Functional Abdominal Pain in Children and Adolescents in a Biopsychosocial Perspective

Diagnostic classification, characteristics, predictive– and prognostic factors

An epidemiological and a clinical cohort study

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2011

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Series of dissertations submitted to the
Faculty of Medicine, University of Oslo
No. 1098

ISBN 978-82-8264-018-3

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Printed in Norway: AIT Oslo AS.

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gå til Per i hagen,
sett deg på en stein og gnag på et bein
så blir du bra i magen

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ACKNOWLEDGMENTS

I would like to express my gratitude to each of you who have supported me and contributed to the accomplishment of this work. In particular I would like to thank:

The children, adolescents and parents for participating in the BAMBI and the TOPP study and thereby providing the base for this project.

Hanne Kristensen, Director, Clinical Research, Centre for Child and Adolescent Mental Health, Eastern and Southern Norway, and my main supervisor, for substantial contributions to conception of my research project, and for envisioning me with professional competency, patience and friendliness, and for her splendid quick perception and clarity of mind.

Trond Markestad, Professor, Haukeland University Hospital, research counsellor at Innlandet Hospital Trust and my co-supervisor, for substantial contributions to conception and conduction of the BAMBI study, for sharing his pediatric and scientific expertise and for envisioning me with enthusiasm and encouragement.

Berit Grøholt, Professor at the University of Oslo, for representing my contact with the University of Oslo.

Bjørg Antonsen and Hedda Døssland, Head and previous Head of Department of Child- and Adolescent Psychiatry Gjøvik, for being my mentors, for valuable help in getting started and for encouragement.

Sonja Heyerdahl, Research Director, Centre for Child and Adolescent Mental Health, Eastern and Southern Norway, for being a catalyst initiating my research career, for advices, and for revising one of my manuscripts critically.

Kristin S. Mathiesen, Director of the Department of Child- and Adolescent Mental Health, Norwegian Institute of Public Health, for generously providing the data from the TOPP study, for good advices and for revising the TOPP manuscript critically.

Gro Flagstad, paediatrician at the outpatient clinics at Gjøvik and Lillehammer, for being a research partner, for valuable contribution in the medical assessment of the pediatric patients in the BAMBI study, and for cooperation on two of our papers.

The staff at the four pediatic outpatient clinics at Innlandet Hospital Trust, in particular **Pål Christensen**, Head of Department of Pediatrics Lillehammer/Gjøvik, and **Jon Grøtta,** Head of Department of Pediatrics Hamar/Elverum, **and the other pediatricians,** for meeting my project with interest and support, and thereby making possible the practical conduction of the BAMBI study.

Leiv Sandvik, Professor at Ullevål University Hospital, for sharing statistical competency with exuberance.

Jocelyne Clench-Aas, Project leader for the Health Profile Study (conducted by the Norwegian Health Services Research Centre in 2002) and **Betty Van Roy**, psychiatrist at Akershus University Hospital and researcher, for providing the reference data form the health

profile study. Betty also for help in data analysis and for revising one of the manuscripts critically.

Anne Marie Skaaden and Aud Ryen Eide, nurses at the outpatients clinics at Hamar/Elverum and Lillehammer and research staff, for conscientious and responsible assistance in including patients in the BAMBI study and acquisition of data.

Turid Skundberg, nurse at Gjøvik outpatient clinic, for practical help, but also for interest and warm support.

Torill Ueland and Katrina Stewart for skilful help in translation of questionnaires.

Gunvor Steine Fosnes and Solveig Ligaarden, my good research colleagues and lunch fellows at the Innlandet Hospital, for fruitful discussions, genuine interest, friendship, valuable support and comfort.

My deepest appreciation to my family: My parents**,** for giving me valuable "luggage" for life. Inger Helene Vandvik, my mother in law, for generously sharing her expertise and wisdom when I asked for help and for reminding me of the importance of a clinical perspective. My husband, Per, for inspiring me and teaching me scientific thinking, for help, unflagging enthusiasm, tolerance and generosity, but most of all for being my soul mate. Our children, Anders, Olav and Elida, for joy and for reminding me of life.

Financial support:

I gratefully acknowledge financial support from:

- Innlandet Hospital Trust , Department of Psychiatry and the Research Unit
- Centre for Child and Adolescent Mental Health, Eastern and Southern Norway
- Lundbeck AS

LIST OF PAPERS

1. Helgeland H, Flagstad G, Grøtta J, Vandvik PO, Kristensen H, Markestad T

   Diagnosing pediatric functional abdominal pain in children (4-15 years) according to the Rome III criteria: Results from a Norwegian prospective study

   Journal of Pediatric Gastroenterology and Nutrition 2009;49:309-315

2. Flagstad G, Helgeland H, Markestad T

   Fecal calprotectin concentrations in children with functional gastrointestinal disorders diagnosed according to the Pediatric Rome III criteria

   Acta Paediatrica 2010;99:734-737

3. Helgeland H, Van Roy B, Sandvik L, Markestad T, Kristensen H

   Functional abdominal pain in children: Significance of child and maternal somatic and mental health on levels of abdominal pain and disability

   Submitted

4. Helgeland H, Sandvik L, Mathiesen KS, Kristensen H

   Childhood predictors of recurrent abdominal pain in adolescence: A 13-year population-based prospective study

   Journal of Psychosomatic Research 2010;68:359-367

LIST OF ABBREVIATIONS

API	Abdominal Pain Index
CSI	Children's Somatization Inventory
CI	Confidence Interval
FAP	Functional Abdominal Pain
FDI	Functional Disability Inventory
FGID	Functional Gastrointestinal Disorder
HSCL-10	Hopkins Symptom Checklist, the 10-item version
NLE	Negative Life Events
OR	Odds Ratio
PRC-II	Pediatric Rome II criteria
PRC-III	Pediatric Rome III criteria
RAP	Recurrent Abdominal Pain
SD	Standard Deviations
SDQ	Strengths and Difficulties Questionnaire
SHC	Subjective Health Complaints
QPGS	Questionnaire on Pediatic Gastorintestinal Symptoms

1. INTRODUCTION

With few exceptions chronic and recurrent abdominal pain in children did not receive much attention in pediatric literature before the late 1950s.[1] In 1958 Apley and Naishe published results from a population-based study of schoolchildren, and introduced the term "recurrent abdominal pain" (RAP) defined as at least three episodes of pain, severe enough to affect activities, over at least three months in the preceding year.[2] Their definition soon became common in use and has been applied in clinical pediatric practice and research since then. However, with enhanced knowledge and understanding, both clinicians and researchers have recognised weaknesses with this term. RAP is a description, not a diagnosis. The definition is wide and general and includes heterogeneous disorders of abdominal pain, including those with organic and non-organic etiology. The vast majority of children and adolescents with RAP have non-organic abdominal pain.[3] This heterogeneity of RAP has made research and treatment difficult. To make a distinction from organic disease, the term "functional gastrointestinal disorders" (FGIDs) has been established. These are chronic or recurrent gastrointestinal symptoms not explained by structural or biochemical abnormalities.[4] The term "functional abdominal pain" (FAP) encompasses the pain related FGIDs.[4]

As a physician working in a child- and adolescent outpatient clinic in secondary health care it was my impression that patients with psychosomatic problems were almost absent from our patient population and that very few patients were referred to us because of such problems. Inspired by my husband who did research on FAP in adults, I started asking my patients about presence of abdominal pain. I soon discovered that not only such symptoms, but also other unspecific somatic symptoms such as headache, back- and limb pain were common. In some patients the symptoms had a huge impact on their daily functioning. Exploring patient somatic symptoms in relation to their emotional and behavioral problems in parallel with going

through relevant literature stimulated a growing interest and fascination for children with FAP and the intricate communication between mind and body. I also realised that compared to abundant research on adults with FAP, far less research has been conducted in children and adolescents. However, children are not small adults, and results from research on the adult population may not be applicable to children.

This thesis is based on two cohort studies that included a clinical sample of patients (4-15 years) in general pediatric outpatient clinics and a population-based sample of adolescents (14 years). The objective of the thesis was to study diagnostic classification and characteristics in children and adolescents with FAP, and further explore predictive- and prognostic factors of FAP.

2. EMPIRICAL BACKGROUND

2.1. Prevalence and characteristics of children with FAP

FAP is a common pain syndrome in children and adolescents. Previous studies indicate a prevalence between 10% and 15%. Some studies have reported two peaks in prevalence, first below five year of age, and then between 8 and 10 years,[2, 5, 6] whereas another study found a progressive increase in prevalence in children below 12-15 year of age.[7] It appears that girls have a higher prevalence of FAP than boys (female/male ratio 1.4:1) with a female predominance seeming to become evident around puberty.[2, 5-7] FAP is also reported to account for 2–4% of all pediatric office visits.[3, 8]

Children and adolescents with FAP experience a great variation with respect to quality, location, intensity, frequency and duration of abdominal pain symptoms.[3, 4] They are further characterized by co-morbid (i.e., co-occurrence of) somatic (e.g., headache, back pain, limb

pain) and emotional symptoms (e.g., anxiety, depressive-) symptoms.[9-13] However, the control groups in earlier studies are small and represent selected groups of children.[9-12] Comparisons between pediatric patients with FAP and a representative sample of children in the general population have, to our knowledge, not been performed. Also the parents of children and adolescents with FAP are reported to have more somatic and emotional symptoms compared to healthy controls.[9, 10, 13-15] Moreover, with few exceptions,[16] children with FAP are found to report higher levels of negative life events compared to healthy individuals.[17-19] However, level of negative life events is not found to discriminate between patients with FAP and other patients groups.[3]

Some children with FAP experience substantial functional disability due to limitations in physical and psychosocial functioning reflected in restrictions in everyday activities, missed school days and physician visits.[20-22] It is a common clinical experience that children reporting the same levels of abdominal pain symptoms (e.g., intensity and frequency) report very different levels in functional disability. Thus, other factors than merely the level of abdominal pain are likely to influence child pain and disability. Both emotional and somatic co-morbidity, parental health and responses to pain in their children, and negative life events are reported to negatively affect pain and disability in children with FAP.[20, 23-26]

Patterns of disability and illness behavior can establish in childhood and may extend into adulthood in some people.[21, 27] There is a need for increased understanding of the relation between pain and disability in children with FAP *and* factors such as child co-morbid symptoms, parental health and negative life events. Enhanced knowledge may be helpful in understanding factors important for development and maintenance of FAP in children.

2.2. Conceptual model, causes and mechanisms

Complex disorders such as FAP and the other FGIDs can not be explained by a simple biomedical disease-based model. A biopsychosocial model is far more comprehensive and seems to be the best prevailing model to conceptualize the pathogenesis and course of these disorders.[28-30] According to this model, FAP in children can be achieved via different etiological pathways. The model also implies that there is an intricate and dynamic interplay between biological, psychological and environmental factors which may act as predisposing (e.g., genetics, early-life experiences), provoking (e.g., gut inflammation, psychosocial stress) and/or modifying factors (e.g., gender, gut flora, dietary components, personality, parental responses to child pain).[31] Interactions between such factors may lead to disease onset and influence outcome.

According to this model, FAP and the other FGIDs are more specifically believed to be caused by a dysregulation of the so called "brain-gut axis" which allows a bidirectional communication between emotional and cognitive centers of the central nervous system and the gastrointestinal tract.[32, 33] Alterations at different levels of the local nervous system of the gut (i.e., the enteric nervous system), the autonomic and/or central nervous systems, or a disturbance of the dynamic interplay between these systems are thought to give rise to the brain-gut dysfunction.[32, 33] However, the underlying pathophysiological mechanisms remain unclear. A variety of biological, psychological and environmental factors may interact via the brain-gut axis.[32, 33] These interactions are thought to contribute to alterations in nerve receptors in the gut wall and the enteric nervous system, modulation of sensory transmission in the peripheral or central nervous system, and central pain processing (cortical perception and pain memories).[30] The resulting changes in gastrointestinal sensitivity, motility and secretion are further believed to give rise abdominal pain symptoms.[33]

Observational studies with a cohort design may increase our understanding of predictors (i.e., variables associated with development of a disease/disorder) and prognostic factors (i.e., variables that predict patients to do better or worse) of FAP. However, despite a growing body of research in this field, relatively few longitudinal studies have been conducted. The prospective design of the two studies included in this thesis is therefore of interest.

The following sections give a brief overview of *some* possible factors that may be involved in the pathogenesis of FAP. Despite the categorization into predisposing, provoking and modifying factors, it is likely that some of the factors classify into several categories.

2.2.1. Predisposing factors

The existence of more somatic and emotional symptoms in children with FAP and their parents when compared to healthy individuals is well known from previous cross-sectional studies,[9, 12, 13, 15] although little longitudinal research exists. Of what there is, one population-based study found parental anxiety and maternal somatic symptoms in the first year of a child's life to predict FAP (i.e., RAP) in their offspring five years later.[34] Another population-based prospective study found somatic symptoms other than abdominal pain and psychosocial difficulties in children to predict new onset of chronic abdominal pain in adolescents.[35] There is a need for longitudinal research to confirm these findings. The associations between parental and child symptoms appear to reflect both environmental and hereditary influences although the relative contribution of genetic and environmental factors is unclear (see section 6.3.2. for more details).[33, 36, 37]

2.2.2. Provoking factors

Immunological alterations and low-grade inflammation in the gut, and changes in the central response to psychosocial stress have received increased attention in the field of gastroenterology.[38] Based on research in adults with irritable bowel syndrome, the most common FAP, low-grade mucosal inflammation and immunological alterations in the gut wall (maybe as a result of alterations in gut flora and permeability) have been suggested to contribute to physiological dysfunction of the gut.[38] Markers of gastrointestinal inflammation (e.g., calprotectin, lactoferrin and humant β-defensin-2) may provide knowledge about the inflammatory mechanisms involved.[39]

Calprotectin, an unspecific marker of inflammation, is a cytosolic protein found in inflammatory cells (primarily in neutrophil granulocytes, but also in monocytes and macrophages), and can be measured in feces, plasma and in other body fluids.[40, 41] High fecal concentrations of calprotectin are found in patients with inflammatory bowel disease (i.e., ulcerative colitis and Crohn's disease) and reflect flux of neutrophils into the gut wall, their turn over and migration into the gut lumen as a consequence of mucosal inflammation and tissue damage.[40] When the present study was planned, several studies of children with FAP had reported no differences in fecal calprotectin concentrations when compared to healthy controls.[42-45] To our knowledge, no study has investigated potential differences in fecal calprotectin concentrations between subgroups of children with FAP classified according the the pediatric Rome criteria.

Psychosocial stress (e.g., low birth weight, sexual or physical abuse, parental emotional and physical distress/illness, serious illness in self or others) may be of importance for the *central* dysregulation of the brain-gut axis.[33] This dysregulation is thought to involve alterations in

the autonomic nervous system and the hypothalamic-pituitary adrenal axis which are parts of the central stress response system.[33, 46, 47] Long-term activation of the stress response system may have secondary, undesirable consequences including physiological dysfunction, increased vigilance toward innocuous visceral afferent information from the gut and maybe also other parts of the body, and emotional disturbance.[46, 48]

2.2.3. Modifying factors

Several biopsychosocial factors appear to modify the gut immune activation and the stress-response elicited. Alteration in the gut flora, dietary components (i.e., food allergens) and psychosocial stress may contribute to a prolonged stimulation of the immune and nervous system of the gut.[31] Furthermore, a person's interpretation of stress is influenced by severity and duration of the stressful events, but also by individual factors such as age, gender, illness, previous life experiences, personality and cognitive style (e.g., catastrophic thinking about pain).[33, 48] The extent of fear and threats evoked influences the emotional reaction and the coping strategies used, which in turn is likely to be reflected in the physiological stress response elicited.[48] Accordingly, a prospective study of pediatric patients with FAP showed that those who accepted pain and used accommodative coping strategies had better outcomes than those who felt most threatened by pain used passive coping strategies.[49]

2.2.4. Outcome and prognostic factors

Prospective studies have shown that abdominal pain persists in almost one third of the children with FAP.[50] Moreover, former FAP patients do not only experience higher levels of abdominal pain, but also higher levels of emotional, other somatic symptoms and functional disability compared to healthy individuals.[21, 51-54] However, previous cohort studies investigating prognosis of FAP have mainly been conducted in relatively small samples of

referred children in specialist health care settings.[50] Of the few long-term cohort studies, one birth cohort study reported that childhood FAP increased the likelihood of developing irritable bowel syndrome, the most common FAP, in adulthood.[55] In contrast, another birth cohort study reported that FAP in childhood predicted psychiatric disorders and was modestly associated with other common somatic symptoms in adulthood.[56]

Somatic and emotional symptoms in children and their parents, and negative life events are reported to be *prognostic factors* associated with pain persistence in some children, although relatively little prospective research exists[23, 24, 26, 57] A short-term population-based study of children with FAP found child headache and a maternal history of anxiety measured when the children were six years old to be associated with sustained abdominal pain one year later.[26] A five year prospective study of a clinical sample of pediatric patients with FAP in tertiary care found that somatic and emotional co-morbidity in the children were associated with persistent pain,[57] and three prospective (two short term and one long term [five years]) clinical studies found higher levels of negative life events to be associated with symptom maintenance in patients with FAP.[23, 24, 57] There is a need for longitudinal research on prognostic factors of FAP.

