies, hand search (based on titles only) of reference lists were made and provided six additional papers. Another limitation of the search strategy was that only published papers written in English were included. Detailed inclusion and exclusion criteria were made, and the pairwise inter-rater agreement, the kappa (k) [98] was estimated as a measure for agreement between the reviewers. Any disagreements on inclusion were subsequently discussed by all three authors in order to avoid biased selection of papers and that relevant papers were excluded.

*Study quality*

Currently, no agreed gold standard appraisal tool to systematically measure the methodological quality in observational studies exists**.** In a systematic review on tools to assess quality and susceptibility to bias in observational studies, the Newcastle–Ottawa Scale (NOS) [99] applied for case-control studies was proposed to be suitable for future use [100]. We therefore chose to use this simple check list to systematically evaluate the methodological quality of the studies included in the review. The original form was applied for case-control studies, and a later modified version for cohort studies [101] for the evaluation of cross-sectional studies. The strengths of the NOS scale are 1) it is specifically developed to be used for systematic reviews and meta-analyses to assess the quality of non-randomised studies, 2) it is easily applicable and 3) it assesses control of confounding. In addition, the modified version for cohort studies also included items concerning used statistics. However, some of the limitations are that the development of the tool is not described in detail and that the psychometric properties are not properly studied.

*Data synthesis*

A narrative synthesis of the data was performed because only a small number of studies could be included for the final analysis, and the data could not be lumped together in a meta-analysis due to different study designs and measures. Because of the narrative synthesis, it was not possible to calculate the effect sizes that examined the strength (or lack thereof), and further if a meta-analysis could have been performed, this could potentially have provided a more unbiased view at the data. However, in order to avoid a biased view, a Data Extraction Sheet was developed and used to gather information regarding main results in a standardised way. All three authors made an independent data extraction to avoid potential errors, and the extraction was then discussed jointly to form the narrative synthesis. In addition, the level of evidence was evaluated according to the criteria described by [102]

**Part II**

**A family case-control design (Paper II+III)**

*Pilot testing*

Prior to the main study, a pilot test was performed to test the recruitment, practical procedures and the face validity of the questionnaire battery to the child and parents. Twelve families participated; five children with a mother with severe HA, four children with a mother with RA and three children with a healthy mother. The pilot test gave the impression that the procedure for recruitment could be optimised in that overall 52% of the invited mothers (N = 13) declined participation. A specific issue related to the HA group was that a main reason for declining was that mothers feared that their child could be armed by participating and being presented for questionnaires concerning illness and death.

To optimise the recruitment procedure and thereby increase the participation rate, the following modifications were therefore made:

- Revision of the participant information towards more pictures and less text, i.e. making it more inviting and readable.
- Individual feedback to families regarding the child's self-reports of HA and physical symptoms after participation was offered.
- The possibility to perform the assessment at home was made available.
- All participating families received a compensation of 75 dollars.
- Five additional departments took part in the recruitment process (2 departments specialised in outpatient treatment of somatoform disorders and 3 in rheumatoid arthritis).
- Not only newly referred mothers with severe HA but also mothers who participated in a treatment programme or had received prior treatment at any of the three specialised departments could be included.

**Study population and the representativeness of the sample**

*Participants with HA*

Initially, the plan was to recruit participants from only one clinic (the Research Clinic for Functional Disorders and Psychosomatic, Aarhus, Denmark). However, due to an unexplained shift in the pattern of referred patients to the clinic towards less women with children in the right age group and more younger males and the fact that a higher proportion than expected did not want to participate in the study, we had to recruit from other clinics as well. This hampered the process of ensuring that all potential consecutive participants from the

other clinics were invited to participate and of ensuring that everyone declining participating was systematically registered as "decline to participate". However, those who took part in the recruitment from the two other hospital departments had received instructions on how to record all patients who declined to participate.
Indeed, the modifications made as a result of the pilot test increased the participation rate significantly to 66.7%. In comparison, a case-control study on parents with somatoform disorders and their offspring had a participating rate of 60% [77]. Thus, the participation rate in the current study seems to be satisfactory for this patient group, but despite of this, the participation rate was moderate and selection bias cannot be ruled out. The main reason for declining participation was still - as found in the pilot study - concerns about whether the children could be harmed by participation, and the mothers often described their child as being particular sensitive. This may have led to exclusion of mothers with the most severe health worries related to their child and perhaps, although speculative, also those children with higher levels of HA thereby leading to an underestimation of potential differences on the examined parameters between the children in the case and two control groups.

A further selection bias could be the recruitment of mothers with severe HA referred to specialised psychiatric clinics as this group may represent mothers who understand their disorder as a psychological problem rather than physical, and therefore also may be more willing to receive psychological treatment. Again, this possible higher level of 'psychological insight' in this particular group compared to mothers with severe HA in general, may have led to an underestimation of our results as it is likely that mothers without such insight would not try to resist their worries and thereby potentially impose these more strongly on their child. Also, the fact that we extended the inclusions criteria by including mothers who already had received treatment for severe HA or currently were in a treatment programme, which may have reduced their symptoms or even cured some of them. This could also have reduced the exposure of the child and thereby a possible transmission of HA symptoms from mother to child.
In sum, selection bias might have occurred leading to a sample of mothers with severe HA, but probably without those most affected by their disorder and who had the highest level of HA by proxy, which all together might have led to an underestimation of the results described in both paper II and III.

*Participants with RA*
Mothers with RA were recruited from three different university hospital departments and one regional hospital, all with a specialised outpatient function related to this disorder. Initially, this group was planned to be recruited from one department (the Department of Rheumatology, Aarhus University Hospital, Denmark), but due to the fact that 1) the majority of the patients were women without children in the age group 8-17 years and 2) more than expected had comorbid diseases (e.g. severe asthma and diabetes mellitus I) that excluded participation, we had to recruit from other departments as well. The participation rate in this group was high (83.1%), but despite a satisfactory participation rate, it can not be ruled out that those with the lowest functional level declined participating, e.g. due to the lack of energy. Thus, strict exclusion criteria were applied where those with a severe comorbid somatic disorder were excluded, which may have led to a selected group with a relatively high functional level.
In summary, it is likely that RA outpatients with a relatively high functional level were overrepresented in this study. Having a mother with a chronic physical disorder who has a high functional level despite of her disease may perhaps serve as a protective factor rather than a risk factor for the development of HA symptoms in the offspring [103]. If this were the case, it may actually work against the a priori hypothesis in this project, where children of mothers with RA were hypothesised to display lower levels of HA symptoms than children of mothers with HA, but with higher levels than children of healthy mothers due to the exposure of early experience of serious illness in a significant other, which, as mentioned previously, has primarily been regarded as a risk factor for HA.

