From the Department of Women's and Children's Health,
Karolinska Institutet, Stockholm, Sweden

EPIDEMIOLOGIC STUDIES ON ACUTE APPENDICITIS IN CHILDREN

Markus Almström

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Epidemiologic Studies on Acute Appendicitis in Children

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By

Markus Almström, M.D.

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Principal Supervisor:
Tomas Wester M.D. Ph.D.
Karolinska Institutet
Department of Women's and Children's Health
Division of Paediatric Surgery

Co-supervisors:
Anna Svenningsson M.D. Ph.D.
Karolinska Institutet
Department of Women's and Children's Health
Division of Paediatric Surgery

Jan F Svensson M.D. Ph.D.
Karolinska Institutet
Department of Women's and Children's Health
Division of Paediatric Surgery

Opponent:
Benno M Ure, M.D. Ph.D.
Medizinische Hochschule Hannover
Department of Paediatric Surgery

Examination Board:
Rolf Christofferson M.D. Ph.D.
Uppsala University
Department of Women's and Children's health
Paediatric Surgery Research Group

Joakim Folkesson M.D. Ph.D.
Uppsala University
Department of Surgical Sciences
Division of Gastrointestinal Surgery

Torbjörn Lind M.D. Ph.D.
Umeå University
Department of Clinical Sciences
Unit of Paediatrics

Utan tvivel är man inte riktigt klok

Tage Danielsson

To my wife and my daughters

ABSTRACT

Acute appendicitis is the most common surgical emergency in children. A considerable effort has been made to develop and improve treatment and outcomes. A PubMed search yields over 20 000 publications on appendicitis. Almost 8 000 abstracts are found if the search is restricted to children. Nevertheless, there are still controversies on the diagnostic work-up, treatment and outcome of acute appendicitis and there are many issues to be further explored.

The diagnostic process behind the decision to explore the abdomen and remove the diseased appendix is evolving and novel diagnostic modalities are continuously introduced. Appendectomy as gold standard treatment for simple and complex appendicitis is challenged by non-operative treatment options. Even the fundamental concept of appendicitis as an inevitably progressive disease, ending up in perforation, has been challenged. We have not been able to fully understand nor significantly reduce associated complications including appendiceal perforation, intra-abdominal abscess, postoperative wound infection and adhesive small bowel obstruction, leading to significant morbidity and even death.

The general aims of this thesis were to investigate the epidemiology of acute appendicitis in children and to identify factors important for optimising treatment and reducing morbidity.

Paper I was a retrospective cohort study investigating the correlation between in-hospital surgical delay and the risk for perforated appendicitis. All 2 756 children operated for acute appendicitis in our institution 2006–2013 were included in the study. Secondary outcome measures were markers of postoperative complications. In multivariate logistic regression analysis, increased time to surgery was not associated with increased risk for histopathologic perforation. There was no correlation between the timing of surgery and rate of postoperative wound infection, intra-abdominal abscess, reoperation, or readmission.

In **paper II,** the epidemiology of acute appendicitis and appendectomy was investigated in a population-based cohort of Swedish children. Data was collected from the Swedish National Patient Register (NPR). 64 971 children registered in the NPR 1987–2013 were eligible for the study. A rapidly declining incidence rate of childhood appendicitis was identified in Sweden over the study period, with significantly different trends comparing non-perforated and perforated appendicitis. Incidence rates differed between genders and between health care regions. Data did not reveal explanations on the aetiology of the findings.

In **paper III**, the correlation between provision of care and outcome after appendectomy in children was investigated. Data from the NPR on 55 591 childhood appendectomies in Sweden 1987–2009 were analysed. The risk of postoperative complications was significantly reduced in specialised paediatric surgical centers and in high caseload hospitals, compared to other hospitals. There were only seven deaths within 90 days of appendectomy in the cohort. We concluded that provision of care matters, and that reduced risks for complications may not only be achieved by centralisation to paediatric surgical centers but also by increasing hospital caseload of childhood appendicitis management in other settings.

LIST OF SCIENTIFIC PAPERS

I. **Almström M**, Svensson JF, Patkova B, Svenningsson A, Wester T.
In-hospital surgical delay does not increase the risk for perforated appendicitis in children: a single center retrospective cohort study.
Ann Surg. 2017;265:616–621

II. **Almström M**, Svenningsson A, Svensson JF, Hagel E, Wester T.
Population-based cohort study on the epidemiology of acute appendicitis in children in Sweden 1987–2013.
BJS Open. In Press.

III. **Almström M**, Svenningsson A, Svensson JF, Hagel E, Wester T.
Hospital level and caseload of pediatric appendectomies correlate with risk for complications after appendectomy in children: a population-based study.
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LIST OF ABBREVIATIONS

AIR	Appendicitis Inflammatory Response
CI	confidence interval
CGH	central general hospital
CRP	C-reactive protein
CT	computed tomography
GH	general hospital
ICD	International Classification of Disease
IQR	interquartile range
IRR	incidence rate ratio
MRI	magnetic resonance imaging
NPR	National Patient Register
OR	odds ratio
PAS	Paediatric Appendicitis Score
SD	standard deviation
SPC	specialised paediatric surgical center
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
US	ultrasonography
WBC	white blood cells
yy-mm-dd	year year - month month - day day

1 SUMMARY OF THE STUDIES

Study I: In-hospital surgical delay does not increase the risk for perforated appendicitis in children: a single-center retrospective cohort study

Aim and methods: We aimed to investigate the correlation between in-hospital surgical delay before appendectomy for suspected appendicitis and the finding of perforated appendicitis in children. Secondary outcomes were markers of postoperative morbidity. All children undergoing appendectomy for suspected acute appendicitis at our institution 2006–2013 were reviewed for the exposure of surgical delay. Primary endpoint was the histopathologic finding of perforated appendicitis. The main explanatory variable was in-hospital surgical delay. Secondary endpoints were postoperative wound infection, intra-abdominal abscess, reoperation, length of hospital stay and readmission. To adjust for selection bias, a logistic regression model was created to estimate odds ratios for the main outcome measures. Missing data were replaced using multiple imputation.

Results and conclusions: 2 756 children operated for acute appendicitis were included in the study. 661 (24.0%) had a histopathologic diagnosis of perforated appendicitis. In multivariate logistic regression analysis, increased time to surgery was not associated with increased risk of histopathologic perforation. There was no association between the timing of surgery and postoperative wound infection, intra-abdominal abscess, reoperation or readmission. We concluded that in-hospital delay of acute appendectomy in children was not associated with an increased rate of histopathologic perforation, and that timing of surgery was not an independent risk factor for postoperative complications. The results were not dependent on the magnitude of the surgical delay. The findings were analogous with previous findings in adults and may support planning of utilisation of available hospital- and operative resources.

Study II: Population-based cohort study on the epidemiology of acute appendicitis in children in Sweden 1987–2013

Aim and methods: The aim of this study was to investigate the present epidemiology of acute appendicitis and appendectomy in a population-based cohort of Swedish children. The Swedish National Patient Register was queried for all children with acute appendicitis and/or appendectomy 1987–2013. Population-based absolute incidence rates were calculated. Rates were age- and gender-adjusted and analysed for temporal and regional trends, in a Poisson regression model.

Results and conclusions: 56 774 children with acute appendicitis were identified, of whom 53 478 (94.2%) underwent appendectomy. The incidence rate of acute appendicitis declined by 43.7% over 26 years, from 177.7 to 100.1 per 100 000 person-years 1987–2013. The most significant reduction was for non-perforated appendicitis, from 138.5 to 68.4 per 100 000 person-years during 1987–2009. The incidence rate of perforated appendicitis decreased from 28.0 to 19.9 per 100 000 person-years and negative appendectomies were reduced from 48.5 to 3.6 per 100 000 person-years during the study period. We concluded that the incidence rates of acute appendicitis and negative appendectomies were markedly reduced in Swedish children, with significantly different trends amongst non-perforated appendicitis and perforated appendicitis. The incidence rate of diagnosed appendicitis did not increase, on the long term, after the introduction of radiologic modalities in diagnosing appendicitis. Data did not explain the reason of the reduced rates, which remains unclear.

Study III: Hospital level and caseload of pediatric appendectomies correlate with risk for complications after appendectomy in children: a population-based study.

Aim and methods: The aim of this population-based cohort study was to investigate the impact of hospital administrative level and caseload of paediatric appendectomies on the morbidity and mortality after appendectomy in children. The study included all Swedish children less than 15 years of age that underwent appendectomy for suspected appendicitis 1987–2009. Patient characteristics and data on postoperative morbidity and mortality were collected from the Swedish National Patient Register and the Swedish Cause of Death Register. Data were analysed in regression models adjusting for available confounders, including patient age and appendicitis subtype.

Results and conclusions: The cohort comprised 55 591 children. The risk for postoperative complications, including reoperation and readmission, was reduced in specialised paediatric surgical centers and in high caseload hospitals, compared to other hospitals. There were only seven postoperative deaths within 90 days of appendectomy. We concluded that risk reductions were clinically relevant and that the merit from centralising the management of paediatric appendectomies to specialised paediatric surgical centers may also be achieved by increasing hospital caseload of paediatric appendectomies in non-paediatric surgical units.

2 BACKGROUND

2.1 HISTORICAL REFLECTION

Most probably already the ancient Egyptians were aware of the vermiform appendix; in graves separate jars for the “worm of the bowel” were found, where the appendix is believed to have been put prior to mummification. The appendix is otherwise not mentioned in early history. Neither Aristotle (4th century BC) nor Galenus (2nd century BC) described the appendix in their anatomic works; as human dissections were forbidden their discoveries were based on vivisections using pigs or macaques, both lacking an appendix. The first written descriptions of the appendix did not appear until the renaissance: both Leonardo Da Vinci (1492) and Andreas Vesalius (1543) noted the presence of the organ. In 1544 Jean Fernel, a French physician and philosopher, made the first pathologic description of appendicitis, in a cadaver.[1]

The famous first appendectomy was performed at St George’s Hospital in London by Claudius Amyand in 1735, remarkably in a case of appendicitis occurring in a scrotal hernia of an 11-year old boy. Thus the first appendectomy was performed scrotally.[2]

Still, surgery was exclusive and not widely available during the 18th and 19th century, and surgical treatment of acute appendicitis and its complications was restricted to incising abscesses of the lower right abdominal quadrant. In a paper from 1812, Parkinson was the first to describe a case of “isolated perforated appendix disease”, or what we today would call appendicitis, at autopsy in a five year old boy.[3] In his paper from 1824 Louyer-Villermay of Paris introduced the term “inflammation de l’appendice”, in relation to the aetiology of the inflammatory disease in the lower right quadrant of the abdomen.[4] Despite the evolving arguments for the appendix to be the origin of the condition previously named typhlitis, influential surgeons sustained in the belief that that the caecum rather than the vermiform appendix was responsible for the lower right quadrant abdominal abscess formations, amongst them the French surgeon Baron Guillaume Dupuytren, Chief of Surgery at Hôtel Dieu in Paris 1815.[3]

The modern era of surgical treatment of acute appendicitis did not start until the first appendectomy for the diagnosis of typhlitis, performed by Robert Lawson Tait in Edinburgh 1880.[5] Not much later, in 1886, Reingald Fitz coined the anatomically more correct appellation *appendicitis.*[6] Charles McBurney presented a series of appendectomies in patients with acute appendicitis in 1889, and he was the first to describe an acute appendectomy prior to perforation.[7] In the same year Karl Gustav Lennander performed the first appendectomy in Sweden.[8] The famous muscle splitting procedure bearing McBurney’s name was published 1894.[9]

The evolutionary great steps in appendicitis treatment of the 20th and 21th century include the addition of antibiotic treatment, improved perioperative care and anaesthesia and the development of minimal access surgery. Important reductions in appendicitis-related mortality was achieved after the introduction of sulphonamide (1935) and subsequently penicillin (1943) for the treatment of the infectious complications of appendicitis and appendectomy.[10] The first laparoscopic appendectomy was performed by the controversial pioneer of endoscopic surgery Kurt Semm in 1980,[11] repeated in children by Benno Ure 1982.[12] The first randomised controlled trial comparing non-operative treatment to appendectomy in acute appendicitis was performed at Danderyd Hospital, Stockholm, Sweden in 1995 by Eriksson and Granström.[13] The first randomised controlled trial on non-operative treatment of acute appendicitis in children was performed in our institution in 2014, with results indicating similar outcome in both treatment arms.[14]

2.2 THE APPENDIX

2.2.1 Embryology

The appendix arises from the bottom of the caecum, appearing as an elongating bud, during the fifth to eighth gestational week. The vermiform appendix follows the caecum during the elongation and rotation of the midgut during the tenth to twelfth week, finding its most common position in the right iliac fossa during the second trimester.[15] Differential growth rates of the appendix and caecum, continuing throughout childhood causes the caecal diameter to exceed the diameter of appendix by four times at birth and eight times in the adult.[16]

2.2.2 Anatomy and histology

The worm-shaped vermiform appendix extends most inevitably from the junction of the taenia coli at the bottom of the caecum. The position of the appendix body is variable; in most cases it is retrocaecal or lies inferiorly towards the pelvis, but it may extend in any direction. It may lie free or be covered by the peritoneum. The topographic position of the base of the appendix is fairly constant and is most often found at the junction of the lateral and middle third of a line between the superior iliac spine and the umbilicus, the McBurney's point.[9] The histologic composition of the wall of the appendix is similar to the intestinal wall of the colon and small bowel: the innermost mucosa is covered by submucosa, the circular and the longitudinal muscle layers and the serosa.[17] The most specific histologic feature of the appendix wall is the presence of lymphoid follicles in the submucosa and lamina propria, much resembling the Peyer's patches of the small intestine.[18]

2.2.3 Normal function

The function of the normal appendix is unknown. It has been postulated to be an evolutionary remnant of lower standing mammalians, where it originally may have aided the digestion of cellulose with the aid of residential microorganisms. More recent research has focused on an immunological function, suggesting the appendix to act as a "safe-house" for the intestinal flora, enabling re-culturing of the colon after infectious diarrhoea and other disturbances of the normal colonic flora.[19] The lumen of the appendix was recently shown to contain an active microfilm, creating a probiotic environment stimulating for bacterial growth, further supporting a “safe-house” theory.[20]

2.3 ACUTE APPENDICITIS

Initial symptoms in acute appendicitis are vague and non-specific. Diffuse periumbilical pain is typically followed by nausea, anorexia and indigestion. Vomiting may be encountered and body temperature rises moderately. The classic migration or shift of pain to the right iliac fossa develops when the initial mesenteric referred pain is overtaken by local peritoneal nociception. Andersson investigated the clinical characteristics and laboratory markers and found peritoneal irritation and migration of pain to be the strongest predictors associated to appendicitis.[21] The histopathologic features of acute appendicitis include mucosal ulceration, neutrophilic leukocyte invasion of the mucosa, submucosa and muscularis and, probably only in a proportion of cases, subsequent perforation and serositis.[22]

2.3.1 Aetiology

Although multiple possible aetiologies have been postulated, there is no consensus on the origin of acute appendicitis. Obstruction and infection were early recognised as important factors in experimental appendicitis models. Wangsteen and Bowers performed an early series of experiments in dogs, concluding that neither induced obstruction nor inoculated infection alone produced the inflammatory progress to acute appendicitis, which was seen after combining the two.[23] In Sweden, Arnbjörnsson and Bengmark found an association between increased intraluminal pressure and signs of obstruction at surgery for gangrenous appendicitis in children, not seen in phlegmonous appendicitis.[24] In a case-control study Arnbjörnsson also found reduced dietary fibre intake to be a risk factor for acute appendicitis.[25] A positive family history increases the risk for appendicitis three-fold,[26] but no specific predisposing gene has been identified. Several infectious agents have been associated with acute appendicitis; including viral, bacterial, fungal, and parasitic organisms, as extensively reviewed by Lamps.[27] Yet the causal relationship between these patogenes and appendicitis has not been described. Investigating the bacterial phylae of appendicitis cultures, the presence of *Fusobacterium species* correlated to disease severity and risk for perforation. There are numerous reports on acute appendicitis emerging after local blunt abdominal trauma, indicating a possible association in selected cases.[28,29] In the majority of cases, nevertheless, the aetiology of acute appendicitis remains unknown.