2.3. Diagnosis

2.3.1. Development of the Rome Criteria for functional gastrointestinal disorders

Because there is no diagnostic biological marker for diagnosing FAP, symptom-based, diagnostic criteria have been developed as an attempt to classify specific diagnostic entities based on typical constellations of gastrointestinal symptoms. Based on gastrointestinal symptoms in adults the Manning criteria were presented in 1978.[58] The Rome I criteria followed in 1992 and have been revised two times (i.e., Rome II and III) since then.[59] The

international *pediatric* Rome II criteria (PRC-II) were introduced in 1999 as a first attempt at classifying FGIDs in children and adolescents.[60] The PRC-II differed from the adult criteria in that they were organized according to main symptoms instead of being organ-targeted.[60] Based on evolving research that pointed out the need for refinement and clarification, the PRC-III were published in 2006.[4] Notable changes were: introduction of new entities (e.g., adolescent rumination syndrome), modification of established categories (i.e., abdominal migraine, functional constipation and childhood functional abdominal pain), reduction of the required duration of symptoms for all disorders except cyclic vomiting and abdominal migraine (from three to two months), and reduction of the required number of episodes of pain for cyclic vomiting and abdominal migraine (from ≥ 3 to ≥ 2 episodes in the preceding year).[4] The PRC-III for FGIDs in children aged 4-18 years are given in the appendix.

Originally, the Rome classification was based on consensus among experts.[32] Evolving research has to some extent supported the existence of different diagnostic subgroups in children (e.g., irritable bowel syndrome, functional dyspepsia, abdominal migraine and childhood functional abdominal pain).[3] Other subgroups are still classified more or less by consensus (e.g., aerophagia). Evidence to support that the Rome criteria are capable of differentiating subgroups of FAP is of crucial importance for implementation in clinical practice and research. Compared to research on the adult criteria, very little research on the ability of the pediatric Rome criteria to capture distinct and clinical meaningful constellations of gastrointestinal symptoms in children has been published. Thus, further studies on the PRC-III are needed.

2.3.2. A positive symptom-based approach

Recent clinical guidelines recommend using the symptom-based Rome criteria in making a positive diagnosis of FAP. A *positive symptom-based diagnostic approach* implies an "immediate" recognition of the patient's abdominal symptoms *combined* with a normal physical examination and the absence of alarm symptoms (e.g., blood mixed with stool, documented weight loss, unexplained fever, significant vomiting).[61, 62] This approach does not abolish the need for additional investigations in children. Additional investigations should be carefully considered on the basis of the history and physical findings, but are typically not necessary for a diagnosis of FAP.[61]

A positive symptom-based approach in parallel with limited medical investigations is believed to reduce unnecessary and harmful investigations, and to convey approval of the legitimacy of the patient's symptoms, reduce fear of serious illness in children and their parents, and facilitate a good therapeutic physician-child/parent relationship.[62, 63] On the other hand, a *diagnosis by exclusion approach* alone, may lead to unnecessary and potential harmful and expensive investigation and increased uncertainty and worries among children and parents. Still, for many clinicians and researchers FAP remains a diagnosis of exclusion, and there is an ongoing debate of the clinical utility of the Rome criteria and the symptom-based approach.[62]

2.4. Treatment

In harmony with the biopsychosocial model, treatment of children with FAP should not only alleviate their symptoms of abdominal pain, but also relieve factors that influence illness experience and behavior (e.g., somatic and emotional co-morbidity, parental emotional and somatic health, fear of serious illness in the child and their parents and other relevant

social/environmental factors). Most likely, a multicomponent targeted therapy that matches the patient's symptomatology (severity and nature), functional limitations and the social and emotional context of the patients is of importance. Treatment that targets a single mechanism is probably not sufficient.

Reflecting the complexity of FAP, a variety of treatments is suggested: Dietary interventions (low lactose diets, dietary fiber supplement, lactobacillus supplementation), pharmacological treatment (famotidine, pizotifen, peppermint-oil) and psychological interventions (cognitive behavioral therapy, family interventions, relaxation, biofeed back, hypnotherapy). However, methodological limitations in several of the previous studies have made interpretation of results difficult.[64-66] Thus, relatively little empiric evidence exists. Interestingly, there seems to be some evidence for beneficial effects of psychological treatment strategies (e.g., cognitive-behavioral therapy, hypnotherapy) which are developed to change psychological processes thought to contribute to pain and disability in children with FAP.[64, 67, 68] Moreover, it remains unclear whether children classified in different entities according to the Rome criteria, are likely to respond differently to treatment.[64, 69]

3. AIM AND RESEARCH QUESTIONS

This thesis is based on two cohort studies that included a clinical sample of patients (4-15 years) in general pediatric outpatient clinics and a population-based sample of adolescents (14 years). The objective of the thesis was to study diagnostic classification and characteristics in children and adolescents with FAP, and further explore predictive- and prognostic factors of FAP. The following research questions are addressed in paper 1-4.

1) In referred pediatric patients (4-15 years) with non-organic abdominal pain, what is the proportion of patients meeting the criteria for one or more diagnoses of functional gastrointestinal disorders according to the PRC-III, what is the distribution of diagnoses, and further, what are the reasons for failure to meet these diagnostic criteria (paper 1)?

2) Do fecal calprotectin concentrations vary between subgroups of referred pediatric patient (4-15 years) with FAP classified according to the PRC-III (paper 2)

3) A. Do referred pediatric patients with FAP experience more emotional and frequent somatic symptoms compared with school children in a large, population-based reference sample of school children (paper 3)?

   B. Do emotional and somatic symptoms in pediatric patients (8-15 years) with FAP and their mothers predict level of abdominal pain and functional disability measured at a follow-up consultation after 6-9 months (paper 3)?

4) Do maternal and child emotional symptoms, physical health and negative life events in childhood predict self-reported recurrent abdominal pain in adolescents at age 14 years (paper 4)?

4. MATERIAL AND METHODS

This thesis is based on two cohort studies, the BAMBI study (paper 1–3) and the TOPP study (paper 4). BAMBI is an acronym for ”**Ba**rn med **M**agesmerter ved **B**arnepoliklinikker i Sykehuset **I**nnlandet” (i.e., Children with Abdominal pain in Outpatient clinics at Innlandet

Hospital Trust), whereas TOPP is an acronym for "**T**rivsel og **Opp**vekst – Barndom og Ungdomstid" (i.e., Tracking Opportunities and Problems – from Childhood through Adolescence).[70]

4.1. The BAMBI study

4.1.1. Design

The BAMBI study is a prospective study designed to identify and follow up a representative sample of referred pediatric patients (4-15 years) with FAP in four general pediatric outpatient clinics (secondary health care) at Innlandet Hospital Trust. The study was conducted from February 2006 to April 2008 and included assessment at two time points (i.e., baseline and follow-up after 6-9 months). The follow-up consultation was arranged as part of the study. At both time points all patients included underwent a consultation by one of the pediatricians and questionnaire data were collected from the participants.

Since we also wanted to assess to what extent pediatric patients with FAP differed from children in the general population with respect to emotional and somatic symptoms, a representative sample of Norwegian school children that participated in a health profile survey in 2002 constituted the reference sample (description below).[71, 72]

4.1.2. Clinical sample and reference sample

The four outpatient clinics at our hospital are the only pediatric referral clinics serving approximately 330,000 inhabitants in the counties of Oppland and Hedmark in Norway, with the exception of one pediatrician working part time in a small practice. In Norway, pediatric consultations are only accepted based on referrals from general practitioners. Only new referrals of Norwegian speaking patients (4-15 years), without abdominal pain of known

organic etiology were eligible. Patients with abdominal pain of known organic etiology were excluded. The inclusion criterion was chosen to obtain results that are representative for a population of children with abdominal pain referred to secondary health care, at least in Norway.

Overall, 192 consecutive patients (4-15 years) were referred from general practitioners to the outpatients clinics for evaluation of recurrent abdominal pain during the inclusion period. Fourteen patients cancelled the appointment because of spontaneous improvement and one because of emergency admission. Of the 177 eligible patients evaluated for abdominal pain, 25 (14%) were excluded (22 due to missing consent from one parent, 2 had recently been evaluated by a pediatrician, and 1 did not speak Norwegian), leaving 152 (86%) patients in the study (142 with FAP, 10 patients with abdominal pain of organic etiology). These patients constituted the sample in paper 1 and 2.

Furthermore, patients old enough (i.e., school grade three to ten) to give self-report and who were diagnosed with FAP by the pediatricians were extracted from the above mentioned clinical sample of 152 patients. The extracted patients (n = 94) with all their mothers constituted the clinical sample in paper 3. Eighty-two (87%) teachers reported on the patients. Since the reference sample only encompassed school children in grade three to *seven*, seventeen patients of older age (i.e., grade eight to ten) were excluded from the clinical sample in the comparison analyses (thus, leaving 77 patients in the comparison analyses).

The reference sample consisted of 14 000 Norwegian school children (school grade three to seven) who participated in a health profile survey undertaken in Akershus County by the

Norwegian Health Services Research Centre in 2002 (84% participation rate, mean age [SD] = 10.5 [0.01] years, 50% girls). All the 22 municipalities in the county participated in the study. Classes at each school were selected at random to obtain a sample representative of the county as a whole. The random selection of classes, the high participation rate and the size of the reference sample most likely make this sample of school children a valid comparison group.[71-73]

4.1.3. Non-participants at baseline, patients lost to follow-up and missing data

The twenty-five of the 177 (14%) eligible patients who were not included in the BAMBI study, did not differ significantly from the participants with respect to age and gender (data not shown). Moreover, six of the 94 (6%) patients that constituted the clinical sample in paper 3 were lost to follow-up. By inspection of baseline data, these children did not appear to represent any outliers with respect to the investigated variables compared to the 88 participants that met for follow-up. At the clinics a member of the research team checked the questionnaires for missing answers, and gave the participants opportunity to complete the items. Thus, the number of missing answers was small. Missing answers were replaced by the mean score for the completed items.[74]

4.1.4. Medical assessment of the pediatric patients

All 152 patients included underwent a consultation by one of several pediatricians at the outpatient clinics. In general, each patient met the same pediatrician at both consultations. A diagnosis of FAP was based on the pediatrician's exclusion of organic disease through medical history and physical examination according to their usual practice, a set of laboratory investigations (including measurement of fecal calprotectin) through a predefined protocol

(appendix) and the clinical 6-9 months follow-up to confirm the diagnosis. Results of supplementary investigations and reported alarm symptoms (e.g., blood in the stools, involuntary weight loss, significant vomiting, chronic severe diarrhea, unexplained fever, a family history of inflammatory bowel disease) were registered by reviewing the electronic medical records after both consultations. Beyond this no information about medical history or physical examination was retrieved from the medical records. Diagnostic procedures and results are described in paper 1.

4.1.5. Classification of symptoms of abdominal pain in the patients

Child gastrointestinal symptoms were classified by parent report with the Questionnaire on Pediatric Gastrointestinal Symptomst – the Rome III version (QPGS-RIII [appendix]) which is scored according to the PRC-III (appendix).[75] The QPGS-RIII is a structured questionnaire and is an adaptation and abbreviation of the original QPGS-Rome II version which has undergone preliminary validation.[75, 76] The form is recommended for use by parents of 4-18 year old children. The QPGS-RIII comprises five sections: pain or discomfort in the upper abdomen above the umbilicus, pain or discomfort in the lower abdomen around and/or below the umbilicus, bowel habits, other gastrointestinal symptoms (nausea and vomiting), and impairment (limitation in activities) because of symptoms.

4.1.6. Measurement of patient and maternal somatic and mental health

Measurement of variables beyond the medical assessment was based on questionnaire data. Although we primarily sought to use validated questionnaires in our study, we also used some additional non-validated questions. These are marked in the text below. After an overview of

questions and questionnaires used in the BAMBI study is given, a more thorough description of the validated questionnaires follows.

Measurement in both the clinical sample and the reference sample

To enable us to compare the clinical sample with the reference sample in paper 3, mothers of the pediatric patients answered identical questions about child somatic and mental health as previously answered by parents in the reference sample of school children.[71, 72] *Somatic symptoms* in children in both samples were assessed by the following question (not validated): "During the last six months, how often has the child had the following complaints?" Abdominal pain, headache, back pain, neck/shoulder pain and dizziness were rated from 0 ("seldom or never") to 4 ("almost every day"). A criterion of once a week or more often was used as a cut-off for dichotomizing each symptom into frequent or infrequent/never somatic symptoms. *Mental health* (i.e., emotional and behavioral problems) in patients and school children were measured by the Strengths and Difficulties Questionnaires (SDQ) completed by the parents.[77]

Measurement in the clinical sample

Dependent variables (outcomes): Patient abdominal pain (Abdominal Pain Index [API],[78] and functional disability (Functional Disability Inventory [FDI]) were reported by self-report. [20, 79]

Independent variables (potential predictors): Patient extraintestinal somatic symptoms (Children's Somatization Inventory [CSI]) were reported by self-report.[10] Patient emotional symptoms and behavioral problems were reported by mothers and teachers only (Strengths and Difficulties Questionnaire [SDQ]).[77] The mothers also reported on somatic and emotional

symptoms in themselves (Subjective Health Complaints [SHC] and Hopkins Symptom Checklist-10 [HSCL-10]).[80, 81 82]

4.1.7. Description of questionnaires

The Abdominal Pain Index (API) comprises five items assessing the frequency, duration and intensity of the child's perceived abdominal pain in the previous two weeks.[78, 83] Frequency of pain, in terms of days, is rated from 0 ("not at all") to 5 ("every day"), and, in terms of times per day, from 0 ("none") to 5 ("persistent"). Duration of pain episodes is measured from 0 ("no pain") to 8 ("most of the day"). Typical and maximum pain intensity is measured on two scales ranging from 0 ("no pain") to 10 ("the most possible pain"). Scores on each item were standardized using z scores and were added to produce an overall score. The alpha reliability for the API in the clinical sample was 0.82.

The Functional Disability Inventory (FDI) is a 15- item questionnaire assessing perceived difficulty in physical and psychosocial functioning in multiple contexts (home, school, social activities, sleep) as a result of the child's physical health in the last two weeks.[20, 79] Each item is rated from 0 ("no trouble") to 4 ("impossible"). A total score (0–60) is obtained by summarizing the ratings on each item. The FDI has demonstrated reliability and validity in previous research.[20, 79] The alpha reliability for the FDI in the clinical sample was 0.91. In addition, to dichotomize the FDI score, we chose a cut-off point of 10. This cut-off point has been used in previous studies to separate children in the low range of functional disability from children in the moderate to high range.[84, 85]

The Children's Somatization Inventory (CSI), short version, assesses the child's experience of 18 somatic symptoms (i.e., "headaches," "abdominal pain," "pain in arms/legs") in the last two weeks.[10] Each item is rated from 0 ("not at all") to 4 ("a whole lot"). A total score is obtained by summarizing the items. The CSI has demonstrated adequate reliability and validity.[10] The alpha reliability for the CSI in the clinical sample was 0.87. To avoid overlap in measurement of abdominal complaints, six items on gastrointestinal symptoms were excluded from the CSI. A somatic co-morbidity score (0–48) was created by summarizing the ratings the remaining items.

The Strengths and Difficulties Questionnaire (SDQ) is a questionnaire for assessing emotional and behavioral problems in children and adolescents (www.sdqinfo.com), consists of 25 items rated from 0 ("not true") to 2 ("certainly true"), and composes five subscales (emotional symptoms, conduct problems, hyperactivity, peer problems, and prosocial behavior).[77] A total difficulties score (0–40) is obtained by summarizing the scores of the first four subscales (0–10). The instrument has previously been used in epidemiological and clinical research,[86, 87] including studies of children with different chronic illnesses.[13, 88-90] The SDQ is a well validated screening questionnaire.[91-93] The internal reliability and test-retest stability of the SDQ has been considered satisfactory, despite modest levels of internal reliability for some of the subscales.[94, 95] Corresponding previous research, the alpha reliabilities for the SDQ in the clinical sample were: 0.79 for the total score, 0.68 for emotional symptom–, 0.45 for conduct problem–, 0.79 hyperactivity-inattention problem–, 0.56 for peer problem–, and 0.65 for prosocial behavior scale.[91, 93]

The Hopkins Symptom Checklist (HSCL-10) is a 10-item questionnaire for assessing emotional symptoms (i.e., anxiety and depressive symptoms).[82] Each item is rated from 1

("not at all") to 4 ("extremely"). An average score (1–4) is calculated by summarizing each item score and dividing by 10. The HSCL-10 has approximately as high sensitivity and specificity as the more widely used HSCL-25,[96] and correlates at 0.97 with the 25-item version.[97] The reliability and the validity of the HSCL-25 is well established.[82, 96, 97] The alpha reliability for the HSCL-10 in the clinical sample was 0.91.

The Subjective Health Complaint Inventory (SHC), previously known as the Ursin Health Inventory is a 29 item questionnaire for assessing 29 common health complaints (e.g., "headache," "back pain," "stomach pain") experienced during the last month.[80, 81] Each item is rated from 0 ("not at all") to 3 ("severe"). A total score is obtained by summarizing the items. The internal reliability and test-retest stability of the SHC has been considered satisfactory.[98, 99] The alpha reliability for the SHC in the clinical sample was 0.87. To avoid overlap in measurement of emotional symptoms, five items on anxiety/depressive symptoms were excluded. A somatic symptom score (0–72) was created by summarizing the ratings of the remaining 24 items.