*Healthy participants*
This group was planned to be recruited through general practitioners who systematically were supposed to ask healthy mothers if they would like to participate in the study. However, this was not possible within the given time frame due to lack of time among the general practitioners. Therefore, this group was self-referred by announcements on facebook, in the waiting rooms in eight general practices and on the intranets on six public schools. This may have lead to selection bias if it attracted mothers with a particular interest in this study, e.g. mothers of children displaying symptoms of HA or other anxiety problems.
Contrary to the two other groups of mothers, the healthy mothers were recruited in the Aarhus area and not from the entire country which could have caused sociodemographic bias. However, the three groups did not differ with regard to level of maternal education.

All in all, selection bias might have been present in all groups of mothers, which potentially could have blurred the results, especially in relation to our main aims in the PhD dissertation; 1) differences in HA symptoms and related constructs between the three groups of children and 2) the report of HA by proxy. Thus, children of mothers with HA and RA were probably less exposed to maternal illness worries and illness than the "true sample of patients from the different hospital departments". In addition, the children themselves may also have been selected. Children of mothers with severe HA, who were described as sensitive by the mother were not included, and the group of included children of healthy mothers might have attracted those displaying HA symptoms.

**Procedure of collection of questionnaire data**
Children and mothers separately filled in an electronic questionnaire battery on an iPad or tablet to avoid mutual influence on their responses.
Participants with a long travelling distance were offered that the assessment took place in their own home. Otherwise, the assessment took place at four different hospitals across the country. A research assistant was present during the entire assessment helping with the technical procedures and to help with any questions regarding the questionnaire battery.
The research assistant was not blinded with regard to the child's risk status which may have induced information bias due to specific expectations toward the child if it needed help understanding a question (if the assistant systematically facili-

tated the answers in a certain direction depending on which group the child belonged to). However, a detailed manual was made to ensure that all questions were reformulated in the same manner, and the research assistants (two medical students at their last year of medical school) were thoroughly instructed by the PhD student in how to use the manual.

**Validity of used measures**

*Procedure for translation of the questionnaires into Danish*

Four questionnaires were translated into Danish for use in the PhD study;

1) the Adult Responses to Children's Symptoms (ARCS, protect scale, parent and child version)
2) the Illness worry scale (IWS-P)
3) the Children's Illness Perception Questionnaire (CIPQ).

The translation into Danish and back translation followed international guidelines for translation and cultural adaptation of questionnaires after permission from the original authors [104]. The guidelines were used to reach equivalence between the original source and the translated Danish version of the questionnaires.

However, two exceptions from the guidelines were made; 1) the back translation was only performed by one native speaker and 2) the Danish version was not pre-tested on 30-40 persons as recommended in the guidelines, but the overall face validity was tested in the pilot study.

*Procedure for modification of the questionnaires*

Three questionnaires were modified for the use in the present study (for the description of the modification of CIPQ).

*The ARCS protect scale*

The original version was developed to measure parental protective behaviour towards the child when it had stomach ache or abdominal pain [105]. For the current study, physically healthy children were included, and therefore it would be too limiting only to ask for parental protective behaviour towards the child when it had stomach ache (i.e. if the child rarely had it). Therefore, the initial wording of the questionnaire was slightly modified to evaluate parental protective behaviour towards the child when "it feels unwell" (e.g. having a cold, stomach ache). However, this modification was relatively unspecific and some may have responded the questionnaire according to when they were sick (e.g. with fever), and others when they felt unwell but not sick. This could have influenced the answers so that those who completed the questionnaire according to when they were sick rather than "just" unwell, would probably have rated a more protective parenting style.

*Illness Perception Questionnaire (B-IPQ)*

The original version measures illness perception and consists of nine items (consequences, timeline, personal control, treatment control, illness identity, comprehensibility, causal attributions, concern, and emotional representations) [106]. The questionnaire was modified to capture participants that were either healthy or had a physical or mental disorder. The word "illness" was replaced with "symptoms", and the item "how much do you experience symptoms from your illness" was left out. Only those with symptoms during the past 4 weeks were asked to fill in the questionnaire. In this study, we included participants with emotional symptoms and participants with physical symptoms with very different impairment which could have reduced the validity. However, the questionnaire's internal consistency in the current study was good ($\alpha$= 0.81).

*Face validity*

The face validity of the questionnaire battery (checking if items in the questionnaires covered the intended topic clearly and unambiguously) [107] was pre-tested on 10 children and then tested in a pilot test involving 12 children and their mothers. The youngest children (age 8-9) in general had problems reading the whole questionnaire battery themselves, and it became clear that some of the questions were difficult to understand or answer for this age group (e.g. "have you had enough money for your expenses", "have you got along well with your teachers", "how many doctors have you seen in the past year"). This may have influenced the validity of the collected data.

*Test of internal reliability*

The Chronbach's alpha coefficient (the extent to which the items are inter-related) was used to estimate the internal consistency of the modified and translated questionnaires. A coefficient above 0.7 was regarded as acceptable for psychometric scales [107]. Further, an exploratory factor analysis was performed on the IWS-p since it was not previously validated. The IWS-p captures parental worries regarding the child's health and consists of 10 items. The exploratory factor analysis showed that the items best fit a two-factor model with items 1-7 as one subscale named "illness worries" and items 8-10 as a second subscale named "disability". Crohnbach's alpha was satisfactory on both subscales; 0.87 (illness worry subscale) and 0.76 (disability subscale).

**Statistical considerations**

Prior to inclusion, a statistical power calculation based on the average CIAS total score (total score=59, SD=9.41) reported in a normal Canadian population of school children [80] was performed. At that time, these were the only reported data on the questionnaire, and the results from this questionnaire were the main outcome of the study. The power calculation was based on different scenarios for CIAS total scores in the three groups (children of mothers with HA: 66-85; children of mothers with RA: 62-70; and children of healthy mothers 59 and SDs (8-11). This power calculation showed that data from 50 subjects in each of the three groups should offer sufficient stability for statistical analysis to demonstrate a difference between the groups (power=0.9).

