Paediatric surgical care in Sweden. Studies on incidence, outcome and access

Omling, Erik

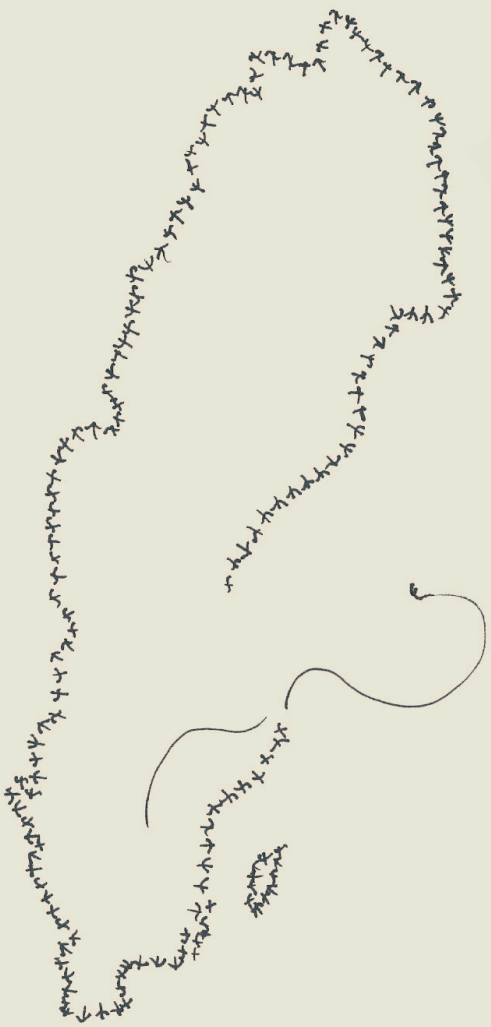
2019

Document Version:
Publisher's PDF, also known as Version of record

Paediatric surgical care in Sweden

Studies on incidence, outcome and access

ERIK OMLING
FACULTY OF MEDICINE | LUND UNIVERSITY



Paediatric surgical care in Sweden

Paediatric surgical care in Sweden

Studies on incidence, outcome and access

Erik Omling

LUND
UNIVERSITY

DOCTORAL DISSERTATION
by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at Grubb lecture room, BMC, Lund, March 15, 2019, at 9 a.m.

Faculty opponent
Professor Jerome Loveland
University of Witwatersrand, Johannesburg, South Africa

Supervisor
Associate professor Lars Hagander

Co-supervisor
Professor Jonas Björk

Organisation LUND UNIVERSITY	Document name **DOCTORAL DISSERTATION**
	Date of issue **15 MARCH 2019**
Author **ERIK OMLING**	Sponsoring organisation

Title and subtitle

PAEDIATRIC SURGICAL CARE IN SWEDEN – STUDIES ON INCIDENCE, OUTCOME AND ACCESS

Abstract

Background: Advanced paediatric surgery is increasingly centralised in Sweden in order to improve treatment outcomes and reduce surgical risks. However, the overall need for surgery in the paediatric population has not been estimated, and the association between geographic access to surgical facilities and timely treatment for common surgical conditions in children is largely unknown.

Aims: To estimate the overall incidence of surgery for Swedish children (I); to describe disease-specific incidences, treatment characteristics and surgical risks for one paediatric non-emergent surgical condition (cryptorchidism) (II) and one acute surgical condition (appendicitis) (III); and to assess for associations between distance to surgical facility and timely treatment with adjustment for medical and socioeconomic risk (IV-V).

Methods: National healthcare and population registers of the total Swedish paediatric population, or subsets of it, for the years 2001-2014, were analysed in five observational cohort studies. The overall incidence of surgery was estimated in the Swedish paediatric population, and the disease-specific incidences were analysed for cryptorchidism and appendicitis. Treatment characteristics and surgical risks were presented, and the associations between travel time to hospital and treatment delay were analysed for these two conditions. Regression methods and survival analysis have been applied to estimate associations and calculate cumulative incidences.

Results: On average, every year of childhood, 1 in 20 children had some kind of surgical procedures (6784 operations per 100,000 person-years), and 27% of all paediatric hospital admissions involved surgical procedures. >67% of all operations were performed as day surgery.

1.4% of Swedish boys were treated for cryptorchidism by age 14, and 1.8% were treated by 18 years of age, with prematurity and low birth weight being strongly associated with this risk. Only a minority (<6%) were treated during their first year of life according to the recommendations, with considerable regional variations. There was no postoperative mortality detected, and the risk of postoperative infection was low (1.4%), with no geographic variations. There was an association between travel time to hospital and timely treatment at 3 years of age, adjusted for birth-related risk factors and socioeconomic determinants (per 30-minute increase in travel time: aHR 0.91 [95% CI 0.88-0.95], p<0.001).

1 in 40 Swedish children (2.5%) had appendicitis during childhood. One in 6 (17%) had a more severe type of appendicitis, with increased postoperative infection rate (5.9% versus 2.3%, aOR 2.6 [2.2-3.2]) and readmission rate (5.5% versus 1.2%, aOR 4.8 [95% CI 4.1-5.5]), and higher risk for small bowel obstruction later on (0.2% versus 0.7%, aHR 3.9 [95% CI 2.6-5.8]). These risks were also associated with treatment modality; postoperative infection rates (aOR 0.6 [95% CI 0.5-0.8]) and small bowel obstruction rates (aHR 0.3 [95% CI 0.1-0.6], p=0.002) were lower after laparoscopic surgery, as compared to open appendectomy. There was no observed association between travel time to treatment and the risk for more severe type of paediatric appendicitis in Sweden.

Significance: In this thesis, the overall *incidence* of surgery in Swedish children has been estimated. One elective condition and one emergency surgical condition have been anlysed for *outcomes* in terms of timing of treatment and surgery-related risks. *Access* to timely surgical treatment have been estimated in the elective and the emergancy care settings. Findings from these studies may be relevant to consider on a regional and national level in future planning of paediatric surgery.

Key words

Public health, paediatric surgery, cryptorchidism, undescended testis, appendicitis, socioeconomic, access

Supplementary bibliographical information		Language **ENGLISH**
ISSN and key title **1652-8220 PAEDIATRIC SURGICAL CARE IN SWEDEN**		ISBN **978-91-7619-750-9**
Recipient's notes	Number of pages 110	Price
	Security classification	

Signature  Date 2019-02-07

Paediatric surgical care in Sweden

Studies on incidence, outcome and access

Erik Omling

LUND
UNIVERSITY

Cover layout by Martiné Wlosinska

Back cover photo by Pär Omling

Lund University, Faculty of Medicine Doctoral Dissertation Series 2019:21
Department of Paediatrics

ISBN 978-91-7619-750-9
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2019

Media-Tryck is an environmentally certified and ISO 14001:2015 certified provider of printed material. Read more about our environmental work at www.mediatryck.lu.se

MADE IN SWEDEN

To my beloved little family

Table of Contents

List of publications

This thesis is based upon the following papers, referred to as paper I-V:

I. **Population-based incidence rate of inpatient and outpatient surgical procedures in a high-income country**
Omling E, Jarnheimer A, Rose J, Björk J, Meara J G, Hagander L
British Journal of Surgery 2018; **105**(1): 86-95

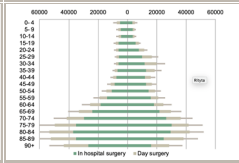
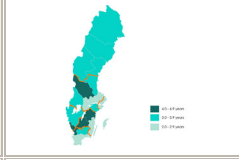
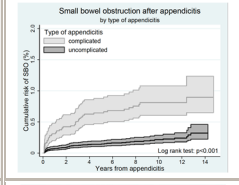
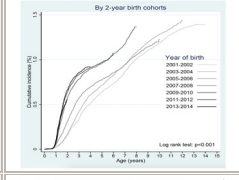
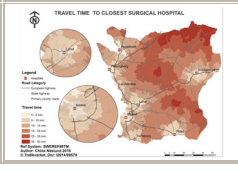
II. **Cryptorchidism in Sweden: a nationwide study of prevalence, operative management, and complications**
Bergbrant S, Omling E, Björk J, Hagander L
Journal of Pediatrics 2018; **194**: 197-203.e6