2.3.2 Epidemiology of appendicitis in general

The life-time risk of acute appendicitis has been estimated to 7–8% and appendicitis occurs somewhat more often in men than women.[30] Globally, acute appendicitis remains one of the major contributors to morbidity, mortality and burden of disease.[31] A strong relationship between age and incidence rate of acute appendicitis has been established, with a peak incidence found in adolescence; as reported from Sweden and England ages 10–14,[32,33] Norway ages 16–20,[34] and the USA ages 10–14 in boys, 14–19 in girls.[30]

In a paper published in the Journal of the Swedish Medical Society, Arnbjörnsson identified a steadily increasing incidence of acute appendicitis during the first half of the 20th century. The incidence decreased, markedly 1950–1965 with a less steep decrease 1965–1980.[35] The incidence of appendicitis of all grades, in both adults and children, in a local hospital in Norway decreased in the middle 20th century (1943–1972) as reported by Noer.[36] A falling incidence was also reported from the United States, with a 15% reduction from 1970 to 1984 with a crude incidence rate of 110 cases per 100 000 person-years 1979–1984.[30] Also from the United Stated, Livingston reported a J-shaped trend with declining incidence of non-perforated appendicitis 1970–1995 followed by an increased incidence rate 1995–2004. The incidence of perforated appendicitis increased over the study period.[37] From Leicester, England, Williams and co-workers reported a decreasing incidence rate from 184 to 117 per 100 000 person-years 1975–1994.[38] In another English study, Kang and co-workers reported declining admissions for acute appendicitis 1989–2000, from 80.9 to 68.8 per 100 000 person-years in men and 68.6 to 55.3 per 100 000 person-years in women.[33] From Canada the overall incidence rate of acute appendicitis was reported to decline by 5.1% from 78 to 74 cases per 100 000 person-years 1991–1998.[39] Notably, the absolute incidence of perforated appendicitis increased by 13% during the study period. In a Swedish national cohort, incidences were reported to be stable 1989–1993 for both perforated and non-perforated appendicitis (110 per 100 000 person-years) in a time of declining incidence of appendectomies.[40] Also from Stavanger, Norway, a stabilised incidence rate of overall acute appendicitis by 84 per 100 000 person-years was confined 1989–1998 in a histology-confirmed prospective study by Körner et al.[34] In opposition to the reduced rates cited, two recent American papers report increased incidence rates of acute appendicitis. Buckius et al reported increased hospitalisation rates for appendicitis from 76.2 to 93.8 cases per 100 000 person-years in the USA, 1993–1998,[41] and Jamie Anderson et al reported a 25% increase of acute appendicitis, from 100 to 120 cases per 100 000 person-years in California 1995–2009.[42]

2.3.3 Epidemiology of appendicitis in children

Appendicitis is more common in children, compared to adults, and both perforation and postoperative complications are more commonly occurring in children.[30] Most epidemiologic studies focus on adults, or do not restrict inclusion to specific ages. However, there are some studies exclusively including children.

Livingston et al found a u-shaped secular trend in incidence of acute appendicitis in children in the USA in a population-based study from 1979 to 2006. They reported an initial incidence rate exceeding 160 cases per 100 000 children and year in 1980, with a nadir approximating 80 cases per 100 000 children and year in 1995, and thereafter a slight increase was noted.[43] A Danish paediatric study based on the Danish National Patient Registry reported a markedly decreasing incidence of non-perforated appendicitis by 13–36% 1996–2004, whilst noting a 10% reduction in the incidence of perforated appendicitis.[44] In 2001 Aarabi et al reported an overall childhood appendicitis incidence rate of 94 per 100 000 person-years in New England.

The incidence rate declined by 9.7% 2000–2006, whilst the proportion of perforated appendicitis as well as the proportion of negative appendectomies decreased.[45]

In our institution, Kaiser et al investigated the incidence rates of overall acute appendicitis, perforated appendicitis and negative appendectomies in children during the introduction of ultrasonography (US) and computed tomography (CT) for appendicitis diagnostics, and found a stable overall incidence rates of 117–132 cases per 100 000 children and year 1991–2000, a stable perforation ratio, but a significantly reduced number of negative appendectomies.[46]

The aetiology of shifting incidences rates of acute appendicitis in adult and children has been poorly described and investigated. Dietary and social factors have been proposed and seasonal variations and cluster outbreaks of appendicitis further indicate that environmental factors and possibly infections can play a part.[47] The increased availability of surgery and modern anaesthesia during the first half of the 20th century are also likely to have influenced the number of patients having their appendicitis properly diagnosed and thus registered.[10] Importantly, reported incidence rates are based on the ratio of diagnosed (registered) cases per number of persons per time unit. Shifts in appendicitis diagnosis definitions or alterations in the threshold for appendectomy reducing the actual number of operated and thus registered appendicitis cases, may impose bias to reported incidence rates of appendicitis.

2.3.4 Natural course

Appendicitis was for long believed to be an inevitably progressive disease, sooner or later ending up in perforation.[48] This eventually led to the concept of early surgery in all cases of suspected appendicitis, to avoid perforation and associated complications, at the cost of accepting a high rate of negative appendectomies. However, based on more recent discoveries, arguments for other understandings of the disease have been raised.

In 1964, Howie presented a comparison of two groups of surgeons adopting different strategies, either expectant or more radical, to patients with signs of acute appendicitis. Although the results indicated that a more expectant strategy may increase the relative proportion of advanced disease, the more conservative surgeons performed 50% fewer negative appendectomies, meanwhile reducing the absolute number of complicated cases with 34%. This early insight strongly indicated that acute appendicitis may be self-limiting and that urgent surgery might not be needed in all cases of acute appendicitis.[49]

The Andersson group has published several papers on the subject of spontaneously resolving appendicitis. In an epidemiologic study on appendectomy for suspected appendicitis, the incidence rate of perforated appendicitis was, in contradiction to previous misbeliefs, independent of the total appendectomy rate.[50] In Andersson's own institution, adopting more expectant strategies to surgery for suspected appendicitis, there were lower incidence rates of non-perforated appendicitis and of negative appendectomies, compared to other Swedish hospitals.[51] In an attempt to better describe the natural course of acute appendicitis Andersson published a paper 2007 further stating that it is the denominator – the total number of appendectomies performed – that causes the proportion of perforations to differ between centers, rather than a difference in the absolute incidence rate of perforated appendicitis. He postulated a new, alternative theory of the natural course of acute appendicitis, where a minor proportion of appendicitis progress to perforation, whilst a significant proportion of non-perforated appendicitis seems to resolve spontaneously.[50] A disconnect between the incidences of non-perforated and perforated appendicitis was also described by Livingston et al 2007.[37]

Yet another study from the Andersson group found differences in the inflammatory response between patients operated for gangrenous and phlegmonous appendicitis, respectively.[52] This again supports a classification with differentiation between two distinct types of acute appendicitis: simple and possibly self-limiting appendicitis which does not progress to gangrene and perforation and complex appendicitis which rapidly progress to gangrene and perforation. This theory was also discussed by Bhangu et al in a recent review.[47]

2.3.5 Diagnosing appendicitis

The differentiation of appendicitis from other causes of abdominal pain was originally based on patient history and clinical examinations alone. Laboratory tests, radiologic investigations and scoring systems have been added to the toolbox, increasing the diagnostic accuracy and avoiding both negative and positive misdiagnosis, i.e. missed appendicitis and unnecessary negative appendectomies. Still, there is no gold standard for appendicitis diagnosis and for differentiating complex cases from simple appendicitis, without surgically removing the appendix.

Laboratory tests

White blood cells (WBC) are usually elevated in acute appendicitis. However, a positive test alone is a highly non-specific marker of inflammation, and the power to discriminate appendicitis from non-appendicitis is low.[53] Also C-reactive protein (CRP) is a poor discriminator of overall appendicitis, yielding better performance discriminating perforated appendicitis from non-perforated cases.[21,54] Wu et al found increasing discriminating power for CRP during the first three days from symptom onset.[55] Body temperature as a single test has poor diagnostic significance in acute appendicitis but repeated measures or serial examinations may increase the discriminatory power.[53] There are several studies on combinations of available laboratory markers; Shogilev et al reviewed them and concluded that outcome varied significantly depending on study design and methodology, selected marker combinations, cut-off levels, and study population, warranting better studies.[53]

In attempts to improve the diagnostic accuracy in acute appendicitis, novel biomarkers have been proposed. Interleukin-6 levels increase early in appendicitis and correlate to the degree of inflammation, but the test failed to improve the diagnostic precision in acute appendicitis.[53] Riboleukograms, in combination with cytokine profiles, were investigated in children by Muenzer et al in a small study with promising sensitivity and specificity, although the findings have to be repeated in larger studies.[56] Granulocyte colony stimulating factor was shown to discriminate appendicitis in children and to correlate to histopathology grading of appendicitis in a prospective small study by Allister et al.[57] Elevated Urine Leucine-Rich α-2-Glycoprotein in urine was highly predictive for acute appendicitis in children, analysed by an advanced and not commercially available laboratory technique. Disappointingly, using a commonly available test for clinical use, the power of the test did not remain.[58]

Imaging techniques

In 1981, Fish et al published the first paper on computed tomography (CT) in the diagnosis of appendiceal disorders,[59] and Baltazar et al described 38 cases of acute appendicitis diagnosed by CT in 1986.[60] The same year Puylaert published a series of investigations by ultrasonography (US) in 60 consecutive patients with suspected appendicitis, identifying 25 of 28 (89%) patients with surgically confirmed with appendicitis.[61] In our hospital, Kaiser et al prospectively randomised 600 children with suspected appendicitis to US alone or US+CT. Sensitivity and specificity was 86% and 95%, respectively, for US and 99% and 89%, respectively, for US+CT. It was recommended to use of US first, and add CT in equivocal cases.[62] In meta-analysis, CT had a higher sensitivity compared to US in diagnosing appendicitis in children and adults, albeit at the cost of potentially harmful radiation, particularly important in children.[63] Low-dose CT was shown to reduce radiation with comparable diagnostic performance compared to standard-dose CT in adults[64] and in young adults.[65] With increased availability, magnet resonance imaging (MRI) has become an interesting alternative to CT. Alone, MRI was comparable to US with conditional CT in discriminating perforated appendicitis.[66] Comparing a US+MRI-protocol to a US+CT-protocol, neither negative appendectomy rates nor perforation rates differed significantly,[67] demonstrating a potential and more readily accessible pathway for diagnosing appendicitis in children without ionising radiation. A recent meta-analysis concluded that MRI displayed excellent diagnostic performance and clinical outcome data in suspected appendicitis in children.[68]

An important aspect of the introduction of radiologic investigations in appendicitis diagnostics is that the new modalities may alter the probability of diagnosing mild appendicitis that under other circumstances would not have been diagnosed, and thus not been treated and registered as appendicitis cases. This sampling bias may increase or reduce the fraction of actual appendicitis cases ending up diagnosed and registered. Yet, there are no studies, except for the study by Kaiser from 2004[46] evaluating the impact of radiologic imaging pathways on the appendicitis incidence.

Scoring systems

In an attempt to increase the diagnostic accuracy in acute appendicitis Alvarado retrospectively analysed data from 305 patients presenting with suspected acute appendicitis. He isolated eight predictive factors and created a novel scoring system for the diagnosis of acute appendicitis.[69] There have been several attempts to validate the Alvarado score. Altogether, in meta-analysis, a low Alvarado score had an excellent sensitivity of ruling out appendicitis, in children and adults. However the specificity for "ruling in" appendicitis at higher scores was poor.[70] Further, later studies have failed to reproduce the high sensitivity presented in the meta-analysis above.[53] Samuel constructed a Paediatric Appendicitis Score (PAS) using eight variables selected by logistic regression of clinical and investigative parameters in acute appendicitis.[71] Andersson and Andersson combined data from a meta-analysis and a local Swedish cohort to form a new Appendicitis Inflammatory Response (AIR) Score, performing similar sensitivity and specificity compared to the Alvarado score while reducing the number of patients in the intermediate or equivocal group.[72] In comparison to a senior surgeon assessment, the Alvarado and AIR-scores performed similar discriminating capacities for overall appendicitis, whilst the AIR-score outperformed the Alvarado Score and the senior surgeon in positive predictive value and specificity.[73] In children the AIR-score proved to outperform the Alvaro and PAS scores in a recent retrospective study.[74]

Appendicitis scoring systems are still not widely used for appendicitis diagnosis. In common, they are created using data from the same local setting where they subsequently are validated, and their initially published accuracy has not been possible to reproduce when applied elsewhere. To date, the AIR-score has had the best reproducibility.[73,74] Further studies on generalisability and the use of scoring in combined clinical and radiologic pathways may increase the future clinical relevance and use of appendicitis scoring systems.