Descriptive statistics were used to characterise the participants, the family functioning and the mothers' satisfaction with the latest visit at the general practitioner with their child. Sum scores of scales and questionnaires were calculated in agreement with existing manuals (with the exception of IWS-p as no manual exists), and all scores were summarised using a percentage, the mean and standard deviation (SD) or the median and inter quartile range (IQR). For the non-normally distributed variables as well as those that did not have equal standard deviation within the three groups, we used the Kruskal-Wallis and Wilcoxon's ranksum tests to compare the distribution of the groups.

For all other continuous variables, the between-group comparison was done using a one-way ANOVA, whereas in cases

where the dependent variable was dichotomous, a $\chi^2$-test was used.
When relevant, Bonferroni was used to adjust for multiple testing [108].
In general, there were very few missing data, and in order to take these into account, participants who had answered < 50% of the items in a questionnaire were not included in the analysis with regard to the specific questionnaire (complete case analysis).
The responses in two of the questionnaires were dichotomised (EUROPEP/ PSCQ-7 and FAD) in an attempt to make the results more communicable even though dichotomisation entails loss of information.
The items regarding satisfaction with general practitioners, based on items from the EUROPEP, were categorised according to principles used in a previous study [109] with a dichotomisation of the two most positive answers (very good/excellent) vs. the three last answer options (poor/fair/good). The same procedure for dichotomisation was made for the items from the PSCQ-7 questionnaire [110] as it seemed sensible to dichotomise these into "a lot/very much" vs. "not at all/little/some" because this would group those who were most satisfied with their last visit at the general practitioner.
The dichotomisation of the items regarding the family function was done by combining strongly agree/agree vs. disagree/strongly disagree making it possible to examine the descriptive differences in perceived family function in the three groups.
All analyses were performed using Stata 13.

**Generalisability**
As discussed, there may have been methodological issues which have led to both selection and information bias in our case-control study and thereby reduced the generalisability of the results. Because we included mothers with severe HA recruited from specialised hospital settings, they might represents those with the most severe HA, which may hamper the generalisation of the results to patients being less affected. However, due to a moderate participation rate, those with the most severe HA or health worries towards their child might also have been more prone to decline participation. This suspicion is supported when comparing the WI-7 score for participating mothers with severe HA in the present study to participants in another study conducted at the Research Clinic for Functional Disorders, Aarhus, Denmark. This other study recruited 126 adult patients with severe HA for a treatment programme, and they had a higher score on the WI-7 (0-100 score), mean = 56.9 [70] indicating more HA symptoms compared to the participants in the present study WI-7 (0-100 score), mean = 49.3.
Further, we excluded mothers with RA who had a comorbid severe somatic disorder and thereby those included in the study may also have represented those with a relatively high functional level thereby reducing the generalisability to the general population of outpatients with RA. A new study on consecutive outpatients with RA may confirm this assumption in that it found lower mental (MCS, mean = 41.7) and physical (PCS, mean = 31.7) health-related quality of life measured by the SF-36 [111] compared to the present study (MCS, mean = 54.8) and (PCS, mean = 42.3) - a higher score on the SF-36 indicating a higher health-related quality of life.
Finally, the self-referral of the healthy group of mothers could have attracted individuals with a special interest in the study, although the baseline characteristics (HA symptoms, physical and mental well-being) validated their healthy health status. However, the CIAS total score in the group of children of healthy mothers was 54.8 in the current study compared to 51.9 found in a Danish cohort of children aged 11-12 years [34]. This higher score and hence more HA symptoms in children of self-referred mothers could support the suspicion regarding selection bias in this group with the inclusion of children with a higher degree of health worries than children of healthy mothers in general.
Furthermore, we only included mothers and not fathers with either HA or RA, which limits the generalisability since it may affect children differently whether they are exposed to paternal or maternal illness. Thus, this study can only conclude on the influence of maternal health exposures and can not further investigate the impact on the child if both parents has HA (dose-responses relationship) [112]. Information bias may also have affected the validity and generalisability of the results as the IWS-P was not validated and other measures were modified (ARCS, B-IPQ). Therefore, the results from the IWS-p have to be interpreted with caution, and the modified questionnaires are not comparable with other studies that have used the original versions of the questionnaires. The youngest children had difficulties reading the questionnaire battery themselves, and some of the questions were difficult for them to understand and answer, which may have lowered the validity of their answers.
Finally, recall bias could be an important error source, e.g. if mothers with HA due to their worries better recall the number of visit to the general practitioner with their child as well as the child's physical and emotional symptoms than the two other groups [113]. This potential artefact could alone explain a higher report of contacts to the general practitioner in the group of mothers with severe HA and their higher reporting of symptoms in their children.

**PRESENTATION OF RESULTS**
**Main results in relation to Paper I**
The review included 25 papers based on 23 studies.
Sixteen papers used a cross-sectional design and nine a case-control design.
Only four papers included children and adolescents.
The included papers were categorised under three different key headings (some of the papers were categorised under more than one of the headings):
1. Childhood learning (n = 9), divided into the subgroups
   a. transmission of HA and illness beliefs .
   b. vicarious and instrumental learning.
2. Negative life events (n = 15), divided into the subgroups
   a. traumatic childhood experiences.
   b. childhood experiences with illness and/or death.
3. Attachment (n = 10), divided into the subgroups
   a. attachment styles.
   b. parental care and protection.

The study quality in the included studies varied. The cross-sectional studies in general had low scores regarding 1) the sample size which was not justified and satisfactory and/or 2) the description of non-respondents (comparability between respondents and non-respondents). The case-control studies especially had methodological problems with regard to 1) case representativeness (not consecutive or obvious representative series of cases), 2) selection of controls (the control series used

was not derived from the same population as the cases), 3) validity of the exposure assessment (e.g. interview not blind to case/control state) and finally 4) the description of the non-respond rate (e.g. not same rate for the case and control groups).

The narrative synthesis of the results showed a trend towards an association between the presentation of HA and intergenerational transmission of negative illness beliefs, illness experiences during childhood and an anxious attachment style. A developmental model based on the synthesis of the findings from the review was proposed as inspiration for future research.