III. **A nationwide cohort study of paediatric appendicitis: how disease severity and treatment modality correlate with short- and long-term risk for adverse outcome**
Omling E, Salö M, Saluja S, Bergbrant S, Olsson L, Björk J, Hagander L
(Submitted manuscript)

IV. **Risk factors for cryptorchidism and delayed treatment: a nationwide cohort study**
Omling E, Bergbrant S, Persson A, Björk J, Hagander L
(Submitted manuscript)

V. **Appendicitis in a nationwide paediatric cohort: the association between travel distance and complicated disease**
Omling E, Salö M, Saluja S, Bergbrant S, Olsson L, Persson A, Björk J, Hagander L
(Submitted manuscript)

Thesis at a glance

	Background and aims	Methods	Main findings	Teaser	Significance
I. Incidence of paediatric surgery in Sweden	5000 operations per 100,000 population has been proposed as a target for national surgical output. The relative importance of paediatric surgery is not known.	All surgery in Swedish hospitals and clinics 2006-2013 was studied. Incidence of surgery was calculated per gender and age, with trends over time.	In 2013, >20,748 operations were performed annually per 100,000 population overall, and >66.9% was day surgery. 1 in 20 children had surgery each year; surgery occurred in 27% of all paediatric admissions.		Paediatric surgery affects 1 in 20 children each year and occurs in 1 in 4 paediatric hospitalisations. Outpatient surgery needs to be included in estimates of surgical output.
II. Elective paediatric surgery -Treatment and outcome	Cryptorchidism is a common cause of elective surgery in boys. Recommended age at treatment is <1 year. The rates of timely and delayed treatment in Sweden are unknown.	All cases of cryptorchidism in Sweden 2001-2014 were evaluated for treatment characteristics and complications. Incidence and age at treatment were assessed.	1.8% of all boys were treated until age 18 years. Prematurity and low birth weight were risk factors. 96% were >1 year old at surgery, with large regional differences. 1.4% developed surgical site infections.		Cryptorchidism surgery was associated with low complication rates. It is unclear why only 1 in 20 are operated at recommended age, with large regional differences.
III. Emergency paediatric surgery -Treatment and outcome	Appendicitis is a common cause of emergency surgery in children. Timely treatment reduces disease progression. Postoperative risk by disease severity and treatment modality is unknown.	All paediatric appendicitis in Sweden, 2001-2014, were evaluated for treatment characteristics and short- and long-term complications.	Complicated appendicitis was associated with higher risk for all evaluated adverse outcomes. Laparoscopic appendectomy was associated with fewer post-operative infections and less small bowel obstruction (aHR 0.3 [95% CI 0.1-0.6], p=0.002).		Short- and long term morbidity after complicated appendicitis in children is considerable. Laparoscopic appendectomy may reduce these risks.
IV. Elective paediatric surgery -Access	Centralised surgery for cryptorchidism is recommended for children <1 year of age. Distance to hospital and socioeconomic background may impact on access to timely treatment.	All Swedish boys born in 2001-2014 were assessed for birth-related and socioeconomic risk factors. The association between travel distance and age at treatment was determined.	Adjusted for known risk factors and potential confounders, every 30-minute increase in distance was associated with reduced chance of treatment at age 3 (aHR 0.91 [95% CI 0.88-0.95], p<0.001).		Centralisation of cryptorchidism treatment may reduce access to timely surgery, particularly for children with long distance to paediatric surgery facility.
V. Emergency paediatric surgery -Access	Prehospital delay is associated with more complicated appendicitis. Increased distance to hospital may reduce access to timely treatment for children.	All paediatric appendicitis in Sweden, 2001-2014, was evaluated. Associations between travel distance and complicated disease were assesed.	When adjusting for confounders including socioeconomic determinants of health, there was no clear association between travel distance and complicated appendicitis in Swedish children.		There is no clear evidence that increasing geographical distance to hospital correlates with worse outcome in children with appendicits.

Background

Surgery and public health

Surgery and public health concern the provision, organisation, distribution and quality of *surgical* care in a wider societal perspective, in entire populations and healthcare systems.

The healthcare organisation is a frequent topic of debate among politicians, professionals and laypeople. In Sweden, healthcare spending accounts for more than one-tenth of the economy, and about 50,000 SEK[1] on average are spent per capita each year (1). Provision of the highest quality healthcare, equitably accessible to all citizens regardless of social background or geographical circumstances, is one of the most important responsibilities for national and regional administrations (2–4). Does the population get what is intended? And if so, do all citizens benefit from these services? Or is access restricted for parts of the population, perhaps due to geographical or other types of barriers? How do we even know that? Which detectors of public health can provide relevant answers to these questions?

Healthcare providers, funding bodies and governmental and private bodies in the healthcare sector have strong motives to improve quality and reduce costs. However, decision-making when it comes to healthcare planning requires expertise in economics and organisational matters, as well as evidence-based quality improvements and public health statistics.

There are strong public interests in making healthcare more universally accessible to the population, more resource-effective and more reliable in terms of treatment outcomes and safety. A widely held view among professionals, hospital administrators and politicians has been that centralisation of resources is the key to meet the ever-increasing demands of specialised care. Centralisation as a phenomenon seems to come with positive expectations, without reflections. During the last decades, hospitals have merged, clinics have been co-localised, and smaller healthcare providers have been drained of resources, in order to improve cost-effectiveness and capacity at a smaller number of centres of excellence.

[1] Equals about 5500 USD or 4800 EUR (2019).

The centralisation process is logical and rational; numerous evidence points at the benefits of concentrating certain kinds of advanced medical and surgical treatments, including cardiothoracic surgery and transplant surgery, advanced cancer treatment and neonatal care, and rare or complex paediatric surgical conditions such as biliary atresia. In the 1990s, Swedish paediatric cardiothoracic surgery was centralised to two centres, informally since 1993, and formalised by the Swedish Board of Health and Welfare in 2007 (5,6). In 2018, specialised neonatal surgery was also considered of national, rather than of regional interest, and surgical treatment of oesophageal atresia, congenital diaphragmatic hernias, anorectal malformations and a few more neonatal conditions were centralised to two designated centres in Sweden (7,8).

These processes have not been straightforward. Whereas evidence points out that certain conditions may be better treated at high-volume centres, this may not necessarily be generalisable to all types of conditions, and extrapolations may be misleading.[2] Overall, very limited attention has been directed at the potential risks associated with centralisation and evidence is lacking.

In 2015, the report 'Practice makes perfect' [Swedish: Träning ger färdighet, authored by Måns Rosén on the assignment of the Swedish Government] concluded that surgical outcomes, including overall survival, is a function of facility caseload volume of surgery (9). The author suggested that an estimated 500 lives may be spared in Sweden each year, if not only highly specialised or risky surgery, but *all* surgery was performed in high-volume centres. The report caused a heated public debate about the consequences of the centralisation-related drainage of surgical resources and competence from smaller hospitals, and the validity of the report has been questioned (10–12). The lack of evidence for centralisation interventions became very apparent.

Historical perspectives and global outlook

Public health issues related to surgical care have historically gained little academic attention. Public health statistics and advocacy, brought to public attention by inspiring personalities such as the late Professor Hans Rosling, have focused primarily on the massive global burden of disease related to infectious diseases, malnutrition and child and maternal mortality. Impressive improvements have been achieved by tremendous efforts and successful interventions within these areas.

Yet, the *epidemiologic transition*[3] in low- and middle-income countries has introduced a *double burden of disease* in many of these populations; meanwhile

[2] Further discussion on centralisation benefits are found later in the *Background*-chapter, in the section on *Organisation of paediatric surgery*.

[3] The epidemiological transition refers to the dramatic societal and demographic shift, seen when populations in low- and middle-income countries face increasing economic standard and

poor nutrition and living conditions in sections of a population may still lead to a large societal burden of communicable diseases and nutrition deficiencies: the general increase in living standard and nutrition introduces a panorama of non-communicable conditions, such as diabetes, arthrosis, and increased burden of cancer and cardiovascular diseases. This double burden of disease is, naturally, a financial and organisational challenge to handle for healthcare systems.

