CHILDHOOD NON-SPECIFIC ABDOMINAL PAIN

in General Practice

Marieke Gieteling

Childhood Non-Specific Abdominal Pain in General Practice

Course and Relation with Mental Health Problems

Marieke Gieteling

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Course and Relation with Mental Health Problems

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Chapter 1

General introduction

BACKGROUND

Abdominal pain is one of the most common complaints amongst children. Depending on age and the definition used, open population and school based studies have reported a prevalence of chronic abdominal pain ranging from 0.5% to 19.2%.[1] Approximately 57% of the children and adolescents (from now on referred to as children) with chronic abdominal pain consult a physician with regard to this complaint.[2] Usually no organic abnormalities are found explaining chronic abdominal pain.[3]

Definition of abdominal pain

Childhood abdominal pain often can be characterized by the following three aspects; I) usually no organic abnormalities can be found explaining the pain, II) the abdominal pain tends to have a prolonged or recurrent course and III) the abdominal pain affects the child's daily life and wellbeing. In literature a variety of expressions are used describing this pain syndrome: recurrent abdominal pain;[1,4-7] chronic abdominal pain;[8,9] functional abdominal pain;[10-16] non-organic abdominal pain; non-specific abdominal pain,[17,18] medically unexplained abdominal pain.[19] These expression lack well defined, generally accepted criteria and every medical specialty elaborates the three above described characteristics of the abdominal pain slightly differently. The extent of additional testing, for example, depends on the facilities available for medical testing which in turn depends on the medical specialty and on when and where the testing took place. Most expressions enclose a minimal duration of abdominal pain, usually 3 months. This "time criterion" derives from Apley *et al*[4] who were the first describing this pain condition, using the term recurrent abdominal pain. As organic abnormalities will usually become manifest within time, this "time criterion" served in 1958 to reduce the risk of organic pathology in children with recurrent abdominal pain. Nowadays, with easier access to additional testing and new medical technologies available, organic abnormalities may be detected more easily. This "time criterion" also serves to select those children whose abdominal pain is likely to have a prolonged course. However, it is not clear yet which duration of abdominal pain has prognostic value for persistence of abdominal pain. Finally, most descriptions include loss of daily functioning or impact on daily life. However, the extent of functional impairment and its measurement lack standardisation.

For research purposes and in order to enhance diagnosis and minimize additional testing, in 1999 secondary and tertiary care specialists developed criteria for childhood abdominal pain.[20] The "Rome committee" defined five different functional gastro-intestinal pain syndromes (FGIDs); functional dyspepsia, irritable bowel syndrome, abdominal migraine, functional abdominal pain, and functional abdominal pain syndrome. In absence of alarm symptoms, these so called "Rome criteria" diagnose functional abdominal

pain based on the presence of symptoms and symptom duration, thus based on history taking and without the necessity to rule out every possible organic disease with abundant additional testing. Whether dividing childhood abdominal pain into distinctive functional gastro-intestinal disorders improves daily clinical practice, remains questionable. It is not known whether these criteria discriminate between patient groups with different aetiology, prognosis or response to various treatment options.

As a consequence of this "definition problem" the study populations of studies on childhood abdominal pain differ. When interpreting the symptoms of the children under study and the result of the studies it is therefore important to take the selection and source of included children into account.

Childhood abdominal pain in general practice

In this thesis we use the term non-specific abdominal pain (non-specific AP) for childhood abdominal pain seen in general practice for which GPs have no specific organic explanation, in other words for which GPs do not suspect organic pathology. As an organic explanation for the pain can never be ruled out definitively and will always depend on the extent of medical testing performed, we considered the expression non-organic AP to be inappropriate. "Functional" abdominal pain suggests that the complaints have a function in expressing psychological distress and therefore implicitly assumes a relationship with psychosomatic aspects.[21] However, this relationship is not well established in childhood abdominal pain. In addition, the term "functional abdominal pain" as defined by the "Rome criteria"[20] as part of the functional gastrointestinal disorders would include only part of the children presenting with non-specific AP seen in general practice, therefore we chose not to use this term. Furthermore, as in general practice patients present in the beginning of their illness, non-specific AP does not enclose a minimum duration of abdominal pain.

Prognosis of childhood abdominal pain

The prognosis of abdominal pain in children is generally unknown. Information on the natural course and the long-term outcome of abdominal pain is important knowledge for good counselling but also for establishing treatment effects.

Childhood abdominal pain and mental health problems

While most of the children with abdominal pain are managed in general practice almost all knowledge of childhood abdominal pain comes from secondary and tertiary care based studies. As referred children are a selection of those seen in primary care, findings of referred children are not directly generalisable to primary care. Referred children with non-specific AP are found to have more mental health problems than children consulting specialist care for other problems.[22-26] It is important to find out whether

children with non-specific AP in general practice are also at increased risk for mental health problems. It would influence the general concept of childhood abdominal pain. Disentanglement of the relation between non-specific AP and mental health problems will allow for a more effective management of both the abdominal pain and the mental health problems.

AIM OF THE THESIS

The overall objective of this thesis was to study childhood abdominal pain and its possible relation with mental health problems. In the literature we studied the prognosis and the prognostic factors of childhood chronic and recurrent abdominal pain, in a large national database we studied the incidence of childhood non-specific abdominal pain in Dutch general practice, and we examined the relation in time between abdominal pain and mental health problems, in a cohort of children aged 4 to 17 years, presenting with abdominal pain to their GP.

Outline of the thesis

Chapter 2 comprises a clinical review of childhood chronic abdominal pain.
Chapter 3 and 4 are systematic literature reviews concerning the prognosis of chronic or recurrent abdominal pain and the prognostic factors for persistence of abdominal pain in children with chronic or recurrent abdominal pain.
In **Chapter 5** we determined with record data from the Second Dutch National Survey of General Practice the incidence rate of childhood non-specific AP in general practice and we studied the GP's management for non-specific AP.
Chapter 6 evaluates the prevalence at baseline of mental health problems of children with non-specific AP. These children with non-specific AP were part of a cohort of children presenting to general practice with a new episode of abdominal pain.
Chapter 7 describes the 1 year prognosis of the mental health problems of a cohort of children presenting to general practice with a new episode of abdominal pain.
Chapter 8 reflects on the main findings of the previous chapters, discusses implications for clinical practice and includes recommendations for future research.

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Chapter 2

Clinical Review

Chronic abdominal pain in children

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BMJ 2007; 334: 997-334

INTRODUCTION

Chronic abdominal pain is a common disorder in children and adolescents worldwide. It affects the child's wellbeing and the costs from missed school days and use of health-care resources are high. Children with chronic abdominal pain represent a heterogeneous population comprising both organic and functional gastrointestinal disorders. Functional disorders are those that cannot be explained by structural or biochemical abnormalities. Differences in prevalence of organic disease are reported depending on the setting, ranging from 5% in an open population to 40% in a paediatric gastroenterologist practice.[1] General practitioners feel confident in labelling chronic abdominal pain as an easy to manage functional disorder. After minimal further testing, these children and their parents are reassured by explaining that the symptoms are common and rarely associated with disease. However, when diagnostic uncertainty increases, pain does not resolve over time or parents are hard to reassure, extensive testing and referral easily set in. As a consequence paediatricians perceive chronic abdominal pain as a time-consuming and therapy resistant disorder.

Sources and selection criteria
We used the Cochrane library to identify relevant systematic reviews that evaluate the effectiveness of pharmaceutical, psychological and complementary interventions.
Medline searches were used to find relevant systematic reviews on diagnosis and treatment of abdominal pain in children using the keywords "abdominal pain", "systematic review", "meta-analysis", "diagnosis" and "treatment". We limited our searches to "all child". Statements on prognosis of chronic abdominal pain were derived from a systematic literature search in Medline, Embase and PsycINFO of prospective cohort studies on the topic. We took additional references from our personal file.

What are we talking about?

In the late 1950s Apley and Naish introduced the term recurrent abdominal pain in children for pain that waxes and wanes, occurs for at least three episodes within 3 months and is severe enough to affect the child's activities (Box 1).[2] This definition has been criticized for including both organic and non-organic causes. Von Bayer and Walker proposed a two-stage approach to classification.[3] For the first stage a child's presentation needs to be consistent with Apley's criteria, whereas for the second stage subgroups are identified on the basis of medical findings: for example, recurrent abdominal pain with constipation, constipation and anxiety, or no identifiable causes. Both approaches are based on the concept that functional abdominal pain is a diagnosis by exclusion. The suggestion arose to facilitate the diagnosis of functional disorders on the basis of symptoms alone. According to a model used in adults, a panel of experts in childhood gastrointestinal disorders subdivided childhood chronic abdominal pain into several well-defined categories on the bases of symptoms; the Rome criteria (Box 1).

Box 1. Classification systems for abdominal pain in children

Apley and Naish, 1958
Recurrent abdominal pain
Abdominal pain that waxes and wanes, occurs for at least three episodes within three months, and is severe enough to affect a child's activities
Subcommittee on chronic abdominal pain, 2005
Chronic abdominal pain
Longstanding intermittent or constant abdominal pain
Functional in most children, that is without objective evidence of an underlying organic disorder

Rome III criteria, 2006
Functional dyspepsia
Must include all of the following*†:
Persistent or recurrent pain or discomfort centred in the upper abdomen (above the umbilicus)
Not relieved by defecation or associated with the onset of a change in stool frequency or stool form

Irritable bowel syndrome
Must include all the following*†:
Abdominal discomfort (uncomfortable sensation not described as pain) or pain associated with two or more of the following at least 25% of the time:
Improved with defecation
Onset associated with a change in frequency of stool
Onset associated with a change in form (appearance) of stool

Functional abdominal pain
Must include all the following*†:
Episodic or continuous abdominal pain
Insufficient criteria for other functional gastrointestinal disorders

Functional abdominal pain syndrome
Must include functional abdominal pain at least 25% of the time and one or more of the following*†:
Some loss of daily functioning
Additional somatic symptoms such as headache, limb pain or difficulty in sleeping

Abdominal migraine
Must include all the following*‡:
Paroxysmal episodes of intense, acute periumbilical pain that lasts for 1 hour or more
Intervening periods of usual health lasting weeks to months
The pain interferes with normal activities
The pain is associated with two or more of the following: Anorexia, Nausea, Vomiting, Headache, Photophobia, Pallor

*No evidence of an inflammatory, anatomical, metabolic, or neoplastic process that explains symptoms, † Criteria fulfilled at least once a week for at least two months before diagnosis, ‡Criteria fulfilled two or more times in the preceding 12 months

Summary Points

- Chronic abdominal pain in children is usually not caused by organic disease
- Diagnostic triage focuses on the assessment of alarm symptoms by means of history and physical examination
- Additional diagnostic evaluation is not required in a child without alarm symptoms
- Family characteristics rather than patient characteristics influence the chronicity of abdominal pain
- A specific intervention for chronic abdominal pain in children cannot be recommended because of the lack of evidence for a beneficial effect
- The mean challenge is to identify the child at risk for a prolonged course of abdominal pain and its correlated functional disability

These criteria distinguish five functional gastrointestinal disorders related to abdominal pain.[4] At present the Rome criteria are not useful in daily clinical practice. Further research is needed on their prognostic and diagnostic value (for example, whether they discriminate between relevant patient groups) and on their responsiveness to different interventions.[5-7]

Who gets chronic abdominal pain?

The prevalence of chronic abdominal pain in community based studies ranges from 0.5% to 19%,[8,9] and varies according to age and definitions used (Table 1).[w1-w4] Studies that included large age ranges show two age peaks; the first at 4-6 years of age and the second at 7-12 years of age.[w2] The predominance of girls is controversial (Table 1).[w1,w5,w6,w7,8,9]

Do sexually abused children get chronic abdominal pain?

Population-based and clinical studies have consistently suggested that a considerable number of adults with IBS report histories of physical, emotional and sexual abuse.[10] Little is known about the role of sexual abuse and the association with chronic abdominal pain in children. In one case-control study, 72 abused children reported more functional disorders than did controls (48 versus 26).[11] In a prospective study, abused and non-abused boys reported comparable rates of functional disorders; the duration of the problems, however, was significantly longer in abused boys than in non-abused boys (Table 1).[12]

Do children of anxious or depressed parents get chronic abdominal pain?

Both maternal and paternal anxiety in the first year of a child's life are associated with chronic abdominal pain before the age of six years (OR 1.53; 95% CI 1.24-1.89 and OR 1.38; 95% CI 1.12-1.71, respectively).[13] This suggests that anxious parents worried by their symptoms, may respond to their child in a way that strengthens the recurrence of the symptoms.[14] That family factors play a role was emphasized by the finding that children of a parent with gastrointestinal problems are more likely to have chronic ab-

Table 1. Factors related to diagnosis, incidence, and prognosis of functional abdominal pain

Factors	Likely to be related	Inconclusive	Unlikely to be related
Diagnosis:			
Factors or findings that differentiate between functional and organic abdominal pain	Alarm symptoms increase the risk of organic disease	*Helicobacter pylori* and antiendomysial antibody positivity[17] are equally present in children with chronic abdominal pain and children without abdominal pain	Pain characteristics such as frequency, severity, or location; other functional symptoms; anxiety, depression; lactose malabsorption
Incidence:			
Factors related to occurrence of functional abdominal pain	Age of the child; parental anxiety in first year of child's life; parents with gastrointestinal complaints; low socioeconomic status	Female sex; anxiety, depression; stressful life event; sexual abuse	Family functioning; marital status of parents
Prognosis:			
Factors related to persistence of functional abdominal pain	No acceptance by parents that the disorder is functional; parental attention to children's discomfort; parental functional problems; stressful life-event; sexual abuse	Age; female sex; self confidence; other functional symptoms; coping style of parents; low socioeconomic status	Anxiety, depression; severity of pain

dominal pain than children of a parent without such problems (OR 5.3; 95% CI 2.1-13.2) (Table 1).[w1,8]

Why do children get chronic abdominal pain?

The cause and pathogenesis of chronic abdominal pain in children is undoubtedly multifactorial and not well understood. Visceral sensation, hormonal changes, inflammation, disturbances in gastrointestinal motility, psychological factors, and family dynamics have been suggested as contributory factors to chronic abdominal pain of functional origin. It is known that the brain and gut have a constant exchange of information. An example of the complex origin of functional abdominal pain is the observation that patients who develop an intercurrent bacterial colitis are more likely to develop IBS if the infection occurs during stressful life-events.[15]

Biopsychosocial model of illness

A biopsychosocial model provides a conceptual basis for understanding and legitimising gastrointestinal symptoms not easily allocated to specific organic diseases, such as abdominal pain, diarrhoea, and constipation. In a biopsychosocial model of care, the management of a child with functional abdominal pain takes all related factors into ac-

count. Behavioural changes to better cope with the pain may therefore be as appropriate as pharmacological interventions to modulate visceral sensitivity and motility.

How is it diagnosed?

Recently a committee of American paediatric gastroenterologists concluded that there are no diagnostic tools to distinguish functional abdominal pain from organic abdominal pain. Only the presence of alarm symptoms or signs increases the probability of an organic disorder and justifies further diagnostic testing.[16] Alarm symptoms or signs include, but are not limited to, those summarized in Box 2. Children with alarm symptoms need additional laboratory testing (erythrocyte sedimentation rate, comprehensive metabolic panel and stool analysis) to examine the possibility of organic abnormalities such as inflammatory bowel disease, celiac disease or less prevalent abnormalities.

Box 2. Alarm symptoms when a child presents with chronic abdominal pain

Involuntary weight loss
Deceleration of linear growth
Gastrointestinal blood loss
Significant vomiting
Chronic severe diarrhoea
Unexplained fever
Persistent right upper or right lower quadrant pain
Family history of inflammatory bowel disease

What is the diagnostic value of history and physical examination?

When alarm symptoms are not found, there is no evidence that pain characteristics such as frequency, severity or location are able to discriminate between functional or organic disorders. Accompanying symptoms such as headache, anorexia, nausea, constipation or arthralgia occur as much in children with abdominal pain as in a manifestation of a functional disorder as in children with abdominal pain due to an organic disorder.[16] The presence of recent stressful life events, anxiety, depression, or behavioural problems is not useful in distinguishing between functional abdominal pain and organic abdominal pain.[16] Studies evaluating this relationship could not establish whether the children became anxious or depressed because of their abdominal pain or whether anxiety or depression triggered abdominal pain (Table 1). No studies could show that stressful life events significantly differentiates patients with functional abdominal pain from other patient groups (Table 1).[16] Good data evaluating the diagnostic value of physical examination are lacking.

What is the diagnostic value of additional testing?

No studies have evaluated the usefulness of common laboratory tests (complete blood cell count, erythrocyte sedimentation rate, comprehensive metabolic panel, urinalysis, stool parasite analysis) to distinguish between organic and functional abdominal pain in the absence of alarm symptoms. Evidence that radiographic or ultrasonographic examination of the abdomen, oesophageal pH monitoring, or endoscopy and biopsy can discriminate between functional or organic abdominal pain is lacking or insufficient.[16] Whenever abnormalities are found their relationship with abdominal pain is questionable. Children with *Helicobacter Pylori* were not more likely to have abdominal pain than children without *H. Pylori*[17] and the same was found for children with a lactose mal-absorption. Anti-endomysial antibody positivity, an indication for celiac disease, was equally present in children with chronic abdominal pain, as in control children.[18]

What do we know about prognosis?

Most children with functional abdominal pain have relatively mild symptoms and are managed in primary care. This is illustrated by the fact that in Dutch general practice less than 2% of all children seen with functional abdominal pain are referred to secondary care.[19] Studies that examined the prognosis of chronic abdominal pain are mainly in children referred to a paediatrician or paediatric gastroenterologist. A recent systematic review of prospective follow up studies in children with chronic abdominal pain showed that the mean percentage of children with continuing abdominal pain was 29.1% (95% CI 28.1-30.2%) (personal communication). Compared to children who did not have chronic abdominal pain at baseline these percentages were considerably higher. (OR 6.28; 95% CI 4.81-8.21). The reported duration of follow-up in the studies ranged from 1 to 29 years (personal communication). Some studies suggest that children with chronic abdominal pain, and in particular girls, develop irritable bowel syndrome as an adult.[w2,20] In addition, there is evidence that children with chronic abdominal pain are at risk for later emotional symptoms and psychiatric disorders, in particularly anxiety disorders.[16]

What factors predict long-term persistence of pain?

From the prospective follow-up studies available it seems that parental factors, rather than psychological characteristics of the child, predict the persistence of abdominal pain (personal communication) (Table 1). Acceptance by parents of the role of psychological factors in the maintenance of symptoms is strongly associated with recovery.[21] Recently Walker et al. showed that parents' attention to children's discomfort was associated with significantly more mention about symptoms than parent behaviour was intended to distract.[14] Children with chronic abdominal pain who experiences stressful life events are at risk of persistent abdominal pain. The presence of a depressive or anxiety disorder

in the child with chronic abdominal pain, however, does not influence whether children will continue to have abdominal pain (personal communication).

Can chronic abdominal pain be treated?

Reassurance is the primary therapy in children with chronic abdominal pain without alarm symptoms; a substantial proportion of clinicians however, prescribe dietary or pharmacological interventions, including analgesics, anti-spasmodics, sedatives and, recently, probiotics. Evidence for an effect of these interventions is based on only 12 randomised controlled trials (RCT's).[22-26] Most studies were small and were carried out in children referred to a paediatrician or paediatric gastroenterologists. Children with psychiatric problems (such as anxiety or depressive disorders) and children with known organic disorders and constipation were excluded from all studies (Table 2).

Table 2. Effectiveness of treatments for abdominal pain in children

Therapy	Definition of disorder	Description of trials	Side effects	Effectiveness
Cognitive behavioural (family) therapy	Recurrent abdominal pain	Three randomised controlled trials in 60 referred and 69 non-referred children compared cognitive behavioural therapy with waiting list or standard medical care	None reported	Beneficial
Famotidine	Recurrent abdominal pain and dyspeptic symptoms	One randomized placebo controlled trial in 25 referred children; children showed improvement on a subjective scale but not on a objective measurement of abdominal pain	Not evaluated	Inconclusive
Added dietary fibre	Recurrent abdominal pain	Two randomized controlled trials in 52 non-referred children and 40 children admitted to hospital	Non evaluated	Unlikely to be beneficial
Lactulose-free diet	Recurrent abdominal pain	Two randomized controlled trails comparing a lactose-containing diet with a lactose-free diet in 38 children	Not evaluated	Unlikely to be beneficial
Peppermint oil	Irritable bowel syndrome using Manning criteria	One randomized placebo controlled trial of peppermint oil for two weeks in 42 children referred to a paediatric gastroenterology centre	Not evaluated	Likely to be beneficial
Pizotifen	Abdominal migraine using Rome II criteria	One placebo controlled crossover trial of pizotifen for one month in 14 referred children	Drowsiness and weight gain	Likely to be beneficial
Lactobacillus GG	Irritable bowel syndrome using Rome II criteria	One randomized placebo crossover trial of Lactobacillus GG in 50 children referred to a paediatric gastroenterology centre	Not evaluated	Unlikely to be beneficial

The effectiveness of analgesics, antispasmodics, sedatives, and antidepressants is currently unknown.

How effective are pharmacological and dietary interventions?

Peppermint oil is thought to relax smooth muscle. In one randomised control trial 42 children with irritable bowel syndrome were given peppermint oil capsules or placebo. Improvements on a scale showing change in symptoms were reported in 71% of the children receiving peppermint oil compared with 43% receiving placebo (relative risk 1.67; 95% CI 0.95-2.93).[24] A committee of American paediatric gastroenterologists concluded that peppermint oil given for 2 weeks might improve symptoms in children with irritable bowel syndrome.[16] In a placebo controlled crossover trial in 14 children with abdominal migraine, the children reported fewer days of pain while taking pizotifen (mean 8.21 pain free days; 95% CI 2.93-13.48).[22] Available evidence is inconclusive for an effect of the H_2 receptor agonist famotidine on symptoms in children with functional abdominal pain. Famotidine improved dyspeptic symptoms only in a subgroup of children with severe dyspeptic symptoms.[22,24] The addition of dietary fibre is not effective (relative risk 1.16; 95% CI 0.47-2.87).[23] Lactose avoidance is unlikely to improve symptoms of functional abdominal pain.[22,24] In one randomised controlled trial in children with irritable bowel syndrome abdominal pain was not reduced with use of lactobacillus GG compared to placebo.[25]

How effective are psychological interventions?

The bio-psychosocial model suggests that functional abdominal pain is related to several causes and in part to learned response patterns. Cognitive behavioural therapy is intended to intervene with learned response patterns. Three randomised controlled trails evaluated the efficacy of a cognitive behavioural program and a cognitive behavioural intervention for the family in the treatment of recurrent abdominal pain.[22,26] In one study improvement occurred more quickly in the intervention group than in the control group, and a larger proportion of children became completely pain free. In the second study a higher rate of complete elimination of pain and lower levels of relapse were found at 6 and 12 months in the intervention group. In the third study the intervention group reported significantly fewer episodes of abdominal pain immediately after the intervention and after one year's follow-up; significantly fewer school absences occurred in the intervention group.[26]

What do guidelines recommend?

Recently a Subcommittee on chronic abdominal pain of the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition presented recommendations for clinicians in primary and secondary care (Box 3).[16]

Box 3. Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

The term recurrent abdominal pain should be retired

Diagnosis
Diagnostic triage to discriminate functional abdominal pain from organic disorders in children aged 4 to 18 years with chronic abdominal pain can be carried out by a general practitioner
Diagnostic triage should be carried out by means of assessment of alarm symptoms or signs and physical examination
Additional diagnostic evaluation is not required in children without alarm symptoms
Testing may be carried out to reassure children and their parents

Treatment
Deal with psychological factors
Educate the family (an important part of treatment)
Focus on return to normal functioning rather than on the complete disappearance of pain
Best prescribe drugs judiciously as part of a multifaceted, individualised approach, to relieve symptoms and disability

Additional educational recourses
Cochrane Library (www.cochrane.org)
Systematic reviews and meta-analyses on the efficacy of treatments for chronic abdominal pain

Useful references
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Chronic multiple functional somatic symptoms. *BMJ* 2002;325:323–326
Mayou R, FarmerA. ABC of psychological medicine.
Functional somatic symptoms and syndromes. *BMJ* 2002;325:265–268
Talley NJ, Phung N, Kalantar JS. ABC of the upper gastrointestinal tract. Indigestion: when is it functional? *BMJ* 2001;323:1294–1297

Information for patients
International Foundation for Functional Gastrointestinal Disorders (www.aboutkidsgi.org/)
The foundation is a non-profit organisation that tackles the problems associated with living with gastrointestinal functional disorders. Membership required.
American College of Gastroenterology (http://gi.org/patients/gihealth/functionalab.asp)
Patient information on functional abdominal pain in children

How can we improve the management of chronic abdominal pain?

Given the multi-factorial onset of chronic abdominal pain and the impact of family factors, the disorder is exceptionally suitable to be managed in general practice. Most knowledge about the prognosis and management of chronic abdominal pain, however, comes from studies carried out in referred children. The paradox should trigger research in primary care. In daily clinical practice a careful medical history and thorough physical examination should be sufficient to recognize children with functional abdominal pain.

Ongoing research

- What factors predict whether abdominal pain becomes chronic in children?
- What interventions are effective in reducing chronicity of abdominal pain in children?
- What interventions are effective in giving symptom relief and reduce its correlated functional disability?
- Do the Rome criteria predict the course of functional abdominal pain and the response to specific treatment in children?

It should not be forgotten, however, that functional abdominal pain has a great impact on the child's well being and that in a considerable number of children it might persist. If time can be reserved to evaluate family coping strategies and psychosocial factors and if appropriate follow-up can be arranged, ineffective use of healthcare resources might be prevented.

A patient's perspective

I am Daphne. I am 12 years old. I have stomach-ache almost every day; the pain can just come on like that, but when I am nervous-for instance, about a test paper-it appears more often. Sometimes my belly contracts with force and I have to run for the toilet, or I have to throw up, or I don't feel good at all. In the beginning I often had to miss school, now I am used to it. I sit down and wait patiently; there isn't much I can do about it. I prefer to go outdoors into the fresh air. I try not to get stressed, because that would upset my stomach even more. I am a little ashamed of it. Some people find it awkward, but I am not badgered about it. Also when I don't feel well I will do my football training. During a training camp, I usually have diarrhoea and have to throw up, but I go anyway. I don't know where it comes from; there is no specific reason. It is not that big deal to me; I have had this for the last four years, and I feel that it's useless to get angry or sad about it because what difference would it make?