**Main results in relation to Paper II & III**

**Sample characteristics**

- The study sample consisted of 150 families: an HA group of 50 families with a mother diagnosed with severe HA, an RA control group of 49 families with a mother diagnosed with RA and a healthy control group of 51 families with a healthy mother.
- Mothers with RA were significantly older than the two other groups of mothers; HA group 41.1 years (SD 4.2), the RA group 45.1 years (SD 5.5) and the healthy group 42.3 years (SD 5.2), (F(2,147) = 8.30, p<0.001, ANOVA) and had the lowest physical health-related quality of life; HA group; mean: 50.3 (SD 6.2), RA group; mean: 42.3 (SD 9.8), healthy group; mean 52.5 (SD 5.9); p<0.001, (Kruskall Wallis).
- Mothers with HA had significantly more HA symptoms as measured by WI-7 (HA group: median = 46.4 [IQR 28.6-64.3]; RA group: median = 7.14 [IQR 0.0-14.3] and the healthy group: median = 0.0 [IQR 0.0-7.1], p< 0.001, Kruskall Wallis).
- The children did not differ significantly with regard to age: the HA group 11.8 years (SD 2.40), the RA group 12.3 years (SD 2.50) and the healthy group 11.6 years (SD 2.32), (F(2,147) = 1.17, p = 0.314, ANOVA), nor with regard to gender: The ratio for girls/boys in the three groups: HA group: 58% (29/50), RA group: 45% (22/49), healthy group: 55% (28/51), Chi2(2) = 1.859, p = 0.395.
- For fathers, no statistically significant differences were found between the three groups with respect to degree of HA symptoms or physical and mental health-related quality of life (all p-values > 0.05).

**Paper II**

**Child self-reports**

Children of mothers with HA reported statistically significantly, although weakly, more HA symptoms compared to children of mothers with RA (p = 0.041, ANOVA), but not compared to children of healthy mothers (p = 0.167, ANOVA) (Table 1).
A cut-off value of ≥ 62 on the CIAS total score was made to define a probable case of HA, and a significantly higher proportion, i.e. 24.0 %, of children of mothers with severe HA, reported HA symptoms at a level defined as "being a probable case of HA" compared to only 4.0 % (Chi2(1): 8.09, p = 0.004 of the children who had a mother with RA, whereas there was only a trend towards a difference in comparison with children with healthy mothers (21.6%) (Chi2(1): 0.08, p = 0.771).
The children of mothers with severe HA did not differ on the reports on physical symptoms during the past 2 weeks compared to children of mothers with RA: HA vs. RA, p < 0.495 and healthy mothers: HA vs. healthy p < 0.562), (ANOVA).

No statistically significant differences in the total sum score on self-reported anxiety symptoms were seen between children of mothers with severe HA and the two control groups; (HA: median 20 [IQR 14-32], RA: median 19 [IQR 9-27], healthy: median 19 [IQR 11-27]; HA vs. RA, p = 0.223, HA vs. healthy p = 0.141, Kruskall Wallis).

The three groups of children did not differ significantly in their self-reported health-related quality of life: psychological well-being: (HA: mean 51.4 (SD 7.5), RA: mean 52.8 (SD 7.8), healthy: mean 51.9 (SD 7.5); HA vs. RA, p < 0.353 and HA vs. healthy p < 0.727, ANOVA), and physical well being: (HA: mean 50.0 (SD 7.3), RA: mean 49.8 (SD 10.1), healthy: mean 52.7 (SD 8.3); HA vs. RA, p < 0.906 and HA vs. healthy p < 0.129, ANOVA).

**Maternal proxy reports of physical and anxiety symptoms**

Mothers with HA reported statistically significantly more physical symptoms in their child compared with the two other groups of mothers; HA vs. RA, p < 0.006 and HA vs. healthy p < 0.004, (ANOVA) (Table 1). They also reported more total anxiety symptoms in their child compared with the two other groups; HA: median 11 [IQR 6-23], RA: median 8 [IQR 5-14], healthy: median 8 [IQR 4-14]; HA vs. RA, p < 0.029, HA vs. healthy p< 0.011, (Kruskall Wallis). When corrected for multiple testing, there was no longer a statistically significant difference with regard to anxiety symptoms.

**Table 1. Child health anxiety, physical symptoms and illness-related behaviour**

| | HA group (N = 50) | RA group (N = 49) | Healthy group (N = 51) | HA vs. RA p-value | HA vs. healthy p-value |
|---|---|---|---|---|---|
| *Child report* | | | | | |
| Health anxiety (CIAS), mean (SD) | 57.1 (9.2) | 53.6 (6.9) | 54.8 (8.7) | **0.041**[1] | 0.167[1] |
| Physical symptoms (CSI-24), mean (SD) | 9.7 (8.0) | 10.8 (8.3) | 8.7 (8.5) | 0.495[1] | 0.562[1] |
| *Maternal proxy report* | | | | | |
| Physical symptoms (CSI-24), mean (SD) | 8.0 (10.3) | 4.3 (3.7) | 4.1 (3.4) | **<0.006**[1] | **<0.004**[1] |
| Contacts to the GP past year, ≥ 3 times, N (%) | 13 (26.0) | 3 (6.1) | 6 (11.8) | **0.007**[2] | 0.067[2] |
| Painkiller past 2 weeks (yes), N (%) | 7 (14.0) | 6 (12.2) | 9 (17.6) | 0.796[2] | 0.616[2] |
| School absence past year due to illness, N (%) | | | | 0.296[2] | 0.390[2] |
| *No* | 9/50 (18.0) | 14/48 (29.2) | 12/51 (23.5) | | |
| *Yes (< 1 week)* | 29/50 (58.0) | 27/48 (56.3) | 32/51 (62.7) | | |
| *Yes (≥ 1 week)* | 12/50 (24.0) | 7/48 (14.6) | 7/51 (13.7) | | |

HA = health anxiety; RA = rheumatoid arthritis; CIAS = the Childhood Illness Attitude Scales; SD = standard deviation; CSI-24 = the Children's Somatization Inventory; GP = general practitioner; 1ANOVA; 2Chi2.