Surgical care in low- and middle-income countries has been considered too advanced in infrastructure, too expensive and too unreliable in terms of financial sustainability and know-how to be implemented in resource-scarce settings. In 2008, surgery was attributed as 'the neglected stepchild of global health', and the field quickly expanded in the following years (13). The vast insufficiency and skewed distribution of the global surgical resources are now gaining increasing attention (14–16). It has become clear that a large proportion of morbidity and mortality worldwide could be prevented simply by adequate surgical care; surgical conditions account for 15% of disability-adjusted life years (DALY) globally and surgical conditions are among the top 15 causes of disability (17,18). Additional studies revealed the cost-effectiveness of basic surgical interventions such as inguinal hernia repair, basic trauma care, club-foot treatment and cataract surgery in resource-scarce settings. The estimated cost per averted DALY for these surgical interventions was on par with many immunisation programmes and far less than oral rehydration therapies, HIV mother-to-child transmission prevention or short-course tuberculosis treatment (19–21).

In 2015, the Lancet Commission of Global Surgery estimated that 5 billion people worldwide do not have access to safe and affordable anaesthesia and surgical care when needed; that 143 million additional procedures are needed each year to meet basic population demands[4]; that 33 million people face catastrophic health expenditure directly related to basic surgical care each year, and that more than twice this number are financially ruined just by the effort to obtain anaesthesia and surgical care (22). The Lancet Commission on Global Surgery also concluded that safe surgery is affordable, saves lives, prevents disability, and it is a good investment for countries as it promotes economic growth.

A number of surgical indicators and targets were proposed by the Commission for national health systems to monitor. These indicators are now incorporated in the

improved living conditions for parts of the population. This shift in living conditions leads to a general decrease in child and maternal mortality, less susceptibility to epidemics and communicable diseases and higher median age in the population. The epidemiological transition can be rather quick, in a demographical context, and may occur within one or two generations.

[4] It could be argued that these numbers provide an overly simplified picture of the reality in discrete countries, as they were derived by extrapolations from data provided only by a few countries [authors' comment].

WHO's Global Reference List of 100 core health indicators, the World Bank's World Development Indicators, and the Sustainable Development Goals. They include *Specialist surgical workforce density* (number of surgical, obstetric and anaesthesia specialists per 100,000 population) and *Perioperative mortality and surgical volume* (annual procedures per 1000 or 100,000 population) (23,24). Through this process, the field of Global Surgery was defined and settled.

Studies on sustainable surgical systems in relation to global trends in population growth, economic transition, epidemiological shifts, and health system development are key questions in the field of Global Surgery. As advanced by this thesis, such science is also equally relevant for national health system strengthening in high-income countries.

Controversies in measures of surgical output

Measures of surgical care, in terms of *incidence*, *outcome* and *access*, require uniform definitions in order to make the results meaningful and interpretable. Defining surgery is not straightforward, however. Debas and colleagues proposed a widely used definition of surgery as:

> 'Anything that requires suture, incision, excision, manipulation, or other invasive procedure that usually, but not always, requires local, regional or general anaesthesia' (25).

This rather wide definition may be correct. Nonetheless, Debas definition proves less useful for the purpose of measuring surgical output on a population level, as it is too inclusive. An alternative and less inclusive definition of surgery, widely used in the global surgery and public health settings, refers to:

> 'Any procedure requiring general or neuroaxial anaesthesia, sometimes with the procedures performed in a hospital operation theatre' (26,27).

There have been efforts to estimate population-level surgical output (26,28). Based on such estimations, the Lancet Commission on Global Surgery proposed that a minimum annual output of 5000 surgical procedures per 100,000 population may meet basic surgical needs in most populations (22).

Problems arise when significant parts of the healthcare system are not included in the analysis of surgical output. Relevant procedures may be performed in other places than the operating theatre of a hospital, such as in the radiology department, the emergency room or in the outpatient clinic, and surgical procedures may be performed with or without anaesthesia according to local guidelines and available resources.

Controversies in defining surgical needs for a population

Indicators of surgery, in terms of *incidence*, *outcome* or *access* are sensitive to the data input. Estimations on surgical need in healthcare systems have commonly been derived from measures of operative volumes in relation to the population at risk. Collection of surgical data currently exists in 74 countries worldwide. Many countries started their systematic collection of data only recently, and the comparability is limited due to diverging definitions of surgery (29).

Measures of surgery reflect a) the dimensions, organisation and financial incitements of the healthcare system itself, b) the health insurance system serving the population, and c) the general population characteristics. Thus, surgical indicators (for example, surgical output, such as annual number of procedures per 1000 or 100,000 population) reflect the need for surgery in a certain population, but may also be a product of demographics and expectations in that specific population, or reflect limitations in access to surgical care (such as financial or geographical barriers). Therefore, to some extent surgical indicators are population-specific as well as system-specific (or legislation-specific).

Table 1. Sources of information of surgical output.
Hospital records from operation wards or hospital administration, health insurance companies documentation of costumers utalization of healthcare, and national databases, can provide valuable information on surgical data.

Source of surgical output	Comment on appropriateness
Hospital output derived from operation records	Widely used, even if the population at risk (i.e. the population served by that specific hospital) may be less well-defined.
Private health insurance databases	Have the advantage that the population at risk is well-defined. These datasets are commonly restricted to certain kinds of treatments, depending on the extent of health insurance, and the population covered by a certain health insurance may not be representative of the total population in a specified region or country.
National healthcare databases	Rare but valuable, as they tend to include the entire population. Several national databases include the public sector only. Procedures performed in outpatient settings (day surgery), or within the private sector are seldom included. In this context, the Swedish national healthcare databases are rare (yet not unique) exceptions as they includes private and public healthcare in both inpatient and specialised outpatient settings and day surgery.

Depending on the administrative infrastructure available, various methods have been applied for estimations of population surgical needs (Table 1). Critiques of surgical indicators point out that facility-based surgical measures (such as hospital records) are unreliable, as they are merely surrogate measures of the true 'population need' of surgery, but rather the 'met need', or even, in some settings, the expectations in the population (30). Epidemiological survey studies may be more accurate in estimating the 'unmet need' for surgical morbidity, than deriving it from population-based national records (31).

Knowledge gap – the population need for paediatric surgery

The efforts to put surgical care on the agenda have brought new insights to the role of surgery in public health. However, previous estimations of surgical need on population level have come with major limitations. Most estimations are derived from scarce data sources, based on diverging definitions of surgery, and either including only the public, or the private sector of the healthcare system. Surgical needs in females have not been differentiated from those in males, and various age groups have not been explored. In particular, surgical needs in the paediatric population have never been analysed. Therefore, earlier extrapolations of population need of surgery have been overly simplified. Such estimations would potentially improve if they could adjust for demographic variations. Age- and gender-specific incidences are therefore needed.

Only very few studies have considered the surgical care provided for children and adults in outpatient settings, such as day surgery. Excluding outpatient surgery is problematic, as a large proportion of surgical care is transitioned from inpatient settings to day surgery (27,32,33). This transition has been facilitated by achievements in anaesthetic and surgical techniques, but also a consequence of the reduction of hospital beds over the last decades. The number of hospital beds per 1000 population has been reduced or unchanged in all OECD country between year 2000 and 2015, except in China and Korea (34). In Sweden, this development has been dramatic; hospital beds were reduced from 3.6/1000 population in the year 2000, to 2.3/1000 population in the year 2017. In comparison, the OECD average was 4.7/1000 population in 2015 (34,35).

In summary, the reliability of population surgical volumes would improve if:

(a) All parts of a healthcare system were studied including both public and private sector, and both inpatient and outpatient care,

(b) All kind of surgery were studied, regardless of whether it was performed in an operating theatre, in a hospital or elsewhere, and independent of the anaesthetic method, and

(c) The entire population was eligible to seek care with no considerable financial or other barriers.

Addressing these knowledge gaps formed the rational for the first part of this thesis.