A parent's perspective

I am Daphne's mother. Daphne has stomach-ache since the age of seven years. The family doctor prescribed laxatives but they were not effective in relieving the pain. Subsequently Daphne was referred to a paediatrician. Blood, faeces and urine tests revealed no abnormalities. Even endosonography and endoscopy were performed which also showed no cause for the pain. Each time we came to the outpatient clinic Daphne had to tell her story over and over again. At a certain moment I thought, "what am I still doing here, they can not do anything anyway". So we stopped seeing the paediatrician. But I often still ask myself if there should be more behind it. I then hesitate about a second opinion. I feel so powerless when Daphne has pain or when she is on the toilet that long. In the beginning I was very considerate and kept her from school, but at the same time I did not want to spoil her too much, because I feared that then the pain would predominate. Happily enough she now manages quite well. As a family we reckon with it but we give up nothing. We always have a toilet role in the car and if necessary we stop on the hard shoulder. Daphne is a victim of heredity because both my husband and I have the same trouble.

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Chapter 3

The prognosis of chronic or recurrent abdominal pain in children. A systematic review

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ABSTRACT

Background

Chronic or recurrent abdominal pain (CAP) is a common childhood complaint, rarely associated with organic disease. CAP is classified into various Functional Gastrointestinal Disorders (FGIDs) by the paediatric Rome criteria. With the modern diagnostic technologies new organic abnormalities are found in children with CAP. The utility of this classification system and the relevance of these organic abnormalities found are being studied.

Objectives

To investigate how often the abdominal pain persists in children with CAP and to investigated whether extensive medical tests, such as laboratorial tests, imaging, and endoscopy, have additional prognostic value to history taking and clinical examination.

Methods

A systematic search was conducted in MEDLINE, EMBASE and PsycINFO for prospective cohort studies published from 1960 until October 2005. The most common keywords of medical literature for CAP were used in our search strategy. The methodological quality of studies was determined. Clinical heterogeneity between studies was analyzed. The percentages of children with abdominal pain after follow-up were pooled.

Results

The search yielded 2620 citations of which 18 studies met the inclusion criteria. In total 1331 children were followed for 5 years (median, range 1-29 years). In total 29.1% (95% CI 28.1-30.2) of the patients with CAP had abdominal pain after follow-up. The prognosis of CAP diagnosed clinically was similar to that diagnosed after extensive medical testing.

Conclusions

CAP persisted in 29.1% (95% CI 28.1-30.2) of children. In the absence of alarm symptoms additional diagnostic tests did not influence the prognosis of children with CAP.

INTRODUCTION

Chronic or recurrent abdominal pain (CAP) is a prevalent problem in children that has major implications for the child's wellbeing and the use of health care systems.[1,2] Apley and Naish (1958) were the first to study children with this pain syndrome.[3] They introduced the term recurrent abdominal pain (RAP) for children with clinically apparent non-organic chronic or recurrent abdominal pain. RAP was defined as three or more episodes of abdominal pain that occur over a period of three months and that are severe enough to interfere with the child's daily activities. Because the term RAP was simply a description of a pattern of symptoms without aetiological assumptions, their definition did not exclude children with organic causes of the pain. Because serious organic pathology would have become manifest within the time limits sets, they assumed that the risk for organic abnormalities was low.[3] For this reason it still is customary clinical practice to avoid excessive diagnostic tests in children. History, clinical examination and the presence of so-called "red flags or alarm-symptoms", differentiate between organic and non-organic causes of the pain and provide indications for further testing. However, over time and with the advances in medical technology, new biochemical abnormalities are detected in children with CAP. Nowadays, in up to 30% of the children with clinically apparent CAP organic abnormalities can be detected,[4] including oesophagitis, H. Pylori gastritis, lactase deficiency and coeliac disease. It still needs to be established however, whether there is a causal relationship between these organic abnormalities and the abdominal pain.[5-8] At the same time further classifications of the symptom complex of CAP have been developed, and the updated Rome criteria (Rome III) have recently been published.[9] The Rome criteria classify non-organic CAP into 5 functional gastrointestinal disorders (FGIDs); i.e. childhood functional abdominal pain, childhood functional abdominal pain syndrome, irritable bowel syndrome (IBS), functional dyspepsia, and abdominal migraine. Structural biochemical abnormalities should be absent. The extent of medical testing to exclude underlying organic pathology is at the discretion of the clinician, the setting of care, and the medical possibilities available. The publication of the Rome criteria and the discovery of new organic abnormalities resulted in an explosion of clinical research. The clinical relevance and consequences for prognosis of this fine tuning of CAP are not yet clear and need to be studied. To be able to do so, one needs a reference of the overall prognosis of CAP. Because, to our knowledge, there is no overview of the current literature on the prognosis of CAP, we performed a systematic review on cohort studies of children with chronic abdominal pain. In this study our primary focus was to investigate how often abdominal pain persisted in children with CAP, or with a subtype of CAP. Our secondary interest was to investigate whether extensive medical testing (ie, laboratorial tests, imaging, and endoscopy) had additive prognostic value after history taking and clinical examination.

METHODS

Search strategy

The MEDLINE database was searched from 1965 to October 2005, PsycINFO from 1970 to October 2005, and EMBASE from 1980 to October 2005. In MEDLINE we searched with a sensitive PubMed clinical query to identify prognostic studies.[10-12] For EMBASE we used the search strategy for detecting prognostic studies recommended by Wilczynski AND Haynes.[13] For PsycINFO we used the search strategy (incidence or mortality or follow-up or prognosis or predict* or course* or epidemiol*). To describe the abdominal pain, the following keywords were used: "abdominal pain", "chronic or recurrent abdominal pain". We limited by age, but no language restriction was used. The reference lists of the relevant retrieved studies were checked to identify additional published research.

Study selection

Two reviewers (M.J.G. and M.Y.B.) screened all of the abstracts of the identified published articles for eligibility. Full articles were retrieved if the abstract provided insufficient information to enable selection or if the paper had passed the first eligibility screening. An article was eligible if it met all of the following criteria: the study population concerned children or adolescents 4 to 18 years of age; the abdominal pain was described according to the criteria defined by Apley and Naish,[3] by von Baeyer and Walker,[14] or by Rasquin-Weber et al,[15] or by using words like "nonorganic abdominal pain", "recurrent abdominal pain", "functional abdominal pain"; the article determined the prognosis of CAP and the prognosis was given as the percentage of children with CAP who had abdominal pain after follow-up; and the outcome was determined prospectively. Decisions regarding the inclusion of studies were made independently, and any disagreements were resolved through consensus or by arbitration of a third person (S.M.A.B-Z).

Methodological quality assessment

Two reviewers (M.J.G. and S.M.A.B-Z.) independently scored the quality of the studies. The instrument used was a modified version of an established criteria list used in systematic reviews of prognostic studies.[16,17] We modified the criteria list on the basis of the framework for assessing internal validity of studies of prognosis as described by Altman.[18] The final list consisted of 11 items (Table 1), each having an answer option of "yes"/ "no"/ "don't know". The operationalization of the criteria list is available from the first author (Appendix 1). A positive score indicated sufficient information and a positive assessment. A negative score indicated sufficient information, but potential bias due to inadequate design or conduct. If an item was scored as unclear it meant that the paper provided insufficient information about these criteria. A score of 1 point is given only to a criterion that was assessed with "yes"; the criteria assessed as "no" or "?" did not receive

Table 1. Criteria for assessing methodological quality[18-20]

Criteria	Score
Study Population	
A. Inception cohort (defined in relationship to onset of symptoms)	+/-/?
B. Description of relevant inclusion and exclusion criteria	+/-/?
C. Description of study population	+/-/?
Follow-up	
D. Prospective data collection	+/-/?
E. Follow-up of at least 1year	+/-/?
F. Drop-outs/loss to follow-up < 20%	+/-/?
G. Information completers versus loss to follow-up/drop-outs	+/-/?
Treatment	
H. Treatment in cohort is fully described/standardised	+/-/?
Outcome	
I. Assessment of standardised outcome measurement	+/-/?
J. Independent assessment of outcome measurement	+/-/?
Data presentation	
K. Data presentation of the outcome measurement	+/-/?

any points. Equal weights were applied to all of the items. This results in a maximum score of 11 points. Disagreement was resolved through consensus or by arbitration of a third person (M.Y.B.).

Data extraction

M.J.G. extracted the information regarding study population, inclusion and exclusion criteria, the study setting, follow-up period, numbers lost to follow-up, and outcome measures on a standardised form. A second observer (M.Y.B.) verified the data.

Data analysis

The inter-assessor agreement on the methodological quality was calculated by use of κ scores (> 0.7 = a high level of agreement between assessors; 0.5-0.7 = a moderate level of agreement, and <0.5 = a poor level of agreement).[21] The prognosis was measured as abdominal pain after follow-up and was given as the percentage of patients who have not recovered from CAP, with corresponding 95% confidence intervals (exact binominal). To take into account the large variation in group size, a weighted pooled percentage was calculated. Each reported percentage was weighted by dividing it through its squared standard error. A sensitivity analysis was performed to estimate the effect of the number of patients lost to follow-up.

The influence on prognosis of the following variables was studied by stratifying three factors: inclusion and exclusion criteria (as a result of the shift of the definition of CAP

over time), the setting of care (inpatients/outpatients and secondary/tertiary based), and the durations of follow-up (1 to < 5 years, 5 to < 10 years, and ≥ 10 years).

The influence of different inclusion and exclusion criteria was studied by comparing studies with a clinical diagnosis of CAP-that is without alarm symptoms ("red flags")- with studies that diagnosed CAP after extensive testing-, and studies conducted before and after 1980. We compared studies before and after 1980, because we hypothesized that with the introduction of for example the fiberoptic endoscopy and the detection of H. Pylori more organic abnormalities could be detected. The percentages of CAP patients with abdominal pain after follow-up of the strata were compared with the X^2 test.

RESULTS

Search results

The search strategy resulted in 2620 citations (MEDLINE 1071, EMBASE 1517, PsycINFO 32) of which 60 full publications were evaluated. Two publications from Czechoslovakia were excluded from further evaluation because of the inability to translate the manuscripts. In total 17 studies fulfilled the inclusion criteria. One study defined CAP after follow-up as at least 1 episode of abdominal pain in six months.[22] This frequency was low in comparison with the frequency of abdominal pain presented at baseline and with the frequency used in the other selected studies. We decided that this outcome was not comparable with the outcome used in the other studies and we excluded the study from further analysis. Two additional studies[23,24] were detected by screening the reference lists of the studies and of two recently published reviews of RAP.[2,25] Finally, 18 articles were included.[23,24,26-41]

Methodological Quality

Table 2 shows the results of the methodological quality assessment. The reviewers agreed on 92.5% of the quality items. The inter-observer reliability of the methodological quality assessment ($\kappa = 0.85$) was good. Studies that scored 0 on item D retrospectively identified the patients by using medical records, but the outcome was determined prospectively.[27-30,35,36,38,39,41] The most important methodological shortcomings concerned the following items. None of the studies identified the cohort at a unique point in the course of the disease (item A). In more than 50% of the studies the study population was not clearly defined (item B, C). Only 4 studies compared the patients lost to follow-up with those who were followed up (item G).[27,32,36,41] Only six studies described the treatments that the patients received (item H).[23,28,35,38-40]

Table 2. Results of the methodological quality (MQ) assessment

	A	B	C	D	E	F	G	H	I	J	K	MQ
Stordal et al.[26]	0	1	0	1	1	1	0	0	1	1	1	7
Lindley et al.[27]	0	1	1	0	1	1	1	0	0	0	1	6
Crushell et al.[28]	0	0	1	0	1	1	0	1	0	0	1	5
Campo et al.[29]	0	1	0	0	1	0	0	0	0	0	0	2
Croffie et al.[30]	0	1	0	0	1	0	0	0	0	0	1	3
Hyams et al.[23]	0	1	1	1	1	1	0	1	0	0	1	7
Walker et al.[31]	0	0	0	1	1	1	0	0	1	0	1	5
Hotoph et al.[32]	0	0	0	1	1	0	1	0	1	1	1	6
Walker et al.[33]	0	1	0	1	1	1	0	0	1	0	1	6
Borge te al.[24]	0	0	0	1	1	1	0	0	1	0	1	5
Oymar et al.[34]	0	0	0	1	1	1	0	0	0	0	1	4
Bury et al.[35]	0	0	0	0	0	0	0	1	0	1	1	3
Magni et al.[36]	0	0	0	0	1	0	1	0	0	0	1	3
Stickler et al.[41]	0	0	0	0	1	1	1	0	0	1	1	5
Liebman et al.[40]	0	0	0	1	1	1	0	1	0	0	1	5
Christensen et al.[39]	0	0	0	0	1	1	0	1	1	1	1	6
Apley et al.[38]	0	0	0	0	1	0	0	1	0	0	1	3
Dahl et al.[37]	0	1	1	1	1	1	0	0	1	1	1	8
Total quality score	0	7	4	9	17	12	4	6	7	6	17	89
Cohen's K	1	0.63	0.63	0.77	1	1	0.67	0.55	1	0.72	0.64	0.85

Study characteristics

The main characteristics of the studies included are given in Table 3. In total, the 18 studies evaluated 1747 patients ages 4 to 18 years with CAP. The sample sizes ranged from N=22[36] to N=356[30] For 1331 patients follow-up data were given (23.8% lost to follow-up). The follow-up period ranged from a minimum of 1 year[27] to a maximum of 29 years[39] (median 5 years, SD 7 years 2 months). In 9 studies, CAP was diagnosed after additional medical testing before patients were included in the studies (tested nonorganic)[27-29,31,32,35,36,39,41] In the remaining 9 studies CAP was clinically diagnosed (clinically nonorganic)[23,24,26,30,33,34,37,38,40] In four of the latter 9 studies children were additionally tested after inclusion in the study and the authors described the abnormalities found.[23,26,30,33]

Two studies explicitly stated that no organic diseases had been diagnosed during follow-up (mean duration of follow-up 8 years 5 months, number followed up 118).[26,35] Three studies reported that organic diseases that were diagnosed during follow-up. In one study (duration of follow-up of ≥5 years, number followed up 161) three patients had Crohn disease, two patients underwent appendectomy, one underwent adhesiolysis, and one underwent ovariocystectomy.[41] In the second study (mean duration of follow-

Table 3. Characteristics and prognosis of patients in the included studies

Source	MQ	Clinical setting Study period	Inclusion criteria	Exclusion criteria	Composition of the study population	N	Duration follow-up	N follow-up	Outcome (95% CI)
Stordal et al. 2005[26]	7	Secondary care Outpatients 1997-1998	RAP: Apley's criteria	Suspicion of IBD Hepatitis	Clinically apparent nonorganic RAP patients. After inclusion: 24 nonorganic (10 IBS, 13 functional abdominal pain, 1 abdominal migraine) and 20 organic (12 GERD, 7 constipation, 1 lactose intolerance)	44	5 y	40 20 non-organic, (9 IBS, 11 functional abdominal pain) 18 organic (11 GERD, 7 constipation) (2 not described)	Presence of recurrent abdominal pain in past 3 mo 40% (24.9–56.7) 7 non-organic (3 IBS, 4 functional abdominal pain) 8 organic (5 GERD, 3 constipation)
Lindley et al. 2005[27]	6	Tertiary care inpatients 1997-2001	Functional Abdominal Pain: Rome II criteria Evidence of visceral hypersensitivity	Not mentioned	Selection of nonorganic RAP patients based on medical evaluation before inclusion.	23	1 y	21	Abdominal pain no better: 43% (21.8–66.0)
Crushell et al. 2003[28]	5	Tertiary care Inpatients 1995-2000	Non-organic RAP: Apley's criteria	Concomitant chronic illness such as cystic fibrosis	Selection of nonorganic RAP patients based on medical evaluation before inclusion.	30	Mean: 3.56 (range 1-6 y)	28	Ongoing abdominal pain: 50% (30.6–69.3)
Campo et al. 2001[29]	2	Tertiary care Inpatients 1980s	RAP: Apley's criteria 6-17 y	Abdominal pain with atypical symptoms or findings suggestive of a physical disease Acute or chronic physical disease Development disability	Selection of nonorganic RAP patients based on medical evaluation before inclusion.	28	Mean: 11.1 y	28 (lost to follow-up not provided)	Complaints of RAP in previous year: 51.9% (45.9–57.6)
Croffie et al. 2000[30]	3	Tertiary care outpatients 1990-1992	RAP: Apley's criteria 3-18 y	< 3 y Symptoms suggesting an inflammatory bowel disease	Clinically apparent nonorganic RAP patients After inclusion: 247 nonorganic (155 no diagnosis, 92 IBS), 109 organic (13 constipation, 47 inflammation of oesophagus, stomach or duodenum, or ulcers in stomach or duodenum, 7 renal abnormalities, 38 other)	356	2-4 y	157 106 nonorganic (no diagnosis n=59, IBS n=47) 51 organic (constipation n=7, GI and extra GI abnormalities, such as oesophagitis, gastritis, reflux, urine tract abnormalities etc.=44)	No improvement of symptoms: 26.7% (19.3–36.2) 29 non-organic (no diagnosis n=19, IBS n=10), 13 organic (constipation n=5, GI and extra GI abnormalities n=8)

Hyams et al. 2000[23]	6	Tertiary care outpatients 1996-1997	>5 y RAP or discomfort for nausea ≥ 1 mo duration Dyspepsia according to predefined criteria	History of faecal soiling Regular use of NSAIDs Swallowing difficulties	Clinically apparent nonorganic RAP patients After inclusion: 35 nonorganic dyspepsia, 21 organic dyspepsia, 71 no endoscopy	127	2 y	113 34 normal endoscopy, 19 mucosal inflammation, 60 no endoscopy	No improvement: 22.1% 14.9–30.9%) 10 normal endoscopy, 4 mucosal inflammation, 11 no endoscopy
Walker et al. 1998[31]	6	Tertiary care outpatients Period not mentioned	RAP≥ 3 mo No evidence of organic disease, IBS or constipation 6-18 y	A concomitant chronic illness An organic explanation for the pain Mental retardation Physical disability	Selection of nonorganic RAP patients based on medical evaluation before inclusion	90	5 y	76	Abdominal pain, more than once a week in past year: 44.7% (33.3–56.6)
Hotopf et al. 1998[32]	6	Population-based national birth cohort of children born in 1 week of March 1946	Patients who reported abdominal pain over the previous year at ages 7, 11 and 15 y	A defined organic cause of the pain (reported in hospital record)	Selection of nonorganic RAP patients based on the evaluation of medical records before inclusion	73	20 y	52	Persistent abdominal pain: 13.5% (5.6–25.8%)
Walker et al. 1998[33]	6	Tertiary care Outpatients Period not mentioned	6-18 y RAP ≥ 3 mo	Chronic health condition Physical handicap Mental retardation	Clinically apparent nonorganic RAP patients After inclusion: 90 nonorganic, 63 organic (primarily minor peptic disease)	153	5 y	129 80 nonorganic, 49 organic	Not recovered; abdominal pain ≥1 mo + certain level of disability: 32.6% (24.6–41.4) 30 nonorganic, 13 organic
Borge te al. 1994[24]	5	Population-based birth cohort born in 1981	Recurrent stomach ache at 4 y old: frequent (≥3 times/wk) or infrequent (≤2/wk)	Not mentioned	4 y; no selection based on aetiology of stomachache, no further description of medical evaluation to clarify the aetiology after inclusion.	48	6 y	48	Persistence of abdominal pain (≥1 mo): 54.2% (39.2–68.6)
Oymar et al. 1993[34]	4	Secondary care outpatients 1989 -1991	RAP: Apley's criteria	Not mentioned	Clinically apparent nonorganic RAP patients. After inclusion: 61 nonorganic (1 IBS, 60 not further specified), 7 organic (2 constipation. 1 dyspepsia, 1 gastritis, 1 lactose intolerance, 1 celiac disease, 1 renal abnormality)	68	16-34 mo	65	Same abdominal pain: 15.4% (7.6–26.5)

Source	MQ	Clinical setting Study period	Inclusion criteria	Exclusion criteria	Composition of the study population	N	Duration follow-up	N follow-up	Outcome (95% CI)
Bury et al. 1987[35]	3	Secondary care outpatients 1973-1982	RAP with ≥ 3 attacks in >2 mo	Organic cause of the pain	Selection of nonorganic RAP patients based on a medical evaluation performed before inclusion	103	0-7 y	78	No improvement or worse abdominal pain: 23.1% (14.3–34.0)
Magni et al. 1987[36]	3	Tertiary care inpatients 1965-1974	RAP: Apley's criteria Negative laboratory findings and instrumental tests at evaluation	Not mentioned	Selection of nonorganic RAP patients based on a medical evaluation performed before inclusion	22	≥10 y	16	Persistent abdominal pain: 50% (24.7–75.3)
Stickler et al. 1979[41]	5	Referral clinic outpatients 1962-1967	<15 y Diagnosis in records of: functional abdominal pain, psychosomatic-, recurrent abdominal pain of undetermined aetiology, abdominal pain, separation anxiety and school phobia Symptoms ≥ 1 mo	Not mentioned	Selection of nonorganic RAP patients based on a medical evaluation performed before inclusion	170	≥5 y	161	Persistent abdominal pain (unchanged/ worse/ failed to indicate the severity of the abdominal pain): 23.6% (17.3-30.9)
Liebman et al. 1978[40]	5	Tertiary care outpatients 1973-1976	RAP with no apparent organic cause	Not mentioned	Clinically apparent nonorganic RAP patients No further description of the medical evaluation to clarify the aetiology after inclusion	119	4 y	112	Relapses of abdominal pain: 24.1% (16.5-33.1)
Christensen et al. 1975[39]	6	Secondary care inpatients 1942-1943	RAP: Apley's criteria 2-13 y	organic disease	Selection of nonorganic RAP patients based on a medical evaluation performed before inclusion	38	28-30 y	34	Persistent abdominal pain symptoms: 52.9% (35.1-70.2)
Apley et al. 1973[38]	3	Referral centre 1960s 1/6 inpatients 5/6 outpatients	≥3 episodes of abdominal pain Pain ≥ 3 months Pain affecting the child's activities	Not mentioned	Clinically apparent nonorganic RAP patients No further description of the medical evaluation to clarify the aetiology after inclusion	120	8-20 y	60	Persistent abdominal pain: 38.3% (26.1-51.8)
Dahl et al. 1969[37]	8	Secondary care Not clear 1956-1965	Recurrent, nonorganic abdominal pain	age <1 y	Clinically apparent nonorganic RAP patients No further description of the medical evaluation to clarify the aetiology after inclusion	135	Mean 5 y (range 1-10)	116	Persistent abdominal pain: 36.2% (27.5-45.6)

up: 29 years, number followed up: 34), duodenal ulcer developed in two patients.[39] In the third study (duration of follow-up: 8-20 years, number followed up: 60) one patient experienced duodenal cancer and one patient had dermoid cysts in her ovaries.[38] The remaining 13 studies did not describe whether organic diseases had been diagnosed during follow-up.

In total, 9 studies were conducted in tertiary care facilities (paediatric gastroenterology),[23,27-31,33,36,40] 5 were conducted in secondary care clinics,[26,34,35,37,39] and one was population based.[24] In three studies, the setting was not clearly reported.[32,38,41] Ten studies were conducted in outpatients,[23,26,30,31,33-35,38,40,41] and 5 studies in hospitalized patients,[27-29,36,39] and in the remaining 3 studies, it was not clear whether inpatients or outpatients were involved.[24,32,37] The studies were performed during a wide time span. In one study the diagnosis of CAP was made in the 1940s,[39] in 5 other studies in the 1960s,[32,36-38,41] and 2 studies were performed in 2005.[26,27]

In six studies[24,26,29,31,32,39] the authors performed a nested case control study; they described a prevalence of abdominal pain at follow-up of formerly well patients and compared this percentage with the percentage of CAP children with abdominal pain at follow-up.

Prognosis of abdominal pain

Of the 1331 children with CAP who were followed up for a median of 5 years (range 1-29, SD 7 years 2 months), 415 had abdominal pain after follow-up. The mean pooled percentage of children with abdominal pain after follow-up was 29.1% (95% CI 28.1-30.2%, range 13.5-54.2%). If all the patients who were lost to follow-up had recovered, the crude percentage of CAP patients with abdominal pain after follow-up would have been 23.7% (95% CI 21.7-25.8%). If all of the patients who were lost to follow-up had persistence of their abdominal pain after follow-up, this would have been 47.6% (95% CI 45.2-49.9%). Five studies described the percentages of children with abdominal pain after follow-up of subtypes of CAP.[23,26,27,30,33] These results are shown in table 4.

Factors that influenced the prognosis of CAP

Table 5 shows the prognosis of abdominal pain stratified according to inclusion criteria, setting of care, and duration of follow-up. CAP that was clinically diagnosed after history taking and physical examination had a prognosis comparable to that of CAP diagnosed after additional medical testing. CAP studied before and after 1980 had comparable prognoses. Inpatients had a statistical significantly worse prognosis than did outpatients. There were no differences in prognoses between studies performed in secondary and tertiary care. The longer the duration of follow-up, the worse was the prognosis. Four studies additionally tested a group patients in whom CAP was clinically diagnosed.[23,26,30,33] In 137 of the 378 (36.2%) patients organic abnormalities were found;

Table 4. Prognosis of subtypes of CAP

Subtype of CAP	Criteria for diagnosis	Number of studies	Number of patients with abdominal pain at follow-up/ number of patients at follow-up	Patients with abdominal pain at follow-up, % (95% CI)
IBS	Rome II	1[26]	3/9	33.3% (7.5-70.1)
IBS	Not specified	1[30]	10/47	21.3% (10.7-35.7)
Functional abdominal pain	Rome II	2[26,27]	13/32	40.6% (23.7-59.4)
Constipation	Not specified	2[26,30]	11/17	64.7% (38.3-85.8)
Functional dyspepsia	Talley et al.[42]	1[23]	10/34	29.4% (15.1-47.5)
Organic dyspepsia	Talley et al.[42]	1[23]	4/19	21.0% (6.0-45.6)
Dyspepsia not further classified	Talley et al.[42]	1[23]	11/60	18.3% (9.5-30.4)
GERD	Not specified	1[26]	5/11	45.4% (16.7-76.6)
Minor peptic disease	Not specified	1[33]	13/49	26.5% (14.9-41.1)

IBS = Irritable Bowel Disease, GERD = gastro-oesophageal reflux disease

38 of these 137 patients had abdominal pain after follow-up [27.7% (95% CI 20.4-36.0%)], in comparison with 76 of the 241 patients in whom no organic abnormalities were found [31.5% (95% CI 25.7-37.8%), (X^2 test NS, p=0.4)]. The organic abnormalities were poorly defined and included gastro-esophageal reflux disease, gastritis, *H. Pylori* gastritis, esophagitis, constipation, lactose intolerance, celiac disease, and urinary tract

Table 5. Patients with abdominal pain after follow-up, stratified by factors that may influence prognosis

Variable	Number of studies	N of patients with abdominal pain at follow-up/n of patients at follow-up	Patients with abdominal pain at follow-up,% (95% CI)*	X^2-test
Inclusion and exclusion criteria				
Clinically nonorganic	9[23,24,26,30,33,34,37,38,40]	254/837	30.3% (27.2-33.6)	
Tested nonorganic	9[27-29,31,32,35,36,39,41]	161/494	32.6% (28.5-36.9)	NS (p=0.39)
Diagnosed <1980	5[37-41]	148/480	30.8% (26.7-35.2)	
Diagnosed ≥1980	13[23,24,26-36]	267/851	31.4% (28.3-34.6)	NS (p=0.84)
Setting of care				
Inpatients	5[27-29,36,39]	64/127	50.4% (41.4-59.4)	
Outpatients	10[23,26,30,31,33-35,38,40,41]	270/991	27.2% (24.5-30.1)	p<0.01
Secondary care	5[26,34,35,37,39]	104/330	31.5% (26.5-36.8)	
Tertiary care	9[23,27-31,33,36,40]	217/680	31.9% (28.4-35.6)	NS (p=0.99)
Duration of follow-up (y)				
1-5	7[23,27,28,30,34,35,40]	146/574	25.4% (21.9-29.0)	
5-10	6[24,26,31,33,37,41]	198/567	34.9% (31.0-38.8)	
≥ 10	5[29,32,36,38,39]	71/190	37.4% (30.5-44.2)	p<0.001

* Crude percentages

abnormalities (Table 3). All of the studies reported that the children received treatment, although the type of treatment was not specified.