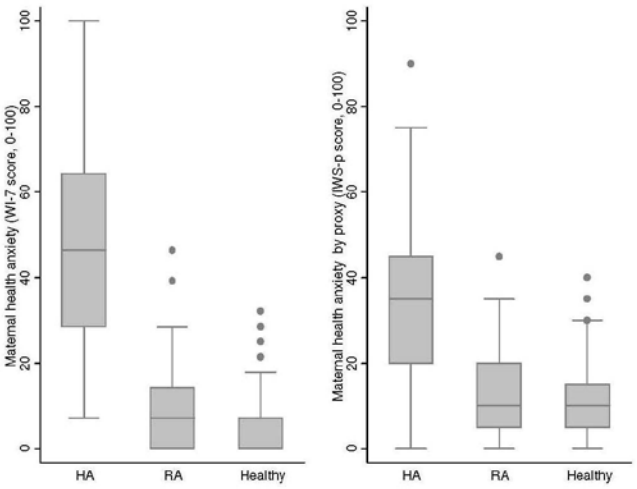
Significantly more mothers with HA reported 3 or more visits to their general practitioners with their child during the past year compared to mothers with RA, (HA vs. RA p = 0.007, Chi2), but not compared to healthy mothers (HA vs. healthy, p = 0.067, (Chi2) (Table 1).

**Paper III**

**Maternal health anxiety by proxy**

Mothers with severe HA reported significantly more worries regarding their child's health on the IWS-p (median 35 [IQR 20-45]) than mothers with RA (median 10 [IQR 5-20]); p < 0.001 and healthy mothers (median 10 [IQR 5-15]; p < 0.001 (Figure 1).

**Figure 1. Maternal score of health anxiety and health anxiety by proxy related to her child.**




HA: health anxiety: RA: rheumatoid arthritis. Median and inter-quartile range.

**Maternal illness perception**

Overall, mothers diagnosed with severe HA reported more negative illness perceptions measured by the sum score on the modified B-IPQ (Table 2).

**Table 2. Maternal illness perceptions of most troublesome symptoms within the last 4 weeks.**

| *B-IPQ item* | HA group Respondents 48/50* Median (IQR) | RA group Respondents 48/49* Median (IQR) | Healthy group (N= 51) Respondents 39/51* Median (IQR) | HA vs. RA p-value** | HA vs. healthy p-value** |
|---|---|---|---|---|---|
| Consequences | 6 (3-8) | 3 (2-5) | 2 (1-3) | **<.001** | **<.001** |
| Timeline | 7 (4-8) | 4 (2-9) | 3 (1-4) | .079 | **<.001** |
| Personal control | 8 (5-10) | 5 (3-7) | 3 (1-5) | **<.001** | **<.001** |
| Treatment control | 3 (1-6) | 2 (1-6) | 3 (1-9) | .565 | .478 |
| Concern | 7 (5-10) | 3 (2-5) | 2 (1-3) | **<.001** | **<.001** |
| Understanding | 5 (4-7) | 3 (1-4) | 1 (1-3) | **<.001** | **<.001** |
| Emotional response | 8 (7-10) | 3 (2-5) | 2 (1-3) | **<.001** | **<.001** |
| *Total sum score* | *39 (34-47)* | *23 (18-32)* | *16 (11-24)* | ***<.001*** | ***<.001*** |

HA = health anxiety; RA = rheumatoid arthritis; IQR = Inter-quartile range; B-IPQ = Brief Illness Perception Questionnaire. Single item score: range 0-10, total sum score: range 7-70. High scores indicate more negative illness perceptions.

* The questions were only to be answered if the mother had experienced symptoms during the past 4 weeks.

** Kruskal-Wallis test.

**Maternal protective behaviour**

Measured with the modified version of the ARCS protect scale, mothers with severe HA reported more protective parenting when their child felt unwell (median 18 [IQR 11-32]) than mothers with RA (median 14 [IQR 8-22]), p=0.031, but not compared to the healthy mothers (median 20 [IQR 11-25]), p = 0.596.

**Maternal satisfaction with the general practitioner**

The between-group difference on the overall maternal evaluation of her last consultation at the general practitioner with her child was near significant with a lower proportion of mothers with HA being satisfied than the mothers in the control groups (HA 69.4%, RA 90.1%, healthy 89.2%; HA vs. RA p=0.053, HA vs. healthy p=0.052). This pattern was also seen in general in the descriptive presentation of maternal evaluation on various qualitative aspects of the consultation and on service availability.

**GENERAL DISCUSSION OF RESULTS**

The first section of this chapter discusses findings from the systematic review (Paper I) and will focus on the results regarding two of the key headings examined, namely social learning and illness experiences during childhood. These key headings are the most relevant in relation to the subsequent family case-control study, whereas I refer to the overall discussion in paper I regarding the last heading 'attachment'. In the second part of this chapter, I will discuss and evaluate the results from the family case-control study (Paper II and III).

**Paper I**

**Main conclusions**

The findings from the review showed a small trend toward a positive association with the development of HA and intergenerational transmission of HA symptoms/negative illness beliefs, childhood experience with illness and an anxious attachment style. However, due to high heterogeneity and methodological problems in the studies along with a small number of existing studies for comparison, the evidence is weak and needs to be interpreted with caution.

**Childhood learning**

Social learning (i.e. vicarious and instrumental learning) and intergenerational transmission were categorised under one key heading called *childhood learning*. Due to the complex interplay between genetics and different environmental factors including social learning that are believed to be involved in the transmission of HA/negative illness behaviour [90] it can be discussed whether this categorization is adequate. However, since our focus in the review was early psychosocial aspects involved in the development of HA - and social learning could be involved in the intergenerational transmission of HA - these two factors were combined under one key heading.

**A critical discussion of the methods used in the included studies regarding social learning**

The intergenerational transmission of HA symptoms/negative illness beliefs from a parent to a child was investigated in three studies included in the review [76,77,79]. They all used a dimensional approach (i.e. questionnaires) to collect data on HA symptoms/negative illness beliefs at the same point in time for both child and parent thus avoiding recall bias.

Two of the studies [76,79] used a cross-sectional design, and therefore the data warrant caution with regard to interpretation on causality. Finally, one study used a case-control design [77] with a small sample size (n=33) and included parents with any somatoform disorder, not specifically HA.

In sum, very little research has been done regarding the intergenerational transmission of HA symptoms/negative illness beliefs from a parent to a child, and none of the previous studies have been designed to investigate more specific mechanisms involved in a potential transmission.