Organisation of paediatric surgery

Paediatric surgery in Sweden and abroad

Paediatric surgery is the surgical speciality to care for children with diseases requiring surgical intervention during infancy, childhood and adolescence. Traditionally, paediatric surgeons treat conditions of the thoracic or abdominal cavity, the genito-urinary system, trauma, solid tumours and vascular malformations. In addition, conditions of the musculoskeletal system, ear-nose-throat surgery, surgical conditions affecting the central nervous system and plastic surgery may be considered under the umbrella of paediatric surgery by some institutions.

In Sweden, advanced paediatric surgery is centralised to the university hospitals, whereas most surgical clinics provide general paediatric surgery. Even if there is no clear age cut-off, children of age 15-18 years or older are considered to be beyond the paediatric surgery spectrum of diseases and they are referred to general surgery clinics for care.

Studies have indicated that increasing volume and experience of rare paediatric conditions, or conditions requiring advanced medical care, are associated with better treatment outcome in terms of survival, complications and patient satisfaction (36–38). Consequently, surgical care for such conditions has been targeted for centralisation, including surgery for advanced congenital anomalies (5,39–43). The Nordic countries are considered suitable for centralisation of paediatric surgery, as the populations are relatively small and widespread (44).

In Sweden, advanced paediatric surgery has been centralised to four regional clinics: Uppsala University Hospital, Astrid Lindgren's Children's Hospital/Karolinska University Hospital in Stockholm, Queen Silvia's Children's Hospital/Eastern Hospital in Gothenburg and Children's Hospital/Skåne University Hospital in Lund. To improve the quality of care for a number of rare diseases, further centralisation of paediatric surgical care was implemented in 2018 when the National Board of Health and Welfare allocated all surgery for congenital diaphragmatic hernias, oesophageal atresia, anorectal malformations and Hirschsprung's disease to two national paediatric surgery centres (Stockholm and Lund) (7,8).

Controversies in centralising surgery

Centralisation of surgical care is a balance between creating centres of excellence on the one hand, and the drainage of resources elsewhere on the other. There are controversies related to this balance: while there is plenty of evidence that increasing volumes and experience of rare conditions or advanced treatment lead to improved outcome, less is known about the negative effects related to centralisation.

Increasing distance to the hospital also forces some patients to travel longer for optimal treatment, and this may become a barrier to optimal care (45). Allocating advanced surgical care to a limited number of surgical facilities may also have negative effects on more common conditions. As surgeons at low-volume general surgery facilities face a narrower spectrum of diseases, and their exposure to complicated cases becomes diluted, their familiarity with advanced surgery is reduced.

To what extent procedures need to be allocated to fewer hands has been debated within the surgical profession and academia. Reports suggest that common surgical procedures such as inguinal and femoral hernia repairs, have lower complication rates and lower risk of recurrence when treated at high-volume centres or by experienced surgeons (46,47). However, proper comparisons of outcomes are not performed easily (48), and there is diverging evidence of the beneficial effects of volume. No clear effect of further centralisation was seen in the treatment for paediatric appendicitis, and surgery by surgeons performing at least four pyloromyotomies annually was not associated with significantly more complications than surgery performed by surgeons at high-volume centres (49).

Knowledge gaps

Only a few studies have focused on the potential negative effects of centralisation of surgical care. Risk factors for suboptimal treatment due to access problems to paediatric surgery are largely unknown. To what extent family background, socio-economic status or language barriers influence children's chances to obtain proper and timely medical care is unclear. Do children need their parents to be healthcare literate, or financially stable to successfully attain the optimal level of care? Do they need their parents to access social networks in order to access timely surgery? Are there threshold effects, so that those children who are offered optimal surgical care do well, as intended, whereas some children are at risk of never really reaching all the way through these barriers?

If so, does it matter whether the child needs emergency surgical care or surgery that can be identified and planned well in advance?

The elective care example – Surgery for cryptorchidism

Early in their training, paediatric surgeon trainees will learn to identify, diagnose and treat cryptorchidism. This is one of the few conditions in boys that is seen frequently. It is not emergent or overly complex, yet timely treatment with the right level of care is recommended to avoid perioperative complications or comorbidities later in life. Therefore, the diagnosis and treatment of cryptorchidism is suitable to study as an indicator for outcome and access of non-emergent paediatric surgery.

Normal testicular development

Early in foetal development, during gestation week 6-7, gonadal tissue located in the genital ridge differentiates into testicular structures. As Leydig cells develop in the testicles, local testosterone levels rise. This stimulates the formation of Wolffian structures, which form into the epididymis and vas deferens. The testicles and the kidneys are formed adjacent to the internal inguinal ring in the abdominal cavity. As the foetus grows, the kidneys migrate in a rostral direction to their retroperitoneal position in the posterior part of the upper abdomen where they are protected by the lower ribs. Meanwhile, the testicles remain in position at the internal inguinal orifice, presumably anchored to this position by the gubernaculum. The gubernaculum then plays an active role in guiding the testicles downward through the inguinal canal, and down to the scrotum, where the gubernaculum transforms into a fibrous structure in the lower part of the scrotum (50,51).

The entire process is directed by the hormonal interplay between activating and inhibiting factors (52,53). The process of testicular descent is not fully understood, and several theories of gubernaculum physiology have been proposed. The migration through the inguinal canal is initiated in gestation week 22 and usually completed by week 27, even if evidence suggests that this process takes only a few days (50). By week 32, most testicles are in the scrotal position. Some normal variation in this migration process exists, and the rate of undescended testicles at birth is relatively high in full-term infants as well as those who are premature (54–57). In clinical praxis, however, it is considered that further testicular descent after 6 months of age is unlikely (52,58,59).

Cryptorchidism

Cryptorchidism[5] is the most common genital anomaly in boys. Previous studies have reported prevalence between 1.0-10.7% (54,57,60–62). The wide range in

[5] Greek: *kryptos* = hidden, *orchis*= testicle. See Text box 1 for a discussion on the nomenclature.

prevalence[6] can be attributed to variation in methods and classification of cryptorchidism, and to the accuracy of the diagnosis. The testicular development is a dynamic process and, therefore, the prevalence is sensitive to the age at evaluation. The prevalence also varies in different population and risk groups (55,57). The term *secondary* cryptorchidism refers to cases where a testicle has been properly positioned in the scrotum, and later ascends up to a suprascrotal position.

Text box 1

Cryptorchidism, undescended testis and retractile testicle

There are terms for cryptorchidism that are used interchangeably, and a few words on the nomenclature would be appropriate.

Whereas **undescended testes** relate to a testicle that is retracted in the descendance to the scrotum, **cryptorchidism** relates more broadly to a testicle that is not properly palpable in the scrotal position. A cryptorchid testicle may thus be undescended, or ectopic (i.e. descended to an improper position, such as the groin, the perineum, femoral canal, perineum, or even the contralateral hemiscrotum), or absent (due to aplasia or testicular atrophy) (53).

A **retractile testicle**, in contrast to the cryptorchid testicle, has a clear tendency to retract to a position superior to the scrotum, usually by an active cremaster muscle. The retractile testicle can be pulled down to the scrotum when the cremaster muscel is relaxed, and the condition is not considered to be pathological. No treatment is indicated, yet active follow-up should be consiedered with regular intervals until the testicular position is fully acceptable.

The term cryptorchidism will be used throughout this thesis. The rational for this is that the exact cause of a clinical unpalpable testicle, will in some cases remain unknown until the surgery is performed, yet the same diagnostic workup and treatment algorithm is applicable.

Aetiology and risk factors for disease

As outlined, the physiology of the normal testicular development and descent is complex. Several hormonal and genetic factors have been identified to cause disturbances in the hormonal interplay, including diseases affecting androgen secretion and functioning (Table 2) (63,64). However, associated abnormalities are found only in 15% of children with cryptorchidism, and in most cases the aetiology is unknown. Risk factors for secondary cryptorchidism include previous inguinal or scrotal surgery, where the testicle or the cord may be trapped and retracted due to the scarring. Well-established risk factors for cryptorchidism include birth characteristics associated with prematurity and poor intrauterine development, which can be expected as the normal testicular descent occurs in the third trimester of pregnancy. Thus, shorter pregnancy length, lower birth weight and being born smaller sized than expected are all associated with higher risk of high testicular position at birth (54–56,60). Even if large variations have been reported between countries, it is unclear as to what extent environmental or genetic factors impact on the risk (55). Recently, two large epidemiological studies based on Swedish and Danish register data on risk factors during pregnancy suggested that maternal

[6] In study II, the term *prevalence* is used to report cryptorchidism in the population, whereas in study IV, *incidence* is used. See Text box 2 for discussion on prevalence and incidence.

smoking and obesity (measured as maternal BMI during pregnancy) were associated with higher risk of cryptorchidism (65,66). Since smoking and obesity are associated with preterm birth and intrauterine growth retardation, it is unclear to what extent smoking and obesity explain the general risk of prematurity and low birth.