4.1.8. Procedure

Before start of the BAMBI study, the four questionnaires (Questionnaire on Pediatric Gastrointestional Symptoms, Abdominal Pain Index, Children's Somatization Inventory and Functional Disability Inventory) were translated into Norwegian after the following procedure: The PhD-candidate made translation drafts. Two physicians with academic competency (one psychiatrist and one paediatrician) independently commented the items in the drafts. New drafts were made and again discussed with the two physicians. When consensus was reached, the final drafts were back-translated into English by another fourth person. The person involved in the back-translation was fluent in both languages with English

as first language. The back-translated versions were all approved by one of the originators. The Strengths and Difficulties Questionnaire and the Hopkins Symptom Checklist are previously translated into Norwegian, whereas the Subjective Health Complaints Inventory is an instrument of Norwegian origin.[80, 81]

The Questionnaire on Pediatric Gastrointestional Symptoms (QPGS) was sent by mail to all referred children with parents together with the appointment for the first consultation. Parents were asked to complete the QPGS at home before the first consultation and bring it to the clinic if they wanted to participate in the study. At the clinic, but before the first consultation by the pediatrician, patients and parents individually completed the other questionnaires. Children completed the forms apart from their parents under assistance by the PhD-candidate or a study nurse. Questionnaires to the non-meeting parent were sent home by the spouse or by mail and were returned to the clinics by mail in a prepaid return envelope. The parents who did not return the questionnaires were given one reminder. When participants agreed, teachers were asked to complete a questionnaire and return it by mail. After the first pediatric consultation, a study nurse gave the parents detailed oral and written information on the procedure for collecting a stool sample for determination of calprotectin concentrations. The stool sampling procedure was conducted at home. At the clinic, but before the follow-up consultation by the paediatrician, the children reported again on the outcome variables. Although data from mothers and fathers were retrieved, only maternal data were used. The completeness of maternal data and a wish to reduce the amount of data were the main reasons for this choice.

The PhD-candidate was responsible for planning, monitoring and conducting the BAMBI study. Two nurses working at the outpatient clinics at Lillehammer, Hamar and Elverum were

responsible for inclusion and follow-up of 96 of the 152 patients included in the BAMBI study. The PhD-candidate was responsible for inclusion and follow-up of 56 children at the clinic at Gjøvik.

4.1.9. Statistics

All statistical analyses were conducted by the PhD-candidate under supervision by a statistician. The Statistical Package for the Social Sciences (SPSS) version 15.0 was used in the statistical analyses. The statistical methods are described in the separate papers.

4.1.10. Ethics

The BAMBI study was approved by the Regional Committee on Medical Research Ethics and the Norwegian Data Inspectorate. General ethical guidelines for research have been followed. Written information about the study was sent by mail to the parents of the referred children together with the appointment for the first consultation. A shorter and more "child friendly" version was also distributed to children of 12 years or older. Oral information was given by a member of the research team at the clinic before the first consultation. Written consent was obtained from all parents and children of 12 years or older. Each child was given two tickets for the cinema as a token of appreciation.

4.2. The TOPP study

4.2.1. Design

The TOPP study is an ongoing population-based observational study that has followed a cohort of 916 mothers with children from the age of 18 months (1993) until the age of 14 years (2006). The participants were recruited from child health clinics (preventive health

care). The cohort was assessed by questionnaires at six different time points (*t*1–*t*6). Child self-report was obtained from the age of 12 years (*t*5).

4.2.2. Sample

Routinely, more than 95% of all Norwegian families with children attend a public health program during the first four years of the children's lives. All families attending 19 child health clinics in seven municipalities in eastern Norway (Nittedal, Bærum, Halden, Fredrikstad, Kåkerøy, Onsøy and Borge) in 1993 for the scheduled 18-month vaccination visit were invited to complete a questionnaire (*t*1). Only maternal data were used in the analyses because few fathers participated. Of the 1081 eligible families, 916 mothers (85%) agreed to participate.

In paper 4 we chose to focus on data from *t*1 and *t*5 versus *t*6. *T*5 was especially chosen because of the use of child self-report which is considered to be a valid measure for assessing pain.[100] *T*1 was chosen to attend to the longest time span from *t*1 to *t*6. Furthermore, approximately 50% of the participants were lost to follow up from *t*1 to *t*6. Therefore, to ensure continuity of mothers across time points only participating mothers at *t*5 with *t*1 data were included in the analyses at *t*5. A total of 456 adolescents (56% girls) completed the RAP questions at the last assessment and were included in the cross-sectional analyses at *t*6. Mothers (at *t*1 and *t*5) and children (at *t*5) with RAP data by adolescent self-report at *t*6 were included in the longitudinal analyses of possible predictors for RAP. Table 1 gives the number of participants at each assessment and participants in the longitudinal analyses.

Table 1. Number of participating mothers and adolescents, and number of participants with endpoint data of RAP at *t*1and *t*5

Time point	Children's age	Mothers, n	Adolescents, n	Mothers of adolescents with RAP data at *t*6, n	Children with RAP data at *t*6, n
*t*1	18 months	916		436	
*t*5	12 years	590	546	380[a]	380
*t*6	14 years	478	456		

Abbreviations: RAP, Recurrent Abdominal Pain; *t*1, *t*5 and *t*6, time point 1, 5 and 6.

[a]Only participating mothers at *t*5 with baseline data were included in the analyses at *t*5.

4.2.3. Non-participants, mothers lost to follow-up and missing data

In the TOPP study, 165 of the 1081 eligible mothers (15%) did not participate in the study. Non-respondents at baseline (*t*1) did not differ significantly from respondents with respect to maternal age, education, employment status, number of children and marital status. Morover, as common in many cohort studies, there was a substantial loss of participating mothers from *t*1 to *t*6. Of 916 mothers included at *t*1, 436 (48%) mothers with data on adolescent abdominal pain at *t*6 were available for the longitudinal analyses. The non-participating mothers (n = 480) were significantly younger, less educated and reported more anxiety/depressive symptoms than participating mothers. The number of missing answers in the questionnaires used in the TOPP study was small. Missing answers were replaced by the mean score for the completed items.[74]

4.2.4. Measurement

Assessment in the TOPP study is based on questionnaire data only. Although we primarily sought to use validated questionnaires, we also used some additional non-validated questions. These are marked in the text below. After an overview of questions and questionnaires used in the TOPP study is given, a more thorough description of the validated questionnaires follows. More details about the non-validated questions are given in paper 4.

Outcome measure

As outlined in the introduction of this thesis, the vast majority of children and adolescents with recurrent abdominal pain (RAP) have FAP (i.e., abdominal pain without demonstrable evidence of a pathologic condition). However, since the adolescents in the TOPP study did not undergo any medical investigation, we found it more appropriate to use the term RAP instead of FAP.

Thus, the outcome measure in paper 4 was self-reported RAP in the adolescents (*t*6). The adolescents answered one main question (not validated): "During the last year, have you had abdominal pain [not related to the menstrual period] at least once a month in three consecutive months?" (yes/no). Adolescents with a positive answer also answered the following sub-question (not validated): "Has the abdominal pain led to: school absenteeism, termination of hobbies or activities, taking medication, visiting a doctor or changing the diet?" Each domain was rated yes or no. A positive answer in the main question and at least one of the sub-questions were necessary to fulfil the criteria of RAP.

Potential predictors

The following potential maternal predictors by self-report were assessed: *Maternal anxiety and depressive symptoms* (Hopkins Symptom Checklist [HSCL], the 25-item version at *t*1 and the 10-item version at *t*5),[82, 96] *maternal physical health* at *t*1 and *t*5 (one non-validated question: "During the last 12 months, have you experienced problems with your own physical health [functional disability, somatic illness]?") and *negative life events* experienced by the mother in the last year at *t*1 and *t*5 (a non-validated checklist of 10 items constructed on the basis of established life events lists).[101, 102]

The following potential child predictors by maternal report were assessed: *Child colic* at *t*1, *symptoms of vomiting/diarrhea/constipation* at *t*1 and *t*5, *abdominal pain* at *t*5 (all measured by separate non-validated questions) and *child depressive symptoms* at *t*5 (Short Mood and Feeling Questionnaire for children and adolescents from 8–18 years, parent version).[103]

The following potential child predictors by self-report at *t*5 were assessed: *Depressive symptoms* (Short Mood and Feeling Questionnaire for children and adolescents from 8–18 years, child version),[103] *frequent (≥ 1–3 times per week)* a*bdominal pain, frequent (≥ 1–3 times per week) extraintestinal pain* (i.e. headache, back pain, limb pain) in the last year (both measured by separate non-validated questions), and n*egative life events* in the last year (a non-validated checklist of 6 items).

Sociodemographic variables measured were child gender, maternal age and education.

4.2.5. Description of questionnaires

The Hopkins Symptom Checklist exists in a 10-item (HSCL-10) and a 25-item (HSCL-25) version for assessing emotional (i.e., anxiety and depressive–) symptoms.[82, 96] In the TOPP study we used the 25-item version at *t*1 and the 10-item version at *t*5. In contrast to the HSCL-10, the HSCL-25 can be subdivided into categories of anxiety (the 10 first items) and depression (the 15 last items). The items "thoughts of ending your life" and "loss of sexual interest or pleasure" were excluded from the 25-item version questionnaire at *t*1 because some of the mothers who participated in a pilot project perceived them as offensive. In both versions of the questionnaire each item is rated on a scale from 1 ("not at all") to 4 ("extremely"). The mean total scores and the two subscale scores on HSCL-25 range from 1–4, with high scores reflecting higher severity of anxiety/depressive symptoms. To obtain sufficient participants in the analyses and in accordance with conventional cut-off points, we chose a cut-off point of 1.55 on the HSCL-25 (including the two subscales) and 1.85 on the HSCL-10.[96, 104] In addition, we made the variable "*maternal history of psychological distress*" to express the number of times (from *t*1–*t*5) the mothers reported an HSCL score equal to or above the cut-off point. A criterion of one or more times was used as a cut-off for dichotomizing this variable.

The Short Mood and Feeling Questionnaire (sMFQ) is a 13-item questionnaire assessing depressive symptoms in children and adolescents from 8–18 years.[103] The questionnaire exists in parallel child and parent versions. Each item is rated on a three-point scale ("not true," "sometimes true" and "true"). The total scores range from 0–26 with high scores reflecting higher severity of depressive symptoms. In the present study, one item about poor concentration was omitted because of space limitations in the questionnaire. However, we still chose to use the conventional cut-off point of eight, which is considered an indicator of

depression.[103, 105] The MFQ has demonstrated reliability and validity in previous research,[105, 106] has been shown to correlate strongly with the Children's Depression Inventory (CDI),[103] and has previously been used in both population-based and clinical research.[103, 107] The alpha reliability for the short MFQ in this study was 0.86.

4.2.6. Procedure

All families attending 19 child health clinics in eastern Norway in 1993 for the scheduled 18-month vaccination visit were invited to complete a questionnaire. Nurses at the health centers obtained informed consent from the mothers and administered the collection of data for the three first assessments. In the latter assessments, questionnaires were sent by post to the families.

The PhD-candidate was not involved in planning and conduction of the TOPP study, but was invited to include questions about recurrent abdominal pain (RAP) in the questionnaire used at the sixth assessment (*t*6) and to use the data from the previous assessments (*t*1-*t*5). The PhD-candidate received a complete data file with raw data ready for analyses.

4.2.7. Statistics

All statistical analyses were conducted by the PhD-candidate under supervision by a statistician. The Statistical Package for the Social Sciences (SPSS) version 15.0 was used in the statistical analyses. The statistical methods are described in the separate papers.

4.2.8. Ethics

The TOPP study was approved by the Regional Committee on Medical Research Ethics and the Norwegian Data Inspectorate. General ethical guidelines for research have been followed.

Informed written consent has been obtained from the participants. Analyses have been conducted on anonymous data.

5. SUMMARIES OF RESULTS

Paper 1 *Diagnosing pediatric functional abdominal pain in children (4-15 years) according to the Rome III criteria: Results from a Norwegian prospective study*

In this study we wanted to determine the proportion of referred pediatric patients with non-organic abdominal pain meeting the criteria for one or more diagnoses of functional gastrointestinal disorders according to the PRC-III, and explore the distribution of diagnoses. We also wanted to investigate reasons for failure to meet these diagnostic criteria.

Of 152 consecutively referred patients (4-15 years) with recurrent abdominal pain, 142 (93%) patients were diagnosed with FAP, whereas 10 (7%) were diagnosed with an organic gastrointestinal disease. Of the 142 patients with FAP (mean age = 9.4 years, 89 [63%] girls), 124 (87%) met the criteria for at least one specific diagnosis of an FGID. IBS was the most common diagnosis (43%), followed by abdominal migraine (23%), aerophagia (15%), functional abdominal pain (15%) and functional dyspepsia (10%). Eighty-two (66%) children were given one FGID diagnosis, 36 (29%) two, and six (5%) three diagnoses. The most frequent combinations were IBS and aerophagia (38% of the children with overlapping diagnoses) and IBS and abdominal migraine (33%). Eighteen patients (13%) did not fulfil any diagnostic criteria. A pain frequency less than that required (i.e., less than once a week) was the dominating cause (83%).

Paper 2 *Fecal calprotectin concentrations in children with functional gastrointestinal disorders diagnosed according to the Pediatric Rome III criteria*

In this study we wanted to determine whether fecal calprotectin concentrations vary between four groups of pediatric patients with FAP classified according to the PRC-III. The groups were as follows: 1) irritable bowel syndrome (both as the only diagnosis or in combination with other diagnoses [n = 61]), 2) childhood functional abdominal pain (n = 22), 3) a mixed group of patients with abdominal migraine, functional dyspepsia, aerophagia, functional constipation or cyclic vomiting (n = 30), and 4) children with FAP, but unclassified according to the PRC-III (n = 18). The groups were also compared with established age-specific reference ranges.[108]

Of the 152 consecutively referred pediatric patients included in the BAMBI study, 136 (126 FAP, 10 organic) delivered a stool specimen for calprotectin analysis. Of the 126 patients with FAP, 113 (90%) had fecal calprotectin levels within normal limits and just slightly elevated for the remaining children. Eighty-three of the 126 [66%] patients had concentrations below the detection limit of 16 mg/kg, 30 [24%] had levels between 16 and 50, and nine [7%] had levels between 50 and 100 mg/kg). Four of the 126 patients (3%) had levels above 100 mg/kg (1 aerophagia, 1 functional abdominal pain, 1 functional constipation, 1 unclassified according to the PRC-III). There were no significant differences in median concentrations between the four groups. The median calprotectin concentration of the 27 patients with IBS as the only diagnosis was less than 16 (range <16-92) mg/kg and did not differ from that of the other groups. Eighteen patients did not fulfil any diagnostic criteria according the PRC-III. Their median calprotectin level was less than 16 (range <16-136) mg/kg.

Paper 3 *Functional abdominal pain in children: Significance of child and maternal somatic and mental health on levels of abdominal pain and disability*

In this study we wanted to explore to what extent do consecutively referred pediatric patients with FAP experience emotional and more frequent somatic symptoms compared with school children in a large, population-based reference sample. We also wanted to investigate the prospective value of somatic and mental health in pediatric patients with FAP and their mothers for level of abdominal pain and functional disability measured at a follow-up consultation after 6-9 months.

The current sample of 94 patients (8-15 years) with mothers was extracted from the original clinical sample of 152 patients (4-15 years) included in the BAMBI study. A representative sample of 14 000 school children constituted the reference sample. The results showed that the patients had significantly more emotional and frequent somatic symptoms (headache [OR, 9.2; 95% CI, 5.9–14.6], pain in neck/shoulder [OR, 7.2; 95% CI, 4.1–12.5] and back pain [OR, 6.6; 95% CI, 3.5–12.6]) when compared with the reference sample. In the multivariate, prospective analyses, patient older age and peer problems at baseline predicted more abdominal pain at follow-up, whereas patient older age, emotional symptoms, prosocial behavior and maternal somatic symptoms predicted disability.

Paper 4 *Childhood predictors of recurrent abdominal pain in adolescence: A 13-year population-based prospective study*

In this population-based study exploring potential childhood predictor of recurrent abdominal pain (RAP) in adolescents (14 years), a total of 456 adolescents (56% girls) completed the RAP questions (outcome) at the last assessment. Of these, 58 (13%) met the criteria for RAP, and 36 (62%) were girls.

By multivariate analyses, the following *maternal factors* predicted RAP in adolescence: maternal psychological distress at children's age18 months (OR, 2.5; 95% CI, 1.3–4.8) and a maternal history of psychological distress at children's age 12 years (OR, 3.2; 95% CI, 1.7–6.2). The following *child factors* measured at age 12 years predicted RAP in adolescence: abdominal (OR, 2.5; 95% CI, 1.3–4.9) and extraintestinal pain (OR, 2.3; 95% CI, 1.2–4.4) by maternal report, self-reported extraintestinal pain (OR, 2.9; 95% CI, 1.4–5.9) and self-reported depressive symptoms (OR, 2.4; 95% CI, 1.1–5.1). Maternal physical health problems and negative life events, and gastrointestinal symptoms in toddlers however, did not predict RAP. None of the sociodemographic factors investigated (child gender, maternal age and education) were associated with RAP in adolescence.