Control group

The prognosis of 278 patients with former CAP was compared with the prognosis of 2901 formerly well patients.[24,26,29,31,32,39] Formerly well patients and patients with former CAP had the same duration of follow-up (mean 12 years 8 months, range 5-19 years). At follow-up, 41.3% (95% CI 35.5-47.4%) of the patients with former CAP patients had abdominal pain compared with 10.1% (95% CI 9.0-11.2%) of the formerly well patients (RR 4.1; 95% CI 3.43-4.89).

DISCUSSION

To our knowledge, this is the first systematic review of the prognosis of CAP in children. The systematic literature search yielded 18 follow-up studies. In total, 1331 children 4 to 18 years of age were followed up for 5 years (median, range 1-29 years, SD 7 years 2 months). The abdominal pain persisted in 29.1% (95% CI 28.1-30.2%) of children with CAP. Children with a history of CAP have four times higher risk of persistent abdominal pain than did children who presented for the first time with CAP. Because of a high drop-out rate of 23.8%, we performed a sensitivity analysis. This analysis showed that even if all of the children dropping out were assumed to become free of abdominal pain almost one fourth of CAP patients would still have abdominal pain after follow-up [23.7% (95% CI 21.7-25.8%)].

The prognoses of specific subtypes of CAP were addressed in only five studies. The numbers of patients studied were too small to enable reliable conclusions about the prognosis of discrete FGIDs.

In studies of children with clinically diagnosed CAP organic abnormality was found in 2% of the children during follow-up. This finding is in accordance with a recent systematic review of the literature in which it was observed that additional diagnostic testing of children with CAP without alarming symptoms did not yield relevant organic disease.[25]

We examined whether extensive medical testing had additive prognostic value above history taking and clinical examination. No differences found between the prognosis of CAP diagnosed clinically and that of CAP diagnosed after extensive investigations. In addition we found no differences in the prognosis of CAP between studies performed at the time of limited diagnostic possibilities and those performed more recently. We found that the persistence of CAP in children without alarming symptoms was not influenced by the detection of abnormalities such as gastro-esophageal reflux disease, gastritis, H. Pylori gastritis, esophagitis, constipation, lactose mal-absorption, celiac disease, and

urinary tract abnormalities. This may indicate that the prognosis would have been worse if these children had not received adequate diagnosis and treatment. From this perspective, it is important to detect abnormalities to minimize persistent abdominal pain. One may argue, however, that the prognosis of the patient with an abnormality should have been better in case of a causal relation between the abnormality and the abdominal pain, given an effective treatment. From this perspective a causal relation between the abnormality and CAP is unlikely, and thus it is not useful to test for these abnormalities in children with CAP to influence the prognosis of CAP. This interpretation is supported by others. Until now an etiologic relation between CAP and H. Pylori gastritis, lactose malabsorption, or celiac disease could not be demonstrated.[5-7,43-45]

From a psychological point of view it should be kept in mind that negative test results do not reassure the child's parents; rather tests reinforce the parent's fear of an unknown organic disease, which makes it harder to introduce the concept of a functional disorder afterwards. This brings us to the conclusion that testing children with CAP without alarm symptoms is not useful and should be avoided or findings endorse the removal of the recommendation for endoscopy for children with CAP without alarming symptoms as recently described in the Rome III criteria for FGIDs.[9]

The results of our study showed that almost twice as many inpatients as outpatients did not improve from CAP. Hospitalisation may reflect the severity of the abdominal pain, existing co-morbidity or the inability of patients and their families to deal with the disorder. Another finding was that almost 1,5 as many patients who were followed up for more than 10 years had persistent abdominal pain compared to those followed up for 1 to 5 years. CAP in children may progress to irritable bowel syndrome in adults.[31,46] The persistence of abdominal pain is a complex multifactorial mechanism that urgently needs further investigation to recognize children at risk for a prolonged course of this disabling condition.

Limitations

The following limitations should be taken into account when interpreting the results of this review. In a literature search there is always a risk of missing studies. This risk may be higher for diseases that lack a clear definition, such as CAP. We tried to avoid this problem by using a sensitive search strategy that included all available words and all known definitions of this pain syndrome. Most studies defined the abdominal pain at follow-up as a pain that resembled baseline pain. However, not all of the studies clearly defined this pain. The outcome measure therefore might be heterogeneous with respect to the frequency and the severity of pain. The presented prognosis for childhood CAP is an overall estimate. Many factors determine a patient's prognosis. We found that inpatients had different prognoses than did outpatients and that the duration of follow-up influenced prognosis. Other factors that might influence prognoses are treatment, the

duration of the pain at baseline, and psychological factors. The identification of these prognostic factors, however, was outside the scope of this study.

Recommendations

There is a need for prognostic research of good methodological quality on CAP in children in a broad range of settings. To establish the clinical utility of a classification system of CAP, the course of disease of the different FGIDs defined should be studied. To grasp the full context of functional disorders, one should add functional disability as outcome measure for prognosis.[47]

Conclusions

CAP persisted in 29.1% (95% CI 28.1-30.2%) of children. In the absence of alarm symptoms additional diagnostic testing did not influence prognosis. There is a need for prognostic research in a broad range of settings on CAP in children.

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SUPPLEMENT 1. CRITERIA FOR ASSESSING METHODOLOGICAL QUALITY

Study population

A.	Inception cohort (defined in relationship to onset of symptoms)	+/-/?
B.	Description of relevant inclusion and exclusion criteria	+/-/?
C.	Description of study population	+/-/?

Follow-up

D.	Prospective data collection	+/-/?
E.	Follow-up of at least 1-year	+/-/?
F.	Lost to follow-up/drop-outs < 20 %	+/-/?
G.	Information completers versus lost to follow-up/drop-outs	+/-/?

Treatment

H.	Treatment in cohort is fully described/standardised	+/-/?

Outcome

I.	Assessment of standardised outcome measurement	+/-/?
J.	Independent assessment of outcome measurement	+/-/?

Data presentation

K.	Data presentation of the outcome measurement	+/-/?

+ positive (sufficient information and a positive assessment); - negative (sufficient information, but potential bias due to inadequate design or conduct); ? unclear (insufficient information in the article to answer the question). Each criteria could be scored as 0 or 1 (+ was scored as 1; - and ? were scored as 0)

Explanation of the criteria

A. Positive if the cohort was approximately uniform with respect to the duration of complaints.

B. Positive if was described:

1) organic or non-organic causes of CAP that were included or excluded
2) relevant co-morbidity like certain organic-, psychological- or psychiatric disorders that would influence prognosis.

C. Positive if was described:

1) in what setting the patients were recruited (i.e. general practice, hospital)
2) referral status (the referral party, the prior investigations etc)

3) age-distribution
4) sex-distribution

D. Positive if a prospective design was used.

E. Positive if the follow-up period was at least 1 year.

F. Positive if the total number of participants was >80% on the last moment of follow-up compared to the number of participants at baseline.

G. Positive if two or more of the following four characteristics: age, sex, SES, initial severity of abdominal pain were presented for completers and those lost to follow-up at the main moment of outcome measurement. Also positive in case of no lost to follow-up.

H. Positive if treatment subsequent to inclusion in cohort is fully described or standardised.

In addition, positive in case of no treatment was given.

I. Positive if the outcome was measured in the same way and at the same follow-up time for every person with an objective method.

J. Positive if the outcome was measured independent from the prognostic variables.

K. Positive if frequency, percentage or mean, median (Inter Quartile Range) and standard deviation/confidence interval (CI) were reported or could be calculated for the outcome measure.

Chapter 4

Prognostic Factors for Persistence of Chronic Abdominal Pain in Children: A Systematic Review

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ABSTRACT

Objectives

The aim of the study was to identify prognostic factors for the persistence of chronic abdominal pain (CAP) in children.

Methods

For this systematic review, MEDLINE, EMBASE and PsycINFO were searched up to June 2008 for prospective follow-up studies of paediatric CAP as defined by the criteria of Apley, von Baeyer, or the Rome committee. The outcome measure of interest was persistence of CAP. Persistent CAP was only considered when the abdominal pain of children with CAP persisted during follow-up at the same level of frequency and severity. For each study the risk for bias was assessed. The evidence for prognostic factors was summarized according to a best-evidence synthesis.

Results

Eight studies, which examined 17 prognostic factors, were included. Moderate evidence was found that having a parent with gastrointestinal complaints predicts the persistence of CAP. Strong evidence was found for an association between female gender and the duration of CAP, and moderate evidence that the severity of abdominal pain does not predict persistence of CAP. There is conflicting evidence as to whether psychological factors prevent, or have no relation with, persistence of CAP.

Conclusions

Because there are few prognostic follow-up studies on paediatric CAP, the evidence for prognostic factors is limited. Physicians should ask about parental gastrointestinal problems, as this is a risk factor for persistence of CAP in children. The hypothesis that psychological factors of the child predict persistence of CAP is not supported by evidence from follow-up studies.

INTRODUCTION

Chronic or recurrent abdominal pain (CAP) is a prevalent disorder that has major implications for a child's wellbeing and the healthcare system.[1] CAP was first described by Apley & Naish (in 1958) as abdominal pain that occurred in at least 3 episodes over at least 3 months and was severe enough to affect a child's activities.[2] Apley & Naish postulated that CAP was a functional syndrome that could not be explained by organic pathology. However, this assumption was difficult to establish using their definition. Therefore, in order to reduce misclassification between functional and organic abdominal pain, the definition of CAP has been revised over the years.[3,4] Baeyer et al. suggested to study children fulfilling criteria for recurrent abdominal pain and describe the tests performed to preclude organic disease in order to become informed about the magnitude of the role of organic disease.[4] In order to define functional abdominal pain as a positive diagnosis rather than a diagnosis "per exclusionism", the Rome committee described symptom-based diagnostic criteria and reported the minimum examinations needed to exclude organic pathology.[3]

CAP is proposed as an altered pain sensation due to a dysfunction of the brain-gut axis resulting from a complex interaction between biological, psychological and social factors. The gut and the brain are highly integrated and communicate in a bidirectional fashion. Emotion, behaviour, gut function and pain are interrelated in this model of thinking.[5] Children with CAP have more anxiety disorders, depressive symptoms and other somatic complaints, and have experienced more negative life events than unaffected children.[6] Parents of children with CAP have more gastrointestinal (GI), anxiety and depressive symptoms than control parents.[7]

Despite treatment, approximately 30% of children with CAP have long-lasting complaints and there is evidence that CAP is a risk factor for the occurrence of irritable bowel syndrome (IBS) in adulthood.[8,9] Psychosocial factors of the child are reported to be associated with the prognosis of CAP.[10] Evidence in favour of such relationship comes mainly from case-control studies; however, such a retrospective study design cannot elucidate whether associated factors cause the pain, influence the course of the pain, or are a result of the pain. Insight into the potential prognostic factors may help clinicians to recognize a child at risk for persistent abdominal pain and guide clinical management.

Although knowledge on factors influencing the clinical course of CAP is important for physicians and patients with regard to patient information, anticipating treatment possibilities and identification of children at high risk, no overview of these prognostic factors is currently available. Good-quality prognostic studies and systematic reviews are the basis for evidence-based guidelines. Therefore, the aim of this review was to systematically describe, investigate and summarize the quantity and quality of all current evidence for potential prognostic factors for the persistence of CAP in children.

MATERIALS AND METHODS

A search was made in the MEDLINE database from 1965 to June 2008, in EMBASE from 1980 to June 2008, and in PsycINFO from 1970 to June 2008. The keywords used to describe the study population were "abdominal pain", "chronic abdominal pain", "recurrent abdominal pain" and "functional abdominal pain". To detect the relevant age group the terms "child", "infant", and "adolescent" were used. Search strategies with a high sensitivity for follow-up studies, as recommended by Altman[11] (MEDLINE), and Wilczynski[12] (EMBASE), were used. No language restriction was applied. Additional strategies to identify studies included hand searching the reference lists of the follow-up studies on paediatric CAP of recently published review articles and of articles written by experts in the field.

Two reviewers (M.J.G. and M.Y.B.) independently screened all abstracts of the identified articles for eligibility. Full papers were retrieved if the abstract provided insufficient information to enable selection, or if the paper had passed the first eligibility screening. An article was eligible if it met all of the following criteria: 1) the study population concerned children or adolescents aged 4-18 years 2) chronic or recurrent abdominal pain was described using the criteria defined by Apley and Naish (see Introduction),[2] von Baeyer and Walker (2-stage classification for RAP: Stage 1: abdominal pain that occurs at least once each month, in at least 3 consecutive months, within the past year and these episodes are usually severe enough to stay home from school, terminate or avoid play, take medication for the pain; and the child rates the pain as moderate to severe, Stage 2; RAP subdivided in either functional or organic disease based on a predefined medical evaluation,[4] or the Rome committee (at least 12 weeks of nearly continuous abdominal pain in school-aged children, no or only occasional relation of pain with physiological events, some loss of daily function, the pain is not feigned, insufficient criteria for other functional gastrointestinal disorder that would explain the abdominal pain, and physical examinations, growth, laboratory test, abdominal ultrasound should be normal)[3] 3) the study determined prognostic factors for persistence of chronic abdominal pain in children with CAP, 4) the frequency and duration of the chronic abdominal pain at follow-up was comparable to that of the CAP at the start of the study, 5) the outcome was determined prospectively. There were no restrictions to duration of follow-up. Any disagreement regarding inclusion was resolved by consensus or by arbitration of a third reviewer (S.M.A.B-Z).

Two reviewers (M.J.G. and S.M.A.B-Z.) independently assessed the risk for bias in each study. The instrument used was a modified version of an established criteria list used in systematic reviews of prognostic factors.[13,14] We modified the criteria list based on the framework for assessing internal validity of studies of prognosis as described by Altman et al., Hayden et al. and the STROBE statement.[11,15,16] The final list consisted of 16 items,

Table 1. Levels of evidence for prognostic factors

Strong evidence	Consistent findings (>75%) in at least 2 low-risk for bias cohorts
Moderate evidence	Consistent findings (>75%) in one low-risk for bias cohort and at least one high-risk for bias cohort
Weak evidence	Findings of one low-risk for bias cohort or consistent findings (>75%) in at least 3 or more high-risk for bias cohorts
Insufficient evidence	Less than 3 high-risk for bias cohorts available
Conflicting evidence	Inconsistent findings irrespective the risk for bias
No evidence	No data presented

each having a 'yes'/'no'/'don't know' answer option: a 'yes' was scored as 1, 'no' and 'don't know' were scored as zero (range 0-16) (Supplement 1). Studies at low risk for bias had high final scores. The inter-assessor agreement on the risk for bias was calculated using kappa scores (> 0.7 = a high level of agreement between assessors; 0.5 to 0.7 = a moderate level of agreement, and < 0.5 = a poor level of agreement).

Data extraction was performed by M.J.G. and verified by a second author (M.Y.B.). Extracted information included patient characteristics, the study setting, follow-up period, numbers lost to follow-up, prognostic factors, and measures of associations. Because the studies were heterogeneous with respect to definition of the study population, study setting, duration of follow-up and the prognostic factors studied, we refrained from meta-analysis (as pooling would give incorrect estimates of the real effects) and instead performed a best-evidence synthesis. The levels of evidence for the associations found are based on the guidelines of Sackett et al.[17] and are presented in Table 1. Studies were defined as being at low risk for bias when they scored more than 55% of the maximum score, i.e. ≥ 9.

Our outcome measure of prognosis of CAP was defined as the percentage of patients with persisting CAP after follow-up. Where possible, the measure of association of a prognostic variable with the percentage of children with persistent CAP after follow-up is presented as relative risk (RR) or an odds ratio (OR; in case of a logistic regression model), with corresponding 95% CI and p-value (Fisher's exact test). If the authors only provided the direction of the association and the statistical significance, this was presented. A $p \leq 0.05$ was considered significant. Prognostic variables with significant RRs or ORs were considered to be associated. To take into account that smaller studies are less likely to find significant associations, in studies with a sample size < 50, we also considered RRs ≤ 0.5 and RRs ≥ 2 to be related.

RESULTS

Search results

A total of 2,968 potentially relevant articles were identified on the first search. Most articles were discarded after analysing the abstracts because they were not follow-up studies. Of the 32 follow-up studies that remained, 14 studies were excluded: 2 because they studied the incidence of CAP,[18,19] 4 because the definition of CAP did not fulfil our criteria[20-23] (the abdominal pain at baseline or follow-up was of shorter duration or of less frequency), and 8 because their outcome measures were different from ours.[24-31] The outcome measures presented in these excluded studies were: health-related functional disability,[26,28,30,31] severity of abdominal pain,[27] a level of somatisation defined as a score on a somatisation index scale (CSI),[24-26,28-30] or as co-existing symptoms after follow-up.[31] Of the remaining 18 follow-up studies, 10 were excluded because they did not study prognostic factors.[32-41] Consequently, 8 studies were included in the final review.[42-49]

Assessment of risk for bias

Details on the assessment of potential biases of the included studies are presented in Table 2. The inter-observer reliability of this assessment (kappa = 0.75) was good. Using our cut-off point of ≥ 9, five studies were classified as studies with a low risk for bias.[42-46]

The most important methodological shortcomings concerned the following items. Most studies did not describe the study population in sufficient detail. For example, in most of the studies, referral status, prior investigations, relevant co-morbidity (items B,C) and the moment in the course of the disease (item A) was not clear. Only two studies

Table 2. Results of the assessment of risk for bias

Item	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Total	RB
References																		
Pace et al. 2006[42]	0	1	0	1	1	1	0	0	1	1	0	1	1	0	1	0	9	LRB
Stordal et al. 2005[43]	0	1	0	1	1	1	0	0	1	1	1	1	1	0	1	0	10	LRB
Lindley et al. 2005[44]	0	1	1	0	1	1	1	0	0	0	0	0	1	1	1	1	9	LRB
Crushell et al. 2003[45]	0	0	1	0	1	1	0	1	0	0	1	1	1	1	1	0	9	LRB
Walker et al. 1998[46]	0	0	0	1	1	1	0	0	1	0	1	1	1	1	1	0	9	LRB
Walker et al. 1998[47]	0	1	0	1	1	1	0	0	1	0	1	1	1	0	0	0	8	HRB
Magni et al. 1978[48]	0	0	0	0	1	0	1	0	0	0	1	0	1	0	1	0	3	HRB
Christensen et al.1975[49]	0	0	0	0	1	1	0	1	1	1	0	1	1	0	1	0	8	HRB
Total score	0	4	2	4	8	7	2	2	5	3	5	6	8	3	7	1		

RB = Risk for Bias, LRB = Low-Risk for Bias, HRB = High-Risk for Bias

The letters A-P correspond with the 16 criteria mentioned in Supplement 1, each criteria could be scored as 0 or 1 ('yes' was scored as 1; 'no' and 'don't know' were scored as 0)

compared the patient and pain characteristics of those lost to follow-up with those who were followed (item G).[44,48] Two studies reported on treatment of the patients during follow-up (item H).[45,49] In addition, in the statistical analysis, one study adjusted for age, gender and baseline severity of abdominal pain (item P).[44]

Study characteristics

The study characteristics and the prognostic factors are presented in Table 3. The sample size of the included studies ranged from 22[48] to 153.[47] The percentage of children with persistent CAP ranged from 28.9%[42] to 52.9%.[49] Six studies used the criteria of Apley & Naish but all these excluded children with organic pathology by medical testing,[43,45,46,47,48,49] and two studies used the Rome II criteria.[42,44] Five studies were conducted in tertiary care (paediatric gastroenterology)[44-48] and three in secondary care (paediatrics).[42,43,49] Four studies investigated inpatients.[44,45,48,49] and three investigated outpatients.[43,46,47] In one article it was unclear whether the study concerned inpatients or outpatients.[42]

Best-evidence synthesis

The results of the best-evidence synthesis are presented in Table 4. Seventeen potential prognostic factors for the persistence of CAP were identified, of which 10 were studied in one study only. Female gender was studied in 6 studies[42,43,44,46,48,49] of which 4 had a low risk for bias.[42,43,44,46,50] Of these 4 latter studies, in one study female gender predicted the persistence of CAP[43] whereas in the remaining three gender was not associated with the outcome. The best-evidence synthesis showed strong evidence that female gender and persistence of CAP are not related.

Four psychological factors were studied in four studies[43,44,45,47] of which three had a low risk for bias.[43,44,45] There was weak evidence that behavioural disturbances and psychological disorders do not predict persistence of CAP. There was conflicting and insufficient evidence that depressive/anxiety disorders and academic competence, respectively, predict persistence of CAP. Altogether, we found conflicting evidence as to whether 'any' psychological factor of the child prevents, or has no predictive value for, persistence of CAP.

The severity of baseline abdominal pain was examined in three studies,[44,47,48] of which one had a low-risk for bias.[44] In all three studies there was no association between the severity of the baseline CAP and persistence of CAP. Consequently, there was moderate evidence that the severity of abdominal pain at baseline does not predict the persistence of CAP.

The effect of negative life events on the persistence of CAP was investigated in only one study with low risk for bias.[44] In that study, more children with high levels of negative life events at baseline had persistence of CAP. Therefore, there was weak evidence that negative life events predict the persistence of CAP.

Table 3. Study characteristics and prognostic factors

Author	Definition of CAP	Duration of follow-up Number of patients at follow-up	Definition of the outcome	Percentage of children with persistent CAP (95% CI)	Prognostic factor	Strength of association (95% CI)
Pace et al. (2006)[42]	RAP as defined by Apley and Naish and IBS as defined by the Rome II committee	Mean: 8.5 years (range: 5-13 years) N=52	IBS-like symptoms	28.9% (17.1-43.1)	Mean age at admission Gender (female vs. male)	IBS symptoms group: 7.7 years versus recovered group: 6.2 years ° RR 1.28 (0.54-3.09) °
Stordal et al. (2005)[43]	RAP as defined by Apley and Naish	5 years N=40	Presence of recurrent abdominal pain in past 3 months	40% (24.9–56.7)	Gender (female vs. male) Behavioral disturbances (CBCL score (high vs. less high)) Duration of pain (long vs. less long)	RR 2.89 (0.98–8.54) °‡ NS NS
Lindley et al. (2005)[44]	Functional abdominal pain as defined by the Rome II committee	1 year N=21	Abdominal pain not improved	43% (21.8–66.0)	Age (young vs. older) Gender (female vs. male) Severity of abdominal pain (severe vs. less severe) Parent hostility/aggression towards health care workers (y/n) ^ Psychological disorder (y/n) ^ Involvement of more than 3 consultants (y/n) ^ Parental divorce within two years of illness onset (y/n) ^ Disagreement with psychological referral (y/n) ^ Lack of insight into psychological influence (y/n) ^ Use of hospital complaints system (y/n) ^ Manipulative complaints (y/n) ^	NS NS NS NS NS RR 3.67 (0.96-13.90) °‡ RR 2.50 (0.96-13.90) °‡ RR 2.67 (0.90–7.88) °‡ RR 7.49 (1.14-49.56) [1] NS RR 3.10 (1.03–9.28) [1]
Crushell et al. (2003)[45]	RAP as defined by Apley and Naish	Mean: 3.56 (SD: 1.59, range 1-6 years) N=28	Ongoing abdominal pain	50% (30.6–69.3)	Mean duration of pain Mean age at admission (The mean age at admission was not reported, the authors therefore subtracted the duration from follow-up of the age at follow-up)	Persistent pain group: 3.2 years (SD 3.0) versus recovered group 0.9 years (SD 0.9) [1] Mean age at follow-up in persistent pain group: 12.9 years (SD 3.4) with a duration of follow-up of 3.7 (SD 1.4) versus mean age at follow-up

					Psychiatric diagnosis: a depression or anxiety disorder (y/n) Mother's report of GI-symptoms (high vs. lower)	in recovered group: 14 years (SD 2.3) with a duration of follow-up of 3.4 (SD 1.5) [1] RR 0.48 (0.48–1.07) º‡ Increase outcome [1]
Walker et al. (1998)[46]	RAP as defined by Apley and Naish	Mean: 25 months (SD: 15 months, range 3-25 months) N=146	Abdominal pain in the past year more than once a week	44.7% (33.3–56.6)	Gender (female vs. male)	RR 1.69 (0.95–3.02) º
Walker et al. (1998)[47]	RAP as defined by Apley and Naish	5 years N=129	Non-recovery of abdominal pain	33.3% (25.2-41.5) Logistic regression model	Symptom severity (CSI score: 0-140) Symptom duration (in months) Functional disability (FDI score: 0-60) * Depressive symptoms (CDI score: 0-54) ± Academic competence (subscale SPPC: 0-18)¶	OR 1.13 º OR 0.98 º OR 1.30 [1] OR 1.46 [1] OR 1.34 [1]
Magni et al. (1987)[48]	RAP as defined by Apley and Naish	≥10 years N=16	Persisting abdominal pain	50% (24.7–75.3)	Age (young vs. older) Gender (female vs. male) Duration of symptoms (long vs. less long) Intensity of the symptoms (intense vs. less intense) Other associated symptoms (nausea, vomiting, headache etc.) (y/n) Painful family (y/n) Surgical operation (both appendectomy and tonsillectomy vs. one of the two) Educational level (lower vs. high school) Social class (lower vs. upper-middle class)	NS NS NS NS NS RR 4.2 (0.67-26.3) º‡ RR 2.0 (1.0-4.0) [1] RR 5.4 (0.86-34.6) º‡ RR 7.0 (1.10-44.6) [1]
Christensen et al. (1975)[49]	RAP as defined by Apley and Naish	8-29 years N=60	Persisting abdominal pain	52.9% (35.1-70.2)	Gender (female vs. male)	RR 1.12 (0.50-2.51) º