Table 2. Known comorbidities associated with cryptorchidism (64)

Mechanism affecting testicular development and descendent	Syndrome
Affecting the hypothalamic and gonadal axis	Kallmann syndrome Prader-Willie syndrome Isolated hypogonadotrophic hypogonadism
Testiclular testosterone secretion dysfuntion	Kleinefelter's syndrome Testicular dysgenesis syndrome Noonan syndrome Congenital adrenal hypoplasia
Insufficient testosterone effect	Androgen insensitivity syndrome
Developmental disorders of the abdominal cavity	Gastroschisis Omphalocele Bladder exstrophy Prune belly syndrome

Classification

There is no uniform classification system for cryptorchid testicles, even if most surgeons differentiate the palpable testicle from the non-palpable testicle. The cryptorchid testicle is commonly located in the inguinal region, such as in the inguinal canal or outside the external inguinal ring. The ectopic testicle is usually found deviated slightly lateral to the expected canal down to the scrotum, and less commonly in the groin or even medially towards the peno-pubal or perineal region (53). The ectopic testicle can prove rather difficult to locate with clinical palpation. The non-palpable testicle is usually located just proximal to the internal inguinal orifice, and sometimes the experienced clinician may be able to manipulate the testicle out through the inguinal canal. However, the non-palpable testicle can also be located outside the internal inguinal orifice and the exact position may not be revealed until the time of laparoscopy. In some cases, the suspected non-palpable testicle is in fact an absent testicle, due to aplasia or atrophy.

Text box 2

Prevalence, incidence and cumulative incidence in the case of cryptorchidism

Prevalence (or *prevalence poroportion*) is the *proportion* having the disease in a population at a specified *point* of time, whereas **incidence** (or *incidence rate*) refers to the number of *new cases* of disease in a specified *period* of time. The **cumulative incidence** (or *cumulative incidence rate*) is also a proportion, and describes the risk over time.

While most authors consider incidence rate as the intuitive way of reporting cryptorchidism in populations, some authors argue that prevalence would be more correct in the case of cryptorchidism. The rational to report prevalence is that cryptorchidism is considered a congenital condition, and consequently, the condition is present over time regardless of the timing of diagnosis.

Clinical characteristics and diagnosis

The cryptorchid child is in general a perfectly healthy boy with no specific symptoms or problems (Text box 3). The experienced clinician (or parent) may notice that the affected hemiscrotum is less developed and flatter than expected, and the parent may confirm that only one testicle has been visible.[7] The clinical diagnosis is made when the clinician determines the testicle to be non-palpable, malpositioned or not reducible to the scrotum.

In cases where the testicle is reducible to the scrotum, retractile testis must be ruled out. This is done by gentle traction of the testicle cord to evaluate the tension of the cord and whether the testicle remains in the scrotum when the cremaster muscle is relaxed.[8] A retractile testicle requires no intervention, but active monitoring of the progression is warranted to rule out secondary cryptorchidism. Annual controls are recommended for retractile testes (67,68).

Clinical evaluation by experienced physicians has proven higher in sensitivity than ultrasonography, computed tomography and magnetic resonance imaging, and routine radiological imaging has usually no role in the diagnosis (53). However, imaging can be used as a diagnostic aid in selected cases.

Text box 3

Screening, timely referral and level of treatment

Children in Sweden are enrolled in a healthy child screening programme from birth to school-age. The check-ups are conducted by paediatricians or primary care physicians (usually specialists in general medicine with special interest in paediatrics), or by paediatric nurses. Until 2017, testicular status was assessed by a physician at birth, 4 weeks, six months, and at 12 months of age. Suspected cases of cryptochidism should be referred to a surgical or urological clinic for evaluation when the child is 6 months or older. The treatment is offered at most general surgery or urological clinics, but the lower age for safe anasthaesia and surgery may vary between clinics. Referral to a dedicated paediatric surgical centre is encurraged for all children <12 months of age with cryptorchidism.

In most cases, clinical evaluation provides enough information to decide on surgical treatment. However, bilateral non-palpable testes are considered special cases, where underlying gonadal anorchia (complete lack of gonadal tissue), androgen insensitivity syndrome and chromosomal abnormality must be ruled out (53,67). In the Nordic countries as well as in the American guidelines, endocrinological and genetic workup is recommended in these cases, as diseases of sexual differentiation must be considered, particularly in cases of suspected micro-penis or hypospadias (67,68).

[7] Testicles in neonates and children are usually easy to detect when the child is relaxed and warm, such as when sleeping in a warm bed or having a warm bath. On the other hand, the same testicles can prove rather uncooperative when a clinical evaluation is conducted with cold hands, in a freezing hospital room with a nervous and frightened child (and an equally nervous parent).

[8] At our institution, traction for about 30 seconds has been recommended to exhaust the cremaster muscle in most cases, but this routine may vary between institutions.

Treatment and timing of surgery

Surgical treatment of cryptorchidism is the gold standard. Non-surgical treatment is not recommended in American guidelines (68). According to the European guidelines and the Nordic guidelines hormonal treatment may be an option in selected cases (67,69). Hormonal treatment is rarely used, however, due to the low success rate, high risk of recurrence and problematic side-effects.

The standard surgical treatment is orchidopexy (53,67–69). In cases of cryptorchidism where the testis is palpable, an inguinal or scrotal incision is recommended, and an orchidofundicolysis[9] is conducted (67–69). In this procedure, the processus vaginalis (the fibrous structures covering the funiculum), is dissected and divided, and when a hernia sac is present, this is carefully isolated and ligated. The flexible and gracile vasal duct (vas deferens) and the spermatic vessels are carefully isolated. In most cases, this provides adequate length of the spermatic cord to allow the testicle to be fixed in a subdartos pouch in the scrotum without tension (53,70).

Text box 4

Fowler-Stephens orchidopexy for high abdominal tests.
The Fowler-Stephens procedure is a one- or two-step operation where the spermatic vessels are divided and the testicle either positioned in the scrotum immediately, or left in the intra-abdominal position for about 6 months, to develop collateral blood supply from the cremaster muscle and the vasal vessel surrounding the spermatic duct. In the second operation (Fowler-Stephens II), the testicle is manipulated down the inguinal canal and the operation proceeds with standard orchidopexy with the aim of positioning the testicle in the scrotum.

In cryptorchidism with a non-palpable testicle, laparoscopy is recommended and provides high sensitivity and specificity for the identification and evaluation of an intra-abdominal testicle. The standard technique is to begin with an umbilical port for diagnostic evaluation of the internal inguinal rings. In the presence of a viable testicle, or if testicular vessels enter the inguinal canal, the testicle can usually be manipulated laparoscopically and the operation can proceed with an open inguinal incision. If the spermatic duct or the testicular vessels are short and do not allow for a primary orchidopexy, other techniques may be considered, including the staged orchidopexy or Fowler-Stephens procedure (Text box 4) (71). The laparoscopy-aided orchidopexy has been associated with success rates of 96-100% in various series, as defined by the fixation of the testicle in a scrotal position, or finding of an atrophied testicle (53,68).

[9] The term *orchidopexy* is used consistently in this thesis, in line with the European Association of Urology (EAU), and the European Society for Paediatric Urology (ESPU), even if the American Urology Association (AUA) prefers the term *orchiopexy* for this operation (68,69).

Text box 5

Cohort studies of rare outcomes – an outlook

Risk factors for outcomes that require very long exposure time are not easily determined, and causal relationships can prove very hard to establish. The association between cryptorchidism in childhood and testicular malignancy many decades later in life has been suspected for quite some time; the risk of testicular cancer was increased 2-8 times in men with previous cryptorchidism, and 5-10% of men with testicular cancer have had cryptorchidism. Still, for a long time it was unclear if the association was due to common underlying factors causing both diseases, or if it *de facto* was a causal relationship.