6. DISCUSSION

6.1. Discussion of paper 1

6.1.1. The ability of the pediatric Rome III criteria to identify subgroups of FGIDs in children with FAP

The results presented in paper 1 add evidence of the ability of the pediatric Rome criteria to capture distinct and recognizable constellations of gastrointestinal symptoms in children with FAP.[3, 75, 109-111] The rate of specific FGID diagnoses obtained with the PRC-III in our study is in the upper range (87% versus 55–89%) compared to previous studies conducted in tertiary pediatric gastroenterology centers based on the PRC-II, indicating that the PRC-III are at least as sensitive as the PRC-II in classifying FGIDs in children.[75, 109-111] So far, only one study in addition to the BAMBI study, has explored the ability of the PRC-III to classify FGIDs in children with FAP.[109] Barber et al. compared classification results using the PRC-II and PRC-III for the pain-related FGIDs (irritable bowel syndrome, functional dyspepsia, abdominal

migraine, childhood functional abdominal pain, childhood functional abdominal pain syndrome) in a sample of pediatric patients (8-17 years) with FAP in tertiary health care.[109] Although some small differences, which may be due to differences in study population and inclusion criteria, the distribution of the pain related PRC-III diagnoses are relatively similar to our results (table 2).

Table 2. Distributions of FGID diagnoses according to Rome II versus Rome III criteria reported by different studies [a]

FGID diagnoses	PRC-II [b]	PRC-III Baber et al. 2008[c]	PRC-III Helgeland et al. 2009 [c]
Irritable bowel syndrome	20-45	45	43
Abdominal migraine	1-6	23	23
Functional dyspepsia	14-47	15	10
Childhood functional abdominal pain	0-8	11	15
Functional abdominal pain syndrome	-	6	9
None	11-35	13	13

Abbreviations: FGID, functional gastrointestinal disorder; PRC-II, pediatric Rome II criteria; PRC-III, pediatric Rome III criteria.
[a]Distributions are given in percent
[b]Walker et al. 2004,[111] Schurman et al. 2005,[110] Caplan et al. 2005,[75] Baber et al. 2008.[109]
[c]Baber et al. 2008,[109] Helgeland et al. 2009[112]

The proportion of overlapping diagnoses, however, differed notably (34% in our study versus 14% in the study by Barber et al.).[109] With respect to the PRC-II, only two studies have reported the total proportion of the diagnoses that overlapped (20% in a study by Caplan et al. versus 5% in the study by Barber et al.).[75, 109] One explanation for the differences between these three studies may be that Barber et al. only reported overlap between the pain-related

FGID diagnoses, whereas we (using the PRC-III) and the study by Caplan et al. (using the PRC-II) reported overlap between all the pediatric Rome diagnoses. Despite the differences, it appears that the PRC-III have become somewhat more inclusive at the expense of a greater tendency to overlap.

Although our findings support the ability of the PRC-III to classify subgroups of FGIDs in pediatric patients with FAP, it is a question whether the overlap represent co-morbidity (i.e., co-occurrence) of distinct subgroups of an FGID or artificial categories. For example, the high prevalence of both abdominal migraine and aerophagia in our study must be viewed in connection with their significant overlap with irritable bowel syndrome. Episodes of intense abdominal pain, increased flatulence and abdominal distension are not only symptoms for aerophagia and abdominal migraine, but also common symptoms in patients with irritable bowel syndrome.[4] Hence, a pertinent question is whether abdominal migraine and aerophagia are distinct entities or common symptoms of irritable bowel syndrome. With respect to abdominal migraine, some studies support the existence of this diagnostic entity.[3, 113, 114] There is less evidence to support the independent existence of aerophagia.[115] Accordingly, based on research in *adults,* it has also been questioned whether some of the subgroups defined by the Rome criteria represent distinct disorders or different clinical manifestations of a common disorder (i.e., widespread irritation of the gut), at least in some people.[116, 117] Moreover, it has been suggested somewhat different etiology in patients with/without overlapping FGIDs (i.e., predominantly psychological versus predominantly biological etiology), and, consequently, that patients with overlapping diagnosis may benefit from different and more comprehensive treatment strategies (e.g., psychological treatment) than patients without (e.g., physiologic treatment).[117, 118] Whether this applies to children with FAP needs further exploration. Despite the tendency to overlap found in our study, it is

noteworthy that more than two thirds (66%) of the patients meeting a diagnosis according to the PRC-III fulfilled the criteria for only one diagnosis. A better understanding of the background and the implication of the overlap of symptoms is necessary.

6.1.2. The use of the Rome criteria in diagnostic evaluation of patients with recurrent symptoms of abdominal pain

An important task for clinicians is to identify children having an organic gastrointestinal disease. Although our study was not designed to determine the accuracy of the PRC-III to discriminate between functional disorders and organic diseases, this aspect deserves some attention. It has been claimed that it is somewhat meaningless to discuss the ability of the Rome criteria to exclude organic disease since the criteria primarily are designed to classify FGIDs which is defined only by exclusion of structural disease.[119] However, two recent meta-analyses on previous symptom-based criteria (e.g., Manning-, Rome I- and Rome II criteria) for irritable bowel syndrome in adults conclude that the symptom-based criteria *alone* are only moderately helpful in excluding organic disease.[120, 121] This may argue for more extensive investigations in patients with recurrent abdominal pain in order to rule out organic disease. On the other side, results from previous research indicate that the likelihood of organic disease is small in the absence of "red flags" (e.g., unexplained fever, significant weight loss, blood in the stool).[121] These findings argue against an extensive diagnostic investigation in the absence of "red flags" in patient populations with a low prevalence (low pretest probability) of organic gastrointestinal. The presence of "red flags", on the other hand, indicates a higher likelihood (higher pretest probability) of organic disease and may therefore call for additional diagnostic testing.[3, 121]

The low prevalence of organic gastrointestinal disease in our study (7%) is in harmony with previous findings and supports a similar approach as recommended in recent clinical guidelines.[3, 27] The rather low prevalence of patients with alarm symptoms and abnormal test results in our sample may therefore limit the number of patients in need for more extensive investigations.

6.1.3. The utility of the Rome criteria

The purpose of the Rome criteria is to ”promote clinical recognition and legitimization of the FGIDs” and “to develop a scientific understanding of their psychopathological mechanisms to achieve optimal treatment”.[122] However, a criticism has been that the criteria up to now have worked better for research purposes than clinical practice.[122] The development of the criteria has resulted in standardization of inclusion criteria in clinical studies. This has provided better patient homogeneity in the clinical studies and has made comparison of results easier. With respect to the clinical utility on the other hand, a recent American study of pediatric gastroenterologists reported that although knowledge about the Rome criteria is common, incorporation in clinical practice is not.[123] A previous Norwegian study revealed that general practitioners in Norway did not know or use the Rome II criteria to diagnose FGIDs in adults.[124] A similar situation for the pediatric version of the criteria would probably have been revealed had it been assessed. It is also my impression that the pediatric criteria were not incorporated into clinical practice among the pediatricians that participated in our study.

Several factors may prevent the dissemination of the Rome criteria in clinical practice. First, it is possible that clinicians do not find the criteria useful because the criteria as yet do not identify subgroups that differ in etiology and responsiveness to treatment.[64, 69] It is also a

question whether the criteria are too detailed and time consuming to use in clinical practice. Second, in accordance with the biomedical tradition for understanding any disease, the fact that there are no biological markers for FAP may reduce the interest for and knowledge about functional disorders. This may in turn affect the clinicians' willingness to incorporate the criteria in their clinical practice. Third, a possible gap between current clinical guidelines and education of clinicians may also be a factor that prevents dissemination of the Rome criteria in clinical practice.

6.1.4. In conclusion

The existing PRC-III seem to represent important steps in the development of knowledge towards enhanced understanding of FAP and thereby better management. The ability of the PRC-III to classify the patients in our study shows promise for improving diagnosis and support the use of the criteria as a diagnostic tool. However, the criteria are still insufficient, controversy exists and the criteria do not seem to be implemented in clinical practice.[62, 123] In the absence of diagnostic markers and as long as the etiology of FAP is unrevealed, it is likely that future use of symptom-based criteria, although maybe different from the current version, is a reasonable way of diagnosing FAP in patients, when used in combination with patient history and physical findings.

6.2. Discussion of paper 2

6.2.1. Fecal calprotectin concentrations in pediatric patients with FAP

In harmony with previous research, the vast majority of the patients in the BAMBI study had fecal calprotectin concentrations within the normal range, although differences in sample selection (e.g., different definition of FAP, age and study setting) make direct comparison of

results somewhat difficult.[42-45] Since our study was performed, other studies of children and adults that support our findings have been published.[39, 125] Only one study published in 2008 reported moderately elevated fecal calprotectin concentrations in 76 pediatric patients with FAP when compared with 46 healthy controls.[126]

Our results suggest that fecal calprotectin concentrations do not differ between subgroups of patients with FAP in the BAMBI study. The majority of patients (66%) had fecal calprotectin concentrations below the detection limit of 16 mg/kg and just slightly elevated for the remaining. Thus, a possible limitation of the current study is lack of statistical power making the study insensitive to small differences between the groups. Furthermore, we did not examine histopathologically whether a low grade mucosal inflammation was present in our patients or not. Thus, our conclusion in paper 2 (i.e., gastrointestinal inflammation is not a significant part of the pathogenesis of FAP) is not appropriate. The role of low grade mucosal inflammation as an etiological factor in FAP (e.g., irritable bowel syndrome) is receiving considerable attention.[38] Although several studies report negative results with respect to fecal calprotectin, it is possible that inflammatory cells other than neutrophils play a more prominent role in the gastrointestinal mucosal inflammatory processes.[33, 127-129] A recent study of adults found another inflammatory marker than fecal calprotectin (e.g., human β-defensin-2) to be a better indicator of the inflammatory changes involved in the pathophysiology of FAP.[39]

The utility of fecal calprotectin appears to be more relevant in clinical practice as a diagnostic test to differentiate symptoms of FAP from organic gastrointestinal disease. Fecal calprotectin has been promoted as an inexpensive, non-invasive marker of inflammatory bowel disease among patients with chronic or recurrent gastrointestinal symptoms.[43, 130, 131] Accordingly, of

all patients included in the BAMBI study, those with a value beyond 100 (six patients) underwent gastroscopy and colonoscopy (with exception of one child with a slightly elevated value and who recovered from pain before the endoscopies). The two patients diagnosed with inflammatory bowel disease in our sample both had markedly elevated fecal calprotectin

6.2.3. In conclusion

The vast majority of pediatric patients with FAP have fecal calprotectin concentrations within the normal range and the fecal calprotectin concentration do not appear to differ between subgroups of patients FAP. It appears that other inflammatory markers than fecal calprotectin are better indicators of the inflammatory changes involved in the pathophysiology of FAP.

6.3. Discussion of paper 3 and 4

6.3.1. Somatic and emotional co-morbidity in children and adolescent with FAP

Although our findings of more emotional (i.e., anxiety and depressive) and frequent somatic (i.e., headache, back pain, pain in shoulder/neck, dizziness) symptoms in pediatric patients with FAP than in school children in the general population echo previous findings, the control groups in earlier studies are small and represent selected groups of children (paper 3).[9-12] The use of the large, representative reference sample and the large differences between the clinical sample and the reference sample in paper 3 are therefore noteworthy. The odds ratios and the lower border of the confidence intervals clearly support that differences are likely to exist. However, the exact differences between the samples must be interpreted with caution because inaccurate estimates may have been introduced due to the small clinical sample. Also in the TOPP-study (paper4) we found that the majority of adolescents with FAP (i.e., RAP) suffered from more somatic co-morbidity than the adolescents without FAP (i.e., RAP). We did not

measure emotional symptom in the adolescents, but such symptoms would probably have been present had it been assessed.[22] A recent population-based study reported 6-year old children with FAP to have more somatic (i.e., headache, limb pain) *and* emotional symptoms (i.e., anxiety) than children without FAP.[13] Thus, it is likely that somatic and emotional co-morbidity is a feature of children with FAP in general, and not only a feature of patients referred to secondary health care.

6.3.2. Predictive- and prognostic factors

Our findings of maternal psychological distress at children's age 18 months and a maternal history of psychological distress at children's age 12 years to predict FAP (i.e., RAP) in the adolescents (14 years) in the TOPP study are noteworthy (paper 4). The prospective design and the long follow-up period of the TOPP study is a contribution to research literature which to date has relied heavily on cross-sectional and retrospective designs to understand FAP. Our results correspond to one of very few previous prospective studies that found parental anxiety and maternal somatic symptoms in the first year of children's life to predict FAP in the children six years later.[34] Thus, maternal psychological distress from early childhood may play a role in the development of FAP, though a causal relationship can not be established. The lack of a predictive value of maternal *physical health* in the TOPP study must be interpreted with caution. An information bias may exist since maternal physical health was only measured by one single question.

Parental somatic and emotional health is also reported to affect the *course* of FAP in children.[26] Again, little prospective research has been conducted. Although the BAMBI study is prospective in the most minimal form (i.e., short follow-up period and assessment at only

two time points), our finding of maternal somatic symptoms to predict functional disability in the patients at follow-up adds previous research (paper 3).[26]

Our findings of extraintestinal somatic and emotional (i.e., depressive) symptoms in preadolescent children (e.g., 12 years old) to independently predict FAP (i.e., RAP) two years later (paper 4) support that such symptoms in children may play a role in development of FAP. The results correspond in part to one population-based prospective study that found somatic symptoms other than abdominal pain (i.e., headache) and psychosocial difficulties to predict new onset of chronic abdominal pain in adolescents.[35] In the TOPP study we did not select adolescent with new onset FAP. Therefore, we can not conclude that emotional and somatic symptoms are "true" predictors for FAP in our sample.[132] Some of the 56 adolescents with FAP (i.e., RAP) most likely had symptoms of abdominal pain when they were 12 years old. However, somatic symptoms (e.g., abdominal pain, headache, limb and musculoskeletal pain) in children and adolescents are likely to coexist and appear to persist in some children.[133-136]

In the TOPP study, the predictive value of child emotional (i.e., depressive) symptoms at age 12 years for FAP (i.e., RAP) two years later is also noteworthy (paper 4). Again little longitudinal research exists, and interestingly, the association between FAP and anxiety/depressive symptoms reported in previous studies has mainly been examined without taking the co-morbidity with other somatic symptoms, a possible confounder, into consideration. There seems to be an association between *somatic* and anxiety/depressive symptoms in general, not just between FAP and anxiety/depressive symptoms.[133, 137, 138] However, the causal direction of the associations cannot be established from most of these studies because of their cross-sectional design.

The fact that higher levels of emotional symptoms in the patients in the BAMBI study also were found to predict more functional disability at follow-up (paper 3) underscore the importance of co-morbid symptoms as prognostic factors. Previous research has reported emotional *and* somatic co-morbid symptoms to negatively affect the prognosis in children with FAP, although little prospective research has been conducted.[26, 57] It is possible that children with FAP and emotional and somatic co-morbidity are more vulnerable to adopt a chronic sick role than children with less co-morbid symptoms. Such an explanation corresponds to previous findings of somatic and emotional symptoms, as well as disability to be associated with less efficient coping of life stress in this patient group.[139-141]

The reason why child somatic co-morbidity and maternal emotional symptoms did not predict level of abdominal pain or functional disability at follow-up in the BAMBI study is difficult to explain, but may be due to methodological limitations, at least partly. Like most previous research we explored children with FAP as one group. Thus, variations within the group may have been masked. For example, the *mean* level of disability was low, despite variations in disability within the sample. This may be contributing to the negative findings of significant associations between some of the potential baseline predictors and functional disability at follow-up.

The associations between parental and child symptoms reflect, as mentioned in the background section, both environmental and hereditary influences.[36] The relative contribution of genetic and environmental factors, however, is still disputed and the results from twin studies are conflicting, but there appears to be a strong environmental influence.[33, 37, 142] Social learning and reinforcement of child illness behavior have been suggested as

possible mechanisms.[36, 143] Parents' own health, health experiences and cognitions (worries, beliefs and fears) may affect their responses to symptoms and illness in them selves and their children, thereby affecting their child's responses to pain.[144-146] With respect to genetic factors, some studies of twins have reported a genetic influence on development of FAP (i.e., irritable bowel syndrome),[142, 147-149] but controversy exists.[150] The possible heritable component and the genetics are poorly understood.[37] A genetic disposition can give rise to physiological effects, but can also make a child more vulnerable to environmental or social factors that in turn affect the gastrointestinal functioning via the brain-gut axis.[36] Various gene polymorphisms are suggested to be relevant for the pathogenesis of FAP, but more research is needed in this field. [33] Previous research has also raised the issue whether there are common genetics predispositions for FAP *and* a vulnerability to anxiety and somatization. [33, 37]

Negative life events (NLE) in childhood did not predict FAP (i.e., RAP) in the adolescents in the TOPP study (paper 4). Unfortunately, we did not measure NLE in the BAMBI study. Thus, we did not have an opportunity to explore NLE as a potential prognostic factor. Prior research suggest *major* NLE to precede onset and exacerbations of symptoms in adult patients with FGIDs,[151, 152] and NLE are also reported to predict symptom maintenance in both adult and child samples.[3, 153, 154] However, the experience of life events is influenced by factors such as emotional health, illness attitudes, personality traits and coping strategies.[19, 36, 155] This complicates inferences of associations between NLE and FAP. A possible explanation of the negative results in the TOPP study may be the relatively long period between the reported NLE and the outcome. Moreover, assessment of life events by questionnaires may not give valid information. In general, measures based on interviews are thought to give more valid information.[48, 156]

6.3.3. In conclusion

Results from the TOPP (paper 4) and the BAMBI (paper 3) study support that somatic and emotional symptoms in parents and children may be of importance in development and maintenance of FAP in children. Despite some discrepancies and the somewhat scarce findings especially in the prospective analyses of data from the BAMBI study, the main findings in paper 3 and 4 in general are in harmony with previous research and the prevailing understanding of FAP in a biopsychosocial perspective. The discrepancies from previous research may in part be due to methodological differences (e.g., differences in sample selection and measurement) and lack of statistical power due to the relative small samples in both our studies. However, the discrepancies are also likely to reflect the complexity of FAP and the intricate relationship between the investigated factors when these are explored in multivariable regression models.