º no statistical significance, [1] statistical significance, ‡ effective association (small study), N = number of patients, CBCL = Child Behavioral Check List, CSI = Children's Somatization Inventory, FDI = Functional Disability Inventory, CDI = Children's Depression Inventory, SPPC = Self-Perception Profile for Children/adolescents, RAP = Recurrent Abdominal Pain, OR: per unit increase of the prognostic factor, ^ adjusted for age, gender and severity of abdominal pain, * adjusted for symptom severity and symptom duration, ± adjusted for symptom severity, symptom duration and functional disability, ¶ adjusted for symptom severity, symptom duration, functional disability and depressive symptoms

Table 4. Best-evidence synthesis

Prognostic factors	Total number of studies	Number of studies with their risk for bias and the direction of the association with persistent CAP at follow-up	Best-evidence synthesis
1 Patient characteristics			
1.1 Female gender	N=6	4 LRB: 3 NA,[42,44,46] 1 +[43] 2 HRB: 2 NA[48,49]	Strong evidence for no predictive value
1.2 Young age	N=4	3 LRB: 2 NA,[42,44] 1 +[45] 1 HRB: NA[48]	Conflicting
1.3 Low educational level of the child	N=1	1 HRB: +[48]	Insufficient
2 Psychological factors of the child			
2.1 Behavioural disturbances	N=1	1 LRB: NA[43]	Weak evidence for no predictive value
2.2 Psychological disorders	N=1	1 LRB: NA[44]	Weak evidence for no predictive value
2.3 Depressive or anxiety disorders	N=2	1 LRB: -[45] 1 HRB: +[47]	Conflicting
2.4 Self perceived academic competence	N=1	1 HRB: +[47]	Insufficient
2.5 'Any' psychological factor (2.1 + 2.2 + 2.3 + 2.4)	N=4	3 LRB: 2 NA [43,44], 1- [45] 1 HRB: +[47]	Conflicting evidence for no predictive value or a negative predictive value
3 Pain history and associated symptoms at baseline			
3.1 Long duration of abdominal pain	N=4	2 LRB: +,[45] NA[43] 2 HRB: 2 NA[47,48]	Conflicting
3.2 Severe abdominal pain	N=3	1 LRB: NA[44] 2 HRB: 2 NA[47,48]	Moderate evidence for no predictive value
3.3 History of 2 or more surgical operations	N=1	1 HRB: +[48]	Insufficient
3.4 Presence of other associated symptoms such as nausea, vomiting and headaches	N=1	1 HRB: NA[48]	Insufficient
3.5 High levels of functional disability	N=1	1 HRB: +[47]	Insufficient
4 Environmental factors			
4.1 Low SES	N=1	1 HRB: +[48]	Insufficient
4.2 High levels of negative life events	N=1	1 LRB: +[44]	Weak evidence for a positive predictive value
5 Family factors			
5.1 High levels of functional GI-complaints in the family	N=2	1 LRB: mother's +[45] 1 HRB: parent's +[48]	Moderate evidence for a positive predictive value

5.2 Illness perception	N=1	1 LRB: a high number of involved consultants +[44] lack of insight into the psychological influences on the pain +,[44] disagreement with psychological referral +[44]	Weak evidence for a positive predictive value
5.3 Attitude towards health care	N=1	1 LRB: parental manipulative complaining +,[44] complaining through hospital system NA,[44] hostility towards health workers NA[44]	Conflicting

N = number of studies, LRB = low-risk for bias, HRB = high-risk for bias, + = predicts poor outcome (RR ≥ 2, or significant RR > 1 or OR>1),- = prevents poor outcome (RR ≤ 0.5, or a significant RR < 1 or OR < 1), NA = not associated (0.5 < RR < 2 or RR and OR ns)

The effect of having a parent with functional GI complaints on the persistence of CAP was examined in two studies.[45,48] One study was at low risk for bias.[45] In both studies, having a parent with GI complaints was associated with a higher risk for the persistence of CAP. There was moderate evidence that these factors predict the persistence of CAP in children.

One study, at low risk for bias, investigated the association between the perception of parents on the illness of their child and the prognosis of CAP.[44] It was found that having parents who continue to search for an organic explanation of the pain (expressed by a high number of consultants) and parents who refused to consider a psychological influence on the pain (expressed by disagreement with psychological referral) was associated with the persistence of CAP. Therefore, there was weak evidence that parental perception of illness predicts the persistence of CAP in their children.

Due to the small number of studies or conflicting directions of the associations, it was not clear whether age, educational level, duration of CAP at baseline, presence of associated symptoms, a history of two or more surgical operations, and/or social economic status of the family, influenced the course of paediatric CAP.

DISCUSSION

In this systematic review, we investigated and summarized the quantity and quality of all current evidence for potential prognostic factors for persistence of CAP in children. In total 8 prospective cohort studies were included, of which 5 were at low-risk for bias. Seventeen potential prognostic factors for the persistence of CAP were identified, of which 10 were examined in one study only. Consequently, beforehand, the level of evidence for an association between these factors and the persistence of CAP was low.

We found moderate evidence that having a parent with functional GI symptoms predicted the persistence of CAP in children, and weak evidence that parental perception of illness predicted the persistence of CAP. These findings can be explained by the social learning theory of illness behavior.[50] Illness behaviour is the way a person reacts to changes in health conditions. People with an inappropriate illness behaviour, misconceive normal sensations as symptoms of disease and react to stressful events with somatic symptoms such as abdominal pain. Children tend to copy their parents' behaviour and parents subsequently reinforce this heightened illness behaviour by paying positive attention to the complaints. Consistent with this theory is the finding that cognitive behavioural family interventions can successfully reduce the child's pain.[51] In this therapy the pain process is thoroughly explained and parents are thought to reinforce 'well' behaviour and to distract the child during pain episodes.[52] Heredity may also play a role; CAP and IBS can run in families, and genetic factors may contribute to the association of parent and child symptoms.[53]

We found strong evidence that female gender had no predictive value for the persistence of CAP. This was a consistent finding in five out of six studies in the present review and is also supported by others.[54] Two prospective cohort studies, however, reported that girls in comparison to boys had an increased risk to develop CAP.[18,19] Thus, the association between gender, incidence and persistence of CAP is not yet fully elucidated and needs further study. The severity of abdominal pain was not a risk factor for the persistence of CAP in children; this finding applied to all included studies. In addition, we found weak evidence that negative life events predicted the persistence of CAP, which is in accordance with current opinion.

In contrast to current opinion,[10] we did not find evidence for an association between psychological factors of the child and persistence of CAP. On the contrary, we found conflicting evidence as to whether psychological factors of the child 'prevented' or had no predictive value for the persistence of CAP in children. One possible explanation for this finding is that CAP and psychological factors may be triggered by the same underlying mechanisms and occur together, but are not necessarily causally related. Therefore, although children with CAP might be at risk for psychological disorders, the psychological disorders themselves are not the reason for the persistence of abdominal pain. Another explanation for the lack of observed evidence is the small number of studies and the risk for bias in those studies that investigated the prognostic value of psychological factors. An argument for a relation between children's psychological problems and persistence of CAP is that psychological treatments reduce abdominal pain.[51] Thus, in the included studies, children with psychological problems that were less likely to have persistent CAP might have received psychological treatments. However, the authors of the individual studies did not report on the treatment used.

Limitations

The following limitations should be taken into account when interpreting the results of the present review. First, some studies may have been missed during the literature search because CAP is a description of symptoms and there is no single, commonly used name or definition for it. However, the chance that studies are missed is small because a sensitive search strategy was used that included all current names and definitions used for CAP. Secondly, because all studies included in the present review were conducted in tertiary or secondary care centres, the results of these studies are not representative for a community setting or general practice. In addition, it is important to note that the prognosis of CAP is influenced by many factors and that these may interact and increase/decrease each other's effect. Most of the studies in the present review used univariate analysis and did not take possible interactions into consideration.

Currently, there is no internationally accepted method to conduct systematic reviews of prognostic studies. In addition, there are no validated or widely used criteria to assess the risk of bias. Hayden et al.[15] and the STROBE statement[16] have provided some recommendations for the methodological assessment of reviews and we incorporated them in our analysis of bias. Although not recommended, we used an overall score for risk for bias to enable a best-evidence synthesis.

In the present review, strict inclusion criteria were applied. Only CAP as defined by Apley and Naish,[2] von Baeyer[4] or the Rome committee[3] was eligible for inclusion. In our opinion, the inclusion of studies using different criteria for CAP did not make our study population heterogeneous. All studies defined CAP as an abdominal pain of comparable duration and frequency, and all studies excluded children with organic pathology. Therefore, the results of this review are applicable to referred children with CAP in which organic pathology has been ruled out by additional diagnostic testing. Another consequence of our inclusion criteria is that some studies on CAP were not included. Ramchandani et al. described the one-year outcome of 860 children with recurrent abdominal pain.[23] This latter study was not included because their outcome measure was abdominal pain in the previous year (a 'yes/no' question). In their definition, the rate of abdominal pain is not comparable to the rate of abdominal pain in our definition; we doubt whether their reported abdominal pain could be regarded as chronic abdominal pain.

Further research

The present study clearly shows the value of a systematic review as it demonstrates that there is little evidence to support all the current assumptions on paediatric CAP. This emphasizes the need for well-conducted follow-up studies on paediatric CAP, not only in referred children but also in primary care and open populations. The outcome measure should be well defined and, besides the persistence of abdominal pain, should

include functional disability due to abdominal pain. The criterion to rule out organic causes should not be part of the definition of outcome because discussion will always remain as to how much and what kind of medical investigation is needed to be sure of ruling out an organic basis for the abdominal pain. Including this criterion will make the definition impossible to apply, for example, to a community or school population. Multivariable analyses are needed to reveal possible interactions between potential prognostic factors. Such interactions can have important clinical consequences. For example, whereas it is impossible to prevent a child from having negative life events it might be possible to strengthen factors that can diminish their effects.

Clinical implications

Boys and girls were found to be at similar risks for persistence of CAP. This implicates that the clinician should be aware that in both, girls and boys, CAP may persist. Furthermore, our results indicate that the clinician should be aware of the association between parental GI symptoms, parental perception towards the abdominal pain and the persistence of abdominal pain in the child. Adequate follow-up should be part of the management of a child with functional abdominal pain at increased risk for chronicity. By addressing coping strategies and parental cognitions on abdominal pain, the persistence of abdominal pain might be reduced or prevented. Last, our finding that the severity of abdominal pain was not a risk factor for the persistence of CAP in children may be particularly useful for clinicians in their management of paediatric CAP. A child in severe pain is impressive and might therefore lead clinical management. The finding of this review might help to change this behaviour.

Conclusions

Children with parents with GI symptoms are at risk for the persistence of CAP. Female gender and the severity of CAP do not influence the persistence of paediatric CAP. The current opinion that a child's psychological disorders predict the persistence of CAP is not supported by evidence from prognostic studies. Our results are based on a limited amount of studies and should therefore be interpreted with caution.

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SUPPLEMENT 1. CRITERIA FOR THE ASSESSMENT OF THE RISK FOR BIAS

Study population

A.	Inception cohort (defined in relationship to onset of symptoms)	+/-/?
B.	Description of relevant inclusion and exclusion criteria	+/-/?
C.	Description of study population	+/-/?

Follow-up

D.	Prospective data collection	+/-/?
E.	Follow-up of at least 1-year	+/-/?
F.	Lost to follow-up/drop-outs < 20 %	+/-/?
G.	Information completers versus lost to follow-up/drop-outs	+/-/?

Treatment

H.	Treatment in cohort is fully described/standardised	+/-/?

Outcome

I.	Assessment of standardised outcome measurement	+/-/?
J.	Independent assessment of outcome measurement	+/-/?

Prognostic factors

K.	Assessment of standardised prognostic variables	+/-/?
L.	Independent assessment of the prognostic variables	+/-/?

Data presentation

M.	Data presentation of the outcome measurement	+/-/?
N.	Data presentation of the prognostic variables	+/-/?

Data analysis

O.	Appropriate univariate crude estimates	+/-/?
P.	Appropriate multivariate analysis techniques	+/-/?

+ positive (sufficient information and a positive assessment); - negative (sufficient information, but potential bias due to inadequate design or conduct); ? unclear (insufficient information in the article to answer the question) Each criteria could be scored as 0 or 1 (+ was scored as 1; - and ? were scored as 0)

Explanation of the criteria

A. Positive if the cohort was approximately uniform with respect to the duration of complaints.

B. Positive if was described:

1) organic or non-organic causes of CAP that were included or excluded
2) relevant co-morbidity like certain organic-, psychological- or psychiatric disorders that would influence prognosis.

C. Positive if was described:

1) in what setting the patients were recruited (i.e. general practice, hospital)
2) referral status (the referral party, the prior investigations etc)
3) age-distribution
4) sex-distribution

D. Positive if a prospective design was used.

E. Positive if the follow-up period was at least 1 year.

F. Positive if the total number of participants was >80% on the last moment of follow-up compared to the number of participants at baseline.

G. Positive if two or more of the following four characteristics: age, sex, SES, initial severity of abdominal pain were presented for completers and those lost to follow-up at the main moment of outcome measurement. Also positive in case of no lost to follow-up.

H. Positive if treatment subsequent to inclusion in cohort is fully described or standardised.

In addition, positive in case of no treatment was given.

I. Positive if the outcome was measured in the same way and at the same follow-up time for every person with an objective method.

J. Positive if the outcome was measured independent from the prognostic variables.

K. Positive if three or more of the following prognostic determinants were measured at baseline in the same way for every person with an objective method: age, sex, SES, severity of abdominal pain, a psychosocial factor.

L. In case of a retrospective study: positive if prognostic determinants were measured independent from the outcome. Also positive in case of prospective data collection.

M. Positive if frequency, percentage or mean, median (Inter Quartile Range) and standard deviation/confidence interval (CI) were reported or could be calculated for the outcome measure.

N. Positive if frequency, percentage or mean, median and standard deviation/CI were reported or can be calculated for 3 or more of the following prognostic determinants: age, sex, SES, severity of abdominal pain, a psychosocial factor.

O. Positive if univariate OR, RR or differences of continuous variables, with a 95% CI were given or the associations could be calculated.

P. Positive if adjusted OR, RR, differences of continuous variables with a 95% Confidence Intervals were given. Adjustment for three or more of the following prognostic determinants: age, sex, SES, severity of abdominal pain, a psychological factor, if they are associated with the outcome in univariate analyses

Chapter 5

Non-Specific Abdominal Pain in Children in General Practice: Incidence, associated factors and management

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ABSTRACT

Purpose

Non-specific abdominal pain (NSAP) is a common complaint in childhood. In specialist care childhood NSAP is considered to be a complex and time-consuming problem and parents of children with NSAP are found to be hard to reassure. Little is known about NSAP in general practice, but the impression is that general practitioners (GPs) consider it a benign syndrome needing little more than reassurance. This discrepancy calls for a better understanding of NSAP in general practice.

Methods

Data were obtained from the Second Dutch National Survey of General Practice. Using registration data of 91 general practices we identified children aged 4-17 years with NSAP. Incidence rate was calculated, factors associated with childhood NSAP, and referrals and prescriptions were studied.

Results

The incidence rate of NSAP was 25.0 (95% CI 23.7-26.3) per 1000 person years. Most (92.7%) of the newly diagnosed children (N=1480) consulted once or twice for NSAP. Factors independently associated with NSAP were female sex (OR 1.4; 95% CI 1.3-1.5), non-gastrointestinal non-specific symptoms (OR 1.3; 95% CI 1.1-1.5) and health care use. At first consultation of newly diagnosed patients 3% of the patients were referred to specialist care and 1% for additional testing. GPs prescribed medication in 21.3% of the consultations for NSAP.

Conclusions

Childhood NSAP is a common problem in general practice, but GP are only briefly involved. GPs use little additional testing and referrals in their management of childhood NSAP. Despite the lack of evidence for effectiveness GPs commonly prescribe medication for NSAP.

INTRODUCTION

Abdominal pain is a common complaint in children all over the world.[1] It has a considerable effect on a child's well-being and leads to substantial school absenteeism.[2] Childhood abdominal pain is usually not associated with organic disease.[3-5] In this study we use the expression "non-specific abdominal pain" (NSAP) for abdominal pain for which the physician does not suspect organic pathology. Most studies on NSAP are carried out in specialist care and include children with chronic or recurrent abdominal pain.

Little is known about childhood NSAP in general practice. In population and school-based studies prevalence rates range from 4-10%.[1] The occurrence of NSAP in general practice has hardly been studied, nor has the general practitioners' (GP) management. The impression is that GPs consider NSAP in children as a benign disorder needing little more than reassurance of parent and child. This view, however, contradicts the presence of psychological co-morbidity,[6-9] other non-specific symptoms[6,8,10] and the high prevalence of prolonged symptoms,[11] found in children referred to secondary and tertiary care. In specialist care, childhood NSAP is considered to be a complex and time-consuming problem and parents of children with NSAP are found to be hard to reassure.[12,13] For paediatric gastroenterologists NSAP is the most common disorder seen.[14] The discrepancy of childhood NSAP described in specialist care and primary care is challenging and calls for a better understanding of NSAP in general practice.

The aim of the study was to offer a primary care perspective to childhood NSAP. Using record registration data from the Second Dutch National Survey of General Practice, we performed an explorative study estimating the occurrence of childhood NSAP in general practice, studying associated factors and determining the GP's management.

METHODS

In the Netherlands, all non-institutionalized inhabitants are registered with a GP. General practice is very accessible, free at point of service, and the GP usually knows the family well. Access to a medical specialist is only possible after referral by a GP. Paediatricians and surgeons will see referred children only. A general paediatrician will refer a child to the paediatric gastroenterologist only if indicated (i.e. endoscopy).

The data used in the present study were derived from the Second Dutch National Survey of General Practice (DNSGP-2), which was carried out by the Netherlands Institute for Health Services Research (NIVEL) in 2001.[15] The study was carried out according to Dutch legislation on privacy. The privacy regulation of the study was approved by the Dutch Data Protection Authority. According to the Central Committee on Research Involving Human Subjects, obtaining informed consent is not obligatory for observa-

tional studies. For this survey, 195 family physicians in 104 practices recorded data about all contacts with their patients for a period of 12 consecutive months. Data from 13 practices were excluded because of poor quality of the registered data (8 practices) and because of failure to register referrals (5 practices). The survey included a representative 2.5% sample of the Dutch population (N = 394192). All patient contacts, all referrals and prescriptions were registered in the electronic medical records (EMR) of the patients. In the Netherlands, the International Classification of Primary Care (ICPC)[16] is the standard for coding morbidity in general practice. It is included in all electronic patient record (EPR)-based morbidity recording systems. The participating GPs of the DNSGP-2 were additionally trained[17] in coding diagnoses using the ICPC and prescriptions using the Anatomical Therapeutic Chemical index (ATC).[18] The software of the electronic patient record (EPR)-based morbidity recording systems of participating GPs was extended with modules that alerted whenever registration was insufficient.[17] The completeness and accuracy of data registration were monitored.[17] The accuracy of coding was monitored by comparing record data with data from video recordings.[17] Reliability was monitored by inter-physician and inter-practice variation in disease episodes.[17] Written patient cases were used to study the agreement of ICPC coding between GPs and experts. There was an agreement in ICPC for generalized abdominal pain (D06) of 85% and for feeling down/depressive (P03) of 73%.[19] Detailed information about the study design and methods has been reported previously.[15]

The survey was episode orientated; meaning that different consultations concerning the same health problem were clustered into one disease episode.[17] The code (ICPC) of the last consultation within an episode was considered as the episode-diagnosis and coded as such. For example, a patient with an episode that consists of two consultations for abdominal pain, in which the first consultation was coded ICPC D06 "other localized abdominal pain" and the second D88 "appendicitis", the episode-diagnosis was coded as D88 "appendicitis" in both consultations.

Study population

To be eligible for this analysis a child had to aged between 4 and 17 years. Age was determined at the middle of the registration year. All consultations within episodes diagnosed as: "generalized abdominal pain" (D01), "epigastric abdominal pain" (D02), "other localized abdominal pain" (D06), and "irritable bowel syndrome" (D93) were considered as NSAP. As GPs use these codes when they are not aware of any disorder causing the pain. A child was considered as an incident case if the first consultation for NSAP during the registration year was coded as a new problem. A child was considered as a prevalent case if the first consultation for NSAP during the registration year was coded as a known problem.

Factors associated with non-specific abdominal pain

Children were labelled as having a psychological problem, a social problem and a non-gastro-intestinal-non-specific symptom whenever they had made ≥ 1 consultation coded with corresponding ICPC. For a psychological problem we used ICPC chapter P [psychological and psychiatric problems; for example: feeling anxious (P01), transient stress reaction (P02), feeling down (P03), eating problems (P11), conduct problems (P22), learning problems (P24)]. For a social problem we used ICPC chapter Z [social problems, for example; relationship problems parents (Z20), problems with disease of parents/family (Z21), problems with death of parents/family (Z23), problems with friends (Z24), problems with assault or violence (Z25)]. We considered the following codes as non-gastro-intestinal-non-specific symptoms: headache (N01), pain, general/multiple sites (A01), general weakness/tiredness (A04), fainting/syncope (A06), chest pain not otherwise specified (A11).

The general practitioner's management

We first compared the percentage of consultations for NSAP with a prescription and referral to the percentage of consultations for other problems with a prescription and referral. Second, we analyzed additional testing, kind of referrals and type of prescriptions in consecutive consultations for NSAP of incident patients. The following prescriptions were analyzed: drugs for acid-related disorders (ATC code A02), antispasmodics (A03), laxatives (A06), intestinal anti-inflammatory drugs (A07E), anti-infective agents (antibiotics; J01), antipropulsives (antidiarhoica; A07D), painkiller (NSAIDs; M01 and analgesics; N02), benzodiazepine derivatives (N05 and rivotril; N03AE), and antidepressants (N06A). All referrals were analyzed. Referrals to all of the following mental health care specialists could be coded: social work, physiotherapy, primary care psychologist, psychotherapist, and psychiatrist.

Analyses

The incidence rate was calculated by dividing the total number of newly diagnosed cases (numerator) by the total number of person years of the population at risk (denominator). The number of person years was calculated by using the mid-time population. As the registration period was one year, the mid-time population was calculated by taking the mean of the number of listed patients at the beginning of the registration period and the number of listed patients at the end of the registration. Incidence rates were expressed per 1000 person-years. The 95% confidence intervals (CI) were computed around incidence rates assuming a Poisson distribution using STATA version 11.0. The prevalence rate was calculated with the total number of children with a consultation for NSAP as numerator. In order to explore the relation between age and NSAP in more detail we analyzed the incidence rate for boys and girls per year of age.

Table 1. Incidence and prevalence rate of childhood non-specific abdominal pain per 1 000 person years

	Incidence rate (95%CI)	Prevalence rate (95%CI)
Male	20.3 (18.8-22.0)	27.3 (25.5-29.2)
Female	29.9 (28.0-31.9)	39.8 (37.6-42.1)
All	25.0 (23.7-26.3)	33.4 (32.0-34.9)

We compared children with NSAP to children without NSAP (also 4-17 years of age) with respect to age, sex, the number of children with psychological, social and non-gastro-intestinal-non-specific symptoms, and healthcare use. Healthcare use was calculated as the number of consultations for reasons other than NSAP per child per year. Differences between proportions were tested with Pearson's Chi-squared test (level of significance $p<0.05$). With univariable logistic regression analyses we assessed the association between the above enumerated factors and NSAP. Factors that were univariately significantly associated with NSAP ($p<0.05$) were entered in a multivariate logistic regression analysis. The statistical package SPSS version 15.0 was used for these regression analyses (SPSS Inc, Chicago IL, USA).

RESULTS

At the beginning of the registration year our study population consisted of 59 999 children aged 4-17 years, yielding 59 203 person-years. During the registration year 40 781 children (68.0%) consulted their GP and 1 978 children did so for NSAP (4.9% of all consulting children). The control group consisted out of 38 803 children in the age of 4

Figure 1. Incidence rate of childhood non-specific abdominal pain in general practice

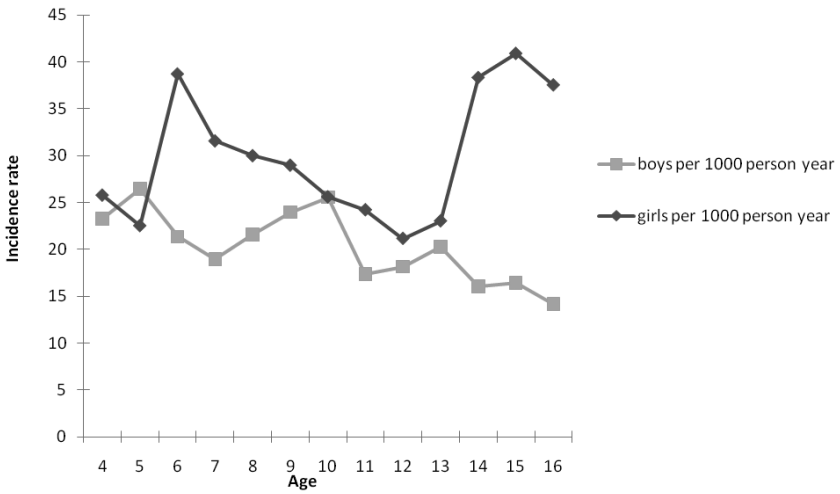

Table 2. Characteristics associated with childhood non-specific abdominal pain (NSAP)

		No NSAP (n=38 803)	NSAP (n=1 978)	Univariate OR (95% CI)	Mulivariate OR (95% CI)
Age in years (mean, SD)		10,4 (3.8)	10,4 (3.8)	1.0 (0.99-1.01)	
Gender	Male	50.6%	41.8%	Ref. cat.	Ref. cat.
	Female	49.4%	58.2%	1.4 (1.3-1.6)	1.4 (1.3-1.5)
Psychological problem	No	93.4%	93.1%	Ref. cat.	
	Yes	6.6%	6.9%	1.1 (0.9-1.3)	
Social problem	No	99.2%	98.7%	Ref. cat.	Ref. cat.
	Yes	0.8%	1.3%	1.6 (1.1-2.4)	1.4 (0.9-2.1)
Non-specific problem	No	95.0%	92.8%	Ref. cat.	Ref. cat.
	Yes	5.0%	7.2%	1.5 (1.2-1.8)	1.3 (1.1-1.5)
Health care use (mean, SD)		3.9 (3.9)	4.6 (4.7)	1.05 (1.04-1.06)	1.04 (1.03-1.05)

Ref. cat. = reference category

to 17 years. In total, 1 480 children consulted their GP for the first time with NSAP. Table 1 shows the incidence en prevalence rate for NSAP in girls and boys. Of the incident cases 1 372 (92.7%) consulted only once or twice for NSAP. Figure 1 shows that the incidence of NSAP for girls had two peaks by age; the first around 6 years and the second around 15 years. The incidence rate for boys decreased by age.