However, when a large cohort of Swedish children was evaluated for the length of the exposure (i.e. age at cryptorchidism) and followed for many decades in medical registers to estimate differences in this rare outcome (testicular malignancy), it was found that lower treatment age was.associated with lower risk of testicular malignancies. A causal relationship is thus likely.

The study was based on data from the National Patient Register and the Swedish Cancer Register and published in the *New England Journal of Medicine* in 2007.

Cryptorchidism increases the risk for complications during childhood and adult life, and this is the motive for early surgical intervention (Text box 5 on testicular malignancy[10]). The risks include impaired semen quality and reduced fertility later in life, and an increased risk of testicular malignancies (72–76). Also, an increased risk of testicular trauma and testicular torsion in cryptorchid testicles has been reported, and this risk is believed to be lowered by surgical fixation in the scrotum.

During the last decades, the recommended age for treatment has been lowered, as the complication risks have been shown to correlate with the treatment age. Currently, guidelines in the Nordic countries recommend that surgery should be performed at 6-12 months of age or, if later, as soon as the diagnosis is established (67). European and American guidelines are somewhat more flexible and recommend treatment before 12 months of age if possible, and no later than 18 months of age (68,69).

Treatment delay

The age at treatment may be adjusted to the circumstances in each individual, such as comorbidities, and the benefits of early treatment may not outweigh the risks or efforts in every case. It has been suspected, however, that disadvantages in socioeconomic circumstances or financial barriers to paediatric surgical care may also increase the risk of treatment delay. Suggested risk factors for treatment delay include low socioeconomic status[11], lower insurance level or rural area of residence (as compared to urban area of residence) (61,77,78). However, the evidence is not entirely conclusive, and socioeconomic risk factors are context-specific, as outlined

[10] References for Text box 5: Petterson et al. (2007)(76).

[11] In most studies, socioeconomic status is measured as the average income level, the average educational level or a weighted index of socioeconomic status for the ZIP-code area.

previously (79). For example, a large Danish study could not establish any association between socio-occupational class and the age at cryptorchidism (80).

Knowledge gaps

When initiating this thesis work, it was unclear to what extent the Nordic guidelines were followed in terms of treatment age, and provision of surgical treatment at paediatric surgery facilities for children under the age of 12 months. Furthermore, it was not known if children were treated equally throughout the country, or if there were regional differences that should be addressed.

It was also unclear as to which extent socioeconomic status was to be considered a risk factor in a country where paediatric healthcare, including surgical care, is free of charge. Previous studies on risk factors for treatment delays have considered insurance status and average socioeconomic status in the area of residence, but have not been able to adjust for these factors on an individual level. Therefore, these estimates were rather proxies of socioeconomic status, than the actual circumstances in the families included for the study.

Despite ongoing centralisation of both paediatric surgery and paediatric anaesthesia, no previous study has addressed the association between distance to hospital and the timing of treatment in the case of cryptorchidism. In fact, very few studies have addressed travel distances to hospital in the paediatric population. Only two studies have been able to include 'rural place of residence' as dependent variables for analysis, with no specification of what the distances or travel times to hospital were and no adjustment for individual-level risk factors (61,77).

The emergency care example – Surgery for appendicitis

In analogy with cryptorchidism, appendicitis is one of the common conditions in general surgery and paediatric surgery that surgeons must learn to diagnose and treat quickly. Unlike cryptorchidism, however, most children with appendicitis require prompt attention and emergency surgery. For these reasons, paediatric appendicitis has generally been considered suitable to study for outcome and access of emergency paediatric surgery (81–86).

Text box 6

Of an inguinal rupture with a pin in the Appendix Coeci, incrusted with stone, and some observations on Wounds in the Guts

The patient was a boy of 11 named Hanvil Anderson, and the hernia had been present from infancy. Amyand decided that an associated faecal fistula could be cured only by cure of the hernia. He explored the scrotal swelling and found the appendix perforated by an encrusted pin. With some difficulty, he separated the omentum and the appendix. The latter was doubled on itself. It was amputated and a stump one inch long was left because a fistula was anticipated. The hernial sac was removed and the fistuolus tract excised. Healing was rapid and the stump ligature separated on the tenth day without incident. This operation took 'near half an hour' – a tribute to the skill of the surgeon and the fortitude of the small boy.

- Published in original in the *Philosophical Transactions in 1736, by Claudius Amyand, surgeon to St George's Hospital, fellow of the Royal Society (as quoted by Dr P. G. Creese, in Surgery, Gynecology & Obstetrics, (1953;**97**:643)*

Appendix vermiformis

The appendix vermiformis is a short blindly-ending segment of the large intestine, usually less than 10 centimetres in length. When the intestines develop in the embryo, the appendix vermiformis is formed as a bud and elongates from the caecum[12], a process starting in the 6th week of pregnancy and is completed in the 12th week.

Even if several theories have been put forward on the physiological function of the appendix vermiformis, its purpose remains a well-hidden mystery of the human body. I am therefore not intending to burden the reader with unproven theories on its physiological function. However, an insight into its function has been provided by observations of how removal of the appendix vermiformis modifies the risk for other diseases (87,88). In the lack of proven use, creative surgeons have introduced

[12] The caecum is the very first part of the large intestine (the large intestine is also known as the colon), where the small intestine ends.

more concrete uses of the appendix vermiformis, including reshaping it as a canal for urinary deviation[13] or for bowel enemas[14].

Appendicitis

Historical outlook

Historically, appendicitis has been a feared condition with high mortality. Prior to the introduction of anaesthesia and abdominal surgical techniques, the treatment of choice was, naturally, a conservative wait-and-see approach. Sporadic reports of appendicitis cases, and more or less remarkable (and successful) attempts to treat it with surgery, have been documented since the early half of the 18th century (89). These early appendectomies were usually incidental, it seems, as many were performed when inguinal or scrotal hernias were ligated (Text box 6). The first description, written in English, of a *perforated appendicitis* was made in London in 1812; a 5-year-old boy deceased with 2 days' history of acute illness and general peritonitis, and the necropsy revealed a perforation of the appendix distal to a faecolith (89).

During the first half of the 19th century, series of appendicitis[15] were reported. In the second half of the 19th century, the first case series of successful surgical treatments was published. In Britain, the conservative regimen prevailed to the end of the 19th century (considering the perioperative risks at that time, conservative treatment may well have had the best outcomes – do no harm, we have all been taught), but in the 1880s, case reports and series of laparotomies for acute appendicitis were published in Britain and other European countries, and in the USA (Text box 7) (89).

[13] The Monti canal is where the appendix vermiformis is disconnected from the bowel and sutured to the urinary bladder instead, with the other orifice placed through the abdominal wall and sutured to the skin. The Monti canal allows urine to be evacuated via the artificial stoma on the abdomen.

[14] The Malone antegrade continence enema (MACE) is where the appendix is still attached to the caecum, and the blind end opened and deviated trough the abdominal wall to be sutured to the skin. This allows the antegrade infusion of enemas in the large intestine, and has proven effective in severe cases of obstipation.

[15] Commonly referred to as thyphilitis or perithyphilitis at the time.

Text box 7

Sir Frederick Treves –the pioneer who introduced the interval appendectomy

Among many pioneers to mention, a few words on Sir Frederick Treves are appropriate. Sir Treves has been attributed to the first appendectomy in Britain (1888), and introduced the concept of interval appendectomy as a safe strategy of appendicitis treatment. He had quite a reputation in the British medical and surgical community at the time, and became famous to the public for the successful drainage of an appendicitis abscess in King Edward VII in 1902. Unfortunately, he lost his own daughteras a result of a generalised peritonitis, most likely due to an perforated appendicitis, which he hesitated to operate upon. [Authors' comment: His hesitation may reflect the perioperative risks related to abdominal surgery at the time]

The interested reader may find the biography on Sir Frederick Treves rather fascinating: Sir Frederick Treves, the extraordinary Edwardian by S Trombley. London, Rutledge, 1989. The book was not easy to locate but is now at the Lund Univerity Library, due to the willing efforts provided by the medical faculty librarians.