2.3.6 Classification

Appendicitis diagnosis can be based on clinical abdominal examination or radiologic investigations, the surgeon's intra-operative grading and histopathology. The clinical diagnosis may be administratively recorded in health care registers, most often according to the International Classification of Disease (ICD).

The histopathologic classification of acute appendicitis was described by Carr, in a comprehensive review of acute appendicitis.[22] Suppurative or phlegmonous appendicitis is characterised by transmural inflammation with neutrophilic infiltration of the mucosa, submucosa and muscularis propria, along with acutely inflamed and often ulcerated mucosa. Oedema, fibrinopurulent serositis and micro-abscesses of the appendix wall may be seen. In gangrenous appendicitis, transmural inflammation and infiltration of neutrophils is accompanied by necrosis of the appendix wall and extensive mucosal ulceration.

Classification of appendicitis in the clinical setting is not strictly defined. Ponsky et al performed a survey among American surgeons, asked to classify appendicitis by appearance on pictures, finding that there was a poor inter-surgeon agreement on the grade of acute appendicitis.[75] Bliss et al investigated the concordance between the surgeon's and the pathologist's classification of acute appendicitis and appendicitis subtypes finding a 90–93% concordance in overall determination of acute appendicitis, comparable between open and laparoscopic operations. Classifying complex appendicitis the concordance dropped to 38% for laparoscopic operations and 52% for open operations. A correct diagnosis of complex appendicitis was highly associated to longer hospital stay and increased risk for postoperative wound infection as compared to discordantly diagnosed cases, indicating that pathologist's report best correlates to outcome.[76] In a recent paper Correa et al investigated 69 appendectomies and found a weak correlation between surgeons' and pathologists' classification – however, without meaningful clinical implications.[77] Tind and Qvist investigated 131 appendectomies in adults identifying a 16–76% concordance between surgeon's and pathologist's classification. In this study both surgeons' and pathologists' classification had a low concordance to positive abdominal cultures, implicating that both classifications may have weaknesses.[78] St. Peter et al investigated the impact of a strict definition of perforated appendicitis stating "a hole in the appendix or a faecalith in the abdomen" on the rate of postoperative abscesses, finding that the strict definition was effective in identifying patients at risk of abscess formation, reimbursing the need for general and strict definitions of appendicitis grades.[79]

Administrative healthcare registers require diagnosis according to the International Classification of Disease (ICD) coding system. Several versions of ICD have been released. Appendicitis classification has differed somewhat over the years, creating possible bias in longitudinal studies. This was obvious as the most recent revision of the Swedish version of the ICD–10 included a modification of specific appendicitis diagnoses not well understood by surgeons, making detailed retrospective studies on appendicitis subtypes impracticable after 2010.[80] Therefore, in Studies II of this thesis, analyses on appendicitis subtypes were restricted to 1987–2009. Correspondingly, the full study cohort in Study III was restricted to 1987–2009.

2.3.7 Treatment options

Surgical treatment

Numerous studies and trials have compared laparoscopic to open surgery in appendicitis. In a meta-analysis by Aziz et al 2006,[81] comparing laparoscopic to open appendectomy, rates of postoperative complications were comparable, except for a reduced risk of wound infection after laparoscopic operation. In a 2010 Cochrane meta-analysis by Sauerland et al,[82] laparoscopic appendectomy in adults was associated with an increased risk of postoperative abdominal abscess and longer duration of surgery but the risk for wound infection, postoperative pain, prolonged hospital stay, and time to return to normal activities were all reduced. In the same study, similar effects were found in children. In a 2012 meta-analysis of 26 studies including 123 000 children, comparing laparoscopic to open appendectomy, laparoscopic operation was superior for all outcome measures, except for postoperative abscess rates, which were comparable. The authors strongly recommended the use of laparoscopy over open surgery for appendicitis.[83] Svensson et al reviewed the introduction of laparoscopic appendectomy in our own institution from 2007, with open appendectomies as reference, finding no significant differences in complication rates between open and laparoscopic appendectomy.[84]

Non-operative treatment

Non-operative treatment for acute appendicitis is not a novel concept. Coldrey treated 471 patients conservatively without appendectomy, with low mortality and morbidity, in 1959.[85] In the modern era Eriksson and Granström performed the first randomised controlled trial on antibiotic treatment vs surgery for acute appendicitis, finding non-operative treatment feasible but associated with a high risk of recurrence during first year.[13] Vons et al randomised adults with appendicitis to antibiotic treatment or surgery concluding that antibiotic treatment was inferior to appendectomy in non-complicated appendicitis.[86] In the 2011 Cochrane meta-analysis where the two trials above were included, conservative treatment was not superior to appendectomy and could not be recommended.[87] In children, Svensson et al performed the first pilot randomised controlled trial randomising 50 children to either antibiotic treatment or appendectomy, showing that antibiotic treatment was feasible.[14] Full-scale statistically powered randomised controlled trials are ongoing, and until otherwise stated appendectomy remains the standard treatment for acute appendicitis.

2.3.8 Surgical delay

The impact of delaying the curative operation with appendectomy in acute appendicitis has been debated. Most published studies were retrospective and did not deal with the selection bias (confounding by indication) introduced when patients with signs of complicated appendicitis on admission have shorter waiting time to surgery.

In children, several studies did not find an increased risk of perforation or complications associated with surgical delay.[88-91] However, the widely referred studies by Surana et al[88] and Yardeni et al[89] were not controlled for important bias. Nevertheless, they have been accepted as evidence for the safety of postponing acute appendectomy, as demonstrated in an audit of the members of the American Paediatric Surgical Association 2012.[92] In opposition, longer delays were associated with increased risk for perforation in children, as stated by Papandria et al 2013.[93] Bonadio et al[94] recently stated that children with delayed appendectomy had an increased risk of perforation, but the study population was highly selected and not well described, therefore the generalisability of the results is probably limited. In adults, several publications[95-100] indicate that at least short surgical delay does not increase the rate of perforated appendicitis. On the other hand, Ditillo et al[101] found an increased rate of perforation in adults with in-hospital delay, but analyses were not adjusted for selection bias. Also Busch et al[102] and Papandria et al[93] reported increased rates of perforation or postoperative complications associated to increased time to appendectomy in adults. Teixeira et al[95] performed a retrospective cohort study in adults finding no association between surgical delay and increased perforation rate, but an increased risk of surgical site infection with surgical delay. A British multicenter cohort study supplemented by a meta-analysis showed similar results in adults and found no increased risk for perforation with short surgical delay.[96]

2.3.9 Provision of care

Dependent of the availability and local arrangement of care, acute appendicitis in children may be treated in county hospitals or regional hospitals by general surgeons, or in specialised paediatric surgical units. The provision of care may affect outcome and results. Several studies report comparable outcomes comparing paediatric appendicitis management by general surgeons to paediatric surgeons. However, there is also evidence of benefits when children with appendicitis are treated in specialised paediatric surgical units.

From the United Stated several papers have been published on the impact of surgeon's speciality licence, the hospital's administrative level and the educational level of the attending surgeon (trainee or resident compared to consultant). Alexander et al reported comparable outcome for children with non-complicated appendicitis treated by either general surgeons or paediatric surgeons at the Cleveland Clinic Foundation. However, in children with perforated appendicitis treated by paediatric surgeons there was a significant reduction of postoperative complications, shorter postoperative length of stay, and reduced number of readmissions and reoperations, as compared to general surgeons' management.[103] Smink et al reported an increased ratio of negative appendectomies in centers performing low volumes of paediatric appendectomies.[104] Still, the hospital operative volume did not correlate to the ratio of perforated appendicitis.[105] In retrospective reviews from California, USA, Emil and Taylor found that a higher proportion of younger children were treated by paediatric surgeons, but restricted for appendicitis grade the outcome did not differ between children treated by paediatric surgeons compared to general surgeons.[106] Lee et al found no differences in postoperative morbidity between a teaching institution involving residents in appendectomies compared to an institution where only consultants attended. Yet, for children with simple appendicitis, the postoperative length of stay was shorter in the teaching institution.[107] In a subsequent paper investigating the impact of patient age, the risk for perforated appendicitis was higher in younger children, but there was a higher risk for abscess drainage in older children, in adjusted analysis.[108]

Collins et al compared appendicitis outcome for children in the UK managed at a district general hospital to outcomes from a regional paediatric surgical unit, concluding that children treated at the latter, using a strict pathway for care, had a lower risk of postoperative complications and readmissions.[109] Tiboni et al also compared appendectomies in children in paediatric surgical units and general surgical units in a UK multicenter observational study finding an increased ratio of negative appendectomies in the general surgical unit, but no difference in complication rate.[110] Mizrahi et al retrospectively compared two campuses where paediatric appendectomies were performed either by paediatric surgeons or general surgery residents, respectively, finding no significant differences in outcome.[111]

This topic was not previously addressed in children in Sweden. However, significantly diverting incidences of overall appendicitis, appendicitis subgroups and negative appendectomies between general hospitals in Sweden was suggested to result from diverging strategies in acute appendicitis management.[51]

3 AIMS OF THE THESIS

The overall aim of the thesis was to increase the knowledge on the epidemiology of childhood appendicitis.

Specific objectives for the conducted studies were:

- To investigate the correlation between time to appendectomy and the risk for perforated appendicitis and postoperative surgical complications.
- To determine and present population-based incidence rates of acute appendicitis, appendicitis subtypes and appendectomies in Swedish children.
- To identify and analyse incidence rate trends, and to compare acute appendicitis epidemiology between Swedish health care regions.
- To investigate the impact of provision of care on the outcome after appendectomy in children, with special focus on the hospital administrative level and the hospital annual caseload of paediatric appendectomies.

4 PATIENTS AND METHODS

4.1 DATA COLLECTION

Data for the studies included in this thesis were collected from two existing databases: the Swedish National Patient Register and a local audit database at the Department of Paediatric Surgery at Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm Sweden. The comprehensive and detailed data from these databases permit retrospective cohort studies on acute appendicitis in children on a national and regional basis.

Since 1947, all Swedish residents are assigned a unique personal identification number, consisting of the six-digit birth-date (yy-mm-dd) combined with a four digit, sex-specific number.[112] The personal identification number allows for exact patient identification in health care registers and linkage of data between different health care registers.[113]

Official Swedish demographic statistics is provided by Statistics Sweden, a governmental organisation responsible for coordinating Swedish official statistics. Demographic data including national and regional population numbers with age- and gender distributions[114] were retrieved for adjusting analyses in Study II.

Results were reported in conjunction with the STROBE guidelines.[115]

4.1.1 Swedish national health care registers

The National Board of Health and Welfare has collected data on patients admitted to hospital since 1964. From 1987 all patients admitted to hospital in Sweden are registered. The National Patient Register (NPR)[116] contains patient data, hospital data, geographical data, administrative data and medical data. Registrations are identified by the personal identification number. Each admission to hospital corresponds to a separate recording in the register. Discharge diagnoses registered in the NPR are coded according to the Swedish version of the International Classification of Disease (ICD-SE), and reported from hospitals according to discharge notes. It was not specified to what degree registrations were based on clinical or histopathologic diagnoses. In review, NPR data has been shown to be highly valid, with an overall predictive value of 85–95%.[117]

The Swedish Cause of Death Register,[118] administered by the National Board of Health and Welfare, has recorded causes of death for Swedish residents from 1952. Complete data with causes of death registered according to the international version of the ICD are available from 1962 to present.

Data on all children 0–14 years of age with a diagnosis of appendicitis and/or appendectomy 1987–2013 were retrieved from the National Patient Register and used in Study II and III. Additional linked data from the Swedish Cause of Death Register was used in Study III. Patient identification and linkage between registers was made by the personal identification number.

4.1.2 Local audit database

At Astrid Lindgren Children's Hospital, Karolinska University Hospital, 350–400 children are annually diagnosed with acute appendicitis. There is a local audit database containing prospectively collected data on all children consecutively diagnosed from 2006 to present, virtually corresponding to all children diagnosed in Stockholm County, Sweden, during that time. Data includes patient characteristics, administrative in-hospital data and detailed pre-, per-, and postoperative clinical data. Data on symptom duration prior to hospital admission were not registered in the database. Data retrieved from the local data base were used in Study I.

4.2 STUDY I

This was a retrospective cohort study on the correlation between surgical delay and the risk for perforated appendicitis and secondary postoperative complications. Data on all children having had an appendectomy for acute appendicitis at our institution 2006–2013 were retrieved from the local audit database. The main explanatory variable was in-hospital surgical delay, defined as time from admission to the emergency department to the time of incision for appendectomy. Appendectomy within 12 hours from admission was set as reference; surgical delay was considered for patients having the appendectomy later than 12 hours from admission to the emergency department. The primary outcome measure was histopathologic diagnosis of perforated appendicitis according to Carr.[22] Secondary outcomes included postoperative wound infection, postoperative intra-abdominal abscess, reoperation, postoperative length of hospital stay and readmission within 30 days of appendectomy.

A univariate assessment of the impact of time to surgery on the primary and secondary outcomes was performed. To adjust for selection bias, in this case confounding by indication; i.e. patients with more severe symptoms or suspected perforated appendicitis being prone for selection to emergent operation, a multiple logistic regression model was created to estimate the odds ratios for the main outcome measures. Regression analyses were adjusted for patient age, sex and available markers disease severity on admission. To account for incongruences between histopathologic grading and surgeon's intraoperative grading of appendicitis severity, and to increase the generalisability of the results, a sensitivity analysis was performed. A revised primary outcome measure "complex appendicitis" was defined, comprising the surgeon's recognition of perforated appendicitis and/or histopathologic perforation.

Missing data were replaced using multiple imputation.[119] 27% of patients had missing data in one or more variables used for adjusting regression analyses. Possible reasons for missing data were reviewed and analysed. No systematic explanation for absent values was found with respect to the main explanatory variable; hence the missing at random assumption was plausible. A total of 10 multiple imputated datasets were produced, using Amelia II.[120]

Analyses of imputated datasets and combination results were performed in R statistical software[121] with Zeilig software.[122]

4.3 STUDY II

This was a retrospective population-based cohort study on the incidence rates and trends of acute appendicitis and appendectomy in Swedish children. The NPR was queried for all children diagnosed with acute appendicitis and/or appendectomy 1987–2013. Population statistics, including annual population-base with age- and sex-distributions, were retrieved from Statistics Sweden.