**Vicarious and instrumental learning**

Six papers investigated vicarious and instrumental learning [58,66,67,114-116]. All studies used a retrospective design,

and the four studies that failed to find any association [58,66,114,115] used study-specific questions with one or two items to explore social learning. The validity of these results can therefore be questioned. The two studies that found an association [67,116] investigated undergraduate students, and therefore the representativeness of the sample and the generalisability of the findings may be reduced. Finally, none of the studies used a prospective design and therefore could not take the child developmental stage into account, and they were all prone to recall bias due to the retrospective nature of the collected information.
Thus, studies investigating social learning as a potential risk factor for the development of HA are few and have methodological problems and therefore it is difficult to draw any clear conclusions based on the findings.

**Discussion of the findings in relation to related disorders**
Empirical research on the intergenerational transmission of anxiety disorders supports the trend found in our review [117], but we could not confirm a clear association with vicarious and instrumental learning and the development of HA, which otherwise is suggested to contribute to the development of anxiety disorders [118]. Beyond vicarious and instrumental learning genetic factors have also been suggested to be involved in the development of anxiety [119-121], and research has indicated that genetic factors may play a role across anxiety disorders in general rather than being disorder-specific [122]. The tendency to shared heredity is also found in a broader group of disorders classified under affective spectrum disorders such as major depression, obsessive compulsive disorders, panic disorders, and functional somatic syndromes e.g. irritable bowel syndrome, and fibromyalgia [123]. If a shared genetic vulnerability for the development of anxiety disorders exists, the shaping into a specific anxiety disorder could be due to a learned childhood behaviour (e.g. parental expression of shame and embarrassment could lead to social anxiety) as suggested in a comprehensive review on childhood learning and anxiety [118]. In our review, only one of the included studies used a specific questionnaire to measure vicarious and instrumental learning around bodily symptoms. The findings from this study showed a significant, positive association between higher levels of HA symptoms in adulthood and vicarious and instrumental learning in childhood [116]. Indeed, the lack of evidence found in our review regarding an association with vicarious and instrumental learning and the development of HA could be due to methodological problems found in almost all included studies in this area.
However, it is important to remember that it is a challenged area of research, where several factors interact [120]. Developmental aspects such as the child's age when being exposed to social learning should be taken into account as well as genetic innovation, where genes become active or decline in influence depending on the child's age [124,125]. Thus, the duration, timing and intensity of parental exposure have to be taken into account in the complex interplay of different factors.

**Childhood experience with illness**
*Discussion of the methodological problems in the included studies*
Childhood experiences with illness in self or significant others were the most researched area in the review. In total, 11 papers investigated a potential association between childhood experience with illness in self or significant others and the development of HA [55-59,65,66,77,114,115,126], and the majority of these studies did provide some support for an association.
All studies which found an association were retrospective, thus recall bias can not be ruled out as an artifact of the findings. Individuals with HA may remember illness related events in childhood better than those without HA in that they may be biased towards a more illness-focused memory [113]. Further, the majority of the studies used single items or non-tested study-specific questions, and hence the validity of the information obtained could be questioned. The fact that some of the studies only found an association with HA and health-related interference in the children's daily life (e.g. school absence) but not with higher reports of illness as such, could reflect an overprotective and symptom-focused parental style as important rather that the exposure for illness [58].
Finally, most of the studies did not have control groups consisting of individuals with other mental disorders, e.g. anxiety or depression, and therefore based on the current research it can no be concluded whether childhood experience with illness is a specific risk factor involved in the development of HA or if it more broadly contributes to the development of mental disorders [126].

**Discussion of the findings in relation to their specificity to health anxiety**
The cognitive behavioural [51] and the interpersonal models [52,53] as well as the DSM-5 [3] all suggest that previous illness experiences can contribute to the origin of HA, and the findings from this review support this suggestion to some extent. However, research also suggests that childhood experiences with illness are associated with other mental disorders, and concerns regarding health are also present in anxiety disorders and obsessive compulsive disorder [127]. A cohort study found that frequent hospitalisations due to physical conditions during childhood increased the risk of different mental disorders later in life [128]. Furthermore, exposure to illness in significant others has also been found to have an association with a broad spectrum of internalising and externalising problems [129].

In sum, the probable complexity of and interaction between various different factors involved in the development of HA have not been explored in the current research. Based on the mixed findings from the systematic review, we developed a model with an integrative developmental approach for the understanding of HA with the intention to provide a starting point and a source of inspiration for future research.

**Strengths and limitations of the review**
The systematic review on childhood and family factors' influence on the development of HA is, to the best of my knowledge, the first of its kind and thereby an important supplement to the existing literature as limited research in this area has been conducted. The focus on HA and not the broader category of somatoform disorders is a distinction not often seen and could provide more specific knowledge on HA. The review was conducted in accordance with the PRISMA statement, and standardised methods for selection of the studies was performed independently by all three authors to avoid selections bias.

The review has some limitations. First of all, the search strategy was limited because it only searched for papers written in English, and we did not search for "grey literature" because it was out of the scope of this dissertation. Therefore, some important studies may have been missed, and because a limited number of studies were included, a more thorough understanding of the influence of childhood and family factors for the development of HA may have been missed. Finally, a narrative synthesis of the data was performed entailing the risk of a biased interpretation of the results, but due to the small number of included studies and the different methods used, it was not possible to perform a meta-analysis.

**Paper II and III**

**Main conclusions in relation to predetermined aims**

This family case-control study found that maternal HA was not a strong risk factor for the development and presentation of severe HA symptoms in children aged 8-17 years. Children of mothers with severe HA had weakly but significantly more self-reported HA symptoms compared to children of mothers with RA, but not compared to children of healthy mothers.
However, the results did indicate that mothers with severe HA perceive their children as having more symptoms, they have far more health-related worries related to their child - a condition we used the term "HA by proxy" for in paper III, and less satisfaction with general practice visits regarding the child compared to mothers with RA and healthy mothers. We also found that mothers with severe HA more often reported that they took their child to the general practitioner and had a more protective behaviour towards their child when it felt unwell, but only in comparison with mothers with RA - not healthy mothers.