7. METHODOLOGICAL CONSIDERATIONS

7.1. Internal validity

The validity of a study can be split into internal and external validity.[157] If the internal validity of a study is low, the quality of evidence that can be derived from a study is poor.[158] The internal validity of a study is considered a prerequisite for its external validity. In general, two types of error may adversely affect the measurement process and limit the internal validity of research results: Random and systematic (i.e., selection bias, information bias and confounding) errors. Features in study design, measurement and analysis may give rise to or limit such errors.

7.1.1. Random error

Random error is unpredictable variability in measurement arising purely by chance, is always present in measurement and can be handled by statistical methods (e.g., p-values, confidence intervals).[159] The amount of random error is reduced as the sample size enlarges. Hence, enlargement of sample size is the most important way to limit random error. The relative small sample size in the BAMBI study may have enhanced the inherent random error, lowered the precision of measurement (as indicated by vide confidence intervals) and thereby opened for type I and II errors. The sample in the TOPP study is fairly large, and the effect of random error is somewhat less.

7.1.2. Selection bias

Factors that influence the selection of participants (how and who we select) and the actual participation (who are the respondents/non-respondents at baseline, who are lost to follow-up) may give rise to selection error (i.e., systematic differences between respondents and non-respondents with respect to the investigating variables and confounding factors).[157] The consecutive recruitment from well described populations and the high baseline participation rates in the BAMBI and the TOPP study most likely resulted in a rather non-biased sampling of participants. In the TOPP study, non-respondents at baseline ($t1$) did not differ significantly from respondents with respect to maternal age, education, employment status, number of children and marital status. In the BAMBI study there was no differences between participants and non-participants with respect to age and gender. Unfortunately, we did not have data to explore possible differences between participants and non-participants with respect to other characteristic.

The high participation rate at follow-up (94%) in the BAMBI study limits the possibility of selection bias due to attrition. By inspection of baseline data, these children did no represent any outliers with respect to the investigated variables compared to the 88 participants. In the TOPP study however, there was a substantial loss of participating mothers from *t*1 to *t*5. The higher levels of psychological distress in mothers lost to follow-up compared to participating mothers may have resulted in an underestimation of the observed association between maternal psychological distress in childhood and RAP in adolescence. The reduction of the sample size also questions the prevalence of RAP found in the TOPP study, though corresponding to results from previous research.[22]

7.*1.3. Information bias*

How we collect information about or from study participants may also be erroneous.[157]
In the BAMBI study, the diagnoses of organic/non-organic (i.e., FAP) abdominal pain were left to the discretion of the pediatricians.Their diagnoses were no subject for further validation. Some of the diagnoses may therefore be inaccurate. However, the rather extensive primary investigation and the 6-9 months follow-up make it unlikely that significant organic disease was missed. This is also supported by previous studies where less than 5% of patients diagnosed with recurrent abdominal pain in a tertiary care centre and 3% of patients diagnosed with an FGID in a primary care setting developed organic disease during the year following the first medical evaluation.[27, 160]

The extensive reliance on questionnaire data in both our studies is likely to reduce the internal validity. Ideally, a combination of several methods (questionnaires, interviews and observational data) provide a more "complete picture". For example, measures based on interviews are thought to give more valid information about negative life events,[48, 156] and

questionnaire data can not replace more detailed psychiatric assessment.[161] The use of non-validated questions may also have reduced the quality of our data, although we used validated instruments and established cut-off points to a large extent. For example, in the TOPP study, maternal physical health problems were measured by only one question which is unlikely to provide a "correct" measure of such problems. The definition of "physical health problems" is also likely to vary between individuals. This may have affected the classification of mothers (i.e., mothers with/without physical health problems). Moreover, the arbitrary cut-off for dichotomizing the score of negative life events in the TOPP study may also have given rise to some degree of misclassification.

In the TOPP study, all baseline (*t*1) variables were reported by the mothers. Maternal characteristics (e.g., emotional and physical illness, personality) and her environmental context may have influenced her perceptions of the child.[162] However, the fact that the outcome variable (FAP in the adolescents) was measured by adolescent self-report most likely prevents, to some extent, inflated associations. In the BAMBI study on the other hand, the sole reliance on child self-reported abdominal pain, somatic comorbidity and functional disability, may have inflated the association between these variables due to shared methods variance.

In the BAMBI study, child emotional symptoms were only measured by the mothers and teachers. Most previous research suggests that third-part informants (e.g., parents and teachers) report lower levels of emotional symptoms than those reported by children, although controversy exists.[163] Parents and teachers may have limited knowledge about children's emotional state and may underreport emotional symptoms.[164] On the other hand, it is possible that parents and teachers of children with chronic pain are more aware of the children's

symptoms and problem behavior.[165]

Finally, in the TOPP study, the recall period was relatively long (i.e., participants had to recall past events in the last 12 months). Thus, we cannot exclude an inaccuracy (overestimation or underestimation) in their reporting.[166] It is also a question whether translation of four questionnaires from English into Norwegian introduced some discrepancies between the original and the translated versions of the questionnaires.[167] A formal validation of the Norwegian versions has not been conducted.

7.1.4. Confounding

The third systematic error that reduces the internal validity of study results is confounding which means confusion or mixing of effects.[157] When the association between an independent and a dependent variable is mixed together with the effect of another variable, which has an effect on both the independent and the dependent variable, this other variable is a confounder.[168] The effect of a confounder can be dealt with by statistical means (e.g., the association between the independent and the dependent variables can be explored together with possible confounders in a multivariate regression model).[169]

The investigated associations in the BAMBI and the TOPP studies are vulnerable for a possible confounding effect of several unmeasured factors. Examples of possible confounders in our studies may be: *Paternal health* was not measured in the TOPP study and was not included in the analyses in the BAMBI study. This factor may have confounded the association between maternal somatic symptoms at baseline and disability in the pediatric patients at follow-up in the BAMBI study (paper 3), or, in the TOPP study, the association between maternal emotional symptoms measured at baseline and FAP (i.e., RAP) in their

offspring 13 years later (paper 4). Further, in the BAMBI study, we did not measure *negative life events* which may be a possible confounder of, for example, the association between child emotional symptoms at baseline and their functional disability measured at follow-up. A last example, *child emotional symptoms* at baseline (*t*1) were not recorded in the TOPP study and may be a confounder of the observed association between maternal emotional symptoms at baseline (*t*1) and FAP (i.e., RAP) in their offspring 13 years later (*t*6).

7.2. External validity

External validity (also called generalizability or representativeness) denotes the extent to which the results of a study can be applied to other groups, settings or situations.[158] The external validity of our results depends primarily on whether the participants in the BAMBI and the TOPP study systematically differ from the target populations. However, the external validity is not considered relevant if the quality of evidence (internal validity) that can be derived from a study is poor.[158]

7.2.1. The BAMBI study

The high participation rates (86% at baseline, 94% at follow-up) and the consecutive recruitment of patients referred from general to pediatric practice within a well-defined geographic area most likely make the results representative for children with sufficient abdominal pain referred to secondary health care, at least in Norway. However, the results may not be similarly applicable to pediatric patients with other FGIDs than FAP, in other age groups, and to children with FAP in the general population. Furthermore, the homogeneous ethnicity in the BABI study may also limit the external validity of our results to more multiethnic populations. Finally, our results may not be representative for other nations or cultures because the tendency to seek medical advice for complaints and referral patterns

within the medical community may differ. With respect to the reference sample in the BAMBI study (paper 2), the random selection of school classes, the high participation rate (84%) and the size of the sample most likely make this sample representative, at least for Akershus county.[71-73]

7.2.2. The TOPP study

The large proportion (95%) of all Norwegian families with children attending a public health program during the first years of the children's life, the consecutive recruitment of participants and the high baseline (*t*1) participation rate (85%) in the TOPP study enhance the external validity of the results. Accordingly, the sample at *t*1 was found to be representative of the diversity of social environments of families with children at age 1-2 years in Norway.[170] On the other hand, the reduction of the sample size during time questions the representativeness of the current sample because of a selection bias. Mothers lost to follow-up were younger, less educated and reported more emotional symptoms than the participating mothers (paper 3). This indicates that the mothers that remained in the study were somewhat better functioning than mothers lost to follow-up.

8. CLINICAL IMPLICATIONS

8.1. Incorporation of the PRC-III in clinical practice?

Although the development of the Rome criteria appears to have contributed to an enhanced awareness, understanding and legitimization of FAP and the other FGIDs in children, it is my impression, as claimed by others, that the criteria still are a better tool for research than clinical practice.[63, 122] The insufficiency of the criteria should not lead to rejection of the criteria or abandonment of the principle of a positive diagnosis, but rather stimulate research on the validity and clinical utility of the PRC-III.

8.2. Screening of co-morbid symptoms in pediatric patients with FAP

Since presence of excess co-morbidity in patients with FAP may identify patients with somewhat different etiology and may be a marker for a negative course,[26, 117, 171] screening of such symptoms as part of the standard medical evaluation can be an important guide for diagnostic assessment and identification of patients at risk for sustained pain. To what extent clinicians *systematically* recognize and incorporate somatic and emotional comorbidity in their evaluation and management of children with FAP is uncertain. A recent study of American pediatric gastroenterologists reported that psychological evaluation was included in "standard" assessment for only 5% of the pediatric gastroenterologists.[123]

Identification of excess co-morbidity in children with FAP can also be an important guide for choice of treatment. Based on research in adults, excess co-morbidity is suggested to be a marker for psychological influences on etiology in patients with irritable bowel syndrome.[116-118, 172] Thus, it may turn out that psychological therapies (e.g., cognitive-behavioral therapy and hypnotherapy) or centrally acting drugs are especially beneficial in these patients.[118, 173].

8.3. Screening of the patients' contextual frame

In general, a family-centred perspective is of importance in treatment of all children. Accordingly, results from the TOPP and the BAMBI study underscore that maternal health is of importance in children with FAP (paper 2 and 3). Parental somatic and emotional health is consistently reported to predict poorer child/adolescent functioning and psychological adjustment across a range of chronic health conditions.[174] Maternal fear about their child's abdominal pain is also reported to differentiate between consulters versus non-consulters.[175] These findings underscore the importance of a focus that is wider than just on the patient's

symptoms. Parent's health problems or fears may maintain pain and disability in their child and oppose progress in treatment of the child. Thus, addressing such factors may be a key to success in treatment of children with chronic and disabling pain.

Identification and treatment of somatic and emotional symptoms in mothers may be another implication of our findings. As far as I know, no study has explored the potential beneficial effects of treating such symptoms in parents of children with FAP. However, there is some evidence that treatment of maternal depression improves children's psychopathology and functioning.[176] Thus, improvement of maternal mental health may be a reasonable strategy as an adjunct when handling children and adolescents with FAP.

8.4. Management of children FAP – a responsibility of specialist health care?

Children with chronic, severe and disabling symptoms may need referral to specialist health care. It is, however, my general impression, although somewhat speculative, that many pediatricians in specialist health care primarily focus on exclusion of organic disease rather than further management of these children. When I worked as a clinician in a child- and adolescent psychiatric outpatient clinic five years ago, it was also my impression that there were very few children with severe and disabling symptoms of FAP among our patients. Although some parents of children without physical findings may resist referrals to mental health services, one might speculate as to whether this situation also reflect that children with FAP seldom are referred to or accepted for further *management* in pediatric and mental specialist health care, at least in Oppland and Hedmark. According to a traditional and biomedical disease-based model, the complexity of FAP (i.e., not being a straight forward organic disease or emotional disorder) may lead to that children with FAP do not belong neither in pediatric nor psychiatric clinics.

The complexity of FAP underscores that children with chronic, severe and disabling symptoms belong in both pediatric and mental specialist health care services and that interdisciplinary cooperation is necessary. Such cooperation is likely to enhance the focus of FAP as a biopsychosocial disorder, open for a broader understanding and exploration of factors relevant for maintenance of patient symptoms and disability, and enhance accomplishment of a tailored, multi-targeted therapy. This may also help the families to accept a diagnosis of FAP, stimulate beneficial coping of the child's pain, and hopefully prevent new consultations, a growing mistrust to the health care system and continuation of child illness behavior.

9. FURTHER RESEARCH

Despite much research on FAP and the other FGIDs in the last years, there is still more to be revealed with respect to etiology, diagnostic assessment and treatment. Compared to abundant research in adults, far less research has been performed in children and adolescents. However, children are not small adults, and results from research on adults may not be applicable in children. Thus, there is a general need for more research in children and adolescents with FAP.

There is a need for further studies to elucidate the etiology of pediatric FAP. Research on possible pathophysiological mechanisms on a molecular and genetic level may support the existence of diagnostic subgroups defined by the existing Rome criteria or identify other subgroups of patients, and may also identify targets for treatment (e.g., inflammatory changes in some patients with FAP may be targets for anti-inflammatory agents).[38] However, it is important to focus also beyond the gut. There is a general need to perform longitudinal

observational studies to increase the quality of evidence, hitherto mostly based on cross-sectional studies. Studies that follow a cohort of children with FAP to adulthood may contribute with knowledge about the natural course of FAP and the evolution and the nature of the observed co-morbidity. Whether different subgroups of FAP as defined by the Rome criteria (or by other phenotypic characteristics) differ in course is unknown. The prognostic value of childhood FAP needs also further elucidation. Few studies have, for example, explored the prognostic value of childhood FAP on development of psychiatric disease in adulthood.[53] Another area for investigation may be the interplay of parental ill health (both in mothers and fathers) *and* adjustment and functional impairment in children with FAP. Enhanced understanding in these areas may lead to a better identification of individuals at risk of a negative outcome, and will thereby benefit both diagnostic and treatment.

Further research should also confirm the existence of the diagnostic categories defined by the PRC-III. A better understanding of the overlap of different subgroups may lead to refinement of the Rome criteria and may facilitate clinical management. In parallel of research on the existing criteria, there is a need for future studies to explore the existence of potential other subgroups classified according to other symptoms than the symptoms included in the PRC-III (e.g., patients with higher/lower levels of co-morbidity). Furthermore, the value of a positive symptom-based approach should also be explored. Beneficial effects of such an approach have been claimed and a symptom-based approach constitutes a fundament in recent clinical guidelines,[61, 62] although there is limited evidence to support it. Finally, the utility of the Rome criteria in combination with different alarm features in diagnosing FAP is another area for investigation. Other acceptable ways of diagnosing FAP without extensive and expensive testing should also be explored.

There is a general need for randomized controlled trials of the different treatment strategies that have been suggested. Taken the complexity of FAP into consideration, research should focus on multicomponent treatment strategies (for example, the effect of education programs and parental counselling in combination with different psychological therapies, or psychological treatment in combination with medication), but also investigate which components actively contribute to improvement. Identification of specific subgroups that benefit from specific interventions should also be explored (e.g., whether pediatric patients with FAP and high level of co-morbidity are more likely to benefit from cognitive therapy or hypnotherapy than those with low level of co-morbidity). Finally, results from the TOPP study suggest that maternal emotional symptoms may be a target for intervention. Whether children with FAP benefit from interventions directed at such symptoms in mothers is largely unexplored.

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ERRATA

Page 7, line 1: “Helgeland H, Flagstad G, Grøtta J, Markestad T, Kristensen H” is corrected to ”Helgeland H, Flagstad G, Grøtta J, Vandvik PO, Kristensen H, Markestad T”

Page 10, section 2.1, line 3: ”.between 8 and years” is corrected to ”between 8 and 10 years”

Page 31, last sentence on the page: “Table 2 gives…” is corrected to “Table 1 gives…”

Page 32, the heading of the table: “Table 2.” is corrected to “Table 1.”

Page 41, table 2, second column, bottom row: ”32” is corrected to “11-35”, and

Page 41, table 2, footnotes, line 4: “[a]Walker et al. …” is corrected to “[b]Walker et al. …...”

Paper 1, page 314, first column, line 10 from the bottom: “…answer whether…” should read “answer whenever…”

Paper 3, Table 3 and 4, first column, line one: “Dependent variables” is corrected to “Independent variables”

Paper 4, page 363, table 3, fifth column, line 8: “111” should read “11” patients with RAP.