Definitions of acute appendicitis and appendicitis subtypes were based on discharge diagnoses in the NPR, according to the ICD-9 and ICD-10 classifications. Negative appendectomy was defined by the combination of appendectomy without appendicitis diagnosis, accompanied by one of several diagnoses that could mimic acute appendicitis, indicating that appendectomy was performed for suspected appendicitis. Incidental appendectomies were excluded. Non-operatively treated appendicitis was included in descriptive analyses but excluded from further analyses due to the poor definitions of this group.

Population-based crude incidence rates of diagnosed and operated appendicitis, appendicitis subtypes and negative appendectomies were calculated and presented. Incidence rates were computed for age subgroups and by sex. Incidence rates restricted to the six health care regions of Sweden were also analysed and presented. A Poisson regression model was created to estimate incidence rate trends. Time (year of event) was set as explanatory variable, 100 000 person-years was used as offset variable. The operative method (laparoscopic or open appendectomy) was introduced to the model to account for possible bias imposed on incidence rates and trends. Overall analyses were age (categorised) and sex adjusted as appropriate. Differences in incidence rate trends between age groups, genders and health care regions were estimated by adding these variables to the model, testing for interaction by time. The incidence rate 2009 or 2013, dependent on data availability, was used as reference. Comparing regional incidence rate trends, the Stockholm region was set as reference. Estimated incidence rate trends were presented graphically.

4.4 STUDY III

The aim of this population-based cohort study was to investigate the correlation between provision of care and the outcome after appendectomy in children. The study included all children less than 15 years in Sweden who underwent appendectomy for suspected appendicitis 1987–2009. Patient characteristics, hospital administrative data, and data on postoperative morbidity were collected from the National Patient Register. Data on mortality within the cohort was collected from the Swedish Cause of Death Register. Appendectomy, acute appendicitis, and appendicitis subtypes were defined by operative diagnosis and discharge diagnoses according to the Swedish versions of the ICD-9 and ICD-10 classifications. Incidental appendectomies and non-operatively treated appendicitis were excluded from this study.

Two explanatory variables were investigated: 1) the hospital's administrative level and 2) the annual hospital caseload of paediatric appendectomies. Three hospital administrative levels were defined: specialised paediatric surgical centers, central general hospitals and general hospitals. The annual caseload of paediatric appendectomies was computed for all Swedish hospitals for each year of the study period. Primary endpoints were postoperative morbidity, including reoperations or readmissions to hospital within 30 days of appendectomy and postoperative length of stay. Mortality within 90 days of appendectomy was also registered.

Patient characteristics and unadjusted distribution of exposures and outcomes were presented. A multivariable logistic regression model, adjusting for age (grouped) and appendicitis subtype was created to analyse the correlation between each exposure and the outcome measures reoperation and readmission. For postoperative length of stay, a negative binomial regression model, accounting for the widely dispersed data, was used. Subgroup analyses restricted for age (categorised) and appendicitis subtype were performed. Mortality was, due to the low numbers, not further analysed. Results were presented as estimated odds ratios with 95% confidence intervals; p-values of less than 0.05 were considered statistically significant.

4.5 STATISTICAL AND ANALYTHICAL METHODS

Descriptive statistics were used to summarise observations and to describe the characteristics of the study cohorts. Univariate analyses were used to assess the distribution of demographics, clinical characteristics and outcome measures amongst exposures and outcomes. Regression models were used to estimate adjusted outcome measures for the exposures of interest. In the following section, the statistical methods used for the studies of this thesis are presented.[123,124]

Fisher's exact test was used to test statistical significance comparing smaller groups of categorical data. The test assumes that the individual observations are independent. It is valid for all sample sizes, but as a consequence of the exact nature of the probability calculation Fisher's exact test is best used for small sample sizes.

Pearson's chi-square test (x^2-test) was another test used for statistical hypothesis testing, comparing categorical data. The test was used to determine whether there were significant differences between the expected frequencies and the observed frequencies in one or several categories. The test assumes independent data. As the chi-square test is an approximate test it is not preferred in analyses of small data samples, but better used with large samples where exact tests were not appropriate.

One-way ANOVA is a parametric test for comparing samples containing continuous variables and requires the assumption of normally distributed data. Analysis of Variance (ANOVA) tests compare the variable means of groups of data. If non-normally distributed data can be transformed to a normal distribution, the test may be used, otherwise other tests must be considered.

Mann-Whitney U test (Wilcoxon rank-sum test) is used to compare the variable distribution of two samples containing continuous or ordinal data. The test is non-parametric and does not assume a specific distribution of data. It is often used in medical science trials to compare the outcomes of two different exposures.

Kruskal-Wallis test is another non-parametric test, used for comparing more than two samples with non-normally distributed (skewed) continuous data. However, the test assumes equally distributed data in compared groups. The result indicates if one group is stochastically dominant to one other group amongst tested groups.

Logistic regression models are used to estimate the probability of a binary outcome based on one or several exposures. The predicted probability of a certain outcome is expressed in the form of an odds ratio (OR). Multiple, or multivariable, logistic regression models estimates the impact of multiple exposure variables on the outcome. Covariates may be added to the model to adjust or account for confounding. To describe the statistical precision, confidence intervals of the odds ratio are calculated. *Odds* must be differentiated from *risk* but in rare outcomes, the *odds ratio* may approximatively correspond to the *risk ratio*. In this thesis logistic regression models were used to estimate the correlations between exposures and outcomes in Study I and Study III.

Poisson regression models are generalised linear models used for count data, assuming the specific Poisson distribution of data. One essential assumption of the Poisson distribution is that the sample mean is equal to the variance. Poisson regression was used in Study II.

Negative binomial regression models are generalisations of the Poisson regression model, often used when overdispersed data is encountered and the Poisson regression model assumptions are not met. Negative binomial regression was used for analysing postoperative length of stay data in Study III, due to the largely dispersed data.

Multiple imputation is a statistical method used to account for missing data. A separate logistic regression model, the multiple imputation model, is created. The model includes co-variables that are statistically associated with the variable that is missing data. By sampling from the model, plausible values for the missing data variable are created, to generate a complete data set. The process is repeated to make multiple imputated datasets, preserving the within and between dataset uncertainty of the imputated values. The statistical analysis of interest is performed separately on the imputated datasets and the resulting multiple estimates are merged to a final multiple imputated estimate, including the variability and uncertainty of included original and imputated data. Multiple imputation was used in Study I.

5 ETHICAL CONSIDERATIONS

In medical research, any potential harm to study participants must be balanced against potential future benefit to patients and to the scientific community. Data for the studies in this thesis were retrieved from two existing patient registers, containing detailed personal and medical data. During computing and statistical analyses, all retrieved data were pseudonymised, and no individual patient was identified or contacted during the studies. Therefore, no consent was retrieved from study participants. In large register based epidemiologic studies the potential harm to individual study objects may be considered negligible.

The studies were approved by the regional Ethics Review Board in Stockholm (ref no 2014/1018-31/4). All research was conducted in accordance with the *Ethical Principles for Medical Research Involving Human Subjects* of the Declaration of Helsinki.[125]

6 RESULTS

6.1 STUDY I. SURGICAL DELAY IN ACUTE APPENDICITIS IN CHILDREN

The local database included 2 888 children having had an appendectomy for suspected appendicitis 2006–2013. 2 864 (99.2%) had a histopathologic diagnosis; of those 108 (3.8%) had a negative appendectomy. 2 756 patients had a histopathologic diagnosis of acute appendicitis and were included in the statistical analysis; 2 095 were non-perforated appendicitis and 661 were perforated appendicitis.

The characteristics of the cohort and missing data are summarised in table 1 and table 2. Lower age, female gender, night-time surgery, higher body temperature, higher CRP and higher WBC at admission were all associated to the finding of histopathologic perforation (table 1).

Table 1. Demographics and Clinical Characteristics of the Cohort by Histopathology

		Non-perforated n=2095	Perforated n=661	Total n=2756	*p*
Age, n(%)	<5 years	78 (3.7%)	107 (16.2%)	185 (6.7%)	
	5-10 years	628 (30.0%)	216 (32.7%)	844 (30.6%)	<0.001†
	10-15 years	1389 (66.3%)	338 (51.1%)	1727 (62.7%)	
Sex, n(%)	boy	1277 (61.1%)	364 (55.1%)	1641 (59.5%)	0.007†
	girl	818 (39.0%)	297 (44.9%)	1115 (40.5%)	
Body temperature, n(%)	<37.5°C	1136 (54.2%)	167 (25.3%)	1303 (47.3%)	<0.001†
	≥37.5°C	933 (44.5%)	486 (73.5%)	1419 (51.5%)	
	missing	26 (1.2%)	8 (1.2%)	34 (1.2%)	
CRP (mg/L), median (IQR)		19 (8, 43)	82 (38, 149)	27 (9, 66)	<0.001‡
	missing	165 (7.9%)	42 (6.4%)	207 (7.5%)	
WBC (10^9/L), mean ±SD		14.3 ± 4.8	17.1 ± 5.6	15.0 ± 5.1	<0.001‡
	missing	486 (23.2%)	114 (17.2%)	600 (21.8%)	
Time of operation, n(%)	00-08	392 (18.7%)	149 (22.5%)	541 (19.6%)	
	08-16	666 (31.8%)	175 (26.5%)	841 (30.5%)	0.013†
	16-24	1037 (49.5%)	337 (51.0%)	1374 (49.9%)	
Time to surgery, n(%)	<12 hours	798 (38.1%)	305 (46.1%)	1103 (40.0%)	
	12-24 hours	899 (42.9%)	268 (40.5%)	1167 (42.3%)	<0.001†
	24-36 hours	305 (14.6%)	66 (10.0%)	371 (13.5%)	
	>36 hours	93 (4.4%)	22 (3.3%)	115 (4.2%)	
Type of operation, n(%)	laparoscopic	1565 (74.7%)	493 (74.6%)	2058 (74.7%)	0.959†
	open	530 (25.3%)	168 (25.4%)	698 (25.3%)	
Operating time (min), median (IQR)		46 (33, 61)	57 (43, 76)	48 (35, 65)	<0.001‡
Wound infection, n(%)		37 (1.8%)	17 (2.6%)	54 (2.0%)	0.199†
Postoperative abscess, n(%)		30 (1.4%)	88 (13.3%)	118 (4.3%)	<0.001†
Reoperation, n(%)		10 (0.5%)	13 (2.0%)	23 (0.8%)	<0.001†
Length of Hospital Stay (hours), median (IQR)		37.4 (23.4, 56.1)	115.1 (87.8, 158.9)	43.3 (25.9, 90.3)	<0.001‡
Readmission, n(%)		45 (2.1%)	67 (10.1%)	112 (4.1%)	<0.001†

Normally distributed data are presented as mean (± standard deviation, SD), skewed data presented as median (interquartile range, IQR). CRP = C-reactive protein. WBC = white blood cell count.
† Fisher exact test. ‡ Non-parametric Mann-Whitney U-test.

Children with surgical delay were more likely to be older, to have a daytime operation, lower body temperature, lower CRP and lower WBC. Analysing crude data, children with surgical delay were less likely to have perforated appendicitis (table 2).

Table 2. Demographics and Clinical Characteristics of the Cohort by Surgical Delay							
		0-12h	**12-24h**	**24-36h**	**36h+**	**Total**	
		n=1103	n=1167	n=371	n=115	n=2756	*p*
Age, n(%)	<5 years	90 (8.2%)	70 (6.0%)	18 (4.9%)	7 (6.1%)	185 (6.7%)	
	5-10 years	359 (32.5%)	350 (30.0%)	102 (27.5%)	33 (28.7%)	844 (30.6%)	0.089†
	10-15 years	654 (59.3%)	747 (64.0%)	251 (67.7%)	75 (65.2%)	1727 (62.7%)	
Sex, n(%)	boy	652 (59.1%)	687 (58.9%)	229 (61.7%)	73 (63.5%)	1641 (59.5%)	0.626†
	girl	451 (40.9%)	480 (41.1%)	142 (38.3%)	42 (36.5%)	1115 (40.5%)	
Body temperature, n(%)	<37.5°C	466 (42.2%)	575 (49.3%)	199 (53.6%)	63 (54.8%)	1303 (47.3%)	<0.001†
	≥37.5°C	619 (56.1%)	578 (49.5%)	171 (46.1%)	51 (44.3%)	1419 (51.5%)	
	missing	18 (1.6%)	14 (1.2%)	1 (0.3%)	1 (0.9%)	34 (1.2%)	
CRP (mg/L), median (IQR)		33 (12, 82)	23 (8, 58)%	21 (8, 53)	18 (8, 59)	27 (9, 66)	<0.001‡
	missing	115 (10.4%)	62 (5.3%)	24 (6.5%)	6 (5.2%)	207 (7.5%)	
WBC (10^9/L), mean ±SD		15.6±5.3	14.8±5.1	14.4±4.8	13.3±5.0	15.0±5.1	<0.001‡
	missing	270 (24.5%)	235 (20.1%)	76 (20.5%)	19 (16.5%)	600 (21.8%)	
Time of operation, n(%)	00-08	250 (22.7%)	222 (19.0%)	52 (14.0%)	17 (14.8%)	541 (19.6%)	
	08-16	131 (11.9%)	597 (51.2%)	83 (22.4%)	30 (26.1%)	841 (30.5%)	0.010†
	16-24	722 (65.5%)	348 (29.8%)	236 (63.6%)	68 (59.1%)	1374 (49.9%)	
Type of operation, n(%)	laparoscopic	790 (71.6%)	872 (74.7%)	301 (81.1%)	95 (82.6%)	2058 (74.7%)	<0.001†
	open	313 (28.4%)	295 (25.3%)	70 (18.9%)	20 (17.4%)	698 (25.3%)	
Operating time (min), median (IQR)		46 (34, 62)	50 (36, 67)	50 (37, 69)	45 (38, 61)	48 (35, 65)	<0.005‡
Histopathology, n(%)	non-perforated	798 (72.3%)	899 (77.0%)	305 (82.2%)	93 (80.9%)	2095 (76.0%)	<0.001†
	perforated	305 (27.7%)	268 (23.0%)	66 (17.8%)	22 (19.1%)	661 (24.0%)	
Wound infection, n(%)		23 (2.1%)	19 (1.6%)	9 (2.4%)	3 (2.6%)	54 (2.0%)	0.600†
Postoperative abscess, n(%)		65 (5.9%)	40 (3.4%)	12 (3.2%)	1 (0.9%)	118 (4.3%)	0.004†
Reoperation, n(%)		9 (0.8%)	10 (0.9%)	2 (0.5%)	2 (1.7%)	23 (0.8%)	0.574†
Length of Hospital Stay (h), median (IQR)		46.9 (29.7, 104.8)	43.8 (26.1, 89.2)	39.4 (22.5, 69.2)	38.7 (25.2, 63.3)	43.4 (25.9, 90.3)	<0.001‡
Readmission, n(%)		56 (5.1%)	38 (3.3%)	13 (3.5%)	5 (4.3%)	112 (4.1%)	0.157†

Normally distributed data are presented as mean (± standard deviation, SD), skewed data are presented as median (interquartile range, IQR).
† Fisher's exact test. ‡ Non-parametric Kruskal-Wallis test. CRP = C-reactive protein. WBC = white blood cell count. h = hours.