Epidemiology

Appendicitis is the most common cause of abdominal surgery in children, and is also the gastrointestinal condition that brings the highest societal costs in children (83,86,90,91). The lifetime risk of appendicitis has been estimated as 9% in males and 7% in females (92).

In Sweden, the overall incidence of perforating and non-perforating appendicitis between 1970-1989 was estimated at 116 per 100,000 population, with a higher risk in males than females (relative risk 1.27 [95% confidence interval 1.16 to 1.38]) (93,94). The risk is increased dramatically during childhood and adolescence and peaks at age 10-20 years, but this risk was mainly attributed to non-perforating appendicitis (92,93,95).

The incidence has decreased during the last decades in most Western countries (91–93,96–98). In Sweden, the incidence of appendicitis in children declined between year 1987 to 2013 from 177 to 100 cases per 100,000 person-years; the decline of non-perforated appendicitis was from 139 to 68 and perforated appendicitis from 28 to 20 per 100,000 person-years) (94). Even if improved diagnostics, including improved specificity in radiology and laboratory testing, explains this decline to some extent, most authors agree that there has been a shift in incidence in Western populations during the last half century.

Aetiology and risk factors for appendicitis

The aetiology of appendicitis has not been clarified.

As indicated by the age variation in incidence, there is a peak in risk for appendicitis during adolescence and childhood, and males are at a generally increased risk compared to females (92–94). However, the youngest children (<5 years of age) rarely suffer appendicitis. Differences in incidence in various parts of the world and

various populations, suggest an impact of either genetic or environmental factors. Whereas appendicitis is relatively common in Caucasian populations, the incidences are lower in Afro-American, Latino and Asian populations (99). This difference is seen on a national level, but also in subgroups of populations in Western countries and in adoptees, suggesting variations in genetic proclivity for disease (100).

Theories of the aetiology of acute appendicitis include changes in the microenvironment and microbiota in the appendix vermiformis. It also seems clear that an obstruction of the appendiceal lumen may lead to appendicitis, supposedly by obstructing the drainage of secretions from the lumen and initiating an inflammation in the tissue, which ultimately leads to perforation. This hypothesis is supported by the numerous radiological and perioperative findings of solid bodies in the appendiceal lumen, just proximal to the inflammation or perforation. Commonly, such bodies consist of hardened faecal matter (faecalith), but may also be seeds from grapes, oranges or other fruits, rice, or parasites. However, faecalith or other visible obstructions of the appendix have been found in 20-30% of paediatric appendicitis cases, and only 41% of those with perforation or gangrene, suggesting other aetiologies in the majority of cases (101,102).

Risk factors for perforated appendicitis

There are a few known risk factors for appendiceal rupture or gangrene: young age, and the presence of a faecalith in the appendiceal lumen are the two factors that are generally accepted (101–103). A few additional factors have been associated with rupture rates; prolonged time with symptoms seems to allow for disease progression and consequently higher rupture rates, whereas, just recently, IgE-mediated allergy[16] has been associated with a reduced risk in children (103,104).

For the last century, it has generally been accepted that prolonged symptoms increase the risk of perforation or gangrene of the appendix. Urgent treatment has therefore been advocated to avoid complications. Results from numerous studies support this 'old truth' (104–106). It must be stressed, however, that most of these studies have methodological limitations, as it is very hard to confirm time chains in the development of appendicitis prospectively. Instead, they commonly rely on self-reported onset of symptoms, and are vulnerable to reporting bias and, more importantly, selection bias.[17]

[16] IgE-mediated allergy is linked to an predominantly Th2-mediated immune response, and the finding of an association between IgE-mediated allergies and less perforated or gangrenous appendicitis is in line with previous results; perforated appendicitis is characterised by a predominantly Th1 and Th17 mediated T-helper cell immune response, whereas non-perforated appendicitis is characterised by a predominantly Th2-mediated immune response (145,146).

[17] The selection bias in studies of appendicitis symptom progression relates to the risk of not including mild cases of appendicitis that resolve spontaneously, and which therefore never reach

The view of appendicitis as an emergent condition has been challenged during the last two decades. Some authors argue that perforation rates are not related to the timing of treatment, but to access of care and, therefore, relate to variations in incidence of either complicated or non-complicated appendicitis, rather than prevented perforations by timely treatment (93,107). The impact of symptom duration is further confused by findings that prehospital, but not in-hospital, delay increases the risk of perforation or complicated paediatric appendicitis (108,109). It must be stressed that these studies are susceptible to severe biases, as they are based on retrospective healthcare records and confounding by indication is highly likely. Also, retrospective observational studies on the risk for complicated appendicitis may be biased by the selection of cases with uncomplicated appendicitis; if mild appendicitis cases seek care early, they will likely be treated with surgery, whereas mild cases with prolonged prehospital delay may as well go in spontaneous regress before even reaching the hospital, and thus never be exposed to the surgeon's eye (107).

Socioeconomic-, societal- and healthcare-related factors have been associated with the risk of perforated or complicated appendicitis, presumably due to treatment delays in certain risk groups. Worse insurance status[18], low average income and low average educational level in the area of residence have been associated with higher risk of complicated appendicitis (81,83,85,95,98,110,111). In addition, rural area of residence has been associated with increased risk (95,98,110,112,113). Even if ethnicity has been associated with perforation risk, it is unclear to what extent complication rates between different ethnic groups reflect genetic or socioeconomic risk (81,109).

Classification

Appendicitis is usually classified as uncomplicated or complicated (see Text box 8 for clinical characteristics and diagnostic aid). This definition does not come with clear criteria. However, perforated appendicitis is always considered complicated, as would most gangrenous appendicitis cases and appendicitis abscesses. Since there is a progressive inflammation, from the mildly phlegmonous appendix to the gangrenous or perforated appendix, and even abscess formation later in the course of perforated disease, the classification may be arbitrary. Until 2010, the Swedish version of ICD-10 classified acute appendicitis based on the perioperative finding

the hospital. Thus, there is a 'selection' of more severe cases in the hospitals, and these are the ones included in the studies (107).

[18] Insurance status as a determinant of health are mainly seen in studies from the United States, and usually refers to the expected principal payer on admission to medical services. Medicaid and private insurances, such as fee-for-service and private pre-payed health insurance plans, are frequently reported. Insurance status is expected to be reported rather accurately in healthcare records.

(or the pathological evaluation), so that perforation, gangrene or abscesses were confirmed by visual inspection. From 2010 and onwards, the classification changed to a clinical determination of the abdominal status, based on the presence or absence of localised or generalised peritonitis (114).

Treatment

The standard treatment for acute appendicitis is open or laparoscopic appendectomy, and the surgical technique in children does not differ from the one in adults. Postoperative intravenous antibiotics are recommended in *complicated* appendicitis[19]. No particular postoperative treatment is recommended in *uncomplicated* appendicitis.

In selected cases, non-surgical (conservative) treatment is provided, usually with fasting, antibiotic and supportive care. Sometimes, drainage of abscess via local incision or laparotomy, with or without appendectomy, may be indicated. Non-surgical treatment is applied when the potential gain of surgical intervention does not motivate the surgical risks. This may be an alternative in selected cases of uncomplicated appendicitis when the symptoms are very mild or already clearly in regress and the patient is doing well, or more often in cases of complicated appendicitis with abscesses where the patient is stable with no signs of deterioration. However, non-surgical treatment is not recommended for uncomplicated appendicitis due to lack of evidence of effectiveness and safety (53).

Appendicitis is a common condition in both children and adults, and most hospitals in Sweden have the necessary routine and experience to diagnose and treat the condition any time of the week. However, radiological resources may be limited during out-of-office hours at some hospitals, particularly ultrasonographical competence, and the surgical or anaesthetic competence may not be adequate for smaller children with appendicitis. Therefore, children may be transferred to clinics with paediatric-experienced surgeons or anaesthetists. The youngest children, or those with comorbidities or particularly advanced disease may be transferred to any of the tertiary paediatric surgery centres for surgery or advanced perioperative care.