Factors associated with non-specific abdominal pain

Table 2 shows the characteristics of children with and without NSAP and the results from the logistic regression analyses. We observed that children with NSAP were more often girls, consulted more for psychological, social problems, and non-specific non-GI complaints, and had more consultations for other reasons. In the multivariable analysis female sex, health care use and unspecified non-GI complaints were independently associated with NSAP.

The general practitioner's management

GPs referred in 5.0% of the consultations for NSAP. This percentage was comparable to that in consultations for other problems (5.1%) (table 3). During the first consultation of new patients GPs referred 3.0% to secondary care and ordered in 1.1% of these patients

Table 3. GP's management during consultations for childhood non-specific abdominal pain (NSAP) and for other problems

	NSAP (n=2 632)	Other problems (n=156 048)	p-value*
No prescription, no referral (%)	73.7	49.7	p<0.001
Prescription (%)	21.3	45.3	p<0.001
Referral (%)	5.0	5.1	p<0.05

*Pearson Chi-square test

Table 4. GP's management during consecutive consultations of incident patients for NSAP

	First consultation (n=1 480)	Second consultation (n=324)	Third and more consultation (n=184)
Consultations with a prescription (n, %)	260 (17.6)	90 (27.8)	75 (40.8)
Drugs for acid-related disorders (%)*	13.1	4.4	1.3
Antispasmodics (%)*	29.2	26.7	24.0
Laxatives (%)*	25.0	32.2	37.3
Osmotic laxatives (Lactulose) (%)*	11.2	15.6	10
Bulking agents (Psylium) (%)*	12.7	14.4	14
Others (%)*	1.2	2	4
Painkillers NSAIDs (%)*	5.4	14.4	14.7
Painkillers Analgesics (%)*	3.8	4.4	5.3
Anti-infective agents (%)*	6.9	5.6	1.3
Consultations with additional testing (n, %)	16 (1.1)	9 (2.8)	0
Consultations with a referral (n, %)	45 (3.0)	19 (5.6)	5 (2.7)
Paediatrician (n)	5	8	3
Surgeon (n)	24	2	0
Radiology (n)	0	1	0
Psychiatrist (n)	1	0	0
Gynaecologist (n)	2	1	1
Cardiologist (n)	1	1	0
Urologist (n)	0	1	0
Physiotherapist (n)	2	2	0
Dietician (n)	2	1	0
Unknown (n)	2	1	1
Other (n)	6	1	0

* Percentages from the total number of consultations with a prescription

(n=16) for additional testing (table 4). The percentage of consultations with a referral increased during the second consultation to 5.6%, but decreased again and stabilized during the third and following consultations (2.7%). During the first consultation 39.3% of the referred children were referred to a surgeon (n=24) in later consultations most of the children were referred to a pediatrician. Only one child was referred to a psychiatrist.

In 21.3% of the consultations for NSAP the GPs prescribed medication; this was significantly less than during consultations for other reasons (45.3%, $p<0.001$) (table 3). During following consultations for NSAP of new patients prescription rate increased (from 17.6% to 40.8% ; table 4). Approximately 1/3 of the total number of prescriptions was laxatives, (25.0%-37.3%) and another 1/3 was antispasmodics (24.0-29.6%). GPs did not prescribe antidepressants or benzodiazepine derivatives for NSAP.

DISCUSSION

With an incidence rate of 25.0 per 1 000 person years (95% CI 23.7-26.3) NSAP is one of the 10 most commonly seen complaints of children in general practice.[16] Annually, a Dutch GP with a practice of average size will see approximately 21 children aged 4-17 years with NSAP. Only few (<7) new patients with NSAP consult more than twice for this problem. In the present study, female sex, health care use and other non-GI unspecified symptoms were independently associated with NSAP. GPs referred in 5.0% of the consultations for NSAP and prescribed medication in 21.3%.

The results of the present study show that childhood NSAP is a common problem in general practice. It is therefore remarkable that it has rarely been studied in this setting. We are aware of only one study that reported the frequency of consultations for NSAP in primary care. In Australia, 1.4 of every 100 consultations of children and adolescents aged 0-24 years concerned NSAP.[20]

In the present study, the incidence of girls consulting for NSAP showed peaks around 5 and 12 years of age, for boys it decreased by age. The incidence rate for NSAP in general practice has not been reported before. The incidence rate for boys and girls separately has not been reported before in any setting. There are open population studies that have presented the prevalence rate of childhood chronic or recurrent NSAP by age.[3,21,22] All studies show a peak in the occurrence of NSAP around 3-6 years of age. Although not studied yet, explanations for this age peak might be school attendance and its associated anxieties. The observed age peak in our study in girls at age 12-16 might be explained by menarche or dysmenorrhoea.

We used the expression non-specific abdominal pain (NSAP) for childhood abdominal pain for which GPs have no specific organic explanation, in other words for which GPs do not suspect organic pathology. NSAP or "medically unexplained abdominal pain" is common in children. A variety of expressions are used describing this pain syndrome: recurrent abdominal pain;[1,3,21,23] chronic abdominal pain;[24,25] functional abdominal pain;[26] non-specific abdominal pain;[27,28] and medically unexplained abdominal pain. Most expressions enclose a minimal duration of abdominal pain, usually 3 months. This "time criterion" was arbitrarily set by Apley et al who were the first describing the pain syndrome in 1958.[3] The 'time criterion" was meant to reduce the risk of organic pathology, as organic abnormalities will usually become manifest within time. In addition to the difference in "time criterion" the extent of additional testing for organic abnormalities depends on the facilities available for medical testing. As a consequence the study populations of almost all studies on childhood abdominal pain differ. It is unknown, what differentiates non-specific abdominal pain in general practice from the above mentioned pain syndrome other then it's probability of a non-organic cause. We assume it will be the duration of the abdominal pain, which makes it mainly a difference in

prognosis. In this study we were not able to explore prognosis or duration of abdominal pain. We looked at contacts for abdominal pain and found that most children contacted once or twice for this complaint. We do not know if children who did not contact more often, were not suffering from abdominal pain. Because of its comparable origin, i.e. a non-organic cause, we consider NSAP in general practice as a hardly studied part of the spectrum of the same pain syndrome.

Although in referred children it has been repeatedly found that chronic or recurrent abdominal pain is associated with psychological symptoms, [6-10] Dutch GPs did not associate childhood NSAP with psychological and social problems. We believe that GPs almost certainly ask for psychosocial complaints in consultations for childhood NSAP, but that they probably regarded these complaints as being too mild to code them with ICPC as a psychological of social problem. Our finding gives room for speculations whether the association found in referred children might be biased due to a selective referral of children with NSAP and (severe) psychosocial problems to secondary and tertiary care. On the other hand it has also been reported that GPs have difficulties in identifying psychological problems in children.[29-31]

During the first consultations of new patients GPs only referred 3% of the new patients to secondary care, and ordered in only 1% additional testing. Given these low percentages we assume that GPs feel comfortable in labelling childhood abdominal pain as NSAP, or "non-organic" abdominal pain. In addition, only few children (< 7%) re-consulted their GP for NSAP. These findings are remarkable, because in referred children it has been shown that NSAP has a chronic course,[11] and parents are found to be demanding and difficult to reassure.[12,13] Maybe GPs successfully manage early stages of NSAP. That is the GP reassures child and parents that there are no severe underlying disorders and teaches families how to deal with the abdominal pain of the child. Given the rising health care, this might be a finding supporting the cost effectiveness of primary care.[32] In contrast , however, we do not know whether the children who do not re-consult will be free of abdominal pain, or are able to cope with their abdominal pain. It has been reported that children look for help elsewhere, e.g. complementary therapy and homeopathic products.[33,34] Future research should further explore the prognosis of non specific abdominal pain in general practice and the effect of the management of the GP.

With respect to treatment GPs do not adhere to published evidence. Despite the lack of evidence for a positive effect of any medication in NSAP,[35] in 21% of the consultations GPs prescribed medication (predominantly laxatives and antispasmodics). GPs seem to believe that laxatives are effective in NSAP or they hesitate between a diagnosis NSAP and constipation. However, the effectiveness of laxatives for NSAP is not supported by clinical evidence[35,36] and should be studied first. In addition, with criteria described in literature, GPs should be capable in distinguishing constipation from NSAP.[26] These cri-

teria, however, are based on consensus of specialized clinicians and studies of referred children and therefore we do not know whether these criteria are applicable to primary care children. Dutch GPs did not prescribe anxiolytics or antidepressants to children with medically unexplained AP. These drugs have been used outside Europe.[37]

Study limitation

A limitation of our study is its dependence on the quality of EMR registration by GPs. However, the record registration data used in this study were derived from the Second Dutch National Survey of General Practice (DNSGP-2). This survey was carried out by a well known research institute of the Netherlands (NIVEL) and was set up to study morbidity. GPs were trained to accurately code all contacts. Validity of data collection was constantly monitored.[17,19] The big advantages of a record registration database is that it provides cheap and relatively easy access to large volumes of data.

Another drawback of this record registration database it was not possible to study the duration of the abdominal pain. Recently our study group showed that 47% of children consulting general practice with a new episode of abdominal pain has chronic complaints (≥3 months abdominal pain) at first presentation.[39] We feel we studied the same pain syndrome as previously reported studies on recurrent or chronic abdominal pain. The differences with other studies will be the time-frame studied and the probability of a non-organic disorder.

There is always a chance of misclassifying organic abdominal pain as non-organic, non-specific abdominal pain. This risk may be higher for diseases that lack an official ICPC code, such as NSAP. We assume that GPs code NSAP with the existing ICPC codes that describe abdominal pain without a specific organic abnormality. This assumption was based on our own clinical experience with ICP, logical thinking (these are the best ICPC codes for NSAP these are), and on the observation that 85% of the participating GPs (n=161) coded a written patient case regarding NSAP with ICPC D01 (generalized abdominal pain).[19] In addition, to reduce misclassification, we selected our cases by using the final diagnosis of a health problem. At the end of a health problem (cluster of consultations concerning in this case abdominal pain) the uncertainty of its origin of the abdominal pain small as the GP has ended his diagnostic process of GPs and time has gone by.

Conclusions

Childhood NSAP is a common complaint in general practice. Less than 7% of children NSAP consult more than twice for this problem. GPs diagnose non-specific abdominal pain by using few additional tests and few referrals. Despite the lack of evidence for effectiveness, GPs frequently prescribe laxatives and antispasmodics for childhood NSAP.

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Chapter 6

Mental health Problems in Children with Non-Specific Abdominal Pain in General Practice

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Submitted

ABSTRACT

Purpose

Childhood non-specific abdominal pain (NSAP) is a frequent complaint in general practice. In specialist care, childhood NSAP and mental health problems are related. Whether this relationship is due to a selective referral or characteristics of the abdominal pain is unknown. Because co-existing mental health problems might influence general practitioners' management for NSAP, we studied the association between childhood NSAP and mental health problems in general practice.

Methods

We quantified the prevalence of mental health problems in a cohort of 171 children aged 6-17 years presenting to general practice for NSAP and compared the prevalence to that of controls consulting for common primary health care problems. Abdominal pain characteristics were measured with standardized questionnaires. Depressive and anxiety problems and having multiple non-specific somatic symptoms were measured with the Child Behaviour Checklist.

Results

Of the children with NSAP, 28.1% (95% CI 21.3-34.8%) had a depressive problem, 15.2% (95% CI 9.8-20.6%) an anxiety problem and 60.8% (95% CI 54.0-67.7%) reported multiple non-specific somatic symptoms. Children with NSAP had 3.0 (95% CI 1.3-7.2) times more often a depressive problem and 8.2 (95% CI 3.2-21.1) times more often multiple non-specific somatic symptoms compared to controls. The duration, frequency and severity of NSAP were not related to mental health problems.

Conclusions

This study shows that in general practice childhood NSAP and mental health problems are associated also. The consequences of this association on prognosis of NSAP and possible interventions need further study.

INTRODUCTION

Abdominal pain is a common complaint in children.[1] In general practice childhood abdominal pain is usually not associated with organic disease. In this study we use the expression "non-specific abdominal pain" (NSAP) for abdominal pain for which physicians do not suspect organic pathology. Most studies on NSAP include children with chronic or recurrent abdominal pain. Chronic NSAP has great impact on daily functioning of the child and its family.[2]

Chronic NSAP is usually defined as abdominal pain with a minimum duration of 3 months and a minimum frequency of 1 attack per months. This "time criterion" derives from Apley and Naish[3] who were the first to study this pain syndrome in school children in 1958, using the term recurrent abdominal pain. As organic abnormalities will usually become manifest within time, this "time criterion" served to reduce the risk of organic pathology. In specialist care, children consulting for NSAP almost always will have chronic abdominal pain at first presentation. This in contrast to general practice, where children consult in the beginning of their illnesses and NSAP of shorter duration will be presented as well. The challenge for the general practitioner (GP) is to recognize the child that will have a prolonged course of its NSAP.

In specialist care, 26-85% of children with chronic or recurrent NSAP have mental health problems, such as internalizing/introvert behaviour problems,[4-6]anxiety disorders,[4,7-9] and depressive disorders.[8,9] Whether these mental health problems are the cause of the NSAP or caused by (long-lasting) NSAP is unknown. However, although most children with NSAP are managed in general practice, studies identifying mental health problems in children with NSAP in this setting are scarce.

We hypothesize that the high prevalence of mental health problems in referred children with NSAP is a consequence of a selective referral. Establishing whether children with NSAP seen in general practice have mental health problems is important for the general concept of NSAP and because it might influence GPs' management. The objective of this study was to study the association between NSAP and mental health problems in general practice. We quantified the prevalence of mental health problems in children presenting to general practice with NSAP. As the decision to actually consult a physician (consulting behaviour) is influenced by psychological factors, we compared the prevalence of mental health problems of children with NSAP to that of children consulting general practice for other reasons than abdominal pain. In addition, we analyzed whether the duration, frequency and severity of abdominal pain were associated with the presence of mental health problems.

METHODS

Patients

Patients were a selection of the Dutch HONEUR abdominal pain cohort.[10] From May 2004 to March 2006, 53 GPs invited all consecutive patients aged 4-17 years presenting with a new episode of abdominal pain to participate in a follow-up study. Exclusion criteria were a previous diagnosis of inflammatory bowel disease, celiac disease, lactose intolerance and parents' inability to complete the questionnaire due to language or cognitive problems. All children aged 6-17 years with NSAP were selected for the present study. The participating general practices represented a total population of 111 000 registered patients, representative for the Dutch population.

The abdominal pain of children was considered to be non-specific if; 1) GPs did not suspect underlying organic cause for the abdominal pain, and if; 2) no organic explanation for the abdominal pain was found in the electronic medical record of the patients up to 3 months after the inclusion visit. The Dutch electronic medical record contain all medical information of the patient including results of additional testing and referrals to secondary care. Dutch GPs are trained to code consultations according to the International Classification of Primary Care (ICPC) with diagnostic criteria based on the International Classification of Health Problems in Primary Care.[11] GPs code abdominal pain without known organic cause with the following symptom codes of ICPC: general abdominal pain/cramps (D01), stomach pain (D02), localized abdominal pain (D06), and irritable bowel syndrome (D93).

Controls

The controls were children aged 6-17 years consulting general practice for common primary health care problems, other than abdominal pain. Controls were selected from the Second Dutch National Survey of General Practice (DNSGP-2).[12] This is a record based registration study carried out by the Netherlands Institute for Health Services Research (NIVEL) in 2001. All contacts of patients of a representative sample of 104 general practices were recorded (368461 registered patients). Morbidity presented to the GPs was electronically registered and coded using the ICPC.[11] A random sample of this population was asked to participate in a health interview survey (response rate 64.5%, N = 2431 children aged 4-17 years), in which parents completed the Child Behaviour Checklist [CBCL 4-18 (edition 1991)].[13] Of these children, we selected those children aged 6-17 years who consulted general practice in the 2 weeks preceding the health interview and excluded children consulting for gastro-intestinal symptoms.

Measures

Abdominal pain

All abdominal pain characteristics were assessed by structured questionnaires. Questions regarding duration and frequency of the abdominal pain were completed by children aged 9-17 years and parents of children aged 6-9 years. The severity of abdominal pain was self reported by all children. Children aged 9-17 years rated the severity of the pain on a 10 point numeric rating scale ranging from no pain (0) to the worst pain imaginable (10). Children aged 6-9 years used a pain faces scale; from happy, no pain at all (0) to the worst pain you can imagine (10).[14] Chronic NSAP was defined as non-specific abdominal pain that occurred at least once each month in three consecutive months.[2]

Mental health problems

Parents' completed the validated Dutch translation of the Achenbach Child Behaviour Checklist [CBCL 6-18 (version 2001)].[15] The CBCL is a well-established questionnaire providing a global measure of psychopathological symptoms in children over the preceding 3 months. The CBCL generates among other scales the anxious/depressed, the withdrawn/depressed and the somatic complaints syndrome scales, which together form the Internalizing Broadband scale. The Internalizing Broadband scale comprises introverted behaviour problems. The CBCL further generates scales orientated on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV, American Psychiatric Association 1994).[16]

Parents rated their children's problems by means of 113 questions. Items were scored on a three-point scale with predefined responses: not true (0), somewhat or sometimes true (1), or very true (2). The scores of items belonging to a scale were summed to raw total scores. CBCL also provides T-scores. T scores are standardized by age and sex and compare the child's ranking on a scale to the distribution of scores obtained by norm children. T-scores are designed to enable a comparison between scales with a different number of items and a different distribution of scores. Norm scores are provided by Achenbach, and are derived from a general population of children with a socio-economic background comparable to our study population.[17] Norm children have not been referred to mental healthcare in the previous year. For the DSM-orientated scales a T-score of ≥ 65 (≥ 93rd percentile of scores of norm children) is considered deviant. A deviant score discriminates between clinical and non-clinical samples of children.[14] A child with a deviant score on the DSM orientated scales has symptoms suggesting a mental disorder conform the DSM-IV classification and is referred to as having a mental health problem. We analyzed the DSM orientated scales for depressive, anxiety and somatic problems. Due to both immaturity and the stipulated duration of symptoms children cannot be diagnosed as having a somatoform disorder. A somatic problem means that the child has multiple non-specific, medically unexplained somatic symptoms. CBCL

asks for the following non-specific somatic symptoms: nausea, stomach ache and vomiting (3 gastro-intestinal symptoms), and dizziness/lightheaded, overtired without good reason, aches/pains other than stomach and headaches, headaches, problems with eyes (not corrected by spectacles), and rashes or skin problems (6 non-gastro-intestinal symptoms).

The CBCL questionnaire was revised in 2001. Consequently parents of patients and controls had completed different versions of CBCL. In the revised edition 3 questions were supplemented (questions nr. 5; there is very little he/she enjoys, 47; nightmares, 49; constipated). In order to compare the scores of the two CBCL editions we only used those questions asked in both versions. We further converted the CBCL version 1991 into the CBCL version 2001 with appropriate ASEBA software (RTS version 1.0).

Analyses

Descriptive statistics are used to report patient characteristics, i.e. the number of children with a depressive, anxiety or multiple non-specific somatic symptoms, and the mean raw and mean T-scores for the different scales of the CBCL. Relative risks (RRs) with corresponding 95% confidence intervals (CI) were calculated for having a mental problem using CIA version 1.0 (MJ Gardner & British medical journal, 1989, London). Differences between the mean raw scores were tested with the independent two-samples-T test (STATA version 11.0). Cohen's δ was used to assess effect sizes of differences between these means. Cohen's δ was calculated by dividing the difference between the means through the pooled standard deviation. Cohen's δ: $0.20 \geq \delta < 0.50$ indicates a small effect size, $0.5 \geq \delta < 0.80$ indicates a medium effect size, and $\delta \geq 0.8$ indicates a large effect size.[18] In order to facilitate comparison of the present results with earlier studies, and to facilitate comparison between scores on the different CBCL scales, mean T-scores were also presented. With logistic regression analyses we evaluated the association between sex, age, duration, frequency and severity of abdominal pain and the presence of a depressive, anxiety problem or having multiple non-specific somatic symptoms. For the regression analyses we used the statistical package SPSS 15.0 (SPSS Inc, Chicago IL, USA).

Ethical approval

The HONEUR abdominal pain cohort-study was approved by the Central Committee on Research Involving Human Subject (CCMO) in the Netherlands. The DNSGP-2 was carried out in accordance with Dutch privacy legislation. Privacy rules and regulations were deposited at the Dutch Data Protection Authority.

RESULTS

Sample characteristics

Patients

In total 171 children aged 6-17 years presenting to general practice with NSAP were included in the present study. Table 1 presents the characteristics of these children. At the moment of their first consultation in general practice 48.5% of the children had chronic NSAP already.

Table 1. Characteristics of 171 children with non-specific abdominal pain (NSAP)

Girls (n, %)	107 (62.6)
Mean age (SD)	9.7 (2.5)
Duration of NSAP (n, %)	
≤ 2 months	58 (33.9)
≥ 3 months and < 12 months	27 (15.8)
≥ 12 months	59 (34.5)
Unknown	27 (15.8)
Frequency of NSAP (n, %)	
≤1x /months	43 (25.2)
>1x /months and < every day	80 (46.8)
≥ Every day	22 (12.9)
Unknown	26 (15.2)
Chronic NSAP (n, %)	83 (48.5)
Severity of the NSAP (mean, SD)	6.0 (2.0)

Controls

In total 54 children aged 6-17 years met our selection criteria, and were used as the control group. Their reasons for encounter were: 5.6% eye problems, 9.3% ear problems, 20.4% musculoskeletal problems, 20.4% respiratory problems, 20.4% skin problems, 16.7% general problems, and 7.5 % other problems. The mean age and sex distribution were comparable in children with NSAP and controls [respectively 10.2 (SD 3.2) vs. 9.7 (SD 2.5) and 63.0% vs. 62.6% girls].

Mental health problems

Table 2 shows the CBCL scores of children with NSAP and controls.

Depressive, anxiety and presence of multiple non-specific somatic symptoms

In total, 28.1% (95% CI 21.3-34.8%) of the children with NSAP had a depressive problem, 15.2% (95% CI 9.8-20.6%) an anxiety problem and 61.4% (95% CI 54.1-68.7) reported multiple non-specific somatic symptoms. Children with NSAP had significantly more often a depressive problem (RR 3.0; 95% CI 1.3-7.2) and reported more often multiple non-specific somatic symptoms (RR 8.2; 95% CI 3.2-21.1) than control children. The risk

Table 2. CBCL scores

CBCL scales	NSAP (N=171)	Controls (N=54)	RR (95% CI)	Cohen's δ
DSM orientated scales				
Depressive problem (%, 95% CI)	28.1 (21.3-34.8)	9.3 (3.1-20.3)	3.0 (1.3-7.2)	
Anxiety problem (%, 95% CI)	15.2 (9.8-20.6)	11.1 (4.2-22.6)	1.4 (0.6-3.2)	
Multiple non-specific somatic symptoms (%, 95% CI)	61.4 (54.1-68.7)	7.4 (2.1-17.9)	8.2 (3.2-21.1)	
Syndrome Scales				
Somatic Complaints (mean raw score, SD)	4.7 (2.7)	1.1 (1.5)*		1.7
Non-gastro-intestinal symptoms† (mean raw score, SD)	2.2 (2.0)	0.8 (1.1)*		0.9
Gastro-intestinal symptoms‡ (mean raw score, SD)	2.5 (1.2)	0.3 (0.6)*		2.3
Internalizing (mean T score, SD)	58.8 (8.9)	47.9 (11.2)		
Anxious/Depressed (mean T score, SD)	56.8 (7.8)	53.5 (6.2)		
Withdrawn/Depressed (mean T score, SD)	55.9 (6.6)	54.6 (5.7)		
Somatic Complaints (mean T score, SD)	64.2 (6.7)	53.7 (5.3)		

†6 questions, ‡ 3 questions, *p-value: <0.001

for an anxiety problem was not significantly higher for children with NSAP than for children consulting general practice for other reasons (RR 1.4; 95% CI 0.6-3.2).

Non-specific somatic symptoms

Children with NSAP had more non-specific somatic symptoms than controls (table 2). These were both non-specific gastro-intestinal symptoms [patients 2.5 (SD 1.2) versus controls 0.3 (SD 0.6), Cohen's δ 2.3 (large effect size)] and non-specific non-gastro-intestinal symptoms [patients 2.2 (SD 2.0) versus controls 0.8 (SD 1.1) Cohen's δ 0.9 (large effect size)].

T scores

In table 2 the mean T scores of the Internalizing Broadband scale and it's subscales are presented. Children consulting for NSAP scored higher than controls on each scale, but they scored particularly high on the Somatic Complaints Syndrome Scale.

Abdominal pain characteristics

In table 3 the results of the univariable logistic regression analyses are presented. We did not find a significant association between the duration, the frequency and the severity of the NSAP and the presence of a depressive, anxiety problem or having multiple non-specific somatic symptoms.

Table 3. Characteristics associated with a depressive and anxiety problem or having multiple non-specific somatic symptoms

		Depressive problem OR (95% CI)£	Anxiety problem OR (95% CI)£	Multiple non-specific somatic symptoms OR (95% CI)£
Age		1.0 (0.9-1.1)	1.0 (0.8-1.1)	1.2 (1.1-1.4)*
Sex	male	ref. cat.	ref. cat.	ref. cat.
	Female	0.8 (0.4-1.5)	0.7 (0.3-1.5)	0.4 (0.2-0.8)*
Duration of NSAP‡	≤ 2 months	ref. cat.	ref. cat.	ref. cat.
	≥ 3months and < 12 months	1.4 (0.5-3.9)	2.3 (0.8-6.8)	1.8 (0.7-4.8)
	≥ 12 months	1.4 (0.6-3.1)	0.7 (0.3-2.1)	1.6 (0.8-3.4)
Frequency of NSAP†	≤ 1x /months	ref. cat.	ref. cat.	ref. cat.
	> 1x /months and < Every day	1.0 (0.4-2.2)	1.3 (0.5-3.7)	1.2 (0.6-2.6)
	≥ Every day	1.8 (0.6-5.3)	1.8 (0.5-6.8)	2.5 (0.8-7.9)
Chronic NSAP	no	ref. cat.	ref. cat.	ref. cat.
	Yes	1.5 (0.8-3.4)	1.5 (0.7-3.6)	1.8 (0.98-3.4)
Severity of the NSAP (0-10)		0.9 (0.8-1.1)	1.0 (0.8-1.2)	0.9 (0.8-1.1)

£ Univariate logistic regression analysis, ref. cat. = reference category, ‡ n=141, † n=145, * P<0.05

DISCUSSION

In the present study 28% of the children presenting to general practice for NSAP met the criteria for a depressive problem, 15% for an anxiety problem and 61.4% had multiple non-specific somatic symptoms. Depressive problems were 3 times and children with multiple non-specific somatic symptoms were 8 times more prevalent in children consulting general practice for NSAP than in children consulting for other reasons. Children with NSAP had both more gastro-intestinal and non-gastro-intestinal non-specific symptoms. The duration, the frequency and the severity of the abdominal pain were not related to the presence of mental health problems.