6.1.1 The risk of perforated appendicitis

In multivariate logistic regression analysis there was no association between surgical delay and the finding of perforated appendicitis at appendectomy (table 3). Sensitivity analyses with non-imputated data did not change the direction or significance of the results. The revised primary outcome measure “complex appendicitis”, including the surgeon’s perception of perforated appendicitis, yielded a cohort of 2 888 of whom 109 had a negative appendectomy. Hence, 2 779 children had an appendectomy for confirmed appendicitis; 846 (30.4%) were complex appendicitis and 1 933 (69.6%) were noncomplex appendicitis. In multivariable regression analysis, results did not differ from the primary analysis; there was no correlation between surgical delay and the operative finding of complex appendicitis. Nor in subgroup analysis of children aged less than five years, there were any associations between surgical delay and the risk for perforated appendicitis.

6.1.2 The risk of postoperative complications

In multivariable logistic regression analysis, adjusted for histopathology, there was no correlation between surgical delay and the secondary outcome measures wound infection, postoperative intra-abdominal abscess, reoperation or readmission. A significant association between moderate surgical delay (24 to 36-hour) and shorter hospital stay was identified, but that was not noted in the 12 to 24-hour or >36-hour surgical delay groups (table 3).

Table 3. Unadjusted and Adjusted Regression Models of the Main and Secondary Outcomes

		Unadjusted model		Adjusted model	
Delay to Operation		**OR***	***p***	**OR***	***p***
Histopathologic perforation†	< 12h	*reference*		*reference*	
	12-24h	0.78 (0.64, 0.94)	0.009	1.09 (0.87, 1.36)	0.453
	24-36h	0.56 (0.43, 0.76)	<0.001	0.79 (0.56, 1.11)	0.174
	>36h	0.62 (0.38, 0.99)	0.049	1.04 (0.60, 1.80)	0.885
Wound infection ‡	< 12h	*reference*		*reference*	
	12-24h	0.78 (0.42, 1.44)	0.421	0.69 (0.35, 1.36)	0.281
	24-36h	1.17 (0.54, 2.56)	0.689	1.08 (0.49, 2.38)	0.856
	>36h	1.27 (0.38, 4.30)	0.700	1.08 (0.32, 3.72)	0.899
Postoperative abscess ‡	< 12h	*reference*		*reference*	
	12-24h	0.57 (0.38, 0.85)	0.006	0.76 (0.48, 1.20)	0.239
	24-36h	0.53 (0.28, 0.99)	0.046	0.80 (0.41, 1.57)	0.522
	>36h	0.14 (0.02, 1.01)	0.052	0.20 (0.03, 1.51)	0.119
Reoperation‡	< 12h	*reference*		*reference*	
	12-24h	1.05 (0.43, 2.60)	0.914	1.13 (0.41, 3.16)	0.810
	24-36h	0.66 (0.14, 3.08)	0.406	0.79 (0.17, 3.74)	0.767
	>36h	2.17 (0.46, 10.19)	0.325	2.65 (0.55, 12.90)	0.227
Readmission‡	< 12h	*reference*		*reference*	
	12-24h	0.66 (0.44, 1.01)	0.053	0.79 (0.49, 1.26)	0.314
	24-36h	0.68 (0.37, 1.26)	0.223	0.87 (0.46, 1.65)	0.673
	>36h	0.86 (0.34, 2.19)	0.750	1.09 (0.41, 2.85)	0.869
		estimate#	***p***	**estimate#**	***p***
Log Postoperative Length of Hospital Stay (hours)‡					
	< 12h	*reference*		*reference*	
	12-24h	-0.106 (-0.17, -0.04)	0.001	-0.035 (-0.09, 0.02)	0.204
	24-36h	-0.280 (-0.37, -0.19)	<0.001	-0.120 (-0.19, -0.05)	0.001
	>36h	-0.256 (-0.41, -0.10)	0.001	-0.099 (-0.21, 0.02)	0.091

*Odds Ratios (95% confidence interval, CI). # Estimate for log[Postop. Length of Hospital Stay] (95% CI).

† Adjusted for Age, Sex, Body Temperature, c-reactive protein (CRP) and White blood cell count (WBC).

‡ Adjusted for Histopathology, Age, Sex, Time of operation, Body Temperature, CRP and WBC

6.2 STUDY II. INCIDENCE RATES AND TRENDS OF ACUTE APPENDICITIS

The demographics and clinical characteristics of the cohort are presented in table 4. 64 971 children registered in the NPR were eligible for the study, according to the inclusion criteria. 56 774 had an appendicitis diagnosis, 3 296 of whom were treated non-operatively. The incidence rate trend for this heterogeneous group was stable over the study period. Appendectomy was performed in 61 675 children 1987–2013: 53 478 (86.7%) had appendicitis, 8 197 (13.3%) had a negative appendectomy. Restricted to 1987–2009, when appendicitis subtype classification in the NPR were reliable, 9 790 (20.5%) had perforated appendicitis and 37 887 (79.5%) had non-perforated appendicitis.

Table 4. Study II: Demographics and Clinical Characteristics of the Cohort

	All Appendectomies 1987-2013			Appendectomy w. Appendicitis 1987-2009		
	Appendicitis all grades	Negative appendectomy	Total	Non-perforated appendicitis	Perforated appendicitis	Total
	n=53 478	n=8 197	n=61 675	n=37 887	n=9 790	n=47 677
Gender, n(%)						
boys	30 570 (89·9%)	3 449 (10·1%)	34 019	21 816 (80·5%)	5 285 (19·5%)	27 101
girls	22 908 (82·8%)	4 748 (17·2%)	27 656	16 071 (78·1%)	4 505 (21·9%)	20 576
Age (years), mean ±SD	10·8 ±2·9	10·3 ±3·1	10·7 ±2·9	11·1 ±2·7	9·9 ±3·5	10·8 ±2·9
Age (categorized), n(%)						
0-5 years	2 566 (81·4%)	585 (18·6%)	3 151	1 019 (46·7%)	1 161 (53·3%)	2 180
5-10 years	15 966 (85·5%)	2 701 (14·5%)	18 667	10 912 (76·8%)	3 300 (23·2%)	14 212
10-15 years	34 946 (87·7%)	4 911 (12·3%)	39 857	25 956 (83·0%)	5 329 (17·0%)	31 285
Type of surgery, n(%)						
Laparoscopic	5 137 (95·3%)	252 (4·7%)	5 389	2 097 (82·6%)	441 (17·4%)	2 538
Open	48 341 (85·9%)	7 945 (14·1%)	56 286	35 790 (79·3%)	9 349 (20·7%)	45 139
Health care region, n(%)						
Northern	5 569 (85·2%)	964 (14·8%)	6 533	4 065 (79·7%)	1 035 (20·3%)	5 100
Stockholm	10 245 (91·1%)	997 (8·9%)	11 242	6 514 (74·7%)	2 203 (25·3%)	8 717
South-Eastern	5 884 (84·6%)	1 073 (15·4%)	6 957	4 268 (79·6%)	1 095 (20·4%)	5 363
Southern	8 334 (85·7%)	1 387 (14·3%)	9 721	6 012 (80·7%)	1 435 (19·3%)	7 447
Uppsala/Örebro	12 225 (86·0%)	1 996 (14·0%)	14 221	8 946 (80·8%)	2 122 (19·2%)	11 068
Western	11 221 (86·3%)	1 780 (13·7%)	13 001	8 082 (81%)	1 900 (19·0%)	9 982
Year of treatment, n(%)						
1987-1989	7 198 (77·9%)	2 045 (22·1%)	9 243	5 961 (82·8%)	1 237 (17·2%)	7 198
1990-1994	10 708 (81·1%)	2 498 (18·9%)	13 206	8 661 (80·9%)	2 047 (19·1%)	10 708
1995-1999	11 298 (87·6%)	1 592 (12·4%)	12 890	8 890 (78·7%)	2 408 (21·3%)	11 298
2000-2004	10 688 (90·5%)	1 121 (9·5%)	11 809	8 336 (78·0%)	2 352 (22·0%)	10 688
2005-2009	7 785 (92·8%)	607 (7·2%)	8 392	6 039 (77·6%)	1 746 (22·4%)	7 785
2010-2013	5 801 (94·6%)	334 (5·4%)	6 135	*n/a†*	*n/a†*	5 801

Data presented as number of patients (n) and row percentages (%). Age was presented as mean ±standard deviation (SD).

† Data on subclassification into non-perforated and perforated appendicitis in the NPR was not valid from 2010. n/a=not available

6.2.1 Incidence rate of appendicitis in Swedish children

The overall incidence rate of appendicitis in Swedish children declined by 43.7% over the 26 years study period, from 177.7 to 100.1 per 100 000 person-years, 1987–2013 (figure 1). The largest reduction was for non-perforated appendicitis with a 50.6% reduction, from 138.5 to

68.4 per 100 000 person-years 1987–2009. For perforated appendicitis there was a 28.9% reduction from 28.0 to 19.9 per 100 000 person-years 1987–2009 (figure 1). Analysed in the Poisson regression model, adjusted for age, sex and operative method, estimated incidence rates of overall appendicitis and appendicitis subtypes were significantly reduced. Estimated incidence rates of non-perforated and perforated appendicitis differed significantly, indicating different epidemiologic features of the two (figure 2).

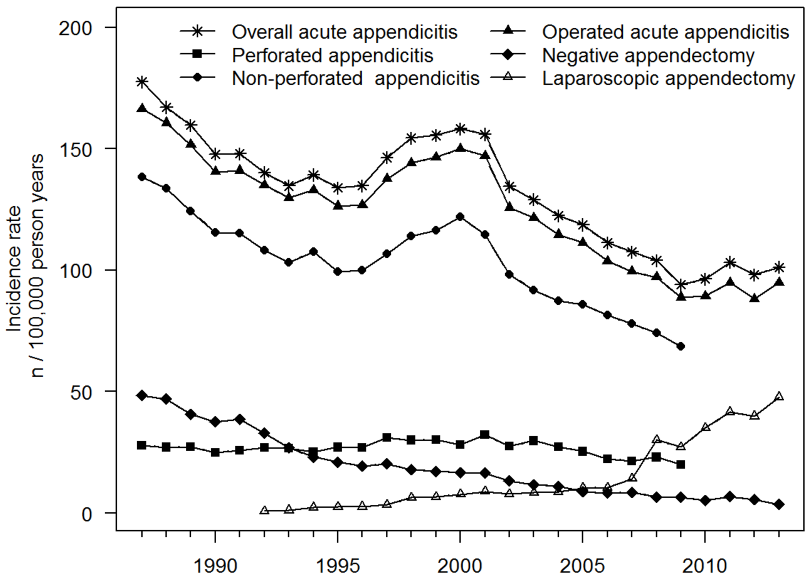

Figure 1. Incidence rates for appendicitis and appendectomies in Swedish children 1987–2013 (number of cases per 100 000 person-years). For subgroups non-perforated and perforated appendicitis data were not available after 2009.

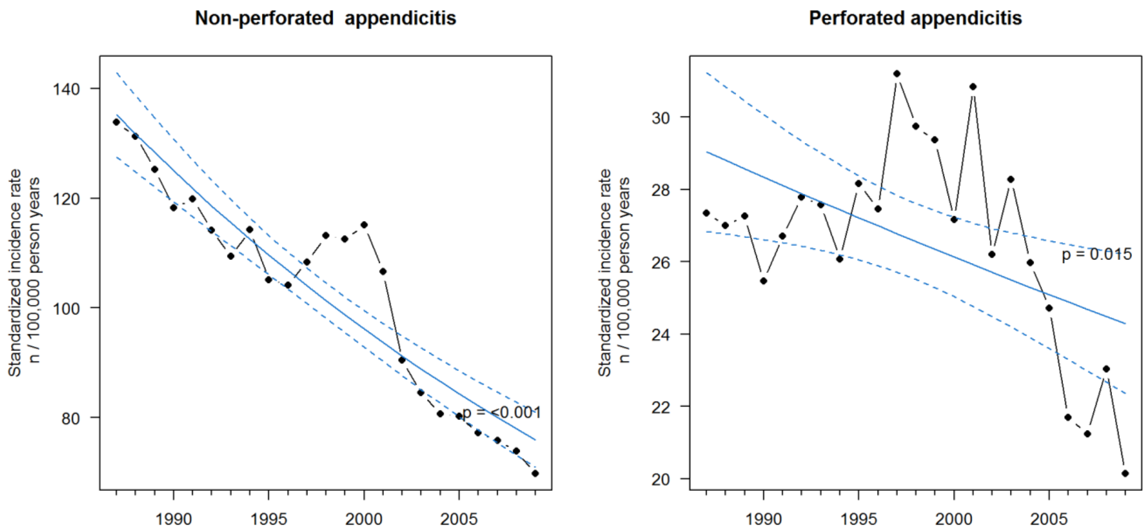

Figure 2. Incidence rates and estimated trends with 95% confidence intervals for nor-perforated and perforated appendicitis. Trends were significantly different from no change over time (p<0.001, p=0.015), respectively.

6.2.2 Subgroup analyses of incidence rates and trends

Age

Over the study period, incidence rates of acute appendicitis and appendicitis subtypes were significantly reduced in all age subgroups. For non-perforated appendicitis, the magnitude of the estimated reduction correlated positively with patient age, with a more pronounced reduction in older children. A similar non-significant correlation was found between perforated appendicitis and age.