APPENDIX

The pediatric Rome III criteria for functional gastrointestinal disorders (FGIDs)

Irritable Bowel Syndrome

Must include *all* of the following:
1. Abdominal discomfort or pain associated with two or more of the following at least 25% of the time.
a. Improved with defecation
b. Onset associated with a change in frequency of stool
c. Onset associated with a change in form (appearance) of stool
2. No evidence of an inflammatory, anatomic, metabolic or neoplastic process

Abdominal Migraine

Must include *all* of the following:
1. Paroxysmal episodes of intense, acute periumbilical pain that lasts for 1 hour or more
2. Intervening periods of usual health lasting weeks to months
3. The pain interferes with normal activities
4. The pain is associated with two or more of the following.
a. Anorexia
b. Nausea
c. Vomiting
d. Headache
e. Photophobia
f. Pallor
5. No evidence of an inflammatory, anatomic, metabolic or neoplastic process

Aerophagia

Must include *at least two* of the following:
1. Air swallowing
2. Abdominal distention because of intraluminal air
3. Repetitive belching and/or increased flatus

Functional dyspepsia

Must include *all* of the following:
1. Persistent or recurrent pain or discomfort centered in the upper abdomen (above the umbilicus)
2. Not relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e., not IBS)
3. No evidence of an inflammatory, anatomic, metabolic or neoplastic process

Functional Constipation

Must include *two or more* of the following.
1. Two or fewer defecations per week
2. At least one episode of fecal incontinence per week
3. History of retentive posturing or excessive volitional stool retention
4. History of painful or hard bowel movements
5. Presence of a large fecal mass in the rectum
6. History of large diameter stools that may obstruct the toilet

Cyclic Vomiting

Must include *both* of the following.
1. Two or more periods of intense nausea and unremitting vomiting or retching lasting hours to days
2. Return to usual state of health lasting weeks to months

Adolescent Rumination Syndrome

Must include *all* of the following:
1. Repeated painless regurgitation and rechewing or expulsion of food that
a. begins soon after ingestion of a meal,
b. does not occur during sleep, and
c. does not respond to standard treatment for gastroesophageal reflux
2. No retching
3. No evidence of an inflammatory, anatomic, metabolic or neoplastic process

Functional Abdominal Pain

Must include *all* of the following:
1. Episodic or continuous abdominal pain
2. Insufficient criteria for other FGIDs
3. No evidence of an inflammatory, anatomic, metabolic or neoplastic process

Functional Abdominal Pain Syndrome

Must satisfy criteria for childhood functional abdominal pain and have at least 25% of the time and *one or more* of the following:
1. Some loss of daily functioning
2. Additional somatic symptoms such as headache, limb pain or difficulty sleeping

BAMBI-STUDIEN
LEGENS ROLLE VED FØRSTE KONSULTASJON

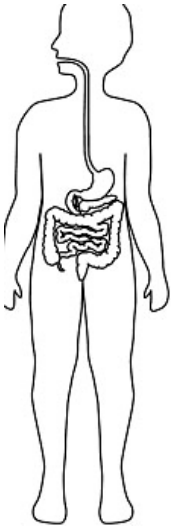
(protokoll for barnelegene)

1. Sjekke at sykepleier har fylt ut skjemaene til Helene Helgeland, inkl. samtykke
2. Sjekke at 3 avføringsprøver er undersøkt for blod (Hemofec) og at urin-stix er avlest
3. Sjekke at veiing, høyde- og blodtrykksmåling er utført
4. Klinisk undersøkelse.
5. Tilleggsundersøkelser:
    - Alle barn: Blodprøve: Hb, LPK med differensialtelling, blodplater, kreatinin, ALAT, GT, amylase, total IgE og matvarepanel, SR, ferritin, serum-folat, cøliakiprøver, hemofec i avføring (3 prøver), urin stix.
    - Alle barn:10 ml blod tas på glass med rød kork – serum separeres på sykehuset. Serum sendes til Laboratoriet med rekvisisjon, Gjøvik for nedfrysing i 70 grader i biobank.
    - Ved mistanke om obstipasjon: Røntgen oversikt abdomen (et enkelt bilde)
    - Én avføringsprøve for undersøkelse av kalprotektin.
        - ✓ Familien får med hjem navnet glass til avføring, samt utfylt rekvisisjonsskjema til Ullevål og konvolutt for prøvesending til Ullevål.
    - Kan gjøres på indikasjon:
        - ✓ Dyspepsi av ulcustype: 24 timers pH-registrering i øsofagus, eventuelt endoskopi.
        - ✓ Andre tilleggsundersøkelser: F.eks. ultralyd- og røntgen-undersøkelser, laktosebelastning.
6. Sørge for at det settes opp til kontroll om 6 måneder. Prosjektsykepleier har ansvar for å koordinere timeavtale mht. tidspunktet.

SPØRRESKJEMA OM MAGE-TARM-SYMPTOMER HOS BARN
Roma III versjon (QPGS-RIII)

Tilpasset etter Spørreskjema om pediatriske gastrointestinale symptomer
(Questionnaire on Pediatric Gastrointestinal Symptoms)
Walker, Caplan-Dover & Rasquin-Weber 2000, revidert 2006

Foreldre rapporteringsskjema
Gjelder barn f.o.m. 4 år



Veiledning

Dette spørreskjemaet handler om ditt barns fordøyelsessystem (spiserør, mage, tynntarm og tykktarm) og problemer man kan ha med det. Noen av problemene kan gjelde barnet ditt, andre ikke.

Forsøk å besvare alle spørsmålene så godt som du kan. Hvis det er umulig for deg å svare på et bestemt spørsmål, kan du svare "Jeg vet ikke" der dette er et alternativ.
Hvis du har noen spørsmål, vil forskningsmedarbeideren gjerne være til hjelp!

Dagens dato: …… Barnets fødselsdato: ……..

Barnets kjønn: (1) Gutt (2) Pike

Hvem fyller ut skjemaet:

(1) Mor (2) Far (4) Andre; hvem:_____

Seksjon A: SMERTE OG FØLELSE UBEHAG I ØVRE DEL AV MAGEN OVENFOR NAVLEN

Den stiplede linjen i bildet nedenfor viser et område OVENFOR navlen hvor barn av og til har vondt, smerter eller har en følelse av ubehag. Noen ord for disse følelsene er magesmerter, kvalme, oppblåsthet, metthetsfølelse eller ikke være sulten etter å ha spist veldig lite.

Ovenfor navlen

Spørsmålene i denne delen av spørreskjemaet er om mage*smerter* og følelse av *ubehag* OVENFOR navlen, og som barnet ditt kan ha hatt i løpet av *de 2 siste månedene*.
Barn kan ha smerter og følelse av ubehag i mer enn et område av magen. I en annen del av dette spørreskjemaet vil du få spørsmål om områdene rundt og nedenfor ditt barns navle.

1. *I de siste2 månedene,* hvor ofte hadde barnet smerte eller følelse av ubehag i øvre del av magen *ovenfor navlen?*
   - 0. € Aldri
   - 1. € 1-3 ganger i måneden
   - 2. € 1 gang i uken
   - 3. € Flere ganger i uken
   - 4. € Hver dag

Hvis barnet ditt ikke har hatt noe smerter eller følelse av ubehag ovenfor navlen de siste to månedene, vær snill å gå direkte til Seksjon B.

2. Hvilke følgende følelser hadde barnet ditt ovenfor navlen de siste 2 månedene? (Dere kan velge flere alternativer)

a. Smerte	0. € Nei	1. € Ja
b. Kvalme	0. € Nei	1. € Ja
c. Oppblåsthet	0. € Nei	1. € Ja
d. Metthetsfølelse	0. € Nei	1. € Ja
e. Ikke være sulten etter å ha spist meget lite	0. € Nei	1. € Ja

3. I de siste 2 månedene, hvor vondt eller hvor stort ubehag hadde barnet ditt i magen *ovenfor navlen*?
   - 1. € Litt
   - 2. € Noe (mellom litt og mye)
   - 3. € Mye
   - 4. € Veldig mye
   - € Jeg vet ikke

4. Når barnet ditt hadde smerter eller en følelse av ubehag *ovenfor navlen,* hvor lenge varte det?

1. € Mindre enn en time
2. € 1-2 timer
3. € 3-4 timer
4. € Det meste av dagen
5. € Hele tiden

5. Hvor lenge har barnet ditt hatt smerter eller en følelse av ubehag *ovenfor navlen*?

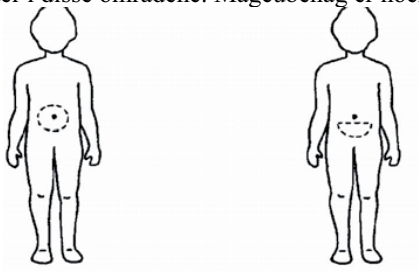
1. € 1 måned eller mindre
2. € 2 måneder
3. € 3 måneder
4. € 4-11 måneder
5. € 1 år eller lengre

Sett RING rundt det tallet du synes passer best til hvert spørsmål nedenfor:

Når barnet ditt hadde magesmerter eller følelse av ubehag ovenfor navlen, i de 2 siste månedene, *hvor ofte*:	**0% av tiden** **Aldri**	**25% av tiden** (en firedel av tiden) **En gang i mellom**	**50% av tiden** (halvparten av tiden) **En god del ganger**	**75% av tiden** (tre firedeler av tiden) **Det meste av tiden**	**100% av tiden** **Alltid**	**Jeg vet ikke**
6. Ble smerten eller følelsen av ubehag bedre etter at barnet ditt hadde en avføring?	0	1	2	3	4	x
7. Var ditt barns avføring (bæsj) mykere og bløtere eller mer vandig enn vanlig?	0	1	2	3	4	x
8. Var ditt barns avføring (bæsj) hardere eller mer klumpet enn vanlig?	0	1	2	3	4	x
9. Hadde barnet ditt flere avføringer enn vanlig?	0	1	2	3	4	x
10. Hadde barnet ditt færre avføringer enn vanlig?	0	1	2	3	4	x
11.Følte barnet ditt seg oppblåst?	0	1	2	3	4	x
12.Hadde barnet ditt hodepine?	0	1	2	3	4	x
13.Hadde barnet ditt vanskeligheter med å sove?	0	1	2	3	4	x
14.Hadde barnet ditt smerter i armene, bena eller ryggen?	0	1	2	3	4	x
15.Følte barnet ditt seg svimmel eller trodde det skulle besvime?	0	1	2	3	4	x
16. Gikk barnet ditt glipp av skolen eller stoppet aktiviteter?	0	1	2	3	4	x

Seksjon B: MAGEUBEHAG OG MAGESMERTE RUNDT OG NEDENFOR NAVLEN

Spørsmålene i denne seksjonen er om områdene RUNDT og NEDENFOR ditt barns navle. Disse områdene er vist med stiplete linjer i bildene nedenfor. Barn har noen ganger mageubehag eller smerter i disse områdene. Mageubehag er noen ganger mildere enn smerter.



Rundt navlen ***Nedenfor navlen***

1. I de siste 2 månedene, hvor ofte hadde barnet ditt mageubehag eller smerter *i området rundt eller nedenfor navlen*?
    1. € Aldri
    2. € 1-3 ganger i måneden
    3. € 1 gang i uken
    4. € Flere ganger i uken
    5. € Hver dag

~~Hvis barnet ditt ikke har hatt noe mageubehag~~ eller smerte i områdene rundt eller nedenfor navlen i de siste 2 månedene, vær snill å gå direkte til Seksjon C.

2. I de siste 2 månedene, hvor vondt hadde barnet ditt vanligvis *i området rundt eller nedenfor navlen*?
    1. € Litt
    2. € Noe (mellom litt og mye)
    3. € Mye
    4. € Veldig mye € Jeg vet ikke

3. Når barnet ditt hadde smerter eller følelse av ubehag *rundt eller nedenfor navlen,* hvor lenge varte det?
    1. € Mindre enn en time
    2. € 1-2 timer
    3. € 3-4 timer
    4. € Det meste av dagen
    5. € Hele tiden

4. Hvor lenge har barnet ditt hatt mageubehag eller smerter *rundt eller nedenfor navlen*?
    1. € 1 måned eller mindre
    2. € 2 måneder
    3. € 3 måneder
    4. € 4-11 måneder
    5. € 1 år eller lengre

Sett <u>RING</u> rundt det tallet du synes passer best til hvert spørsmål nedenfor:

Når barnet ditt hadde magesmerter eller følelse av ubehag ovenfor navlen, i <u>de 2 siste månedene,</u> *hvor ofte*:	**0% av tiden** **Aldri**	**25% av tiden** (en firedel av tiden) **En gang i mellom**	**50% av tiden** (halvparten av tiden) **En god del ganger**	**75% av tiden** (tre firedeler av tiden) **Det meste av tiden**	**100% av tiden** **Alltid**	 **Jeg vet ikke**
5. Ble smerten eller følelsen av ubehag bedre etter at barnet ditt hadde en avføring?	0	1	2	3	4	x
6. Var ditt barns avføring (bæsj) mykere og bløtere eller mer vandig enn vanlig?	0	1	2	3	4	x
7. Var ditt barns avføring (bæsj) hardere eller mer klumpet enn vanlig?	0	1	2	3	4	x
8. Hadde barnet ditt flere avføringer enn vanlig?	0	1	2	3	4	x
9. Hadde barnet ditt færre avføringer enn vanlig?	0	1	2	3	4	x
10.Følte barnet ditt seg oppblåst i magen?	0	1	2	3	4	x
11.Hadde barnet ditt hodepine?	0	1	2	3	4	x
12.Hadde barnet ditt vanskeligheter med å sove?	0	1	2	3	4	x
13.Hadde barnet ditt smerter i armene, bena eller ryggen?	0	1	2	3	4	x
14.Følte barnet ditt seg svimmel eller trodde det skulle besvime?	0	1	2	3	4	x
15. Gikk barnet ditt glipp av skolen eller stoppet aktiviteter?	0	1	2	3	4	x

16. I løpet det **siste året,** hvor mange ganger hadde barnet ditt en episode med **svært sterke smerter** rundt navlen som varte **2 timer eller lengre** og som fikk barnet ditt til å stoppe alt som han eller hun drev med?

0. € Aldri *(hvis aldri, vær snill å gå til neste seksjon C)*
1. € 1 gang
2. € 2 ganger
3. € 3-5 ganger
4. € 6 eller flere ganger

16a. I løpet av en episode med svært sterke smerter, hadde barnet noe av det følgende?

a. Ingen appetitt	0. € Nei	1. € Ja
b. Følelse av kvalme (i magen)	0. € Nei	1 € Ja
c. Oppkast	0. € Nei	1. € Ja
d. Blek (i huden)	0. € Nei	1. € Ja
e. Hodepine	0. € Nei	1. € Ja
f. Lysømfiendtlighet (ubehagelig å få lys i øynene)	0. € Nei	1. € Ja

16b. Mellom episoder med svært sterke smerter, blir barnet ditt igjen like frisk som det pleier i flere uker eller lenger?

€ (0) Nei
€ (1) Ja

Seksjon C. AVFØRING (BÆSJING)

Denne delen av spørreskjemaet spør om ditt barns avføring (bæsjing).

1. I de siste 2 månedene, hvor ofte hadde barnet ditt avføring vanligvis?
   1. € 2 ganger i uka eller sjeldnere
   2. € 3-6 ganger i uka
   3. € 1 gang om dagen
   4. € 2-3 ganger om dagen
   5. € Mer enn 3 ganger om dagen € Jeg vet ikke

2. I de siste 2 månedene, hvordan var ditt barns avføring (bæsj) vanligvis?
   1. € (1) Veldig hard
   2. € (2) Hard
   3. € (3) Verken for hard eller for myk
   4. € (4) Veldig myk eller bløt
   5. € (5) Vandig (vanntynn)
   6. € (6) Det varierer (hans eller hennes avføringer er ikke alltid like) € Jeg vet ikke

   2a. Hvis ditt barns avføringer (bæsj) vanligvis var harde, hvor lenge har de vært harde?
      0. € Mindre enn en måned
      1. € 1 måned
      2. € 2 måneder
      3. € 3 eller flere måneder

3. I de siste 2 månedene, gjorde det vondt når barnet ditt hadde en avføring?
   0. € Nei
   1. € Ja € Jeg vet ikke

Sett en <u>RING</u> rundt det tallet du synes passer best til hvert enkelt spørsmål nedenfor:

I de siste 2 månedene, hvor ofte:	**0% av tiden** **Aldri**	**25% av tiden** (en firedel av tiden) **En gang i mellom**	**50% av tiden** (halvparten av tiden) **En god del ganger**	**75% av tiden** (tre firedeler av tiden) **Det meste av tiden**	**100%** **Alltid**	 **Jeg vet ikke**
4. Måtte barnet ditt skynde seg på do for å bæsje?	0	1	2	3	4	x
5. Måtte barnet anstrenge seg (presse hardt) for å få bæsjen ut?	0	1	2	3	4	x
6. Hadde barnet ditt slim (hvitt, gullig, trådaktig eller seigt materiale) i avføringen sin?	0	1	2	3	4	x
7. Hadde barnet ditt følelsen av ikke å være ferdig etter å ha bæsjet *(som om det var mer som ikke ville komme ut)*	0	1	2	3	4	x

8. I de siste 2 månedene, hadde barnet ditt en bæsj som var så stor at den tettet til toalettet?

    0. € Nei
    1. € Ja

9. Noen barn holder på avføringen (bæsjen) sin selv når det er et toalett tilgjengelig. De kan gjøre dette ved å stivne i kroppen eller krysse bena sine. I de 2 siste månedene, hvor ofte prøvde barnet ditt å holde på avføringen (bæsjen) når det var hjemme?