**Discussion of the results in relation to other studies**

The findings of the present PhD study only partly confirmed our hypothesis that was based on previous studies [76,77,79], which have found a positive correlation between parental and child HA symptoms/negative illness beliefs. Further, it was somewhat conflicting with previous studies where the majority have found an association with childhood exposure to illness from significant others (e.g. parents) and HA [56-59] that children of mothers with a chronic physical disorder characterised by pain and disability (i.e. RA), had the lowest level of self-reported HA in the present study.
Beyond a suggested genetic heredity for HA, although still in its infancy [90,130,131], our findings indicate that children of mothers with severe HA were exposed to more maternal worries regarding their symptoms along with a more symptom-focused parental style compared to the two control groups. However, despite of this exposure, it did not significantly increase their children's level of HA symptoms at this point in their life, nor had it more broadly an influence on their well-being in that their own report of anxiety symptoms and health-related quality of life did not differ from the two control groups of children.
The majority of the included children in the present study (77.7%) were under the age of 14, which could partly explain why our findings differed from previous studies. The mechanisms behind a presumed transmission of HA symptoms may not be similar for all, but is influenced by a wide range of factors, among which the parents' own HA, and the duration and nature of the exposure may be important. A transmission of HA symptoms/negative illness beliefs in younger children could therefore be dependent on a larger parental influence and a longer exposure of a certain parental behaviour before the symptoms become evident, or the symptoms may not appear until adulthood. It is stated in the DSM-5 that HA may arise at any age, although the most common age is proposed to be in early adulthood [3]. It could be that the exposure to sustained parental health worries along with a symptom-focused parental style could form a vulnerability and a lower threshold for the development of maladaptive cognitions around illness in the child. Perhaps in interaction with other environmental factors, such as exposure to illness or stress, could trigger the development of HA symptoms later in life [5].
In the present PhD study, the children had been exposed to severe maternal HA for minimum two years, but beyond that, it was not possible to measure the duration and its potential relation to the child's developmental stage. Furthermore, the study design could not distinguish between the influence of environmental and genetic factors.

In our study, we did find that children of mothers with severe HA were exposed to more protective maternal behaviour when they felt unwell and also had more contacts to the doctor during the past year compared to children of mothers with RA, but not compared to children of healthy mothers. Since we only found a statistically significant difference in HA symptoms between children of mothers with severe HA and children of mothers with RA, but not children of healthy mothers, this finding could indicate that a protective parental behaviour toward the child's health complaints is involved in the development of HA symptoms.
Children and adolescents tend to have high levels of somatic complaints [132-134] and a protective parental style towards the child's health complaints could result in more maladaptive cognitions around illness. As a result of overprotection in relation to health complaints, the child may start focusing on bodily sensations and thereby indirectly increase an emotional reaction leading to a belief that these sensations are threatening [135]. A general overprotective behaviour is found to be a risk factor for the development of mental disorders [136], and it could be that a specific overprotection regarding the child's health is a stronger risk factor for the development of HA than overprotection in general.
Health care utilisation of a child very much depends on the parents [137], and therefore it may be assumed that the health care utilisation of the child is an expression of parental behaviour more than that of the child, and several studies have reported a high health care use in adults with severe HA [8,9,138,139]. In the present study, we found that mothers with severe HA not only had worries regarding their own health, but also had a higher level of health worries concerning their child, i.e. HA by proxy, and compared to mothers with RA had more doctor visits with their child during the past year. This is an overlooked aspect of HA [32], and recognising and addressing this could probably reduce unnecessary health care visits in relation to the child.
Information on the child's own contacts to the school nurse was obtained as part of the present study. These contacts could reflect the independent illness behaviour of the children as they could contact a school nurse without parental involvement as opposed to seeing the general practitioner. However, in additional analyses we found no statistically significant differences between the three groups of children with regard

to number of contacts to the school nurse during the past year. These findings could therefore suggest that the higher uses of health care visits seen in children of mothers with HA compared to children of mothers with RA rather reflects the mothers' illness behaviour, not the children's.
Information on school absence due to illness in the past year was obtained from two different sources; maternal report and data obtained directly from the schools, and no differences were found between the three groups of children regardless of the data source. This could to some degree validate the mothers' replies to the questionnaires as their answers did not differ significantly from the objective data obtained from the schools. Despite the fact that we found a more protective maternal behaviour, this did not cause more school absence regarding their child. This finding may indicate that mothers with severe HA do not encourage their children to a maladaptive behaviour regarding school absence but rather encourage to more doctor visits, which may reflect the mothers' tendency to seek medical reassurance [5].

**Strengths and limitations of the family case-control study**
This case-control study has several strengths. It is the first larger study using a case-control design and including a case group of children of mothers diagnosed severe HA. Previous studies have either used a cross-sectional design [76,79] or a smaller case-control design with children of parents with any somatoform disorder, not specifically HA [77]. Second, using a case-control design with two control groups makes it possible to compare the influence of not only the exposure to maternal HA, but also the influence of having a mother with a chronic physical disorder and a healthy mother. Third, the three groups of children were matched on age and gender in order to control for potential age and gender differences in symptom reports. The age of onset of specific anxiety disorders has been shown to vary in that specific phobias have an early onset, while Obsessive Compulsive Disorder often onsets in mid or later adolescence [140,141]. Gender differences have also been found with regard to self-reported functional symptoms [142]. Fourth, all children underwent a brief physical examination to exclude any undiscovered physical disorder that could lead to increased physical symptoms or health worries.
The present study has some limitations to be considered. As already discussed in the section "Discussion of methods", selection bias could have occurred in all three groups of mothers. In order to reduce selection bias, children of mothers with severe HA were randomly selected to participate if the mother had more than one child available for inclusion. However, this procedure could have resulted in a lower participation rate in this group if the mother declined participation due to her worries about whether the child could be harmed by participation if she perceived the selected child as being particularly sensitive. If this were the case, it could indeed have skewed the results.
To summarise, selection bias could have blurred the picture seen in the present study towards a direction where the group of children of mothers with severe HA may have had a lower level of HA symptoms and children of healthy mothers may have had a higher level of HA symptoms.
Finally, information bias may have occurred as the use of questionnaires to assess complex concepts such as health beliefs and attitudes in younger children may be of limited reliability [143], and the youngest children had difficulties reading the questionnaire battery. Furthermore, the questionnaire regarding HA by proxy (IWS-p) was not validated, and although the internal reliability for the present study was satisfactory, the results concerning this questionnaire have to be interpreted with caution. Finally, maternal recall bias may have occurred - especially mothers with severe HA could have a selected memory regarding health-related areas (i.e. health care visits).