Sex

Absolute incidence rates of acute appendicitis were reduced for both boys ($p<0.001$) and girls ($p<0.001$) during the study period. There was a more pronounced reduction in girls, resulting in an increased difference between sexes over time. In 2013 there was a 30% lower estimated incidence rate of acute appendicitis in girls compared to boys in Sweden ($p<0.001$) (figure 3a).

Negative appendectomy

The incidence rate of negative appendectomies fell by 92.6%, from 48.5 to 3.6 per 100 000 person-years 1987–2013. The reduction was significant for both girls ($p<0.001$) and boys ($p<0.001$). In 1987 the incidence rate of negative appendectomies was two times higher in girls compared to boys. A significantly larger reduction of negative appendectomies in girls resulted in similar absolute incidence rates in 2013. Analysed in the Poisson regression model, the estimated trends of negative appendectomies for girls and boys converged in the later study period: estimated rates were comparable 2013 ($p=0.136$) (figure 3b).

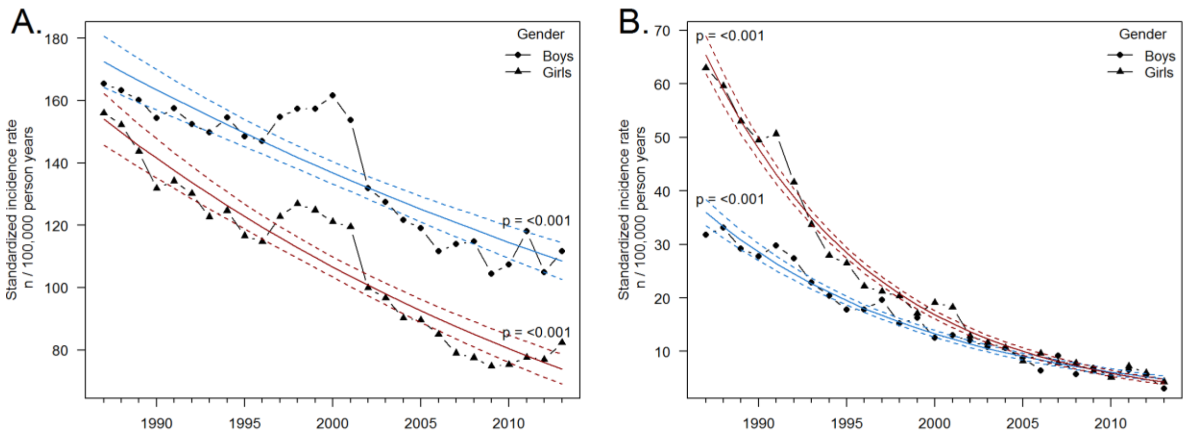

Figure 3. Incidence rates and estimated trends with 95% confidence intervals of A. acute appendicitis and B. negative appendectomies, in girls and boys in Sweden 1987–2013. All trends were significantly different from no change over time ($p<0.001$).

Health Care Region

In the early study period, estimated incidence rates of acute appendicitis were higher in the other health care regions in Sweden compared to the Stockholm region (reference). Over time, incidence rates decreased proportionately more in these other health care regions; in the later study period incidence rate trends were converging across Sweden. In 2013, estimated incidence rates were comparable in the four Central/Northern health care regions, but lower in the Southern and South-Eastern health care regions (figure 4).

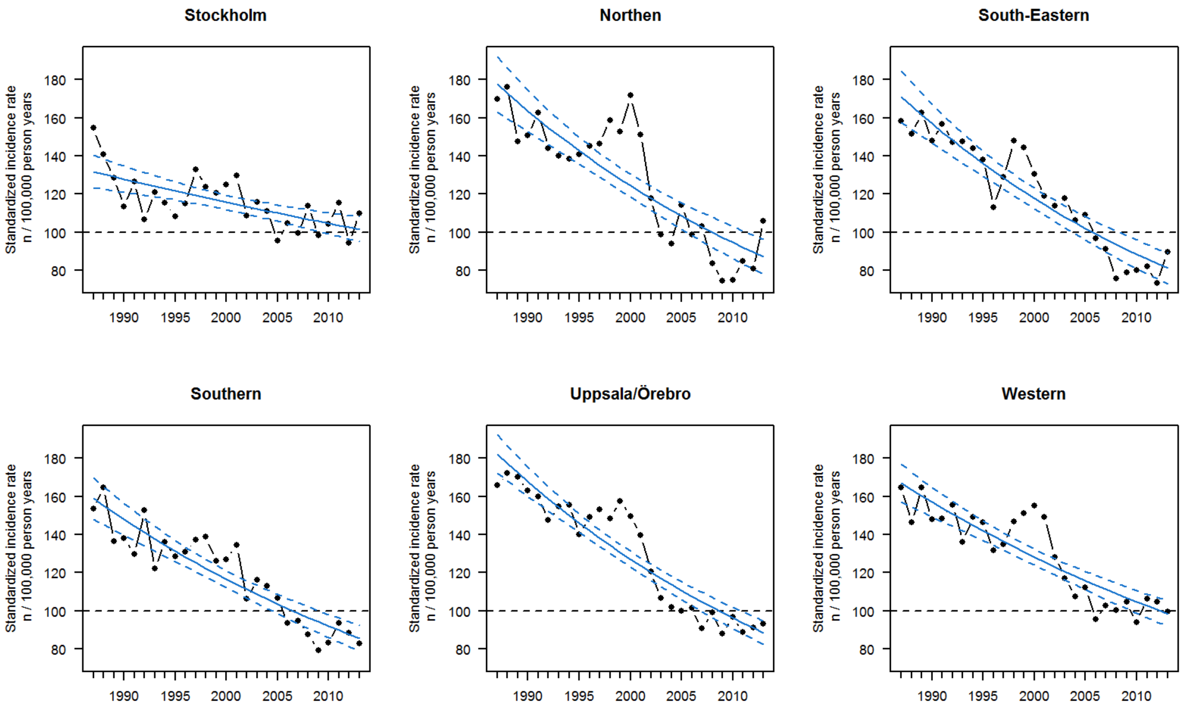

Figure 4: Incidence rates and estimated trends with 95% confidence intervals for overall appendicitis in Swedish children 1987–2013, restricted for health care region.

Transiently increased rates 1997–2002

Transiently increased incidence rates of overall acute appendicitis and appendicitis subtypes were identified 1997–2002 (figure 1). This finding was not changed after adjusting for available confounders, including birth cohort changes, sex-distribution, operative technique (open versus laparoscopic appendectomy) and health care region. The transient increase was more pronounced for non-perforated appendicitis compared to perforated appendicitis, and differed in magnitude between Health Care Regions; being less evident in the Stockholm region (figure 4).

Operative Technique

The first laparoscopic appendectomies in children in Sweden were performed in 1992. The minimal access surgical method has been increasingly used since. In 2013, every second appendectomy in Swedish children was performed by laparoscopy. The use of laparoscopy did not statistically correlate to the declining incidence rates trends for overall appendicitis,

appendicitis subtype or negative appendectomy (figure 1). Nor did the use of laparoscopy correlate to the transiently increased rates noted for the years 1997–2002.

6.3 STUDY III. PROVISION OF CARE FOR CHILDREN WITH APPENDICITIS

55 591 appendectomies were performed in children less than 15 years of age in Sweden 1987–2009. Cohort characteristics and clinical outcomes by exposure are presented in table 5. More than two thirds of children with acute appendicitis were managed in central general hospitals and general hospitals, and the majority of the appendectomies were performed in hospitals with an annual caseload of less than 50 appendectomies in children. Virtually all children were operated at the hospital they were first admitted to, only 0.8% were referred to a higher level of care before the operation. Postoperatively another 0.6% were referred to a higher level of care. The overall perforation ratio in the cohort was 20.6%. Reoperations were rare, 1.4% had a second surgical intervention requiring general anaesthesia. 5.4% were readmitted to hospital within 30 days. The average negative appendectomy rate was 14%, although with a marked reduction over the study period. There were only seven deaths within 90 days of appendectomy, mainly occurring in children less than five years of age and in children managed in specialised paediatric surgical centers. The case fatality rate in the cohort was 0.013%.

6.3.1 Impact of hospital administrative level

Analysing crude data, patients were unevenly distributed; children managed in specialised paediatric surgical centers were younger, presented more often with perforated appendicitis and had fewer negative appendectomies, compared to patients at general hospitals and central general hospitals. Reoperations and readmissions were more common, but the postoperative length of stay was shorter, at general hospitals and central general hospitals (table 5).

In logistic regression analysis there was a twofold increased odds for reoperation, and a 50% increased odds for readmission, after appendectomy at general hospitals and central general hospitals compared to specialised paediatric surgical centers (table 6). Analysing subgroups, restricted for both age (grouped) and appendicitis subtype, the odds for reoperation remained significantly increased at central general hospitals for all subgroups except for children less than age of five years with perforated appendicitis. At general hospitals results remained significant for children with non-perforated appendicitis over five years of age and for children with perforated appendicitis over 10 years of age. For readmission the findings remained significant for appendicitis in all subgroups but two (table 7). Importantly, also non-significant estimates had the same direction, with odds ratios indicating increased risks for reoperation and readmission. The postoperative length of stay was shorter at general and central general hospitals compared to specialised paediatric surgical centers (table 6), and that finding remained significant in the majority of subgroups (table 7).

Table 5. Study III: Cohort characteristics and clinical outcome by exposure

	Hospital administrative level				Hospital annual caseload of pediatric appendectomies					total
	SPC n=15 388	**CGH** n=21 677	**GH** n=18 526	***p***	**<50** n=28 075	**50-99** n=15 556	**100-199** n=2 907	**200-** n=9 053	***p***	n=55 591
Age, n (%)										
0-4 y	975 (6.3)	1 150 (5.3)	574 (3.1)	<0.001	1 091 (3.9)	857 (5.5)	170 (5.8)	581 (6.4)	<0.001	2 699 (4.9)
5-9 y	4 756 (30.9)	6 679 (30.8)	5 385 (29.1)		8 222 (29.3)	4 839 (31.1)	893 (30.7)	2 866 (31.7)		16 820 (30.3)
10-14 y	9 657 (62.8)	13 848 (63.9)	12 567 (67.8)		18 762 (66.8)	9 860 (63.4)	1 844 (63.4)	5 606 (61.9)		36 072 (64.9)
Age, mean ± SD	10.6 ± 3.0	10.7 ± 3.0	11.0 ± 2.7	<0.001	10.9 (2.8)	10.6 (2.9)	10.6 (3.0)	10.5 (3.0)	<0.001	10.8 (2.9)
Laparoscopic operation, n (%)	895 (5.8)	1 204 (5.6)	676 (5.6)	<0.001	1 262 (4.5)	714 (4.8)	47 (1.6)	721 (8.0)	<0.001	2 775 (5.0)
Appendicitis sub-type, n (%)†										
Non-perforated appendicitis	10 401 (75.5)	14 672 (79.5)	12 874 (82.6)	<0.001	19 413 (80.9)	10 430 (80.1)	1 990 (77.0)	6 114 (74.4)	<0.001	37 947 (79.4)
Perforated appendicitis	3 368 (24.5)	3 793 (20.5)	2 709 (17.4)		4 583 (19.1)	2 584 (19.9)	595 (23.0)	2 108 (25.6)	<0.001	9 870 (20.6)
Negative appendectomy, n (%)‡	1 619 (10.5)	3 212 (14.8)	2 943 (15.9)	<0.001	4 079 (14.5)	2 542 (16.3)	322 (11.1)	831 (9.2)	<0.001	7 774 (14.0)
Hospital Annual Case Load, n (%)										
<50	140 (0.9)	11 693 (53.9)	16 242 (87.7)	<0.001	28 075 (100.0)	-	-	-		28 075 (50.5)
50-99	3 591 (23.3)	9 882 (45.6)	2 083 (11.2)		-	15 556 (100.0)	-	-		15 556 (28.0)
100-199	2 604 (16.9)	102 (0.5)	201 (1.1)		-	-	2 907 (100.0)	-		2 907 (5.2)
>200	9 053 (58.8)	0 (0.0)	0 (0.0)		-	-	-	9 053 (100.0)		9 053 (16.3)
Hospital administrative level, n (%)										
SPC	15 388 (100.0)	-	-		140 (0.5)	3 591 (23.1)	2 604 (89.6)	9 053 (100.0)	<0.001	15 388 (27.7)
CGH	-	21 677 (100.0)	-		11 693 (41.6)	9 882 (63.5)	102 (3.5)	0 (0.0)		21 677 (39.0)
GH	-	-	18 526 (100.0)		16 242 (57.9)	2 083 (13.4)	201 (6.9)	0 (0.0)		18 526 (33.3)
Reoperation, 30d; n (%)	125 (0.8)	359 (1.7)	281 (1.5)	<0.001	444 (1.6)	226 (1.5)	21 (0.7)	74 (0.8)	<0.001	765 (1.4)
Readmission, 30d; n (%)	631 (4.1)	1 373 (6.3)	1 019 (5.5)	<0.001	1668 (5.9)	863 (5.5)	132 (4.5)	360 (4.0)	<0.001	3 023 (5.4)
Length of stay, d; median (IQR)	3 (2, 4)	2 (2, 3)	2 (2, 3)	<0.001	2 (2, 3)	3 (2, 3)	2 (1, 4)	3 (2, 5)	<0.001	2 (2, 4)
Mortality, 90d; n (%)	3 (0.019)	3 (0.017)	1 (0.005)	0.504	3 (0.011)	1 (0.006)	2 (0.069)	1 (0.011)	0.049	7 (0.013%)

† Ratio of all appendicitis. ‡ Ratio of all appendectomies.

Normally distributed data are presented as mean (±standard deviation, SD), skewed data are presented as median (inter quartile range, IQR).

Abbreviations: SPC, Specialised Paediatric Surgical Center; CGH, Central General Hospital; GH, General Hospital.