To our knowledge, this is the second study examining the prevalence of mental health problems in children with NSAP in general practice. Earlier, Campo et al. found in a smaller study (N = 42) carried out in paediatric primary care practices in the USA, that 40% of children consulting for NSAP met the criteria for a depressive disorder and 80% for an anxiety disorder [measured with K-SADS (Kiddies' Schedule for Affective disorders and Schizophrenia for School Age Children)].[19] These prevalence's are evidently higher than those in the present study and resemble those found in referred children.[4,7-9] The differences in the prevalence estimates might be due to dissimilarities in study populations and measurement instruments. The referral state and previous healthcare use are not clearly described in the study of Campo *et al*. In the Netherlands all inhabitants are registered in a general practice. General practice is very accessible, free at point of service, and the GP usually knows the family well. Outpatient hospital care and hos-

pital admission require referral by the GP. Medical specialists work exclusively hospital based. Considering this central role of the GP in the Dutch healthcare system, our study population is likely to represent exclusively non-referred children in the begin phase of their illness. In contrast to others,[4,7-9,19] we found a higher prevalence for depressive problems than for anxiety problems. This might be due to (unknown) characteristics of our study population, due to the interaction between GP and patient, or due to an underestimation of anxiety problems. It has been reported that the CBCL predicts the DSM-IV diagnosis Depressive Disorder fair to good, but the DSM-IV diagnosis Anxiety Disorder poor to fair.[20]

The mean T scores on the various CBCL scales of children with NSAP, found in this study, are comparable to those found in tertiary care. The mean T score for internalizing complaints was 58.8 (SD 8.9), for anxious/depressed complaints 56.8 (SD 7.8) and for non specific somatic complaints 64.2 (SD 6.7). CBCL scores found in tertiary care for internalizing complaints range from 59.6-62.8[4-7] for anxious/depressed complaints from 55.5-59.4[4,5,21-23] and for somatic complaints ranging from 62.2-68.5.[4,7,21-23] We had hypothesized that the high prevalence of mental health problems in referred children was a consequence of selective referral . Our results refute this hypothesis. Our findings point towards a simultaneous occurrence of NSAP and mental health problems, which may be related via the same underlying mechanism.[24]

In total 61% of the children seen in general practice has multiple non-specific somatic symptoms, both gastro-intestinal and non-gastro-intestinal. Earlier studies on referred children with NSAP also reported high levels of non-specific somatic symptoms.[4,7,21-23] In our opinion, this finding raises the question whether childhood NSAP is a separate functional syndrome,[25] or only one of the many functional complaints of children with a tendency to somatisation. Whether the presence of high levels of non-specific somatic symptoms can predict somatoform disorders in adult life needs further investigation.

Limitations

A selective inclusion of GPs of children with mental health problems would explain the large number of children with mental health problems found in the present study. However, the participating GPs were not aware of our research questions and as they rarely referred these children with NSAP to mental healthcare (1.5% of children), we believe that selection bias does not explain our findings. Our control group consisted of children whose parents consented to participate in a health interview survey. Parents of children with mental health problems may have been more reluctant to participate in the study, resulting in a lower risk for mental health problems in our controls than in a general sample of children consulting their GP. However, as we found higher CBCL scores for control children than for norm children (general population),[17] we do not think that the controls are a selection of "healthy" children.

In order to compare the CBCL version 2001 to the 1991 version we only used the questions asked in both questionnaires. We omitted 3 new questions of the 2001 version. As the prevalence of mental health problems in both groups was calculated using data of the norm population, the prevalence is a minor underestimation of the true prevalence estimate. This also applies to the scores on the somatic complaints syndrome scale, the withdrawn/depressed syndrome scale and the total Internalizing Broadband scale.

We further used the parent's perception of the child's psychopathological symptoms. It would, of course be better to use multiple perspectives on children's functioning, including their own perspective.[26] Parents might have emphasized the severity of their children's symptoms.[27,28] However, this limitation does not affect the comparability to others because they all used parent-reports.

Clinical implications

Earlier research of our study group showed that Dutch GPs scarcely register psychological co-morbidity in children with NSAP, and seldom refer these children to mental healthcare.[29] We believe that GPs almost certainly ask for psychosocial complaints in consultations for childhood NSAP. But, probably, Dutch GPs regarded these complaints as being too mild to code them with ICPC as a psychological problem. Our results suggest that GPs might underestimate or might have difficulties in identifying mental health problems in children with NSAP. This has been reported before.[30-32] We think, however, that it is too early to recommend GPs to assess the mental health of children with NSAP. The consequences of knowing that a child with NSAP has mental health problems are not clear yet. Although in referred children with NSAP the number of non-specific symptoms has been found to predict the prognosis of abdominal pain, functional disability and healthcare use,[34,35] as well as the risk for a depressive or anxiety disorder[36] , it is unknown whether mental health problems influence prognosis of NSAP[33] in primary care. In addition, it should be studied first whether children with NSAP benefit from early (psychological) interventions.

Conclusions

Our study shows that in general practice childhood NSAP and mental health problems are related independent of the duration, frequency and severity of the abdominal pain. GPs can expect that approximately 30% of children who present for NSAP have a depressive problem and 15% an anxiety problem. In total 61% of children with NSAP have multiple non-specific somatic symptoms, both gastro-intestinal as well as non-gastro-intestinal. The consequences of these mental health problems on prognosis for NSAP and possible interventions for childhood NSAP with mental health problems should be studied.

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Chapter 7

Prognosis of Mental Health Problems in Children presenting with Abdominal Pain to General Practice

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Submitted

ABSTRACT

Objective

To examine the course of mental health problems in children with abdominal pain and to examine the association between abdominal pain characteristics and prognosis of mental health problems

Design

Prospective cohort study with 1 year follow-up

Setting

Primary care in the Netherlands

Participants

281 children aged 4-17 years presenting with abdominal pain

Outcome Measures

The presence of a depressive, an anxiety and a multiple non-specific somatic symptoms at follow-up and the odds ratios of the duration, frequency and severity of abdominal pain with a depressive, an anxiety and the presence of multiple non-specific somatic symptoms at follow-up.

Results

A depressive problem persisted in 32.9% children (95% CI 22.3-44.9), an anxiety problem in 30.2% (95% CI 17.2-46.1) and a multiple non-specific somatic symptoms in 44.1% children (95% CI 36.7-51.6). None of the abdominal pain characteristics were associated with a depressive or an anxiety problem at 12-months follow-up. Only more moments of moderate to severe abdominal pain was associated with the presence of multiple non-specific somatic symptoms at 12 months follow-up (multivariate adjusted OR 1.5; 95% CI 1.1-2.1).

Conclusions

Although mental health problems in children consulting primary care for abdominal pain decrease over time, they continue to be more elevated than in the general population after 1 year of follow-up. Characteristics of the abdominal pain do not influence the prognosis of a depressive and anxiety problem. We recommend following the children consulting primary care with abdominal pain over time.

INTRODUCTION

Abdominal pain is one of the most common complaints in childhood.[1,2] Childhood abdominal pain is usually not associated with organic disease.[3-5] In this study we use the expression "non-specific abdominal pain" (NSAP) for abdominal pain for which the physician does not suspect organic pathology. In literature, a variety of expressions have been used for NSAP; recurrent abdominal pain,[3] chronic abdominal pain,[6,7] and functional abdominal pain.[8,9] NSAP affects the child's wellbeing and the consequences of missed schooldays and health care use are high.[10,11]

In specialist care, 26-85% of the children with NSAP have mental health problems; such as Behavioural problems, anxiety and depressive disorders and other medically unexplained, non-specific somatic symptoms.[12-16] In a systematic review we determined that one third of referred children with NSAP continue to experience long term abdominal pain.[17] However, as follow-up studies on mental health problems of children with NSAP are scarce it is largely unknown whether the psychological symptoms of these children also persist. Furthermore, the association between NSAP and mental health problems has primarily been established in cross-sectional studies. A cross-sectional study design hampers us to determine whether the mental health problems are caused or enlarged by long lasting abdominal pain or whether the abdominal pain is increased by mental health problems. Therefore it is important to study the prognosis and determinants that influence prognosis of mental health problems in children with abdominal pain, preferably in a prospective cohort study.

The present study aims to investigate the course of mental health problems in a cohort of children presenting with abdominal pain in primary care. In addition we evaluated the extent to which abdominal pain characteristics are associated with the prognosis of mental health problems.

METHODS

Participants

The HONEUR abdominal pain cohort is a prospective 1 year follow-up study of children aged 4-17 years presenting with a new episode of abdominal pain in general practice. Detailed methods of the study are described previously.[18] Between May 2004 and March 2006, 53 GPs in the southwest region of the Netherlands invited all consecutive patients to participate in the study. A new episode of abdominal pain was defined as a consultation for abdominal pain not preceded by a consultation for this complaint in the previous 3 months. Exclusion criteria were a previous diagnosis of inflammatory bowel

disease, celiac disease, lactose-intolerance and inability to complete questionnaires due to language or cognitive problems. In total 305 children were included.

Measurements

All data were collected with structured questionnaires and were filled in at baseline and after 3, 6, 9 and 12 months follow-up.

Characteristics of the abdominal pain

We investigated the following abdominal pain characteristics: presence of chronic abdominal pain during the follow-up period (yes/no), duration of chronic abdominal pain, severity of abdominal pain and frequency of abdominal pain (measured at all follow-up moments). Chronic abdominal pain was defined as abdominal pain that occurred at least once each month in three consecutive months.[3] The duration of abdominal pain was calculated as the total number of months during follow-up that the child fulfilled the criteria of chronic abdominal pain. A maximum duration of 15 months could be achieved as we asked for abdominal pain in the preceding 3 months at baseline and at each follow-up moment. The severity of abdominal pain was self reported by all children and rated on a 10 point Numeric Rating Scale ranging from no pain (0) to the worst pain imaginable (10) for children aged 9-17 years. For children aged 4-9 years a pain faces scale was used; 6 faces from happy, no pain at all (0) to the worst pain you can imagine (10). The frequency of abdominal pain in the past two weeks was rated on a 5-point scale; up to 2 days (1), 3 or 4 days (2), 5 or 6 days (3), almost all days (4), to every day (5).[19]

The Functional Disability

The Functional Disability Inventory[20] was measured at all follow-up moments and was used to assess the child's difficulty in his/her physical and psychosocial functioning due to their physical health. Children and parents rated how difficult it was to perform school, home, recreation and social activities on 15 questions with a 5-point scale [ranging from no trouble (0) to impossible (4)]. The items were summed to obtain a total score ranging from 0-60, a higher score indicating more impairment.

Diagnoses of the abdominal pain by the GP

The GP's diagnosis for the child's abdominal pain was used. Dutch GPs are trained to code visits according to the International Classification of Primary Care (ICPC) with diagnostic criteria based on the International Classification of Health Problems in Primary Care (ICHPPC-2).[21] We searched the electronic medical records (EMR) at 3-months follow-up of all included children to record the diagnosis as coded by the GP. The Dutch EMR of a patient contains all medical information of the child (from primary, secondary and tertiary care). We categorized the child to have NSAP if GPs used one of the following

ICPC codes: D01 (general abdominal pain), D02 (stomach pain), D06 (localized abdominal pain) and D12 (functional constipation). All other diagnoses were categorized as organic abdominal pain. If the GP did not code the diagnosis, 2 medical doctors coded the diagnosis with the information from the EMR.

Negative life events

A Dutch life event questionnaire was used to measure life events.[22] It was used as a control variable in the analysis. Participants were asked whether they had experienced 24 predefined life events and whether the event was a negative or a positive experience for the child. We summed the negative experienced life events which took place during the 12 months follow-up period.

Mental Health Problems

Mental health problems were assessed at baseline and at 12-months follow-up with the Child Behavior Checklist (CBCL) parent-report. The CBCL is a well established questionnaire that provides a global measure of psychopathological symptoms in children.[23,24] Parents rated their child's problems on 100 questions (children aged 4-5 years)[17] and 113 questions (children aged 6-17 years).[24] Items were scored on a three point scale with responses: not true (0), somewhat or sometimes true (1), or very true (2). Items were summed to obtain a total score. The CBCL generates (among other scales) scales orientated on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV, American Psychiatric Association 1994).[25] A score on the DSM-IV orientated scales of ≥ 93rd percentile scores of norm children is considered deviant. Norm scores are provided by Achenbach and are derived from a general population of children with comparable cultural and economical background to our study population (norm children 6-17 years n = 1753, 4-6 years n = 700).[26] Norm children were not referred to mental health care in the previous year. The deviant range of CBCL scales discriminates between clinical and non-clinical samples of children.[23,24] A child with a deviant score on the DSM orientated scales has symptoms suggesting a mental disorder conform the DSM-IV classification and is referred to as having a mental problem. We analyzed the DSM orientated scales for a depressive, an anxiety and a somatic problem. As there was little overlap between the deviant scores on the DSM-oriented scales (Pearson correlation coefficients of 0.4 for a depressive problem x anxiety problem, 0.3 for a depressive problem x somatic problem, and 0.3 for an anxiety problem x somatic problem) we analyzed the risk for these problems separately.

According to the DSM-IV classification, children cannot be diagnosed as having a somatisation disorder as they can never fulfil the described criteria of the DSM-IV due to both immaturity and the stipulated duration of symptoms. The CBCL classification a somatic problem means that the children who fulfil this classification have multiple non-specific somatic symptoms.

Statistical analyses

Descriptive statistics were used to summarize characteristics of the cohort. The prevalence of mental health problems as defined by the DSM-orientated scales of CBCL; was calculated at baseline and at 12 months follow-up. The prevalence of mental health problems at baseline was compared to the prevalence at follow-up with the Pearson's Chi-Square test. The cumulative incidence of mental health problems during follow-up was calculated among children who did not have mental health problems at baseline. Among children who had mental health problems at baseline we calculated the percentage of children who had persisting mental health problems at 12 months follow-up. The prevalence of mental health problems at follow-up was compared to the prevalence in norm children (7% of n = 2453) and we calculated relative risks (RRs) with corresponding 95% confidence intervals (CI).

To investigate the association between abdominal pain characteristics and a mental health problems at 12 month follow-up we used logistic regression analysis. A depressive, anxiety and multiple non-specific somatic symptoms were included as dependent variables. The abdominal pain characteristics were included as independent variables and we controlled for age, sex, referral to mental health care by the GP (yes/no), number of negative experienced life events in the follow-up period and baseline scores on the DSM-IV orientated scales of the CBCL. For the latter, we used the continuous baseline scores of the CBCL scales by converting the raw scores into scores on a 0-100 scale. The following characteristics of abdominal pain were included as independent variables; chronic abdominal pain during the follow-up period (yes vs. no), the duration of abdominal pain in months, the severity of abdominal pain, the frequency of abdominal pain and the disability due to the abdominal pain during the follow-up period and finally the GP's diagnosis (NSAP versus organic abdominal pain). The follow-up moments with a moderate to severe abdominal pain (pain score of ≥ 3, range 0-10) were summed and used as a summary measure for the severity of abdominal pain during the follow-up period. In literature this severity is assumed to cause impact on the child's daily functioning.[27] As summary measure for the frequency of abdominal pain during the follow-up period we summed the number of follow-up moments with a frequency of abdominal pain of 5 days or more in the past 2 weeks. The follow-up moments with a disability score of ≥ 10 (range 0-60) were summed and used as summary measure for the disability during the follow-up in a univariate regression analyses We reported adjusted odds ratios (ORs) with 95% confidence intervals (CIs). In case of a significant association ($p<0.05$) between an abdominal pain variable and the risk for a mental health problems we entered all the abdominal pain variables into a multivariable logistic regression analysis. We reported these as adjusted multivariable OR.

RESULTS

In total 281 children (92.1%) of the 305 children of the HONEUR abdominal pain cohort completed the CBCL at baseline and at 12 months. These 281 children were included in the analyses. Two children were excluded from the analyses because of missing questionnaires and 22 children were lost to follow-up. Reasons for being lost to follow-up were; not interested anymore in participating in the study (n = 7), absence of abdominal pain (n = 6), too many problems (n = 5), hospitalized (n = 1), too intrusive (n = 1), without

Table 1. Baseline characteristics of 281 children aged 4-17 years consulting general practice for a new episode of abdominal pain

Characteristic	
Children with a period of chronic abdominal pain during follow-up (n, %)	240 (85.4)
Children with chronic abdominal pain at baseline (n, %)	130 (46.3)
Duration of abdominal pain in months (range: 0-15) (median, IQR)	10.5 (7.5-13.5)
Severity of abdominal pain (range 0-10) (mean, SD)	6.2 (2.2)
Frequency of episodes of abdominal pain in past 2 weeks (n, %)	
up to 2 days	68 (24.2)
3 or 4 days	43 (15.3)
5 or 6 days	45 (16.0)
almost every day	98 (34.9)
every day	26 (9.3)
Functional disability (range 0-60) at baseline (median, IQR)	5.0 (1.0-11.0)
Children with functional disability ≥10 during follow-up (n, %)	117 (41.6)
Diagnosis (n, %)	
Non-specific abdominal pain	242 (86.1)
Generalized abdominal pain	161 (57.3)
Localized abdominal pain	53 (18.9)
Functional constipation	28 (10.0)
Organic abdominal pain	32 (11.4)
Gastro-enteritis	17 (6.0)
Cystitis	5 (1.8)
Appendicitis	1 (0.4)
Other	9 (3.2)
Unknown	7 (2.5)
Gender (girls) (n, %)	175 (62.3)
Age (in years) (median, IQR)	7.8 (5.7-10.4)
Score on the CBCL Scale Depressive problem (range 0-100, deviant score ≥ 27) (median, IQR)	15.0 (5.0-25.0)
Score on the CBCL Scale Anxiety problem (range 0-100, deviant score ≥ 37) (median, IQR)	16.7 (8.3-25.0)
Score on the CBCL Scale Somatic problem (range 0-100, deviant score ≥ 22)(median, IQR)	27.3 (14.3-35.7)
Number of children with ≥ 1 negative life events in past year (n, %)	87 (31.0)
Referred to mental health care by the GP (n,%)	5 (1.8)

reason (n = 2). There were no differences between the children lost to follow-up and those included in the analysis with respect to the prevalence of mental health problem at baseline and with respect to the abdominal pain characteristics.

In table 1 the baseline characteristics of the 281 children are presented. There were 175 girls (62.3%) and the median age was 7.8 years (interquartile range (IQR) 5.7-10.7). The median duration of abdominal pain in months was 10.5 (IQR 7.5-13.5). According to the ICPC codes given by the GPs, 242 children (86.1%) had NSAP, in 32 children (11.4%) the GPs diagnosed an organic disorder, and for 7 children (2.5%) the diagnosis was not coded because of insufficient information in the EMR.

In table 2, 3 and 4 the shift in time of respectively a depressive, an anxiety and the presence of multiple non-specific somatic symptoms is presented. The prevalence of children with a depressive problem decreased statistical significantly during the 1 year

Table 2. Shift in time of a depressive problem

		Follow-up		
		Normal n (%)	Depressive problem n (%)	
Baseline	Normal n (%)	195	13*	208 (74.0)
	Depressive problem n (%)	49	24†	73 (26.0)
		244 (86.8)	37 (13.2)	281

*Cumulative incidence of children developing a depressive problem: 6.3% (13/208), †Cumulative incidence of children with a persisting depressive problem: 32.9% (24/73)

Table 3. Shift in time of an anxiety problem

		Follow-up		
		Normal n (%)	Anxiety problem n (%)	
Baseline	Normal n (%)	219	19*	238 (84.7)
	Anxiety problem n (%)	30	13†	43 (15.3)
		249 (88.6)	32 (11.4)	281

*Cumulative incidence of children developing an anxiety problem: 8.0% (19/238), †Cumulative incidence of children with a persisting anxiety problem: 30.2% (13/43)

Table 4. Shift in time of the presence of multiple non-specific somatic symptoms

		Follow-up		
		Normal n (%)	Multiple non-specific somatic symptoms n (%)	
Baseline	Normal n (%)	93	18	111 (39.5)
	Multiple non-specific somatic symptoms n (%)	95	75	170 (60.5)
		188 (66.9)	93 (33.1)	281

*Cumulative incidence of children developing multiple non-specific somatic symptoms: 16.2% (18/111), †Cumulative incidence of children with a persisting multiple non-specific somatic symptoms: 44.1% (75/170)

Table 5. Logistic regression analysis examining the effects of abdominal pain characteristics on the presence of mental health problems at 12-months follow-up

	OR (95% CI) Depressive problem	**OR (95% CI) Anxiety problem**	**OR (95% CI) Multiple non-specific somatic symptoms**	
	Adjusted Or#	Adjusted OR#	Adjusted OR #	Multivariate adjusted OR€
Chronic abdominal pain in past year (yes vs. no)	0.5 (0.2-1.5)	0.7 (0.2-2.2)	1.9 (0.7-4.7)	1.1 (0.3-4.1)
Duration of abdominal pain in past year in months (range: 1-15)	1.0 (0.9-1.1)	1.0 (0.9-1.1)	1.1 (1.0-1.2)*	1.0 (0.9-1.2)
Nr. of follow-up moments with moderate to severe abdominal pain (VAS score ≥3)(range: 0-5)	1.0 (0.7-1.3)	1.1 (0.8-1.5)	1.7 (1.3-2.1)*	1.5 (1.1-2.1)*
Nr. of follow-up moments with a frequency of abdominal pain of 5 days or more in the past 2 weeks (range: 0-5)	0.8 (0.6-1.1)	1.1 (0.8-1.5)	1.2 (0.9-1.4)	0.8 (0.6-1.1)
Nr. of follow-up moments with a functional disability ≥ 10 (of 0-60) (range: 0-5)	1.1 (0.7-1.5)	1.0 (0.7-1.6)	1.4 (1.1-1.9)*	1.4 (1.0-2.0)
Reason for abdominal pain (non-specific abdominal pain vs. organic abdominal pain)	1.7 (0.3-8.0)	0.4 (0.1-1.2)	1.0 (0.4-2.6)	1.0 (1.0-3.0)

adjusted for age, sex, referral to mental health care by the GP (yes/no), number of negative experienced life events in the follow-up period and baseline scores on the DSM-IV orientated scales of the CBCL, €multivariate adjusted logistic regression model with all abdominal pain characteristics, * statistical significant association

follow-up period (from 26.0 to 3.2%). The cumulative incidence during one year of a depressive problem was 6.3% (95% CI 3.4-10.5%). In 37 children a depressive problem persisted during follow-up (32.9%; 95% CI 22.3-44.9%) and in 49 children the depressive problem normalized (67.1%; 95% CI 55.1-77.7%). After 12-months follow-up more children of the study population had a depressive problem than in the norm population (RR 1.9; 95% CI 1.4-2.6).

The prevalence of an anxiety problem decreased statistical significantly during the 1 year follow-up period (from 15.3 to 11.4%). The cumulative incidence during one year of an anxiety problem was 8.0% (95% CI 5.0-12.2%). In 13 children the anxiety problem persisted during follow-up (30.2%; 95% CI 17.2-46.1%) and in 30 children the anxiety problem normalized (69.8%; 95% CI 53.9-82.8). After 12-months follow-up there were more children with an anxiety problem in our study population than in the norm population (RR 1.6; 95% CI 1.1-2.3).

The prevalence of the presence of multiple non-specific somatic symptoms decreased statistical significantly during the 1 year follow-up period (from 60.5 to 33.1%). The cumulative incidence during one year of the presence of multiple non-specific somatic symptoms was 16.2% (95% CI 9.4-23.1%). In 75 children, multiple non-specific somatic symptoms persisted during follow-up (44.1%; 95% CI 36.7-51.6%) and in 95 children

the multiple non-specific somatic symptoms normalized (55.9%; 95% CI 48.4-63.3%). After 12-months follow-up there were more children with multiple non-specific somatic symptoms in our population than in the norm population (RR 4.6; 95% CI 3.7-5.7).

Details of the association between the abdominal pain characteristics and mental health problems after 12-months follow-up are given in table 5.

DISCUSSION

In this prospective follow-up study we observed that mental health problems in children with abdominal pain decreased in the course of one year. However, the prevalence of children with a depressive and an anxiety problem and multiple non-specific somatic symptoms after 12-months follow-up remained above the prevalence which is found in the general population. After follow-up, one third of the children had multiple non-specific somatic symptoms. None of the abdominal pain characteristics were associated with a depressive or an anxiety problem at 12-months follow-up. More moments of moderate to severe abdominal pain were the only characteristic of abdominal pain that was associated with the presence of multiple non-specific somatic symptoms at 12 months follow-up.

To our knowledge, this is the first follow-up study examining the prognosis of mental health problems of children consulting general practice with abdominal pain. There are few follow-up studies of mental health problems of (predominantly) referred children with NSAP.[28-33] These studies confirm that although mental health problems of children with abdominal pain decrease in time they remain higher than is seen in children from the general population. A reduction of mental health problems over time has repetitively been found in both children referred to mental health care and in children of the general population.[34,35] Factors that might have influenced the decline in our study (besides spontaneous recovery and statistical effects such as regression to the mean) could be the standard clinical care of GPs and other professionals such as: reassurance and explanation to the family how to deal with the complaints. The latest are simple suggestions for Behavioural changes and in referred children with FAP it has been found that cognitive Behavioural therapy reduces both the abdominal pain and symptoms of anxiety and depression.[36]

It has barely been studied if characteristics of the abdominal pain influence the prognosis of mental health problems of children with abdominal pain. The few published studies on prognosis of mental health problems (see above) merely examined the association between psychological factors and course of non-specific somatic symptoms.[28-33] In 2 studies Walker et al. confirmed our finding that after follow-up, children with NSAP had comparable levels of psychological problems as children with organic abdominal

pain.[29,32] However, in 2 other studies the same authors found contradictive results.[28,30] There is only one study that examined the association between abdominal pain characteristics and the prognosis of non-specific somatic symptoms.[33] The authors confirmed our finding that the frequency of abdominal pain was not associated with the level of non-specific symptoms after follow-up. They could not confirm, however, our finding that the severity of abdominal was associated with the level of non-specific symptoms. This difference could be explained by the fact that our summary measure for the severity of abdominal pain also contains the duration of complaints.