    0. € Aldri
    1. € 1-3 ganger i måneden
    2. € 1 gang i uka
    3. € Flere ganger i uka
    4. € Hver dag

10. Har en lege eller sykepleier noen gang undersøkt barnet ditt og sagt at barnet ditt hadde mye avføring innvendig?

    0. € Nei
    1. € Ja

11. I de siste 2 månedene, hvor ofte var ditt barns undertøy flekket eller skitnet til med bæsj?

0. € Aldri. *Hvis aldri, vær snill å gå til Seksjon D*
1. € Sjeldnere enn 1 gang i måneden
2. € 1-3 ganger i måneden
3. € 1 gang i uka
4. € Flere ganger i uka
5. € Hver dag

11a. Når barnet ditt flekket eller skitnet til undertøyet sitt, hvor *mye* var det flekket eller skitnet til?

€ (1) Undertøyet var flekkete (ingen avføring, kun "bremsespor")
€ (2) Liten mengde bæsj i undertøyet (mindre enn en hel bæsj)
€ (3) Stor mengde bæsj i undertøyet (en hel bæsj)

11b. I hvor lang tid har barnet ditt flekket eller skitnet til undertøyet?

1. € 1 måned eller kortere tid
2. € 2 måneder
3. € 3 måneder
4. € 4-11 måneder
5. € 1 år eller lengre

Seksjon D. ANDRE SYMPTOMER

Sett en RING rundt det tallet du synes passer best til hvert spørsmål nedenfor:

I de siste 2 månedene, hvor ofte:	**Aldri**	**1-3 ganger pr. måned**	**Én gang i uka**	**Flere ganger i uka**	**Hver dag**	**Jeg vet ikke**
1. Rapet barnet ditt om igjen og om igjen uten å ville det?	0	1	2	3	4	x
2. Prompet barnet ditt mye *veldig ofte*?	0	1	2	3	4	x
3. Utviklet barnet ditt en tydelig utspilt mage i løpet av dagen (du kunne se at den var utspilt)?	0	1	2	3	4	x
4. Svelget eller slukte barnet ditt ekstra luft? (Du kan ofte høre en klikkende lyd når barnet ditt svelger ekstra luft)	0	1	2	3	4	x

5. I LØPET AV DET SISTE ÅRET, hvor mange ganger kastet barnet ditt opp *om igjen og om igjen uten å stoppe i 2 timer eller lenger*?

0. € Aldri (*Hvis aldri, vær snill å gå til spørsmål nr.6)*
1. € 1 gang
2. € 2 ganger
3. € 3 ganger
4. € 4 eller flere ganger

5a. Hvor lenge har barnet ditt hatt episoder med oppkast om igjen og om igjen uten å stoppe?

1. € 1 måned eller kortere tid
2. € 2 måneder
3. € 3 måneder
4. € 4-11 måneder
5. € 1 år eller lengre

5b. Følte barnet ditt vanligvis *kvalme* når han eller hun kastet opp om igjen og om igjen uten å stoppe?

1. € Nei
2. € Ja

5c. Var barnet ditt frisk i flere uker eller lengre mellom episodene med oppkast om igjen og om igjen?

0. € Nei
1. € Ja

6. I de 2 siste månedene, hvor ofte kom mat tilbake opp i ditt barns munn etter at det hadde spist?

0. € Aldri *(Hvis aldri, vær snill å avslutte spørreskjemaet her)*
1. € 1-3 ganger i måneden
2. € 1 gang i uka
3. € Flere ganger i uka
4. € Hver dag

6a. Skjer dette vanligvis mindre enn en time etter at barnet ditt spiser?

0. € Nei
1. € Ja

6b. Skjer dette mens barnet ditt sover?

0. € Nei
1. € Ja

6c. Føler barnet ditt vanligvis kvalme og kaster opp når dette skjer?

0. € Nei
1. € Ja

6d. Gjør det vanligvis vondt når maten kommer tilbake opp i munnen hans/ hennes?

0. € Nei
1. € Ja

6e. Hva gjør vanligvis barnet ditt med maten som kommer tilbake opp i munnen hans/hennes?

0. € Svelger den
1. € Spytter den ut

Tusen takk for hjelpen!

III

Functional abdominal pain in children: Significance of child and maternal somatic and mental health on levels of abdominal pain and disability.

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ABSTRACT

Objective First, to explore to what extent do consecutively referred pediatric patients with FAP experience somatic and emotional symptoms compared to school children in a large, population-based reference sample. Second, to investigate the prospective value of somatic and mental health in pediatric patients with FAP and their mothers for level of abdominal pain and functional disability measured at a follow-up consultation after 6-9 months.

Methods Ninety-four patients (86% participation rate, mean age 11.1 years, 62% girls) reported on abdominal pain, other somatic symptoms and disability. Mothers and teachers reported on child emotional and behavioral problems. Maternal somatic and emotional symptoms were also assessed. Patient self-reported abdominal pain and disability were measured at follow-up (94% participation rate). A representative sample of 14 000 school children constituted the reference sample.

Results Compared with the reference sample, the patients experienced significantly more emotional symptoms and more frequent somatic symptoms (headache [OR, 9.2; 95% CI, 5.9–14.6], pain in neck/shoulder [OR, 7.2; 95% CI, 4.1–12.5] and back pain [OR, 6.6; 95% CI, 3.5;–12.6]). In the multivariate, prospective analyses, patient older age and peer problems at baseline predicted more abdominal pain at follow-up, whereas patient older age, emotional symptoms, prosocial behavior and maternal somatic symptoms predicted *disability*.

Conclusion Somatic and emotional co-morbidity in general pediatric outpatients with FAP were confirmed. The observed associations between child and maternal somatic and mental health and pain and disability in pediatric patients highlight the importance of a focus that is wider than just the patient's symptoms of abdominal pain.

Keywords: recurrent abdominal pain, co-morbidity, disability, child, mother, health, longitudinal study

INTRODUCTION

Pediatric chronic or recurrent abdominal pain is common, affecting 10–15% of school children and accounting for 2–4% of all pediatric office visits.[1,2] The majority of affected children have functional abdominal pain (FAP).[3-6] These are chronic or recurrent gastrointestinal symptoms that cannot be explained by structural or biochemical abnormalities.[7] Some children with FAP experience substantial functional disability due to limitations in physical and psychosocial functioning.[8-10] According to a biopsychosocial model, a complex relationship exists between child and parental health and pain and disability in children with FAP.[11] Results from previous studies, the majority of which have a cross sectional design, have shown that many children with FAP and their parents experience more emotional and somatic symptoms other than abdominal pain compared to healthy controls.[12-16] Co-morbid (i.e., co-occurrence of) emotional and somatic symptoms in these children are reported to be associated with pain and disability,[9,10] and parents' own health experiences and cognitions (worries, beliefs and fears) may affect their responses to symptoms and illness in them selves and their children, thereby affecting their child's responses to pain.[17-20] Somatic and emotional symptoms in children with FAP and their parents are also reported to negatively influence course of pain and disability in children with FAP. However, few longitudinal studies have been conducted.[3,21,22]

Although it is well known that children with FAP experience more somatic and emotional symptoms than healthy controls, the control groups in earlier studies are small and represent selected groups of children. [12-14,16] Comparisons of pediatric patients with FAP with a representative sample of children in the general population have, to our knowledge, not been performed. Further, since relatively few prospective studies have been conducted, more knowledge about the prognostic value of child and parental health is needed.

In the current study we wanted to explore to what extent do referred pediatric patients with FAP experience somatic and emotional symptoms compared with school children in a large, population-based reference sample. We also wanted to investigate the prospective value of somatic and mental health in pediatric patients with FAP and their mothers for level of abdominal pain and functional disability measured at a follow-up consultation after 6-9 months. We expected that patients would report more somatic and emotional symptoms than children in the reference sample. We also expected that both patients and maternal somatic and emotional symptoms would be associated with level of abdominal pain and disability at follow-up.

METHODS

Design

The current study is part of a prospective study of consecutively referred pediatric patients with FAP at four general pediatric outpatient clinics in Norway. The original study was conducted from February 2006 to April 2008 and included assessment at two time points (i.e., baseline and follow-up as part of the study after 6-9 months). At both time points all patients underwent a consultation by one of the pediatricians and questionnaire data were collected from the participants. A representative sample of school children (school grade three to seven) constituted the reference sample (description below).

Current clinical sample

Patients old enough (i.e., above school grade three) to give self-report on abdominal pain and disability and who were diagnosed with FAP by the pediatricians were extracted from the original clinical sample of 152 patients (4-15 years).[6] The extracted patients (n = 94) with mothers constituted the current clinical sample. Since the reference sample only encompassed

school children in grade three to *seven*, seventeen patients of older age (i.e., grade eight to ten) were excluded from the current patient sample in the comparison analyses.

Original sample

Only new referrals of Norwegian speaking patients (4-15 years), without abdominal pain of known organic etiology were eligible in the original study. Of 192 referred patients 177 were eligible. Of these 25 (14%) were excluded (22 due to missing consent from one parent, 2 had recently been evaluated by a pediatrician, and 1 did not speak Norwegian). Of the152 patients included (86%), ten (7%) were diagnosed with abdominal pain of organic etiology, whereas 142 (93%) were diagnosed with FAP.[6]

A diagnosis of FAP was based on the pediatrician's exclusion of organic disease through medical history and physical examination according to their usual practice, a set of laboratory investigations through a predefined protocol and the clinical 6-9 months follow-up to confirm the diagnosis. Electronic medical records were also reviewed for evidence of organic disease after both consultations. Diagnostic procedures and results are previously described.[6]

Reference sample

The reference sample consisted of 14 000 school children (school grade three to seven) who participated in a health profile survey undertaken in Akershus County by the Norwegian Health Services Research Centre in 2002 (84% participation rate, mean age [SD] = 10.5 [0.01] years, 50% girls)[23,24]. All the 22 municipalities in the county participated in the

study. Classes at each school were selected at random to obtain a sample that was representative of the entire county.[23,24]

The study was approved by the Regional Committee on Medical Research and Ethics and the Norwegian Data Inspectorate.

Child variables measured in both the clinical and the reference sample

Somatic symptoms in children in both samples were assessed by the following question: "During the last six months, how often has the child had the following complaints?" Abdominal pain, headache, back pain, neck/shoulder pain and dizziness were rated from 0 ("seldom or never") to 4 ("almost every day).[23,24] A criterion of once a week or more often was used as a cut-off for dichotomizing each symptom into frequent or infrequent/never somatic symptoms.

Mental health (i.e., emotional and behavioral problems) in both samples were measured by the Strengths and Difficulties Questionnaires (SDQ) completed by the parents.[25] The SDQ consists of 25 items rated from 0 ("not true") to 2 ("certainly true"), and composes five subscales (emotional symptoms, conduct problems, hyperactivity, peer problems, and prosocial behavior). A total difficulties score (0–40) is obtained by summarizing the scores of the first four subscales (0–10). The instrument has previously been used in epidemiological and clinical research.[15,26-28] The SDQ is a well-validated screening questionnaire.[29-31] Corresponding previous research, alpha reliabilities in this sample were: 0.79 for the total score, 0.68 for emotional symptom–, 0.45 for conduct problem–, 0.79 hyperactivity-inattention problem–, 0.56 for peer problem–, and 0.65 for prosocial behavior scale.[29,31,32]

Variables measured in the clinical sample

At baseline, patients and their mothers individually completed questionnaires about child somatic and mental health. The mothers also answered questions about their own somatic and emotional symptoms. When participants agreed, questionnaires were sent by mail to the child's teacher. At follow-up, the patients again reported on their abdominal pain and disability. A member of the research team checked the questionnaires for missing answers, and gave the participants opportunity to complete the forms. Thus, the number of missing values was small.

Child *functional disability* was measured by patient self-report on the Functional Disability Inventory (FDI).[9,33] The 15- item questionnaire assesses perceived difficulty in physical and psychosocial functioning in multiple contexts (home, school, social activities, sleep) as a result of the child's physical health in the last two weeks. Each item is rated from 0 ("no trouble") to 4 ("impossible"). A total score (0–60) is obtained by summarizing the ratings on each item. The FDI has demonstrated reliability and validity in previous research.[9,33] Alpha reliability in this sample was 0.91. In addition, to dichotomize the FDI score, we chose a cut-off point of 10. In previous studies this cut-off point has been used to separate children in the low range of functional disability from children in the moderate to high range.[34,35]

Child *abdominal pain* was measured by patient self-report of the Abdominal Pain Index (API) which assesses the frequency, duration and intensity of the child's perceived abdominal pain in the previous two weeks.[36] Frequency of pain, in terms of days, is rated from 0 ("not at all") to 5 ("every day"), and, in terms of times per day, from 0 ("none") to 5 ("persistent"). Duration of pain episodes is measured from 0 ("no pain") to 8 ("most of the day"). Typical

and maximum pain intensity is measured on two scales ranging from 0 (“no pain”) to 10 (“the most possible pain”). Scores on each item were standardized using z scores and were added to produce an overall score. Alpha reliability for the API in this study was 0.82. In addition, the mothers also answered one question about how long the child had experienced abdominal pain.

Child *somatic symptoms* were measured by patient self-report on the short version of the Children’s Somatization Inventory (CSI) which assesses the child’s experience of 18 somatic symptoms (i.e., “headaches,” “feeling low in energy/slowed down,” “pain in arms/legs”) in the last two weeks.[13] Each item is rated from 0 (“not at all”) to 4 (“a whole lot”). A total score is obtained by summarizing the items. The CSI has demonstrated adequate reliability and validity.[13] Alpha reliability for the CSI total score in the clinical sample was 0.87. To avoid overlap in measurement of abdominal complaints, six items on gastrointestinal symptoms were excluded from the CSI. A somatic comorbidity score (0–48) was created by summarizing the ratings the remaining items.

Child *mental health* were measured by the Strengths and Difficulties Questionnaires (SDQ) completed by the patients’ mothers and teachers (description above).

Maternal *emotional symptoms* (anxiety and depressive symptoms) were measured by the 10-item Hopkins Symptom Checklist (HSCL-10).[37] Each item is rated from 1 (“not at all”) to 4 (“extremely”). An average score (1–4) is calculated by summarizing each item score and dividing by 10. The HSCL-10 has approximately as high sensitivity and specificity as the more widely used HSCL-25,[38] and correlates at 0.97 with the 25-item version.[39] The reliability and the validity of the HSCL-25 is well established.[37-39] Alpha reliability in this sample was 0.91.

Maternal *somatic symptoms* were measured by 24 items selected from the Subjective Health Complaint Inventory (SHC), previously known as the Ursin Health Inventory.[40,41] The SHC consists of 29 common health complaints (i.e., "headache," "back pain," "stomach pain") experienced during the last month. Each item is rated from 0 ("not at all") to 3 ("severe"). A total score is obtained by summarizing the items. The internal reliability and test-retest stability of the SHC has been considered satisfactory.[42,43] Alpha reliability for the total score in this sample was 0.87. To avoid overlap in measurement of emotional symptoms, five items on anxiety/depressive symptoms were excluded. A somatic symptom score (0–72) was created by summarizing the ratings of the remaining 24 items.

Sociodemographic factors recorded included child gender and age, and the mother's highest completed education within four categories: (1) elementary school, (2) middle school, (3) high school and (4) college or university.

DATA ANALYSIS

All statistical analyses were performed using SPSS 15.0 for Windows. Missing values in the questionnaires were replaced by the mean score for the completed items.[44] Differences between the clinical and the population-based samples were analyzed with chi-square- and Mann–Whitney U tests. Non-parametric tests for non-normally distributed data were used. The comparison analyses were rerun with respect to gender post hoc. To assess the predictive value of potential predictors of level of abdominal pain and disability in the pediatric patients, the following analyses were used: Linear regression analyses were used to assess bivariate associations between potential child and maternal predictors for child abdominal pain and functional disability. Multivariate linear regression analyses with backward variable selection

were performed to assess associations between the independent variables and the outcome variables. Only variables significant at the 20% level ($p \leq 0.2$) in the bivariate analyses were included in the multivariate analyses.[45] To avoid child SDQ variables (i.e., emotional and behavioral problems) reported by both mothers and teachers being included in the same analyses, separate multivariate analyses were performed either with maternal or teacher report on these variables included. All multivariate analyses were adjusted for the effect of child gender and age. The Wilcoxon paired sample test was applied to analyze changes in levels of patient abdominal pain and functional disability from baseline to follow-up. To assess the level of agreement between patient emotional symptoms by maternal report and teacher report the intra-class correlation coefficient was computed post hoc. A significance level of 5% was used throughout, except where otherwise specified.

RESULTS

Clinical sample

Of 142 pediatric patients (4-15 years) diagnosed with FAP in the *original clinical sample*, 56 children were considered too young to give self-report (i.e., below school grade three). Thus, 94 patients (mean age = 11.1 years [SD 1.9], 58 [62%] girls) with all their mothers constituted the *current* clinical sample. Eighty-two (87%) teachers reported on symptoms in the patients.

Both parents were Nordic for 89 (95%) of the children. Thirty-four (36%) of the mothers had a college or university degree and a further 54 (57%) had completed high school. All 94 patients had experienced abdominal pain for more than two months, 91 (97%) for more than three months and 65 (69%) children for more than one year. Their typical intensity of abdominal pain in the last two weeks (item four in the API) was in the medium range on a scale ranging from 0 to 10 (mean = 4.3, SD = 2.1). Their level of functional disability (FDI

score) was relatively low (mean = 6.9, SD = 7.7, median = 4, range 0-42). Twenty-eight patients (30%) had FDI scores in the moderate to high range (FDI score > 10). **Table 1** gives descriptives of the patients with mothers at baseline.