Table 6. Study III: Adjusted regression analyses of the outcome measures

Hospital administrative level		***OR****	***p***
Reoperation	SPC	*reference*	
	CGH	2.18 (1.78, 2.69)	<0.001
	GH	2.12 (1.71, 2.63)	<0.001
Readmission	SPC	*reference*	
	CGH	1.66 (1.51, 1.83)	<0.001
	GH	1.50 (1.36, 1.67)	<0.001
		IRR†	***p***
Length of stay	SPC	*reference*	
	CGH	0.83 (0.82, 0,84)	<0.001
	GH	0.77 (0.76, 0.77)	<0.001
Hospital annual caseload		***OR****	***p***
Reoperation		0.978 (0.970, 0.985)	<0.001
Readmission		0.985 (0.982, 0.989)	<0.001
		IRR†	***p***
Length of stay		1.009 (1.009, 1.010)	<0.001

* Odds ratios, OR (95% confidence interval, CI). Logistic regression model, adjusted for age (grouped) and appendicitis subtype.
†Incidence Rate Ratio, IRR; derrivated from exp [estimate log days LoS] (95% CI). Negative binomial regression model, adjusted for age (grouped) and appendicitis subtype.
Abbreviations: SPC, Specialised Paediatric Surgical Center; CGH, Central General Hospital; GH, General Hospital.

6.3.2 Impact of hospital caseload of paediatric appendectomies

In unadjusted analysis, children managed in hospitals with higher caseload were younger and more often had perforated appendicitis, but less often had a negative appendectomy. Reoperations and readmissions were more frequent in hospitals with lower caseload, but the postoperative length of stay was shorter (table 5).

In the Poisson regression model, increased caseload was associated with reduced risk for postoperative complications; the odds ratios for reoperation and readmission were reduced with increased hospital caseload of paediatric appendectomies (table 6). In subgroup analyses (table 8), restricted for age (grouped) and appendicitis subtype, the reduced odds for reoperation remained significant for children over five years of age with non-perforated appendicitis, and for children over 10 years of age with perforated appendicitis, albeit non-significant estimates for younger children followed the same direction. The reduced risk for readmission remained significant in all appendicitis subgroups, but not in negative appendectomy subgroups. Analysed in the negative binomial regression model, higher caseload was associated with increased length of stay (table 6), a finding that was significant for all subgroups (table 8).

Table 7. Study III: Subgroup analysis, adjusted regression analyses of the outcome measures by age group and appendicitis subtype

		0-4 years		5-9 years		10-14 years	
Hospital administrative level		***OR****	***p***	***OR****	***p***	***OR****	***p***
Reoperation							
Non-perforated appendicitis	SPC	*reference*		*reference*		*reference*	
	CGH	4.35 (1.43, 18.79)	0.020	3.14 (1.77, 6.01)	<0.001	2.71 (1.78, 4.25)	<0.001
	GH	3.62 (0.99, 16.92)	0.064	3.66 (2.06, 7.03)	<0.001	2.87 (1.89, 4.52)	<0.001
Perforated appendicitis	SPC	*reference*		*reference*		*reference*	
	CGH	1.40 (0.64, 3.17)	0.396	2.05 (1.24, 3.52)	0.007	1.98 (1.30, 3.07)	0.002
	GH	2.04 (0.81, 5.00)	0.120	1.10 (0.57, 2.10)	0.765	1.83 (1.18, 2.90)	0.008
Negative Appendectomy	SPC	*reference*		*reference*		*reference*	
	CGH	1.31 (0.42, 4.91)	0.661	2.97 (1.01, 12.67)	0.081	1.04 (0.54, 2.09)	0.911
	GH	1.16 (0.30, 4.76)	0.832	2.04 (0.64, 8.97)	0.272	1.09 (0.57, 2.21)	0.793
Readmission							
Non-perforated appendicitis	SPC	*reference*		*reference*		*reference*	
	CGH	3.04 (1.73, 5.68)	<0.001	1.85 (1.45, 2.38)	<0.001	1.82 (1.53, 2.20)	<0.001
	GH	2.23 (1.13, 4.51)	0.020	1.74 (1.36, 2.27)	<0.001	1.66 (1.37, 2.00)	<0.001
Perforated appendicitis	SPC	*reference*		*reference*		*reference*	
	CGH	1.40 (0.96, 2.04)	0.081	1.61 (1.23, 2.12)	0.001	1.53 (1.22, 1.93)	<0.001
	GH	1.72 (1.08, 2.71)	0.020	1.08 (0.78, 1.49)	0.625	1.45 (1.14, 1.85)	0.003
Negative Appendectomy	SPC	*reference*		*reference*		*reference*	
	CGH	1.31 (0.59, 3.10)	0.522	1.71 (1.05, 2.92)	0.037	1.15 (0.84, 1.60)	0.376
	GH	2.35 (1.06, 5.61)	0.041	1.38 (0.83, 2.40)	0.221	1.06 (0.77, 1.47)	0.729
		estimate†	***p***	***estimate†***	***p***	***estimate†***	***p***
Postoperative length of stay							
Non-perforated appendicitis	SPC	*reference*		*reference*		*reference*	
	CGH	0.93 (0.85, 1.02)	0.126	0.86 (0.83, 0.88)	<0.001	0.88 (0.86, 0.89)	<0.001
	GH	0.88 (0.79, 0.98)	0.019	0.77 (0.75, 0.80)	<0.001	0.81 (0.79, 0.83)	<0.001
Perforated appendicitis	SPC	*reference*		*reference*		*reference*	
	CGH	0.86 (0.80, 0.92)	<0.001	0.78 (0.74, 0.81)	<0.001	0.77 (0.74, 0.80)	<0.001
	GH	0.87 (0.79, 0.96)	0.038	0.74 (0.70, 0.77)	<0.001	0.71 (0.68, 0.74)	<0.001
Negative Appendectomy	SPC	*reference*		*reference*		*reference*	
	CGH	0.63 (0.53, 0.74)	<0.001	0.84 (0.78, 0.90)	<0.001	0.71 (0.68, 0.74)	<0.001
	GH	0.55 (0.45, 0.67)	<0.001	0.74 (0.68, 0.80)	<0.001	0.68 (0.65, 0.72)	<0.001

*Odds ratios, OR (95% confidence interval, CI). Logistic regression model, adjusted for age (grouped) and appendicitis subtype.
†Estimate for log[postoperative length of hospital stay] (95% CI). Negative binomial regression model, adjusted for age (grouped) and appendicitis subtype. Abbreviations: SPC, Specialised Paediatric Surgical Center; CGH, Central General Hospital; GH, General Hospital.

Table 8. Study III: Subgroup analysis, adjusted regression analyses of the outcome measures by age group and appendicitis subtype

	0-4 years		5-9 years		10-14 years	
Caseload	***OR****	***p***	***OR****	***p***	***OR****	***p***
Reoperation						
Non-perforated appendicitis	0.953 (0.891, 0.996)	0.072	0.952 (0.925, 0.975)	<0.001	0.966 (0.949, 0.981)	<0.001
Perforated appendicitis	0.990 (0.963, 1.014)	0.443	0.991 (0.973, 1.008)	0.318	0.985 (0.971, 0.999)	0.040
Negative Appendectomy	1.014 (0.971, 1.049)	0.482	0.956 (0.886, 1.001)	0.125	0.992 (0.964, 1.015)	0.541
Readmission						
Non-perforated appendicitis	0.974 (0.950, 0.994)	0.020	0.980 (0.971, 0.989)	<0.001	0.981 (0.974, 0.988)	<0.001
Perforated appendicitis	0.984 (0.971, 0.997)	0.016	0.991 (0.981, 0.999)	0.043	0.990 (0.982, 0.997)	0.008
Negative Appendectomy	0.979 (0.942, 1.008)	0.206	0.985 (0.966 (1.002)	0.121	0.995 (0.983, 1.006	0.418
	IRR†	***p***	***IRR†***	***p***	***IRR†***	***p***
Postoperative length of stay						
Non-perforated appendicitis	1.004 (1.001, 1.008)	0.007	1.009 (1.008, 1.010)	<0.001	1.008 (1.008, 1.009)	<0.001
Perforated appendicitis	1.004 (1.002, 1.006)	0.001	1.008 (1.007, 1.010)	<0.001	1.010 (1.009, 1.011)	<0.001
Negative Appendectomy	1.019 (1.013, 1.025)	<0.001	1.011 (1.008, 1.013)	<0.001	1.013 (1.012, 1.015)	<0.001

*Odds ratios, OR (95% confidence interval, CI). Logistic regression model, adjusted for age (grouped) and appendicitis subtype.
†Incidence Rate Ratio, IRR; derrivated from exp [estimate log days LoS] (95% CI). Negative binomial regression model, adjusted for age (grouped) and appendicitis subtype. Abbreviations: SPC, Specialised Paediatric Surgical Center; CGH, Central General Hospital; GH, General Hospital.

DISCUSSION

6.4 GENERAL STRENGTHS

The large number of patients registered in the NPR, and also in the local database, brings substantial strength the studies in this thesis. There were small numbers of missing data and loss to follow up. In Study I, multiple imputation was used to account for missing data. Thus variables including substantial missing data could be used to adjust for important confounding in the statistical analyses. The NPR was previously shown to have a near 100% coverage and yields highly valid data, allowing high-quality longitudinal epidemiologic studies on population basis.[117] Reliable, detailed population data from Statistics Sweden allows for standardisation and adjustments that further reduced potential bias. Sensitivity analyses were also performed to confirm the robustness of the respective study results.

6.5 GENERAL LIMITATIONS

All three studies included in this thesis were retrospective studies based on register data. In Study I the presence of intra-abdominal abscess and wound infection were retrospectively based on information retrieved from the computerised notes database, potentially introducing bias. Likewise, in Study II and Study III the definition of negative appendectomy and measures of postoperative morbidity were retrospectively defined, according to availability of appropriate variables and information in the registers. This was recently addressed in a proposal for specific guidelines reporting outcomes from studies based on health care register data; the Reporting of studies conducted using observational routinely-collected health data (RECORD) statement.[126] In adjusted analyses in Study I, II and III, co-variables were introduced to account for possible bias. However, residual confounding is always a potential problem in retrospective studies.

The register data available from the NPR did also not include information to investigate the aetiologic reasons behind the significantly shifting trends of appendicitis incidence rates.

6.6 STUDY I

According to the results of Study I, surgical delays can be accepted without increased risks of perforated appendicitis and postoperative complications. Previous studies[88,89] indicating the safety of surgical delay in childhood appendicitis were not controlled for important bias, but were nonetheless accepted as evidence for the safety of postponing appendectomy after confirming the diagnosis, as demonstrated by Dunlop’s audit of members of the American Association of Paediatric Surgeons.[92] By adjusting data for disease severity on admission, the present study adds important evidence for the safety of surgical delay in childhood appendicitis. Our findings were analogous with several previous findings in adults. Teixeira et al performed a retrospective cohort study in adults and found no association between surgical delay and increased perforation rate, however there was an increased risk for surgical site infection with increased surgical delay.[95] The British Multicenter Cohort Study supplemented by a meta-analysis displayed similar results, with no association between short surgical delays and risk for perforated appendicitis.[96] The findings of this and previous studies indicate that the progression to perforation in acute appendicitis is haltered upon admission to hospital. Strict fasting, proper fluid resuscitation and analgesics are cornerstones in the initial treatment of children and adults with appendicitis and may affect the progressive inflammation and stop the process towards perforation. This effect may be further enhanced by preoperative antibiotics treatment, analogous with the development of strategies of non-operative antibiotics treatment of acute appendicitis in children[14] and adults.[86] Most children in the present study were not treated with preoperative antibiotics, indicating that fasting, fluid resuscitation and analgesics alone may play the important role to shift the inflammatory process otherwise leading to perforation. This is also analogous with the hypothesis of spontaneously resolving appendicitis and the strategies of observing rather than exploring patients with suspected or even confirmed acute appendicitis presented by Andersson.[50]

The clinical implications of the results from Study I include possible changes in the management of children with diagnosed appendicitis, shifting focus from the provision of emergent surgery towards focus on providing physiologic homeostasis and preoperative optimisation. The study results also give important support to ongoing and future trials on non-operative treatment for acute appendicitis.

6.7 STUDY II

This was the largest population-based epidemiologic study on acute appendicitis in children to date, including 65 000 children over a 26-year period. Markedly reduced incidence rates of acute appendicitis were identified, with diverging trends for non-perforated and perforated appendicitis, respectively. A more pronounced reduction of appendectomies for appendicitis, and of negative appendectomies, in girls resulted in increased differences among sexes for appendectomies for appendicitis but converging incidence rate trends for negative appendectomies. We did not identify any correlations between the introduction of radiologic investigations in the diagnostic pathways on the long term incidence rate trends.

The incidence rate of non-operatively managed patients discharged with an appendicitis diagnosis was stable over the study period. This was, due to the unreliable diagnosis criteria and the probable heterogeneity of this group, not further analysed in this study. However, it is surprising not to find increasing rates of conservatively treated appendicitis during a period of rapidly reduced rates of appendectomies, as one might expect to follow evolving conservative approaches towards appendectomy in mild appendicitis. The increasing use of laparoscopy have been argued to possibly affect the rate of registered negative appendectomies, as the minimally invasive technique renders the alternative to leave a non-inflamed appendix in situ – i.e. to not perform a negative appendectomy. The reduced incidence rate of negative appendectomies did, however, not correlate to the introduction or the subsequent increased use of laparoscopic surgery for paediatric appendectomies.

The findings of reduced incidence rates of paediatric appendectomies were consistent with previous findings of long-term reduced rates in adults and children. Arnbjörnsson et al reported increased incidence of acute appendicitis in the south of Sweden during the first half of the 20th century.[35] This may have resulted from improved health care standards and availability of surgical care. Rates were reported to decrease rapidly 1950–65 with a more moderate reduction 1965–1980. Continuing reductions were reported from the North America and Europe during the last decades of the 20th century.[30,33,36] Also in children, appendectomies were reduced. A Danish study, based on NPR data, identified a 13–36% reduced incidence rate of non-perforated appendicitis 1996–2004, but a modest 10% reduction of perforated appendicitis.[44] Reduced rates of paediatric appendectomies were also reported from New England, USA, 2000–2006.[45] In contrast, increased rates of appendicitis were reported, from Norway [34] and from the USA.[41,42] Livingston identified a J-shaped trend with increased appendicitis rates towards the end of a 1970–2004 study period.[43] We identified a corresponding, but transient, increase of appendicitis and appendectomies in Swedish children 1997–2002, followed by continued reductions. The temporary increase may be argued to have coincided with the introduction of radiologic investigations in appendicitis diagnosis. There is no general data on the use of radiology in diagnosing appendicitis available from the NPR or other Swedish health care registers. A previous study by Kaiser et al, on the introduction of US and CT in diagnosing appendicitis at out institution, found stable rates before, during and after the introduction.[62] Importantly, on a population basis, the temporary increase identified in the present study was followed by a return to the previous trend of reduced rates. The transient increase also coincides with the conversion from ICD-9 to ICD-10, but no major changes in coding appendicitis, explaining the finding was done at that time.