More moments of a moderate to severe abdominal pain predicted the presence of multiple non-specific somatic symptoms at follow-up. Apparently, in children with persisting moderate to severe abdominal pain also other non-specific somatic symptoms persist. It is striking that at 12-months follow-up still one third of our study population had above normal levels of non-specific somatic symptoms in comparison to 7% of the general population. The co-existence of NSAP and other non-specific somatic symptoms has frequently been found before,[37] and it raises the question whether childhood NSAP is a separate functional syndrome and whether it is a precursor of a somatisation disorder in time.[38]

Strength and limitations

The strength of our study is that we have followed over reasonably long period primary care children with abdominal pain. We have measured the abdominal pain characteristics and the mental health problems in a validated and consistent way over time. Therefore, for the first time the association between abdominal pain characteristics and the course of mental health problems of children with abdominal pain could be examined. Our findings suggest that anxiety and depressive symptoms found in children with chronic abdominal pain are not a consequence of the duration, the severity or the frequency of the abdominal pain. However, as the number of children that developed anxiety and depressive mental health problems during the follow-up period in our study was limited, causal interpretations cannot be drawn.

In order to summarize the duration of abdominal pain, the severity of abdominal pain, the frequency of abdominal pain and the functional disability due to the abdominal pain during the follow-up period we chose cut-off values based on literature[27] and expert opinion. We realize that any cut-off value is to a degree arbitrary. However, sensitivity analysis with other cut-off values did not alter the associations reported (data not shown).

Clinical implications

As children consulting primary care with abdominal pain are at increased risk for persisting mental health problems we recommend to follow these children over time.

We feel it is important to include questions on medically unexplained, non-specific somatic symptoms in other bodily systems such as headaches, limb pains or tiredness in the anamnesis. We think that children with persisting non-specific somatic symptoms particularly need further special attention by GPs by means of further mental health assessment and by means of follow-up as children with multiple somatic complaints have a short and long-term psychosocial impairment.[39,40] As, until now no studied have been performed on the effectiveness of any type of intervention in children with abdominal pain and mental health problems in primary care, there is no evidence to promote an early (psychological) intervention in these children.

Future research

The prognosis of mental health problems of children with abdominal pain should be further studied. Knowledge of factors that influence the prognosis is necessary as they might be targets for intervention and can help the clinician to recognize a child at risk for future mental health disorders. We think it is important to develop treatments for children seen in primary care with multiple non-specific somatic symptoms and to study the effects of early interventions.

Conclusions

Although mental health problems in children consulting primary care for abdominal pain decrease over time, children with abdominal pain still have more mental health problems after 1 year of follow-up than children of the general population. Duration, frequency and severity of abdominal pain did not influence the prognosis of a depressive and an anxiety problem during 1 year follow-up. Persisting moderate to severe abdominal pain was associated with an increased risk for multiple non-specific somatic symptoms. We recommend following the children consulting primary care with abdominal pain over time, especially those with multiple non-specific somatic symptoms.

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Chapter 8

General discussion

INTRODUCTION

Abdominal pain is a frequent complaint in children.[1] In many cases no organic abnormalities are found to explain this pain.[2] In most of the published reports, that mainly concern children referred to a specialist, chronic or recurrent abdominal pain is generally studied.[3] In this thesis we use the expression "non-specific abdominal pain" for abdominal pain in children as seen in general practice for which general practitioners (GPs) do not suspect organic pathology. Although most of the children with abdominal pain are managed in primary care, almost all knowledge on this pain syndrome comes from studies conducted in secondary and tertiary care. However, results emerging from specialist care are not always generalizable to the primary care setting. Moreover, in referred children with chronic or recurrent abdominal pain, mental health problems are frequently found.[4-8] There is an ongoing discussion about the magnitude and direction of the relation between the abdominal pain and the mental health problems of these children. Establishing whether children with non-specific abdominal pain seen in general practice have mental health problems is important, because this may influence the general concept of childhood abdominal pain and will help unravel the relation between non-specific abdominal pain and mental health problems. This, in turn, may lead to more effective management of both the abdominal pain and the mental health problems of the child.

The aims of this thesis were to study childhood non-specific abdominal pain in a general practice setting, and to explore the relation between childhood abdominal pain and mental health problems. This chapter summarizes the findings from this thesis, discusses the results in a broader context, and presents implications for daily practice and recommendations for future research.

MAIN FINDINGS OF THIS THESIS

In our first systematic review on the course and prognosis of childhood chronic or recurrent abdominal pain we found that abdominal pain persisted in 29.1% (95% CI 28.1-30.2) of referred children with chronic or recurrent abdominal pain at presentation. Extensive medical testing had no additive prognostic value above history taking and physical examination in children with chronic or recurrent abdominal pain without alarm symptoms. Subsequently, in a second systematic review, we studied risk factors for persistence of chronic or recurrent abdominal pain. We found no evidence for the assumption that mental health problems were risk factors for persistence of chronic or recurrent abdominal pain in children. However, having parents with gastro-intestinal symptoms, and parents who kept on searching for an organic explanation for the pain,

were risk factors. On the other hand, female gender and the severity of the abdominal pain were not.

In a large record-based registration study we calculated the incidence rate of childhood non-specific abdominal pain in Dutch general practice to be 25.0 per 1,000 person-years (95% CI 23.7-26.3). As few children (<7%) with non-specific abdominal pain returned to their GP, the workload of childhood with non-specific abdominal pain in general practice was relatively low: i.e. 1.7% (95% CI 1.6-1.7) of the total workload. GPs did not register more psychological or social problems in children with non-specific abdominal pain than in children consulting for other problems. In the first contact with new patients, GPs made practically no recommendations for additional testing (1.1%) and very seldom (3.0%) referred the children to secondary care. Dutch GPs prescribed medication in 21.3% of all consultations for non-specific abdominal pain, of which 30% were laxatives and 30% were anti-spasmodics. In total, 5% of the children with non-specific abdominal pain were referred to specialists, but none of them to mental health care.

In a one-year follow-up study of children presenting to general practice with a new episode of abdominal pain, we studied the presence and prognosis of mental health problems. It appeared that when assessed by means of a questionnaire, of all children presenting to general practice with non-specific abdominal pain, 30% had a depressive problem, 15% an anxiety problem, and 61% had multiple non-specific somatic symptoms. Children with non-specific abdominal pain reported more gastro-intestinal and non-gastrointestinal non-specific somatic symptoms than children consulting general practice for other complaints. In children with abdominal pain, 30% of the depressive and anxiety problems persisted at 12 months follow-up, as did 44% of the multiple non-specific somatic symptoms. The course of the mental health problems of children with abdominal pain was not influenced by characteristics of the abdominal pain, such as the duration and severity.

CHILDHOOD NON-SPECIFIC ABDOMINAL PAIN IN GENERAL PRACTICE

Childhood non-specific abdominal pain appears to be one of the 10 most commonly seen complaints of children in Dutch general practice.[9] It is therefore remarkable that this pain syndrome receives so little attention in vocational training and in primary care research.

Based on the small number of children receiving additional testing and/or referred to specialist care during the first consultation, suggests that GPs feel comfortable in labelling childhood abdominal pain as non-organic, non-specific abdominal pain. However, because GPs prescribed laxatives in 25% of the new consultations for non-

specific abdominal pain, it seems that doubt exists between the diagnosis of functional constipation and non-specific abdominal pain, or perhaps GPs believe that laxatives are effective against non-specific abdominal pain. There is, however, no evidence for a positive effect of laxatives for non-specific abdominal pain; nor for supplementing fibres nor for Lactulose or Polyethylene Glycol.[10] The ROME diagnostic criteria for functional gastro-intestinal disorders[3] may help GPs to distinguish between constipation and non-specific abdominal pain. The large number of prescriptions without proven effectiveness suggests that GPs have a problem with treating non-specific abdominal pain. This is interesting because the published reports mainly focus on enhancing diagnosis and minimizing testing.[3,11] In the light of our results, however, more research should focus on the effect of interventions for childhood non-specific abdominal pain in general practice.

This thesis presents a picture of childhood abdominal pain in general practice that is basically similar to that of childhood abdominal pain as seen in specialist care. In our cohort study, we found that GPs usually did not suspect an organic reason for the abdominal pain, half of the children already had chronic abdominal pain at first presentation, and many children presenting for the first time in general practice for non-specific abdominal pain had depressive, anxiety and multiple non-specific somatic symptoms.[2] Our findings complete the total picture of childhood abdominal pain. It seems that psychological co-morbidity or persisting abdominal pain in general practice are not necessarily reasons for referral to specialist care. This suggests that the mental health problems, as found in referred children with abdominal pain, are not a consequence of selective referral or long-lasting abdominal pain.

Children with non-specific abdominal pain in general practice represent a heterogeneous population: including children with uncomplicated short-term non-specific abdominal pain, children with non-specific abdominal pain that persists for a longer period, and children with additional co-morbidities such as multiple non-specific somatic symptoms and depressive or anxiety problems.

CHILDHOOD NON-SPECIFIC ABDOMINAL PAIN AND MENTAL HEALTH PROBLEMS

Mental health problems among children with non-specific abdominal pain of general practice

Mental health problems appear to be common in children consulting general practice with non-specific abdominal pain. In our cohort study, 30% of these children had a depressive problem, 15% an anxiety problem and 61% had multiple non-specific somatic symptoms. Although a similar picture has also been described in referred children,[4-8,12-15]

until now this phenomenon has rarely been studied in primary care.[16] At the moment, during regular care, Dutch GPs do not register more psychological problems in the medical records of children consulting for non-specific abdominal pain than in those of children consulting for other complaints. We believe that GPs almost certainly ask for psychological complaints in consultations for childhood non-specific abdominal pain. But, probably, Dutch GPs regarded these complaints as being too mild to code them in the child's electronic medical record as a psychological problem. Our results suggest that GPs might underestimate or might have difficulties in identifying mental health problems in children with non-specific abdominal pain. This has also been reported previously.[17-19] Another explanation could be that the outcome measure used for mental health problems in the studies presented in this thesis, may not be a valid measure for psychological problems in children with abdominal pain in general practice. However, as the Child Behaviour Checklist (CBCL)[20] is a well-known validated screening tool for psychopathological symptoms, well capable of predicting mental disorders, we think this latter explanation is not likely. A child with non-specific abdominal pain that meets the criteria for a mental health problem scores as high on the CBCL as children referred to mental health care.[20] In the CBCL the number and the severity of complaints are summed. Thus, children with a depressive or anxiety problem have numerous affective and anxiety complaints. Whether these children do indeed have a mental disorder can only be diagnosed by means of a psychiatric interview.

Management of mental health problems of children with non-specific abdominal pain in general practice

Our findings raise the question whether GPs should actively assess mental health problems in children presenting with non-specific abdominal pain. We believe there are several important aspects related to this issue. Arguments against such an active assessment or screening are: i) the one-year prognosis of depressive, anxiety and having multiple non-specific somatic symptoms is to a certain extent favourable (70% of the children with a depressive or anxiety problem improve, as do 60% of the children with multiple non-specific somatic symptoms), ii) there are no indications that the mental health problems influence the course of the abdominal pain, iii) no suitable screening instrument is available to assess mental health problems in children consulting in general practice, and iv) there is no evidence-based effective strategy for the management of mental health problems in children with non-specific abdominal pain in general practice.

Whether the target of intervention should primarily be the abdominal pain or the mental health problems is unknown. Behavioural and cognitive Behavioural treatments for chronic or recurrent abdominal pain are effective in reducing abdominal pain in referred children.[21] As cognitive Behavioural therapy is the psychological treatment

of choice for depressive and anxiety problems, it is easily assumed that mood and disability will also improve with cognitive Behavioural therapy for abdominal pain. To our knowledge, until now, there is insufficient evidence that psychological interventions for any chronic or recurrent pain condition in children, including abdominal pain, improve disability or mood.[22] In conclusion, although asking about psychological symptoms seems to be a natural thing to do, GPs needs to realize that (after asking) the effect on prognosis is not established, nor can we give any recommendation for an evidence-based effective intervention. In other words, at the moment, no uniform psychological treatments for somatic unexplained physical symptoms (such as non-specific abdominal pain) are either clearly described or readily available in the Netherlands.[23] Therefore, it is essential that tailor-made psychological interventions for general practice become a main focus of future studies.

Non-specific abdominal pain and other non-specific somatic symptoms

In our cohort study, 61% of the children presenting to general practice for non-specific abdominal pain had multiple non-specific somatic symptoms (such as headache, limb pains and tiredness) and in 44% of the children with abdominal pain these symptoms persisted during the one-year follow-up period. Referred children with chronic or recurrent abdominal pain are also frequently found to have multiple non-specific somatic symptoms.[6,7,12-14] Until now, very few studies have reported on non-abdominal non-specific somatic complaints at follow-up of children with chronic or recurrent abdominal pain. At follow-up, children with recurrent abdominal pain appeared to have other non-abdominal non-specific somatic symptoms, particularly headaches, but also chronic pain in the pelvis, back, shoulder and limbs.[24-27] In our opinion, these findings raise the question as to whether childhood non-specific abdominal pain should be seen as a distinct functional syndrome or as a symptom of children with a broader functional syndrome[28] and whether, for some children, non-specific abdominal pain is a precursor of a somatoform disorder in later life.

Relation between non-specific abdominal pain and mental health problems over time

This thesis has helped to unravel the relation between childhood abdominal pain and mental health problems. In a case control study performed in general practice, we first showed that childhood non-specific abdominal pain and mental health problems are related. It was observed that this association did not depend on the severity or duration of the abdominal pain. In a systematic review of prospective cohort studies of referred children with chronic or recurrent abdominal pain, we found no evidence that psychological problems had an influence on the prognosis of childhood abdominal pain. In addition, in children from general practice we prospectively showed that the duration

of abdominal pain and the course of mental health problems were not related. Therefore, we think that abdominal pain and psychological factors may be triggered by the same underlying mechanisms and may occur together, but are not necessarily causally related.[29] Thus, although children with non-specific abdominal pain might be at risk for psychological disorders, the psychological disorders themselves are not the reason for the persistence of abdominal pain. Conversely, the persistence of abdominal pain is not the reason for the persistence of mental health problems of these children.

MANAGEMENT OF NON-SPECIFIC ABDOMINAL PAIN IN GENERAL PRACTICE

Our question is: should children seen in general practice with non-specific abdominal pain receive more health care for their abdominal pain. In fact, we found that the prognosis of their abdominal pain is only moderate: 30% of referred children with chronic or recurrent abdominal pain have long-term persistence of abdominal pain, and many children experience continuing impairment such as school absenteeism and social withdrawal. Moreover, GPs have an additional responsibility towards children in general, because the children themselves cannot decide to return to the GP. At the moment, in general, GPs are only briefly involved with these children and few children are referred to specialist care. Because it well established that many families with children with abdominal pain resort to complementary therapy and homeopathic products,[30,31] there seems to be a demand for health care. So the question remains: why do children with non-specific abdominal pain not return to general practice? It seems as though GPs are mainly focused on excluding organic pathology and ignore the fact that it concerns a chronic, non-specific somatic pain syndrome in children. GPs should be considered as experts in dealing with chronic and non-specific somatic conditions. Therefore, despite the absence of a specific evidence-based intervention for childhood non-specific abdominal pain, in our opinion follow-up is certainly justified. The primary goal of follow-up of children with non-specific abdominal pain should be to ensure that the impact of this pain syndrome on the child's daily life is of an acceptable level. Interventions for childhood non-specific abdominal pain in general practice should be developed and their effectiveness thoroughly investigated.

IMPLICATIONS FOR FUTURE RESEARCH

Our group was the first to perform a meta-analysis concerning the prognosis of childhood abdominal pain. We discovered that up, until now, the prognosis of childhood

abdominal pain has not been studied in primary care. For good counselling and in order to establish treatment effects, information about prognosis is essential. Therefore the prognosis of non-specific abdominal pain in general practice should be studied. It can then be established whether or not the parental risk factors for persistence of abdominal pain among referred children are also applicable to general practice. Moreover, childhood abdominal pain encompasses more than abdominal pain alone. Thus, we recommend that, besides the persistence of abdominal pain, also impairment and well-being should be included as outcome measures in prognostic and intervention studies of childhood abdominal pain.

Our group was one of the first to assess mental health problems in children seen in general practice with non-specific abdominal pain. We found that mental health problems measured with the CBCL are prevalent among these children. However, more research is needed to establish whether these children actually have or develop mental disorders, and whether these children require treatment or referral to specialist care. In addition, the effects of these mental health problems on the child's daily life should also be investigated.

Our study clearly shows the urgent need for intervention studies for childhood non-specific abdominal pain in general practice. Based on the results to date, we recommend that informing, advising and reassuring interventions for GPs in a stepped-care model should be the focus of research. Also, because cognitive Behavioural therapy has been found to effectively reduce the abdominal pain of referred children, it seems logical to test the effectiveness of this therapy in primary care children. In addition, we need to establish whether children with non-specific abdominal pain and psychological co-morbidity need a specific approach.

It would be valuable to know whether a general management strategy for childhood non-specific somatic symptoms (including non-specific abdominal pain) can be developed. This would enlarge GPs' experiences and understanding of the treatment of these symptoms and would increase the number of children participating in intervention trials.

The current heterogeneity and frequent use of non-evidence based treatments for childhood non-specific abdominal pain (as found in this thesis) suggest that GPs need additional guidance in managing this pain syndrome. The high incidence and only moderate prognosis justify development of a clinical practice guideline for childhood non-specific abdominal pain. Such a guideline should aim to convert current heterogeneous, non-evidence based management for childhood non-specific abdominal pain into a simple and comprehensible management based on available evidence and expert opinion. Such a guideline will also reveal for which specific treatments we need additional information and evidence.

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Summary

Summary

Abdominal pain is a common complaint in children. Usually no organic abnormalities can be found explaining the abdominal pain of children. While most of the children with abdominal pain are managed in general practice this pain syndrome has hardly been studied in this setting. In this thesis we use the term non-specific abdominal pain for abdominal pain for which general practitioners (GPs) do not suspect organic pathology. In referred children it has been found repeatedly that children with chronic or recurrent non-specific abdominal pain have mental health problems. Establishing whether children with non-specific abdominal pain seen in general practice are at increased risk for mental health problems is important. It may influence GPs' management of children with non-specific abdominal pain and may allow a more effective and preventive treatment of both the abdominal pain and the mental health problems. In this thesis we studied childhood non-specific abdominal pain in general practice, it's course and it's relation with mental health problems.

Chapter 2 is a clinical review of childhood chronic abdominal pain. Based on literature it provides a comprehensive up-to-date overview of childhood chronic abdominal pain. In this chapter the aetiology, possible risk factors for the development, the diagnostic process, the prognosis and the management of childhood chronic abdominal pain are discussed.

Chapter 3 and **chapter 4** are systematic reviews concerning the prognosis and prognostic factors for childhood chronic or recurrent abdominal pain. These systematic reviews aim to investigate and summarize the quantity and quality of all current evidence for the prognosis and for potential prognostic factors of chronic or recurrent abdominal pain in children.

In **Chapter 3** we investigated how often abdominal pain persisted in children with chronic or recurrent abdominal pain and we investigated whether extensive medical tests, such as laboratorial tests, imaging, and endoscopy, had additional prognostic value to history taking and clinical examination. After a systematic literature search in MEDLINE, EMBASE and PsycINFO for prospective cohort studies published from 1960 until 2005, 18 studies were included. None of the studies was performed in general practice. In total 1331 children were followed for 5 years (median, range 1-29 years). In total 29.1% (95% CI 28.1-30.2) of the patients with chronic or recurrent abdominal pain had abdominal pain after follow-up. The prognosis of chronic or recurrent abdominal pain diagnosed clinically was similar to that diagnosed after extensive medical testing.

The systematic review with a best-evidence synthesis described in **Chapter 4** studies the evidence for possible prognostic factors for persistence of chronic or recurrent

abdominal pain in children. After the systematic literature search 8 studies examining 17 prognostic factors, were included. None of the included studies was performed in general practice. Having a parent with gastrointestinal complaints (moderate evidence) or parents that kept on searching for an organic explanation for the pain (weak evidence) were risk factors for persistence of chronic or recurrent abdominal pain. The sex of the child, the duration of the abdominal pain (both strong evidence) and the severity of abdominal pain (moderate evidence) had no prognostic value. It was not clear as to whether mental health problems prevented, or had no relation with persistence of chronic abdominal pain. We concluded that because there were few prognostic follow-up studies examining prognostic factors on paediatric chronic or recurrent abdominal pain, the evidence for prognostic factors was limited. We recommend physicians to ask about parental gastro-intestinal complaints and their perception towards the abdominal pain, as these are risk factors for persistence of chronic or recurrent abdominal pain. We showed that the hypothesis that psychological problems maintain chronic or recurrent abdominal pain is not supported by evidence from follow-up studies.

The objective of **chapter 5** was to determine the occurrence and management of childhood non-specific abdominal pain in general practice. Using medical record data of the Second Dutch National Survey of General Practice (91 general practices) we found that the incidence rate of non-specific abdominal pain in children aged 4-17 years was 25.0 (95% CI 23.7-26.3) per 1000 person years. Most (92.7%) of the newly diagnosed children (N=1480) consulted once or twice for non-specific abdominal pain. At first consultation of newly diagnosed children 2% of the patients were referred to specialist care and in 1% of the children laboratorial testing was ordered. GPs prescribed medication in 21.3% of the consultations for non-specific abdominal pain. GPs did not register more psychological and social problems in children with non-specific abdominal pain then in children without non-specific AP. We concluded that childhood non-specific abdominal pain was a common problem in general practice but that GPs were only briefly involved. We assume that GPs felt confident in labelling abdominal pain as non-organic, non-specific abdominal pain as they used little additional testing or referrals. GPs commonly prescribed medication for non-specific abdominal pain despite the lack of evidence for their effectiveness.

Chapter 6 and **chapter 7** describe the prevalence and the course of mental health problems among children consulting general practice for abdominal pain. The children were part of the HONEUR abdominal pain cohort. In this cohort study 305 children aged 4-17 years presenting to general practice with a new episode of abdominal pain were followed during 1 year. The mental health problems were measured with the Child Behaviour Checklist at baseline and at 12 months follow-up. The outcome measure for mental health problems was a depressive, an anxiety and a somatic problem. A child was considered to have a somatic problem when he/she had multiple non-specific somatic

symptoms. Abdominal pain characteristics were measured with structured questionnaires at baseline and after 3, 6, 9 and 12 months follow-up.

In **Chapter 6** we determined the baseline prevalence of mental health problems of 171 children of the HONEUR abdominal pain cohort presenting with non-specific abdominal pain and compared that to those of 54 children consulting general practice for other reasons. Of the children with non-specific abdominal pain, 28.1% (95% CI 21.3-34.8%) had a depressive problem, 15.2% (95% CI 9.8-20.6%) an anxiety problem and 60.8% (95% CI 54.0-67.7%) multiple non-specific somatic symptoms. Children with non-specific abdominal pain had 3.0 (95% CI 1.3-7.2) times more often a depressive problem and 8.2 (95% CI 3.2-21.1) times more often multiple non-specific somatic symptoms compared to controls. Patients had both more non-specific gastro-intestinal and non-specific non-gastro-intestinal symptoms compared to controls [mean score (SD) 2.5 (1.2) vs. 0.3 (0.6) and 2.2 (2.0) vs. 0.8 (1.1)]. The conclusions of this chapter were that in general practice mental health problems and non-specific abdominal pain were associated. The GP can expect that approximately 30% of children with non-specific abdominal pain have depressive problems, 15% anxiety problems and 61% somatic problems. The consequences of these mental health problems on prognosis and the effectiveness of possible interventions should be studied.

Chapter 7 shows the course of mental health problems of 281 children presenting to general practice with abdominal pain. We evaluated whether characteristics of the abdominal pain during follow-up influenced were associated with the course of mental health problems. A depressive problem persisted in 32.9% children (95% CI 22.3-44.9%), an anxiety problem in 30.2% (95% CI 17.2-46.1%) and multiple non-specific somatic symptoms in 44.1% children (95% CI 36.7-51.6%). Compared to the open population, after 12-months follow-up more children who consulted for abdominal pain at baseline, had a depressive problem (RR 1.9; 95% CI 1.4-2.6) an anxiety problem (RR 1.6; 95% CI 1.1-2.3) and multiple non-specific somatic symptoms (RR 4.6; 95% CI 3.7-5.7). None of the abdominal pain characteristics were associated with a depressive or an anxiety problem at 12-months follow-up. We concluded that although mental health problems in children consulting general practice for abdominal pain decreased over time, after 1 year of follow-up they continued to be more elevated than in the general population. Our findings suggest that anxiety and depressive symptoms found in children with chronic abdominal pain are not a consequence of the duration, the severity or the frequency of the abdominal pain.

Chapter 8 reflects on the main findings of this thesis and it discusses the implications of the results for clinical practice and future research.

Samenvatting

Samenvatting

Buikpijn is een veelgehoorde klacht bij kinderen. Meestal wordt er lichamelijk geen of onvoldoende verklaring gevonden voor de buikpijn. Buikpijn waarvoor de arts geen lichamelijke oorzaak vermoedt wordt in dit proefschrift aspecifieke buikpijn genoemd. Er is nog nauwelijks onderzoek gedaan naar aspecifieke buikpijn bij kinderen in de huisartspraktijk. Kinderen die met aspecifieke buikpijn door een kinderarts gezien worden blijken ook vaak psychische problemen te hebben. Het is onbekend of dit ook het geval is in de huisartspraktijk. Het is belangrijk om te onderzoeken of kinderen die de huisarts ziet met aspecifieke buikpijn ook psychische problemen hebben. Dit gegeven zou het beleid van de huisarts kunnen beïnvloeden en wellicht een meer preventieve en effectievere behandeling van zowel de buikpijn als de psychische problemen mogelijk maken.

Het doel van dit proefschrift was om aspecifieke buikpijn bij kinderen in de huisartsenpraktijk te onderzoeken. De focus lag daarbij op het bestuderen van het beloop van aspecifieke buikpijn bij kinderen en op het vóórkomen en het beloop van psychische problemen bij deze kinderen.

Hoofdstuk 2 is een overzichtsartikel over chronische aspecifieke buikpijn bij kinderen. Het bevat een uitgebreide up-to-date samenvatting van de literatuur. In dit hoofdstuk worden de etiologie, de risicofactoren voor het ontstaan, de diagnostiek, de prognose, en de behandeling van chronische aspecifieke buikpijn bij kinderen besproken. Het artikel bevat een casusbeschrijving van de twaalfjarige Daphne en haar moeder waarin zij hun ervaringen met chronische aspecifieke buikpijn beschrijven.