Clinical sample versus reference sample

Of the 94 patients, 77 (82%) within the same age range (i.e., grade three to seven) as the 14 000 children in the reference sample were included in the comparison analyses. The proportion of girls was higher in the clinical sample than in the reference sample (62% versus 50%; OR, 1.6; 95% CI, 1.1–2.5) whereas children's age and maternal education did not differ significantly between the samples. The patients had significantly more frequent somatic symptoms (**table 2**) and higher scores on the SDQ emotional subscale (median=3.0, range 0-10 versus median=1.0, range 0-10, p<0.001). Scores on the other SDQ subscales did not differ significantly between the samples. When gender specific analyses were rerun post hoc, the differences between the samples remained (data not shown).

Predictors of abdominal pain and disability in patients at follow-up

Eighty-eight of the 94 patients met for follow-up (94%). From baseline to follow-up the API z-score did not change significantly. The median FDI score was significantly reduced (4.0, range 0-42 vs. 2.0, range 0-33, p = 0 .002). The proportion of patients that had FDI scores in the moderate to high range (FDI scores > 10) was significantly reduced from 28 patients (30%) from baseline to 16 patients (18%) at follow-up (p = 0.013).

In the prospective bivariate analyses, being a child of older age ($\beta = 0.31$, p = 0.004) at baseline was the only significant factor associated with higher level of *abdominal pain* at follow-up, whereas the following factors were significant at the 20% level (thus, included in

the multivariate analyses): being a girl (β = 0.16), having somatic comorbidity (β = 0.19) and peer problems (β = 0.19). **Table 3** gives results from the bivariate analyses of potential predictors for *disability* at follow-up.

In the prospective multivariate analyses (child SDQ variables by *maternal* report), children of older age (β = 0.28, p = 0.007) and with peer problems (β = 0.21, p = 0.05) at baseline remained independent predictors for higher level of *abdominal pain* at follow-up (adjusted R^2=0.13), whereas children of older age and having mothers with somatic symptoms predicted higher level of *disability* (**table 4**). When the two multivariate analyses were rerun with child SDQ variables by *teacher* report included, no other significant predictors for abdominal pain scores were found, whereas children with higher scores on emotional symptoms (β = 0.29, p = 0.009), prosocial behavior (β = 0.23, p = 0.04) and being of older age (β = 0.33, p = 0.003) predicted more patient disability at follow-up (adjusted R^2=0.15). The intra-class correlation between maternal report and teacher report of child emotional symptoms (computed post hoc) was low (ICC=0.29).

DISCUSSION

Results from the comparison analyses showed that the patients with FAP reported more somatic and emotional symptoms than the children in the reference sample. Although these results echo previous findings, the control groups in earlier studies are small and represent selected groups of children.[12-14,16] The large differences between the samples in our study are therefore noteworthy. The odds ratios and the lower border of the confidence intervals clearly support that differences are likely to exist, although the differences between the samples must be interpreted with caution because inaccurate estimates may have been introduced due to the small clinical sample. Previous population-based studies have reported more somatic and emotional symptoms in children and adolescents with FAP compared to

those without.[15,46,47] Thus, it is likely that somatic and emotional co-morbidity is a feature of children with FAP in general, and not only a feature of patients referred to secondary health care.

The prospective analyses showed that children with peer problems and of older age at baseline had increased risk for higher levels of abdominal pain at follow-up. However, the predictive value of peer problems must be interpreted with caution because of the low internal reliability of the peer problem score in our study. Nevertheless, lower level of social competence is reported to be associated with higher level of abdominal pain in adolescents and young adults with FAP, and to negatively affect the relationship between pain and disability in girls (cross-sectional data).[8,10] On the other side, peer problems (measured on the SDQ) did not predict sustained abdominal pain in a one-year population-based cohort study of six-years old children with FAP.[22] With respect to the predictive value of child age for level of abdominal pain little research has been published. However, the apparent effect of age in our study may be due to an age related reporting bias and not represent actual differences in the level of perceived pain.

Child emotional and prosocial behaviour predicted functional disability at follow-up, whereas child somatic symptoms did not. Previous studies, the majority of which have a cross-sectional design, have reported emotional *and* somatic symptoms to be associated with disability in pediatric patients with FAP.[8,9,21] One of few existing prospective studies reported somatic and emotional co-morbidity in pediatric patients with FAP in tertiary health care to be associated with somatic symptoms and disability five years later.[21] A population-based one-year cohort study also reported headache and limb pains to predict continued abdominal pain and school absenteeism in children with FAP.[22] It is possible that children with FAP and emotional and somatic co-morbidity are more vulnerable to adopting a chronic

sick role than children with less co-morbid symptoms. Such an explanation is corresponding previous findings of somatic and emotional symptoms, as well as disability to be associated with less efficient coping of life stress in this patient group. [48-50] The reason why child *somatic* co-morbidity did not predict level of abdominal pain or disability at follow-up may be due to, at least partly, the fact that we explored children with FAP as one group. Despite variations in disability within the sample, the *mean* level was low. This may be contributing to the null findings of significant associations between some of the potential baseline predictors (e.g., patient somatic co-morbid symptoms) and disability at follow-up.The predictive value of increasing child prosocial behavior for disability has not been previously reported, is somewhat surprising and seems to contradict possible peer problems within these patients. We have no convincing explanation for this result.

Only somatic, not emotional symptoms in mothers predicted child disability at follow-up. This finding corresponds in part with a previous cross-sectional study that reported maternal distress (i.e., both somatic and psychological symptoms) to be associated with disability in pediatric patients with FAP or migraine headache.[51] Moreover, a one-year cohort study also reported maternal anxiety to predict sustained abdominal pain and school absenteeism in children with FAP in the general population.[22] Although, the effect of parental health on children's experience of pain and disability is likely to be mediated through both genetic and environmental influences, there appears to be a strong environmental influence.[18] Social learning of illness behavior of parents and parental reinforcement of child illness behavior have been suggested as possible mechanisms.[18] Parents preoccupation with their own somatic or emotional symptoms may influence how their child respond to pain.[17,20,52,53] Parental responses such as protectiveness, solicitousness and critical responses are also found to increase level of pain and disabilities in children,[17,54] particularly in children with higher levels of emotional distress.[54]

The finding of that patient level of abdominal pain did not change significantly from baseline to follow-up, whereas level of disability did, may seem puzzling. However, chronic pain is reported to persist in many children. [15,55] The majority (69%) of our patients reported abdominal pain of more than one year duration. Thus, chronicity of abdominal pain may in part explain our finding. The reduction in child disability from baseline to follow-up, however, may be an effect of the first pediatric consultation and the offer of a follow-up consultation. Although level of abdominal pain remained, it is possible that the patients handled their pain in a better way at follow-up.

Some strengths of our study are the consecutive recruitment of patients referred from general to pediatric practice within a well-defined geographic area, the high participation rate and the prospective design. This most likely makes the results representative for referred children with FAP in secondary health care, at least in Norway. Further, the importance of the multi-informant approach is underscored by the finding of child emotional symptoms by teacher report only as a predictor for patient disability at follow-up. The low correlation between mother and teacher reports of child emotional symptoms corresponds with previous research and may, in part, explain our finding. [29,56] Children can behave differently across settings, and mothers and teachers can observe child behavior differently.

The following study limitations should be considered. Firstly, results from this study cannot be generalized to children with pain conditions other than FAP, or to other age groups, and. the results from the comparison analyses cannot be generalized to the oldest patients (i.e., in grade eight to 10) in the clinical sample because these patients were excluded from these analyses. Second, the relatively small sample size allows type II errors and may lead to

inaccurate estimates. Third, we did not control for the fact that multiple regression analyses were run. Thus, the problem of false positive results can not be ignored. Fourth, the sole reliance on child self-reported abdominal pain, other somatic symptoms and functional disability, may bias our findings due to shared methods variance. Fifth, child emotional symptoms were only reported by mothers and teachers in our study. Parents and teachers may have limited knowledge about children's emotional symptoms and may underreport them. [57] On the other hand, it is possible that parents and teachers of children with chronic pain are more aware of the children's symptoms and problem behavior. [58] Finally, the lacking differences between the clinical sample and the reference sample with respect to behavioral problems and prosocial behavior must be interpreted with caution because of low internal reliabilities of the conduct– and peer problem scale in our study.

Despite some discrepancies from previous research and the relatively scarce findings in the prospective analyses it is our impression that the main results are in harmony with previous research and the prevailing understanding of FAP in a biopsychosocial perspective.[59] Although methodological differences and limitations (e.g., differences in sample selection and measurement, lack of statistical power due to the small sample in our study) may in part explain the discrepancies from previous research and the relatively scarce prospective findings, our results are also likely to reflect the complexity of FAP and the intricate relationship between the investigated factors when these are explored in multivariable regression models.

CONCLUSION

This study confirms emotional and somatic co-morbidity in pediatric outpatients with FAP in secondary healthcare as underscored by significantly more emotional and frequent symptoms than the children in a population-based reference sample. Although prospective in the most

minimal form (i.e., short follow-up period and assessment at only two time points), the study also contributes with knowledge about the prospective value of child and maternal somatic and mental health on pain and disability in pediatric patients with FAP. Since patterns of disability and illness behaviour can establish in childhood and may extend into adulthood in some people, the findings highlight, in harmony with a biopsychosocial model, the importance of a focus that is wider than just the patient's symptoms of abdominal pain.[3,8,11]

LIST OF ABBREVIATIONS

FAP; functional abdominal pain

API; abdominal pain index

FDI; functional abdominal pain

CSI, children's somatization inventory

SDQ; Strengths and Difficulties Questionnaire

HSCL-10; Hopkins Symptom Checklist, the 10-item version

SHC: Subjective Health Complaints

COMPETING INTERESTS

The authors declare that they have no financial or non-financial competing interest.

AUTHORS' CONTRIBUTION

HH was responsible for conducting the study and made substantial contributions to conception, design, and acquisition, analysis and interpretation of data. HH was also responsible for drafting and revising the manuscript. BVR made substantial contributions to acquisition and analysis of data, and has been involved in revising the manuscript critically. LS made substantial contributions to analysis and interpretation of data, and has been

involved in revising the manuscript critically. TM made substantial contributions to conception, design, and acquisition of data, and has been involved in revising the manuscript critically. HK made substantial contributions to conception, design and interpretation of data, and has been involved in revising the manuscript critically. All authors have given final approval of the version of the manuscript to be published.

ACKNOWLEDGEMENT

This study received financial support from the Innlandet Hospital Trust and the Regional Centre for Child and Adolescent Mental Health, Eastern and Southern Norway. The authors gratefully acknowledge the children and their parents for their efforts, Gro Flagstad and the other pediatricians at the four outpatient clinics at the Innlandet Hospital Trust for performing the medical evaluations, and the nurses Anne M. Skaaden, Aud R. Eide and Turid Skundberg for invaluable help in recruitment and data collection. We also thank Lynn S. Walker, PhD, for her assistance in the translation of questionnaires (Abdominal Pain Index, Children's Somatization Inventory and Functional Disability Inventory), and Per O. Vandvik, Phd, for discussions of the ideas behind this work and helpful comments on drafts of this manuscript.

TABLE LEGEND

Table 1: Descriptive statistics for baseline variables in the clinical sample

Table 2: The proportions of pediatric patients who had experienced frequent somatic symptoms in the last six months compared with school children in a large population-based sample.

Table 3: Results from the bivariate linear regression analyses of potential baseline predictors for level of child functional disability at follow-up

Table 4: Results from the multivariate linear regression analysis of potential baseline predictors for level of patient functional disability at follow-up

Table 1: Descriptive statistics for baseline variables in the clinical sample

Variables[a]		Mean (SD) or %	Possible range	Observed range
Child variables				
Age (years)	*child self-report*	11.1 (1.9)	8-15	8-15
Gender, girls	*child self-report*	62%		
Abdominal pain (API)	*child self-report*	17.2 (7.6)	0-38	0-31
Functional Disability (FDI)	*child self-report*	6..9 (7.7)	0-45	0-42
Somatic comorbidity (CSI)	*child self-report*	5.7 (5.3)	0-48	0-29
Emotional symptoms[b]	*maternal report*	3.2 (2.0)	0-10	0-10
	teacher report	2.7 (2.4)	0-10	0-10
Conduct problems[b]	*maternal report*	1.3 (1.3)	0-10	0-5
	teacher report	0.7 (1.5)	0-10	0-8
Hyperactivity problems[b]	*maternal report*	3.0 (2.4)	0-10	0-9
	teacher report	2.3 (2.4)	0-10	0-10
Peer problems[b]	*maternal report*	1.5 (1.7)	0-10	0-7
	teacher report	1.3 (1.6)	0-10	0-6
Prosocial behavior[b]	*maternal report*	8.3 (1.7)	0-10	1-10
	teacher report	7.5 (2.3)	0-10	0-10
Maternal variables				
Emotional symptoms (HSCL-10)		1.5 (0.6)	1-4	1-4
Somatic symptoms (SHC)		10.2 (7.5)	0-72	0-33

Abbreviations: API, Abdominal Pain Index; FDI, Functional Disability Inventory; CSI, Children's Somatization Inventory; HSCL-10, Hopkins Symptom Checklist (10-item version); SHC, Subjective Health Complaints.

[a]All variables except age and sex, represent continuous scores.

[b]Denotes Strengths and Difficulties Questionnaire subscale.

Table 2: The proportions of pediatric patients who had experienced frequent somatic symptoms in the last six months compared with school children in a large population-based sample.

Frequent somatic symptoms [a]		**Pediatric patients, n (%)**	**School Children, n (%)** [b]	**OR (95% CI)**
Headache	No	38	12 800	9.2 (5.9–14.6)*
	Yes	39 (51)	1 415 (10)	
Dizziness	No	60	13 766	23.0 (13.2–40.2)*
	Yes	17 (22)	173 (1)	
Pain neck/shoulder	No	61	13 475	7.2 (4.1–12.5)*
	Yes	16 (21)	503 (4)	
Back pain	No	66	13 529	6.6 (3.5–12.6)*
	Yes	11 (14)	349(3)	

* $p < 0.001$

[a]Denotes child somatic symptoms at least once a week in the last six months reported by the mother.

[b]Number of school children varied slightly in each analyses.

Table 3 Results from the bivariate linear regression analyses of potential baseline predictors for level of child functional disability at follow-up

Independent variables measured at baseline		B (SE)	Beta	t	*p*- value
Child factors					
Age, years		1.06 (0.36)	0.30	2.94	0.004
Gender		0.44 (1.46)	0.03	0.30	0.77
Abdominal pain (API z score) [a]		0.03 (0.88)	0.01	0.03	0.97
Somatic comorbidity (CSI score) [a]		0.24 (0.13)	0.19	1.81	0.08
Emotional symptoms [b]	*maternal report*	0.31 (0.35)	0.09	0.86	0.39
	teacher report	0.54 (0.30)	0.20	1.80	0.08
Conduct problems [b]	*maternal report*	0.87 (0.54)	0.17	1.61	0.11
	teacher report	-0.53 (0.56)	-0.11	-0.95	0.35
Hyperactivity [b]	*maternal report*	0.09 (0.30)	0.03	0.30	0.77
	teacher report	-0.11 (0.35)	-0.04	-0.32	0.75
Peer problems [b]	*maternal report*	0.85 (0.42)	0.21	2.01	0.05
	teacher report	-0.07 (0.46)	-0.02	-0.15	0.88
Prosocial behavior [b]	*maternal report*	-0.39 (0.42)	-0.10	-0.92	0.36
	teacher report	0.48 (0.34)	0.16	1.41	0.16
Maternal factors					
Maternal education		0.67 (1.22)	0.06	0.55	0.59
Maternal emotional symptom (HCSL score)		2.38 (1.15)	0.22	2.06	0.042
Maternal somatic symptoms (SHC score)		0.21 (0.09)	0.24	2.28	0.025

Abbreviations: API, Abdominal Pain Index; CSI, Children's Somatization Inventory; SDQ, Strengths and Difficulties Questionnaire; HSCL, Hopkins Symptom Checklist (10-item version); SHC, Subjective Health Complaints

[a]by child self-report

[b]Denotes Strengths and Difficulties Questionnaire subscale.

Table 4: Results from the multivariate linear regression analysis of potential baseline predictors for level of patient functional disability at follow-up

Independent variables measured at baseline	B (SE)	Beta	t	*p*- value
Child age	0.94 (0.35)	0.27	2.67	0.009
Child gender	0.76 (1.44)	0.06	0.53	0.60
Child somatic comorbidity (CSI score) [a]	0.13 (0.13)	0.11	1.03	0.31
Child conduct problems (SDQ subscale score) [b]	-0.24 (0.63)	-0.05	-0.39	0.70
Child peer problems (SDQ subscale score) [b]	0.73 (0.40)	0.18	1.84	0.069
Maternal emotional symptom (HCSL score)	1.35 (1.38)	0.12	0.98	0.33
Maternal somatic symptoms (SHC score)	0.18 (0.097)	0.21	2.05	0.044

Adjusted $R^2 = 0.14$

Abbreviations: CSI, Children's Somatization Inventory; SDQ, Strengths and Difficulties Questionnaire; HSCL, Hopkins Symptom Checklist (10-item version); SHC, Subjective Health Complaints

[a] by child self-report

[b] child SDQ variables by maternal report

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