We were not able to identify any aetiologic reason for the reduced rates of non-perforated and perforated appendicitis in the data. Results may result from a long term change in the attitude towards appendicitis and its consequences, including expectant treatment strategies leading to a reduced proportion of mild, perhaps self-limiting, appendicitis actually being diagnosed and thus registered. That hypothesis also fits well with the pronounced reduction of non-perforated appendicitis, compared to the moderate reduction of perforated appendicitis. The finding of significantly different incidence rate trends comparing non-perforated to perforated appendicitis further supports previous theories stating that the two subtypes of appendicitis have different aetiology and pathogenesis.[37]

Observed differences between genders may be attributed to changed attitudes towards diagnosing and managing acute appendicitis over the study period. In boys, with fewer differential diagnoses to acute appendicitis compared to girls, a lower threshold to early appendectomy may explain the trend of increased incidence rate ratio between sexes. Accordingly, more expectant strategies in combination with increased precision in diagnosing appendicitis and ruling out important differential diagnoses in girls may explain the more marked reduction of negative appendectomies in girls, resulting in comparable rates towards the later study period.

The most important clinical implications of Study II are the changed health care provision perspectives, with further reduced number of hospitalisations and numbers of appendectomies. This will also adversely affect surgeons' caseload and future surgeons' training possibilities.

6.8 STUDY III

The main findings of Study III were clinically relevant risk reductions for reoperations and readmissions to hospital after appendectomies performed in specialised paediatric surgical centers. The risk for reoperations and readmissions were also reduced with increased hospital caseload of paediatric appendectomies. In subgroup analysis, estimated odds ratios were directed towards reduced risks at specialised paediatric surgical centers or high caseload hospitals, also in the minority of subgroups where estimates were statistically non-significant. As it is unlikely that larger cohorts can be collected, we believe that the uniformly directed estimates towards lower risks in specialised paediatric surgical centers and high caseload hospitals are relevant also for the smallest subgroups.

The study adds important results from one of the largest population-based cohort studies on the impact of appendectomy provision, based on highly valid national patient register data, spanning a long period of time, in support of reduced complication rates in paediatric surgical centers. The available markers of postoperative complications includes the important major complications requiring general anaesthesia or readmissions (Clavien-Dindo III–IV[127]) and death (Clavien-Dindo V) but the data source lacks registration of minor complications and deviations from the expected postoperative course (Clavien-Dindo I–II).

The main findings of reduced complications rates at specialised paediatric surgical centers are coherent with previous studies from several different health care settings. From the UK, Giuliani et al[128] identified 11% more complications and 11% more readmissions after paediatric appendectomies in district general hospitals compared to specialised paediatric surgical centers in a large cohort of 83 679 children, whilst Collins et al,[109] in a smaller cohort, identified more than 50% increased risks for reoperations and readmissions in district general hospitals compared to specialised paediatric surgical centers. Comparing paediatric surgical services to general surgical services in a local USA cohort, Alexander et al[103] found reduced risks for postoperative complications (8% vs 33%) and readmissions (25% vs 66%) in perforated appendicitis, but comparable outcomes in simple appendicitis. From South Korea, Kim et al[129] also reported reduced postoperative complication rates in paediatric surgical practice compared to general surgical practice, by identifying less need for peritoneal drainage in the former. In two large cohort studies from the USA, Smink et al[104] and Ponsky et al[130] both identified lower negative appendectomy rates in high caseload hospitals, but these studies did not investigate postoperative complication rates.

However, in a study by Emil et al[131] from California, USA, comparable outcomes between paediatric surgeons' and general surgeons' management in university hospitals were identified. Also, Lee et al[107] found comparable outcomes, comparing management in a teaching institution involving general surgery residents to a non-teaching institution, in California, USA. In a large cohort study from Ontario, Canada, Somme et al[132] found similar complications rates comparing appendectomies performed by paediatric surgeons to those performed by general surgeons. In a local cohort of Israeli children, Mizrahi et al[111] also identified similar rates of postoperative complications and readmissions comparing appendectomies performed by paediatric surgeons to those performed by general surgery residents. Moreover, Tiboni et al[110] found comparable risk measures of adverse outcomes between paediatric surgical units and general surgery units, whilst identifying higher negative appendectomy rates in the latter, in a multicenter UK study including 703 children treated in 73 hospitals.

It is unlikely that systematic differences among hospitals in reporting operative appendicitis diagnosis and outcome measures used would affect the study outcome significantly. The length of stay variable from the NPR was, however, registered as full days without decimals, a low precision value possibly imposing bias in cases of shorter lengths of hospital stay. Also, there may be residual confounding concerning the case mix, even after adjusting analyses for patient age and appendicitis subtype, as the disease severity is not fully explained by those variables. We identified that 0.8% of children were referred to a more advanced care facility before the operation and 0.6% were referred postoperatively. This may impose bias towards the null, or a type II error, as we believe that a sound centralisation of some of the sickest children already does occur. We did not further analyse mortality data in the cohort, as the low numbers disable statistical analyses.

Based on the outcome of this and previous studies, we conclude that paediatric surgical centers' highly specialised care for children with appendicitis results in reduced postoperative complication rates. Amongst factors possibly contributing to the improved outcome we propose selection and interpretation of diagnostic investigations, pre- and perioperative care and anaesthesia as well as early identification of postoperative complications. Structured pathways for appendicitis management may help achieve this. Importantly, it is not likely that all children with appendicitis can be referred to specialised surgical centers, nor is it possible to admit all of them in those services. The main results of this study indicate that the merit from specialised paediatric surgical management of paediatric appendicitis may also be achieved by increasing hospital caseload of paediatric appendectomies, not necessarily at specialised paediatric surgical units. We anticipate the results to be generalizable to similar health care settings, especially together with the results from the large well performed studies by Smink et al and Giuliani et al.

7 CONCLUSIONS

- Surgical delay in paediatric appendicitis was not associated with increased risk for perforated appendicitis. Surgical delay was not an independent risk factor for postoperative complications. Results were robust in sensitivity analyses and may have important implications for the development of non-operative treatments for appendicitis and for the utilisation of surgical resources, especially during night time.

- Significantly reduced incidence rates of appendicitis and appendectomies in children since 1987 were identified in Study II. The current incidence rate of acute appendicitis in Swedish children was 100.1 per 100 000 person-years 2013. Despite a transient increased rate 1997–2002, the reduction of diagnosed appendicitis does not seem to cease.

- The trends of non-perforated appendicitis and perforated appendicitis were both declining and trends diverged significantly supporting that the two are different entities and have different epidemiologic features. Identified regional differences were reduced over the study period and estimated trends converged in the later study period. The register data used did not include sufficient information to investigate the underlying reasons for the results. The rapidly declining rates of childhood appendicitis will have implications for provision of care, for surgeons' training and for future appendicitis research.

- The risk for reoperations and readmissions to hospital was reduced after appendectomies performed in specialised paediatric surgical centers, compared to other hospitals. Similar risk reductions were found with increased caseload of paediatric appendectomies. This will have to be taken into account in planning future provision of care for this patient group. Importantly, the study results indicate that the merit of appendicitis management at specialised paediatric surgical centers may be achieved by increasing hospital caseload in other settings.

8 FUTURE RESEARCH DIRECTIONS

The studies constituting this thesis has contributed with small, but important pieces to the body of scientific understanding, and the results may contribute to improved future management and outcome for children with acute appendicitis.

In a larger context, despite the large number of publications on appendicitis, we still lack the fundamental knowledge on the aetiology, natural course and best treatment options needed to really change the game in treating acute appendicitis and its complications. Recent advances include better understanding of the natural course of non-perforated appendicitis and possible non-operative treatment options. Large multicenter randomised controlled trials on non-operative treatment are underway and the results will, hopefully, bring stronger light to the issue. To further increase the understanding of the pathology and to develop future treatment strategies for acute appendicitis, we must continue the strive for producing high quality prospective trials on the subject.

My intended future research includes both a continuation of the retrospective cohort studies presented in this thesis, upcoming prospective trials and new observational studies. The local audit database includes data on microbiology of acute appendicitis which will be used for cohort studies including studies analysing the present microbiology of acute appendicitis in children, the microbiology of postoperative abscesses, and possible correlations between specific bacteria and the risk for postoperative complications.

As a consequence of recent changes in the health care structures in Stockholm, the management of children aged 10–14 years was relocated from the specialised paediatric surgical unit to a downtown central general hospital in 2016. This was a unique chance to prospectively compare the outcomes after appendectomy at a specialised paediatric surgery unit to the management at a general hospital, and this study is in progress.

Our appendicitis research group are involved in the ongoing APPY-trial, a multicenter international randomised controlled trial, and the offspring of the first pilot randomised controlled trial on non-operative treatment of acute appendicitis in children, the CONSAPP trial published in 2015. In collaboration with the Department of Paediatric Perioperative Medicine and Intensive Care at our hospital, we are investigating new and promising biomarker in an attempt to better differentiate perforated appendicitis from non-perforated appendicitis, already in the emergency department.

I hope to be able to continue exploring this exciting research field, contributing to the future improvement of appendicitis diagnosis and treatment strategies.

9 SVENSK SAMMANFATTNING

Akut bildtarmsinflammation är den vanligaste akuta kirurgiska åkomman hos barn. Trots att ca 7% av befolkningen drabbas under livet och att mycket ansträngning lagts på att utforska ämnet är många aspekter kring blidtarmsinflammation okända. Den traditionella uppfattningen att den tidiga lindriga sjukdomsfasen alltid övergår i allvarlig blindtarms-inflammation och perforation, brusten blindtarm, är djupt rotad men har inte stöd i den moderna vetenskapen. Det har vidare saknats vetenskapliga bevis för vilka eventuella risker fördröjd utredning och behandling av blindtarsinflammation egentligen medför. Det har också visat sig att många blindtarmsinflammationer kan läka utan operation, med hjälp av antibiotika eller till och med utan medicinering. Man har hittills inte klarlagt om eller hur man i förväg kan urskilja vilka skulle kunna läka med annan behandling än operation. Det finns också obesvarade frågor om hur sjukvården skall administreras för att minimera risken för komplikationer i samband med behandling av blindtarmsinflammation hos barn – spelar det någon roll om man opereras vid ett högspecialiserat barnkirurgiskt centrum, eller ett sjukhus som med stor vana att operera blindtarmsinflammation, jämfört med andra sjukhus?

Detta avhandlingsarbete syftade till att besvara några av dessa frågor:

- Vilken roll spelar tiden från att blindtarmsinflammationen upptäcks till operationen för risken att drabbas av brusten blindtarm eller andra komplikationer?
- Hur stor är risken för barn att drabbas av blindtarmsinflammation i Sverige?
- Att identifiera och analysera trender i förekomst av blindtarmsinflammation hos barn i Sverige, och att jämföra trender mellan olika regioner i Sverige.
- Uppnår man motsvarande resultat efter blindtarmsoperationer som utförs vid mindre sjukhus eller sjukhus som opererar få barn jämfört med specialiserade barnkirurgiska kliniker eller sjukhus som opererar fler barn med blindtarmsinflammation?

Studie I syftade till att utreda eventuella samband mellan fördröjd operation och risken för brusten blindtarm. I andra hand utredde vi samband mellan fördröjd operation och komplikationer såsom postoperativa infektioner, längd på sjukhusvistelsen, reoperation och återinläggning. Efter att ha justerat analyserna för olikheter i barnens ålder och sjukdomsgrad vid inläggning kunde vi inte påvisa några samband mellan fördröjd operation och risk för brusten blindtarm eller postoperativa komplikationer. Resultaten tolkades som att inflammationen bromsas av fasta, dropp och vila, och vi hypotiserar att hos många barn med blindtarmsinflammation kan den behandlingen till och med räcka för tillfrisknandet.

I **Studie II** studerades incidenstal för att insjukna i och att opereras för blindtarms-inflammation åren 1987–2013. Vi konstaterade att förekomsten av blindtarmsinflammation minskat kraftigt under den undersökta perioden, och att minskningen var större för icke-brusten blindtarm (50.6%) än för brusten blindtarm (28.9%). Vidare visade vi att förekomsten av operationer för misstänkt blindtarmsinflammation, där blindtarmen konstaterades vara frisk, minskat med drygt 90 % under samma period. Vi visade också att incidensen av blindtarmsoperationer skiljt sig mellan Sveriges sjukvårdsregioner, men att skillnaderna utjämnats över tid, talande för en homogenisering av omhändertagandet av barn med blindtarmsinflammation.

I **Studie III** undersökte vi samband mellan sjukhusets administrativa nivå, definierat som barnkirurgiskt center, länssjukhus, respektive länsdelssjukhus, och risken för komplikationer i samband med blindtarmsoperationen. Vi undersökte också samband mellan sjukhusens årliga antal operationer av blindtarmsinflammation hos barn och risken för komplikationer. Vi fann att barn som opereras vid barnkirurgiska centra löper mindre riska att drabbas av komplikationer som kräver en förnyad operation eller återinläggning på sjukhus, jämfört med andra sjukhus. Vi fann också motsvarande minskad komplikationsrisk också förelåg vid sjukhus som gör många blindtarmsoperationer hos barn, jämfört med de som opererar få. Den skyddande effekten av att opereras vid barnkirurgiskt center eller vid ett högvolymsjukhus gällde både unga och äldre barn, och både barn med okomplicerad och med brusten blindtarmsinflammation. Tidigare studier har påvisat jämförbar eller minskad komplikationsrisk vid barnkirurgiska kliniker jämfört andra sjukhus, men vi anser det viktigt att samma riskminskning verkar vara möjlig att uppnå genom ökat antal operationer även vid andra sjukhus. Det är viktigt, eftersom det inte är möjligt att centralisera vården av alla barn med blindtarmsinflammation till barnkirurgiska kliniker (fyra i Sverige). Det skulle däremot vara möjligt att centralisera vården av dessa barn till färre kliniker och att på så sätt öka dessa klinikers årliga operationsvolymer.

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