Hoofdstuk 3 en hoofdstuk 4 zijn systematische reviews over aspecifieke buikpijn bij kinderen. In een systematische review worden de artikelen die over het betreffende onderwerp zijn gepubliceerd op een systematische manier vergaard. De resultaten uit de gevonden studies worden vervolgens op een transparante manier samengevoegd. Een systematische review heeft tot doel om een zo compleet mogelijk overzicht te geven van het bestaande bewijs voor en tegen bepaalde bevindingen.

In **hoofdstuk 3** wordt de prognose van aspecifieke buikpijn bij kinderen onderzocht. De systematische zoekactie leverde enkel vervolgstudies op naar chronische aspecifieke buikpijn (≥ 3 maanden en ≥ 1x aanval/maand) bij kinderen uit de 2de en 3de lijn. Uit 18 studies bleek dat bij 29,1% (95% betrouwbaarheidsinterval (BI): 28,1-30,2%) van de kinderen deze buikpijn gedurende 5 jaar (mediaan, draagwijdte 1-29 jaar) aanhield. De prognose van chronische aspecifieke buikpijn gediagnosticeerd op basis van het klinische beeld was vergelijkbaar met de prognose gediagnosticeerd na uitgebreid aanvullend onderzoek. De conclusies van hoofdstuk 3 zijn dat bij verwezen kinderen

chronische aspecifieke buikpijn in ongeveer 30% van de gevallen langdurig aanhoudt. Aanvullend diagnostisch onderzoek lijkt niet zinvol bij kinderen met chronische aspecifieke buikpijn zonder alarmsymptomen.

De systematische review met een best-evidence analyse die beschreven wordt in **hoofdstuk 4** onderzoekt prognostische factoren van aspecifieke buikpijn bij kinderen. De zoekactie leverde 8 relevante vervolgstudies op naar prognostische factoren van chronische aspecifieke buikpijn bij kinderen uit de 2de en 3de lijn. Het hebben van een ouder met gastro-intestinale klachten en het hebben van ouders die blijven zoeken naar een organische oorzaak bleken risicofactoren voor het aanhouden van deze buikpijn (matig bewijs). Het geslacht bleek geen prognostische factor te zijn (sterk bewijs), de ernst van de buikpijn ook niet (matig bewijs). Het werd niet duidelijk of psychische comorbiditeit het aanhouden van de buikpijn voorkwam of dat psychische comorbiditeit het beloop van de buikpijn niet beïnvloedde (conflicterend bewijs). De conclusies van hoofdstuk 4 zijn dat er nog weinig onderzoek gedaan is naar factoren die het beloop van aspecifieke buikpijn bij kinderen beïnvloeden. Hierdoor is de bewijskracht voor prognostische factoren bij voorbaat beperkt. Gastro-intestinale klachten bij ouders, en ouders die blijven zoeken naar een organische verklaring voor de pijn zijn mogelijk risicofactoren voor het aanhouden van chronische aspecifieke buikpijn bij kinderen. Er is geen bewijs voor de gangbare hypothese dat chronische aspecifieke buikpijn bij kinderen aanhoudt doordat het kind psychische problemen heeft.

Hoofdstuk 5 geeft een algemeen beeld van aspecifieke buikpijn bij kinderen in de Nederlandse huisartspraktijk. Hiervoor is gebruik gemaakt van de gegevens uit de Tweede Nationale Studie. In deze studie registreerden 104 huisartspraktijken gedurende één jaar de morbiditeit van de patiënten en het handelen van de huisartsen. De incidentie van aspecifieke buikpijn bij kinderen van 4 tot 17 jaar bleek 25,0 per 1000 persoonsjaren (95% BI 23,7-26,3). De meeste kinderen (92,7%) bleken maar 1 of 2 keer bij de huisarts te komen voor deze klacht. Huisartsen bleken bij een eerste presentatie van aspecifieke buikpijn 2% van de kinderen te verwijzen en bij 1% van de kinderen aanvullend onderzoek aan te vragen. Huisartsen schreven tijdens 21,3% van de consulten medicatie voor; bij 30% hiervan ging het om laxeermiddelen en bij 30% om darmtonus beïnvloedende middelen. Huisartsen registreerden niet vaker psychische en sociale problemen bij kinderen met aspecifieke buikpijn dan bij kinderen die de huisarts consulteerden voor andere klachten. De conclusies uit hoofdstuk 5 zijn dat huisartsen regelmatig kinderen zien met aspecifieke buikpijn en dat huisartsen over het algemeen slechts kortdurend betrokken zijn bij dit probleem. Huisartsen stellen de diagnose aspecifieke buikpijn zonder veel aanvullend onderzoek of verwijzingen. Huisartsen schrijven vaak medicatie voor, ondanks dat er een gebrek aan bewijs is voor de effectiviteit van deze middelen.

Hoofdstuk 6 en **hoofdstuk 7** laten het onderzoek zien naar het vóórkomen en het beloop van psychische problemen bij kinderen met buikpijn uit de huisartspraktijk.

De onderzochte kinderen maakten deel uit van het HONEUR-buikpijncohort. In de HONEUR-buikpijnstudie werden gedurende 1 jaar 305 kinderen gevolgd die de huisarts consulteerden met een nieuwe episode van buikpijn. Deze prospectieve studie werd uitgevoerd door de afdeling huisartsgeneeskunde van de Erasmus Universiteit. De psychische klachten werden gemeten bij aanvang en na 12 maanden follow-up met de Child Behavioural Checklist (CBCL). De uitkomstmaten waren depressieve, angst- en somatische problemen. Een somatisch probleem betekende de aanwezigheid van meerdere aspecieke klachten (somatisch onvoldoende verklaarbare lichamelijk klachten ; SOLK). Het beloop van de buikpijn werd gemeten met gestructureerde vragenlijsten bij aanvang en na 3, 6, 9 en 12 maanden follow-up.

In **hoofdstuk 6** wordt de aanwezigheid van psychische problemen bij kinderen met aspecifieke buikpijn vergeleken met die bij kinderen die naar de huisarts komen voor andere klachten (controle-kinderen). Van de kinderen met aspecifieke buikpijn had 28,1% (95% BI 21,3-34,8%) een depressief probleem, 15,2% (95% BI 9,8-20,6%) een angstprobleem en 60,8% (95% BI 54,0 -67,7%) een somatisch probleem. Kinderen met aspecifieke buikpijn hadden 3,0 (95% BI 1,3-7,2) keer vaker depressieve problemen en 8,2 (95% BI 3,2-21,1) keer vaker somatische problemen dan de kinderen uit de controlegroep. Kinderen met aspecifieke buikpijn hadden meer lichamelijk onvoldoende verklaarde gastro-intestinale klachten [gemiddelde score (SD) 2,5 (1,2) versus 0,3 (0,6)] en niet-gastro-intestinale klachten dan controle kinderen [2,2 (2,0) versus 0,8 (1,1)]. In hoofdstuk 6 wordt geconcludeerd dat er een verband bestaat tussen aspecifieke buikpijn en psychische problemen bij kinderen in de huisartspraktijk. De huisarts kan ervan uit gaan dat ongeveer 30% van de kinderen die hij/zij ziet met aspecifieke buikpijn depressieve klachten heeft, 15% angstklachten en 61% andere lichamelijk onvoldoende verklaarde somatische klachten.

Hoofdstuk 7 laat het onderzoek zien naar het 1-jaars beloop van psychische problemen bij kinderen die naar de huisarts komen met buikpijn. In hoofdstuk 7 wordt de relatie beschreven tussen de duur, de ernst en de frequentie van de buikpijn gedurende de follow-up periode enerzijds en de psychische problemen op 12 maanden anderzijds. In totaal hield 32,9% (95% BI 22,3-44,9%) van de kinderen depressieve problemen, 30,2% (95% BI 17,2- 46,1%) angstproblemen en 44,1% (95% BI 36,7-51,6%) somatische problemen. Kinderen met buikpijn hadden ook na 12 maanden, in vergelijking met kinderen uit de algemene bevolking, vaker depressieve problemen (RR 1,9; 95% BI 1,4-2,6), angstproblemen (RR 1,6; 95% BI 1,1-2,3) en somatische problemen (RR 4,6; 95% BI 3,7-5,7). Geen van de buikpijn-kenmerken waren geassocieerd met een depressie- of een angstprobleem na 12-maanden. De conclusies van hoofdstuk 7 zijn dat psychische problemen bij kinderen die naar de huisarts komen met buikpijn in de loop van een jaar meestal afnemen. Echter, deze kinderen houden ook na 12 maanden een verhoogd risico op psychische problemen. De duur en de ernst van de

buikpijn lijken het beloop van de psychische problemen bij kinderen met buikpijn niet te beïnvloeden.

Hoofdstuk 8 geeft een samenvatting van en reflecteert op de belangrijkste bevindingen van dit proefschrift. Tekortkomingen van de studies, de implicaties van de resultaten voor de praktijk en er aanbevelingen voor toekomstig onderzoek worden besproken.

Dankwoord

Dankwoord

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Marieke

Curriculum Vitae

Curriculum Vitae

Marieke Gieteling is geboren op 15 januari 1974 te Havanna (Cuba). Na het behalen van haar Gymnasium diploma aan het Marianum College te Venlo begon zij in 1992 aan de studie geneeskunde aan de Erasmus Universiteit in Rotterdam. In 1997 behaalde zij het doctoraal examen en in 1999 het artsexamen. Aansluitend werkte zij als arts-assistent op de afdeling neurologie in het ErasmusMC in Rotterdam, als basisarts in Arequipa (Peru), als arts-assistent psychiatrie bij Parnassia in Den Haag en als arts-assistent op de spoedeisende hulp in het Vlietland Ziekenhuis in Schiedam. In september 2004 startte zij met de opleiding tot huisarts en onderzoeker (AIOTO) op de afdeling Huisartsgeneeskunde aan de Erasmus Universiteit in Rotterdam. Eind 2008 rondde zij de huisartsenopleiding af. Sindsdien werkte zij als huisarts in opleiding tot onderzoeker en als huisarts in dienst bij een huisarts (HIDHA) in Moordrecht. In 2010 behaalde zij haar Master of Science in de klinische epidemiologie aan het Nederlands Instituut for Health Sciences (NIHES).

Marieke is getrouwd met Kees-Jan Korving, zij hebben 3 kinderen.

PhD Portfolio

PhD Portfolio

1. PhD Training	Year	Workload	
		Hours	ECTS
MsC in Clinical Epidemiology, NIHES, Rotterdam	2005-2010		70
Biomedical English Writing and Communication	2007	40	
Professional education			
Vocational training for general practitioner, Erasmus MC Rotterdam	2005-2008		
Presentations			
WONCA Europe, Italy (two oral presentations)	2006	80	
NHG Science Conference, Rotterdam (oral presentation)	2008	40	
NHG Science Conference, Utrecht (oral presentation)	2009	40	
EGPRN, Italy (poster presentation)	2009	16	
NAPCRG, Montreal, Canada (oral presentation)	2010	40	
National and international conferences			
PGN, Amsterdam	2005	30	
NHG Congress, Rotterdam	2008	8	
2. Teaching			
Education in science to students of the Vocational Training for General Practitioners, Erasmus MC Rotterdam	2009	20	

Appendix

Gedragsvragenlijst voor ouders van kinderen van 4 - 5 jaar

Hieronder is een lijst met vragen over kinderen. Alle vragen gaan over **hoe uw kind *nu is of in de afgelopen 3 maanden is geweest***. Kruis aan wat het beste bij uw kind past. Beantwoord alle vragen zo goed als u kunt, ook al lijken sommige vragen niet bij uw kind te passen.

		helemaal niet	**een beetje of soms**	**duidelijk of vaak**
		(voor zover u weet)		
1.	Pijnklachten (zonder medische oorzaak; geen buikpijn of hoofdpijn)	□	□	□
2.	Doet te jong voor zijn/haar leeftijd	□	□	□
3.	Is bang om iets nieuws te proberen	□	□	□
4.	Vermijdt anderen aan te kijken	□	□	□
5.	Kan zich niet concentreren; kan niet lang de aandacht ergens bij houden	□	□	□
6.	Kan niet stilzitten, is onrustig of hyperactief	□	□	□
7.	Kan er niet tegen wanneer dingen ergens anders staan	□	□	□
8.	Kan niet tegen wachten; alles moet nu gebeuren	□	□	□
9.	Kauwt op dingen die niet eetbaar zijn	□	□	□
10.	Klampt zich vast aan volwassenen of is te afhankelijk	□	□	□
11.	Zoekt voortdurend hulp	□	□	□
12.	Obstipatie; heeft geen ontlasting (zonder dat hij/zij ziek is)	□	□	□
13.	Huilt veel	□	□	□
14.	Wreed tegen dieren	□	□	□
15.	Uitdagend	□	□	□
16.	Wil in alles direct zijn/haar zin hebben	□	□	□
17.	Vernielt eigen spullen	□	□	□
18.	Vernielt spullen van gezinsleden of van andere kinderen	□	□	□
19.	Diarree of dunne ontlasting (zonder dat hij/zij ziek is)	□	□	□
20.	Ongehoorzaam	□	□	□
21.	Verstoord wanneer iets anders gaat dan hij/zij gewend is	□	□	□
22.	Wil niet alleen slapen	□	□	□
23.	Geeft geen antwoord wanneer anderen tegen hem/haar praten	□	□	□
24.	Eet niet goed	□	□	□
25.	Kan niet opschieten met andere kinderen	□	□	□
26.	Kan geen pret maken; doet als een kleine volwassene	□	□	□
27.	Lijkt zich niet schuldig te voelen na zich misdragen te hebben	□	□	□
28.	Wil het huis niet uit	□	□	□
29.	Snel van streek als iets tegenzit	□	□	□
30.	Snel jaloers	□	□	□
31.	Eet of drinkt dingen die eigenlijk niet eetbaar of drinkbaar zijn	□	□	□
32.	Is bang voor bepaalde dieren, situaties of plaatsen	□	□	□
33.	Voelt zich snel beledigd of gekwetst	□	□	□
34.	Bezeert zich vaak; krijgt vaak ongelukken	□	□	□

35.	Vecht veel	□	□	□
36.	Bemoeit zich met alles	□	□	□
37.	Raakt te veel overstuur wanneer hij/zij gescheiden wordt van zijn/haar ouders	□	□	□
38.	Heeft moeite met inslapen	□	□	□
39.	Hoofdpijnen (zonder medische oorzaak)	□	□	□
40.	Slaat anderen	□	□	□
41.	Houdt zijn/haar adem in	□	□	□
42.	Doet dieren of mensen zonder opzet pijn	□	□	□
43.	Ziet er ongelukkig uit zonder duidelijke reden	□	□	□
44.	Boze buien	□	□	□
45.	Misselijk (zonder medische oorzaak)	□	□	□
46.	Zenuwachtige bewegingen of zenuwtrekken	□	□	□
47.	Nerveus, zenuwachtig of gespannen	□	□	□
48.	Nachtmerries	□	□	□
49.	Eet te veel	□	□	□
50.	Is erg moe	□	□	□
51.	Is in paniek zonder duidelijke reden	□	□	□
52.	Pijnlijke ontlasting (zonder medische oorzaak)	□	□	□
53.	Valt mensen lichamelijk aan	□	□	□
54.	Pulkt aan neus, huid of aan iets anders van het lichaam	□	□	□
55.	Speelt te veel met eigen geslachtsdelen	□	□	□
56.	Onhandig of stuntelig	□	□	□
57.	Oogproblemen (zonder medische oorzaak)	□	□	□
58.	Straffen verandert zijn/haar gedrag niet	□	□	□
59.	Gaat snel over van de ene bezigheid naar de andere	□	□	□
60.	Huiduitslag of andere huidproblemen (zonder medische oorzaak)	□	□	□
61.	Weigert om te eten	□	□	□
62.	Weigert om actieve spelletjes te spelen	□	□	□
63.	Bonkt steeds met hoofd of wiegt met lichaam	□	□	□
64.	Verzet zich 's avonds met naar bed gaan	□	□	□
65.	Verzet zich tegen zindelijk worden	□	□	□
66.	Schreeuwt veel	□	□	□
67.	Lijkt niet te reageren op liefde of genegenheid	□	□	□
68.	Schaamt zich gauw of voelt zich niet op zijn/haar gemak	□	□	□
69.	Egoïstisch; wil niet delen	□	□	□
70.	Toont weinig liefde of genegenheid voor anderen	□	□	□
71.	Toont weinig belangstelling voor dingen om zich heen	□	□	□
72.	Toont te weinig angst om zich te bezeren	□	□	□
73.	Te verlegen of timide	□	□	□
74.	Slaapt overdag en/of 's nachts minder dan de meeste kinderen	□	□	□
75.	Smeert of speelt met ontlasting	□	□	□
76.	Spraakprobleem	□	□	□
77.	Staart voor zich uit of lijkt volledig in beslag genomen	□	□	□
78.	Buikpijn of krampen (zonder medische oorzaak)	□	□	□
79.	Snelle wisselingen tussen verdriet en opwinding	□	□	□
80.	Vreemd gedrag	□	□	□
81.	Koppig, stuurs of prikkelbaar	□	□	□
82.	Stemming en gevoelens veranderen plotseling	□	□	□
83.	Mokt veel	□	□	□

84.	Praat of schreeuwt in slaap	□	□	□
85.	Driftbuien of snel driftig	□	□	□
86.	Overdreven netjes of te schoon	□	□	□
87.	Te angstig of te bang	□	□	□
88.	Werkt niet mee	□	□	□
89.	Weinig actief; beweegt zich langzaam of te weinig energie	□	□	□
90.	Ongelukkig, verdrietig of depressief	□	□	□
91.	Meer dan gewoon luidruchtig	□	□	□
92.	Van streek door onbekende mensen of stituaties	□	□	□
93.	Overgeven (zonder medische oorzaak)	□	□	□
94.	Wordt 's nachts vaak wakker	□	□	□
95.	Loopt weg	□	□	□
96.	Wil veel aandacht	□	□	□
97.	Zeuren	□	□	□
98.	Teruggetrokken; gaat niet met anderen om	□	□	□
99.	Maakt zich zorgen	□	□	□

Gedragsvragenlijst voor ouders van kinderen van 6 tot en met 16 jaar

Hieronder is een lijst met vragen over kinderen. Alle vragen gaan over hoe uw kind *nu is of in de afgelopen 3 maanden is geweest*. Kruis aan wat het beste bij uw kind past. Beantwoord alle vragen zo goed als u kunt, ook al lijken sommige vragen niet bij uw kind te passen.

		helemaal niet	een beetje of soms	duidelijk of vaak
1.	Doet te jong voor zijn / haar leeftijd	□	□	□
2.	Drinkt alcohol zonder dat zijn/haar ouders dat goed vinden	□	□	□
3.	Maakt veel ruzie	□	□	□
4.	Maakt dingen waar hij/zij mee begint niet af	□	□	□
5.	Er is heel weinig wat hij/zij leuk vindt	□	□	□
6.	Doet ontlasting (poept) buiten de wc of in de broek	□	□	□
7.	Schept op; doet stoer	□	□	□
8.	Kan zich niet concentreren; kan niet lang de aandacht ergens bij houden	□	□	□
9.	Kan bepaalde gedachten niet uit zijn/haar hoofd zetten; obsessies	□	□	□
10.	Kan niet stilzitten; is onrustig of hyperactief	□	□	□
11.	Klampt zich vast aan volwassenen of is te afhankelijk	□	□	□
12.	Klaagt over zich eenzaam voelen	□	□	□
13.	In de war of wazig denken	□	□	□
14.	Huilt veel	□	□	□
15.	Wreed tegen dieren	□	□	□
16.	Wreed, pesterig of gemeen tegen anderen	□	□	□
17.	Dagdromen of gaat op in zijn/haar gedachten	□	□	□
18.	Verwondt zichzelf opzettelijk of doet zelfmoordpogingen	□	□	□
19.	Eist veel aandacht op	□	□	□
20.	Vernielt eigen spullen	□	□	□
21.	Vernielt spullen van gezinsleden of van anderen	□	□	□
22.	Is thuis ongehoorzaam	□	□	□
23.	Is ongehoorzaam op school	□	□	□
24.	Eet niet goed	□	□	□
25.	Kan niet opschieten met andere jongens of meisjes	□	□	□
26.	Lijkt zich niet schuldig te voelen na zich misdragen te hebben	□	□	□
27.	Snel jaloers	□	□	□
28.	Houdt zich niet aan de regels thuis, op school of ergens anders	□	□	□
29.	Is bang voor bepaalde dieren, situaties of plaatsen anders dan school	□	□	□
30.	Is bang om naar school te gaan	□	□	□
31.	Is bang dat hij/zij iets slechts zou kunnen doen of denken	□	□	□
32.	Heeft het gevoel dat hij/zij perfect moet zijn	□	□	□

33.	Heeft het gevoel of klaagt erover dat niemand van hem/haar houdt	□	□	□
34.	Heeft het gevoel dat anderen hem/haar te pakken willen nemen	□	□	□
35.	Voelt zich waardeloos of minderwaardig	□	□	□
36.	Bezeert zich vaak; krijgt vaak ongelukken	□	□	□
37.	Vecht veel	□	□	□
38.	Wordt veel gepest	□	□	□
39.	Gaat om met jongens of meisjes die in moeilijkheden raken	□	□	□
40.	Hoort geluiden of stemmen die er niet zijn	□	□	□
41.	Impulsief of doet dingen zonder er bij na te denken	□	□	□
42.	Is liever alleen dan met anderen	□	□	□
43.	Liegt of bedriegt	□	□	□
44.	Bijt nagels	□	□	□
45.	Nerveus, zenuwachtig of gespannen	□	□	□
46.	Zenuwachtige bewegingen of zenuwtrekken (schrijf op):	□	□	□
47.	Nachtmerries	□	□	□
48.	Andere jongens of meisjes mogen hem/haar niet	□	□	□
49.	Obstipatie; last van verstopping	□	□	□
50.	Is te angstig of te bang	□	□	□
51.	Voelt zich duizelig of licht in het hoofd	□	□	□
52.	Voelt zich erg schuldig	□	□	□
53.	Eet te veel	□	□	□
54.	Is erg moe zonder reden	□	□	□
55.	Te dik	□	□	□
56.	Lichamelijke problemen zonder bekende medische oorzaak			
	a Pijnen (geen buikpijn of hoofdpijn)	□	□	□
	b Hoofdpijn	□	□	□
	c Misselijk	□	□	□
	d Oogproblemen (waarvoor een bril of lenzen niet helpen)	□	□	□
	e Huiduitslag of andere huidproblemen	□	□	□
	f Buikpijn	□	□	□
	g Overgeven	□	□	□
	h Andere problemen (schrijf op):	□	□	□
57.	Valt mensen lichamelijk aan	□	□	□
58.	Pulkt aan neus, huid of aan iets anders van het lichaam	□	□	□
59.	Speelt met eigen geslachtsdelen in het openbaar	□	□	□
60.	Speelt te veel met eigen geslachtsdelen	□	□	□
61.	Schoolwerk is slecht	□	□	□
62.	Onhandig of stuntelig	□	□	□
63.	Gaat liever om met oudere jongens of meisjes	□	□	□
64.	Gaat liever om met jongere jongens of meisjes	□	□	□
65.	Weigert om te praten	□	□	□
66.	Herhaalt bepaalde handelingen steeds maar weer; dwanghandelingen	□	□	□
67.	Loopt weg van huis	□	□	□
68.	Schreeuwt veel	□	□	□
69.	Gesloten; houdt dingen voor zichzelf	□	□	□
70.	Ziet dingen die er niet zijn	□	□	□
71.	Schaamt zich gauw of voelt zich niet op zijn/haar gemak	□	□	□
72.	Sticht branden	□	□	□
73.	Seksuele problemen	□	□	□

74.	Slooft zich uit of doet gek om op te vallen	□	□	□
75.	Te verlegen of timide	□	□	□
76.	Slaapt minder dan de meeste jongens en meisjes	□	□	□
77.	Slaapt overdag en/of 's nachts meer dan de meeste jongens en meisjes	□	□	□
78.	Let niet goed op of is snel afgeleid	□	□	□
79.	Spraakprobleem	□	□	□
80.	Kijkt met een lege blik	□	□	□
81.	Steelt van huis	□	□	□
82.	Steelt buitenshuis	□	□	□
83.	Spaart te veel dingen op die hij/zij niet nodig heeft	□	□	□
84.	Vreemd gedrag	□	□	□
85.	Vreemde gedachten	□	□	□
86.	Koppig, stuurs of prikkelbaar	□	□	□
87.	Stemming en gevoelens veranderen plotseling	□	□	□
88.	Mokt veel	□	□	□
89.	Achterdochtig	□	□	□
90.	Vloekt of gebruikt vieze woorden	□	□	□
91.	Praat erover dat hij/zij zichzelf zou willen doden	□	□	□
92.	Praat tijdens slaap of slaapwandelt	□	□	□
93.	Praat te veel	□	□	□
94.	Pest veel	□	□	□
95.	Driftbuien of snel driftig	□	□	□
96.	Denkt te veel aan seks	□	□	□
97.	Bedreigt mensen	□	□	□
98.	Duimzuigen	□	□	□
99.	Rookt tabak	□	□	□
100.	Problemen met slapen	□	□	□
101.	Spijbelt; blijft weg van school	□	□	□
102.	Weinig actief; beweegt zich langzaam of te weinig energie	□	□	□
103.	Ongelukkig, verdrietig of depressief	□	□	□
104.	Meer dan gewoon luidruchtig	□	□	□
105.	Gebruikt drugs	□	□	□
106.	Vandalisme	□	□	□
107.	Plast overdag in zijn/haar broek	□	□	□
108.	Plast in bed	□	□	□
109.	Zeuren	□	□	□
110.	Wil dat hij/zij van het andere geslacht is	□	□	□
111.	Teruggetrokken; gaat niet met anderen om	□	□	□
112.	Maakt zich zorgen	□	□	□

Childhood Non-Specific Abdominal Pain in General Practice
Course and Relation with Mental Health Problems

Abdominal pain is a common complaint in children. Usually no organic abnormalities can be found explaining the abdominal pain of children. While most of the children with abdominal pain are managed in general practice this pain syndrome has hardly been studied in this setting. In this thesis we use the term non-specific abdominal pain for abdominal pain for which general practitioners do not suspect organic pathology. Referred children with chronic or recurrent non-specific abdominal pain are found to have more mental health problems than children consulting specialist care for other problems. It is important to find out whether children with non-specific abdominal pain in general practice are also at increased risk for mental health problems. It may influence general practitioners' management and it may allow for a more effective management of both the abdominal pain and the mental health problems. In this thesis we studied childhood non-specific abdominal pain, it's course and it's relation with mental health problems.

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