**FUTURE PERSPECTIVES**
**Future research related to the present PhD study**
As part of the PhD dissertation, data was collected regarding the children's illness perception using a vignette developed for the study. These data can provide information on whether a negative illness perception as seen in the group of mothers with severe HA is transmitted to the children.
A real time assessment - using mobile phone data - was also a part of this PhD dissertation, where the children received four questions by text message 4 times a day during a week in a random sample design. The children were asked about their physical and emotional symptoms. These data can provide more detailed information on the presence of and fluctuations in emotional and physical symptoms and possible differences in the three groups of children when they are in their normal living environment. Furthermore, the feasibility of using text messages to measure physical and emotional symptoms in this particular sample of 8-17 years children can be tested.
Finally, register data can be used to obtain detailed information on whether children of mothers with severe HA had a higher health care use over an extended period of time (both before and after the study period) compared with children of mothers with RA and children of healthy mothers. This can extend the results from the present study, based on the mothers' self-reported data, suggesting that mothers with severe HA more often took their child to see the doctor than mothers with RA.

**Suggestions for future research in general**
Prospective studies gathering information on different potential risk factors associated with the development of HA and their duration and timing in relation to the child's developmental stage are needed. In a prospective study design, it will be possible to investigate whether there is a cumulative influence of multiple types of negative childhood experiences involved in the development of HA, and whether the experience of a single specific risk factor such as early experience of illness in self or significant others could be more important.
Additional research on the family environment, parental characteristics (e.g. their physical and mental disorders, own illness behaviour and overprotection in relation to the child's health with modelling and reinforcement) and the child's underlying personality and attachment style could provide unique information on the putative complex interacting factors that may be involved in the development of HA. As clinical presentations of HA most often origin in adulthood, well-planned and well-conducted long- term, large epidemiological cohort studies with follow-up into adulthood will be optimal.

**Clinical perspectives**
Results from the family case-control study indicate that mothers with severe HA have health worries towards their child and, compared to mothers with RA, also had a higher health care use on behalf of their child - a behaviour that could induce the risk of unnecessary medical investigations of the child. Early identification of the problem (i.e. parental worries)

in medical settings could reduce unnecessary medical investigations of the child and probably reduce family stress and increased health-related worries with regard to the child in the parent as this could be fueled by medical tests and investigations of the child. Acknowledging the clinical phenomenon and also involving these aspects in the treatment of parents with severe HA could be an important target point in preventing the child itself from developing maladaptive illness behaviour. In addition, though speculative, this may prevent parents wrongly being accused for the serious suspicion of being perpetrators of fabricated or induced illness in children and instead offer them proper treatment. However, whether this is a real clinical issue needs to be further elucidated, e.g. through qualitative interviews with both patients and health professionals.

**SUMMARY**

Excessive health anxiety, still designated as hypochondriasis in ICD-10, refers to worries and anxiety about harbouring serious illness. It is common in both primary and secondary health care with prevalence rates up to 9% and causes great suffering for the individual as well as high health care costs when untreated. Growing research suggests that health anxiety may originate in childhood, and studies have demonstrated that cognitive and behavioural features similar to those described for health anxiety in adults may be present.

The development of health anxiety probably has a complex nature involving a number of interacting factors such as genetics and environmental factors. A few studies have highlighted a possible transmission of health anxiety symptoms from a parent to a child and found significant associations between child and parental self-reported health anxiety symptoms. Theoretical perspectives also assume an association between childhood experiences and family factors and a later development of health anxiety.

This dissertation is based on a systematic review and a family case-control study and aims to answer the following questions:

1) What is the empirical evidence for the influence of childhood and family factors for the development of health anxiety?

2) Does exposure to severe maternal health anxiety contribute to health anxiety symptoms in their children or perhaps more broadly affect the children emotionally?

3) Do mothers with severe health anxiety express more health anxiety on behalf of their child, more maladaptive illness perceptions and behaviours compared to mothers with rheumatoid arthritis and healthy mothers?

The first part, the systematic review, was performed in accordance with the PRISMA statement and focused on the current empirical evidence for childhood and family factors involved in the development of health anxiety. In total 25 papers were examined emanating from 23 studies. The results, based on this limited research, suggested potential relationships between the development of health anxiety and 1) the intergenerational transmission, i.e. from parent to child, of health anxiety symptoms, 2) early childhood experience involving illness and 3) the expression of an anxious attachment style.

The second part, the family case-control study, adds to the limited knowledge of health anxiety symptoms in childhood with one paper presenting original data on health anxiety, related symptoms and illness behaviour in three groups of children exposed to different maternal health status. Another paper examines the phenomenon of maternal health anxiety by proxy in mothers with severe health anxiety. The data for these two papers stem from 150 families with a child in the age group 8-17 years. These were grouped into a case group of children of mothers with severe health anxiety and two control groups; children of mothers with rheumatoid arthritis and children of healthy mothers. The children completed a questionnaire battery including items on health anxiety and related constructs. The mothers and fathers filled in questionnaires regarding their own mental and physical health including health anxiety, and the mothers moreover filled in questionnaires regarding illness perceptions, illness worries and illness behaviour related to their children.

The findings suggest that severe maternal health anxiety only weakly affects children's own report of health anxiety symptoms and hence may not be a strong risk factor for the development and clinical presentation of excessive health anxiety symptoms early in life, i.e. in children aged 8-17 years. However, mothers with severe health anxiety perceived their children as having more emotional and physical symptoms compared to mothers with RA and healthy mothers and accordingly more often took their child to see a doctor compared to mothers with rheumatoid arthritis. They reported a more negative illness perception and more health anxiety on behalf of their child, i.e. health anxiety by proxy, as well as more dissatisfaction with their medical consultation in general practice regarding their child compared to mothers with rheumatoid arthritis and healthy mothers. Thus, although we in the first study did not find that the children of mothers with severe health anxiety themselves reported more physical symptoms compared to children in the control groups, the findings of the second study raise the possibility that the upbringing by a parent with negative illness perceptions and health anxiety in the long run could learn the child that minor bodily changes (i.e. feeling unwell) are unusual and need extra attention. Targeting health anxiety by proxy in the treatment of mothers who suffer from severe health anxiety may therefore be important to prevent not only iatrogenic harm to the child but also the exposure of the child to a maladaptive illness behaviour, which potentially could be a risk factor for the child to develop this behaviour itself when growing up.

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