Knowledge gaps

Even if family background, in terms of socioeconomics (income, education, insurance) has been associated with the appendicitis perforation risk, all previous studies have been based on retrospective register data, and used proxies for socioeconomic determinants of health (such as *average* income, *average* education

[19] A treatment length of about 10-12 days has been recommended, with transition from parenteral to oral antibiotics no earlier than postoperative day 5 (or when clinical symptoms have resolved), and 7 days of oral treatment (53,147,148).

or general socioeconomic deprivation index in ZIP-code area of residence) rather than individual-level data.

Even if rural status has been included in previous analyses, this is a vaguely defined variable, and only one study has considered the geographical distance to hospital (112). In that study, distance was estimated by a straight line from the ZIP-code area of residence to the hospital, rather than by analysis of the actual road route net.

Text box 8

Clinical characteristics of appendicitis and diagnostic aid

The classical early symptoms in appendicitis are seen in about 50% of patients, and include abdominal pain, nausea, mild fever and abdominal tenderness in the right lower quadrant. The pain is usually unspecific or localised to the umbilical region initially, and migrates to the right lower quadrant and escalates during the first hours or day. While loss of appetite and nausea are early symptoms, sub-febrility develops later when the inflammation spreads and the fever is usually accompanied by a localised or generalised peritonitis.

Needless to say, symptoms and clinical signs are less pronounced in children and the diagnosis can prove to be a real challenge in the youngest ones. A high degree of suspicion may help.

Laboratory tests may add to the clinical evaluation of suspected appendicitis, but all tests have low specificity. Mild leucocytosis may be detected early in blood samples, whereas elevation of C-reactive protein (CRP) usually requires >6 hours from symptom onset for detection. A urinalysis may be obtained to exclude bacteriuria (suggestive of differential diagnosis such as pyelonephritis), and is usually normal in the case of appendicitis, or may show red and white blood cells due to local inflammation in the vicinity of the urinary tract.

The diagnosis may be confirmed by abdominal ultrasonography (US) or abdominal computed tomography (CT). Both modalities provide high sensitivity (85-95%) and specificity (90-95%), even if US is particularly sensitive to the experience of the radiologist. US is also free from radiation and contrast, which is a clear advantage as compared to CT. Magnetic resonance imaging (MRI) is an attractive option due to very high diagnostic accuracy with no disadvantage of radiation exposure, yet its use is still limited due to low availability and the need to lie still for quite some time to obtain an optimal result. Plain abdominal X-rays may capture faecaliths, but they are of little use, unless a differential diagnosis is more likely (such as bowel perforation with free intra-abdominal gas or bowel obstruction).

Aims of the thesis

The overall purpose of this thesis was to describe the *incidence* of surgery for children and adults in Sweden, and to analyse treatment *outcome* and patient *access* to timely elective and emergency surgical care for Swedish children. Five separate epidemiological studies were conducted. The specific aims and research questions is presented below.

First, population needs of surgery were analysed in adults and children during an 8-year period, and overall *incidences* were determined. Then, two representative paediatric surgical conditions with considerable public health impact were analysed in the entire population of Swedish children – one was an elective and the other was an emergency surgery procedure. Finally, these two conditions were analysed regarding patient *access* to timely surgical care.

The rationale for study I was our hypothesis that previously reported estimates of basic surgical outputs on population level (5000 operations per 100,000 population and year) severely underestimated the surgical needs in high-income populations, as most outpatient surgeries were excluded from these estimates. We aimed to provide gender- and age-specific incidence estimates of surgery, to improve the accuracy in population estimates of surgical needs.

The rationale for studies II and III was the general lack of reliable data on peri-operative and postoperative surgical risks related to paediatric surgery in Sweden. In study II, we specifically aimed to assess whether children were treated equally throughout the country.

The rationale for studies IV and V was our hypothesis that socioeconomic and geographical circumstances had an impact on children's access to optimal and timely surgery. In particular, we hypothesised that the distance to a surgical facility would be a barrier to non-emergent and emergency surgical care for children.

Two paediatric conditions were chosen for evaluation in studies II-V:

a. Cryptorchidism – to exemplify elective paediatric surgery
b. Appendicitis – to exemplify emergency paediatric surgery.

Both conditions are relatively common in children, and both could potentially be treated at most surgical facilities in Sweden.

Aims and research questions in study I

Specific aims were to describe the age- and gender-specific *incidences* and trends of surgical procedures in Sweden, including in both inpatient and outpatient settings. Incidences of surgery in the paediatric population were thereby put in relation to the overall population. A secondary aim was to assess the distribution of surgical procedures across major disease groups.

Specific research questions included:

1. What were the age- and gender-specific incidences of surgery in the Swedish population?
2. To what extent was surgery performed in outpatient settings?
3. To what extent was surgery performed in children, as compared to adults?

Aims and research questions in study II

This study aimed to describe the *incidence* and *outcome* in an elective surgical condition for children, exemplified by the treatment for cryptorchidism. Specific aims were to evaluate treatment characteristics and complications, and differences between geographical regions of the country were assessed. A secondary aim was to evaluate if treatment age was in line with national guidelines throughout the country.

The specific research questions included:

1. What was the risk of cryptorchidism among Swedish boys up to age 18 years?
2. How did the risk of disease correlate with known risk factors, including prematurity, low birth weight and size for gestational age?
3. What kind of hospital (local, regional or university hospital) provided the care, and were there any trends in referrals?
4. To what extent were operations performed as day surgery, and what treatment modalities were used (open procedure or minimally invasive surgery)?
5. At what age were boys in Sweden treated for cryptorchidism? Were there any time trends in treatment age? Does the age at treatment vary within Sweden?
6. What were the surgical risks in terms of 30-day mortality and surgical site infections?

Aims and research questions in study III

This study aimed to describe the treatment characteristics and *outcome* in a condition requiring emergency surgery in children, exemplified by acute appendicitis. Specific aims were to evaluate how paediatric appendicitis was treated in Sweden, and to assess how the complication risks were associated with disease severity and treatment modality.

The specific research questions included:

1. What treatment modalities were used in complicated and uncomplicated appendicitis in children, and were there any trends over time?
2. What were the risks for postoperative complications (surgical site infection, re-admission, re-operation or mortality within 30 days from discharge)?
3. What was the long-term risk of small bowel obstruction after appendicitis? Was the risk different in complicated as compared to uncomplicated appendicitis?
4. Was treatment modality, adjusted for disease severity, associated with the risk of adverse postoperative events?

Aims and research questions in study IV

This study aimed to describe the *access* to timely treatment in an elective surgical condition for children, exemplified by the age at surgery for cryptorchidism. Specific aims were to determine the *incidence* of cryptorchidism in known risk groups of the population, and the timing of treatment for children in potentially unfavourable socioeconomic and geographical risk-groups.

The specific research questions included:

1. What was the risk of cryptorchidism among Swedish boys, by levels of known or suggested risk factors, adjusted for socioeconomic determinants of health?
2. How was the travel distance to hospital associated with timely treatment, when multiple birth-related risk factors and socioeconomic determinants of health were adjusted for?
3. Where there any socioeconomic determinants in particular that were associated with treatment delays (including parental education level, parental employment, family income, social security benefits or parental migration status)?

Aims and research questions in study V

This study aimed to describe the *access* to timely treatment in an emergency surgical condition for children, exemplified by the risk of complicated appendicitis. Specific aims were to describe the *incidence* of paediatric appendicitis in Sweden, and if the risk of suffering complicated appendicitis was higher in potentially unfavourable socioeconomic and geographical risk-groups.

The specific research questions included:

1. What was the childhood risk of appendicitis, and how common was complicated appendicitis in children?
2. Did the risk of complicated appendicitis differ between gender or by age during childhood?
3. Were there any trends in operative volume per surgical facility, suggesting that treatment for paediatric appendicitis had been centralised during the study period?
4. How was the travel distance to hospital associated with appendicitis severity, when socioeconomic determinants of health were adjusted for?
5. Were gradients in socioeconomic determinants associated with higher risk of complicated appendicitis (including parental education level, parental employment, family income, social security benefits or parental migration status)?

Patients and methods

Study population

This thesis was based on the entire Swedish population, or subsets of it, as it was between 2001 and 2015. The population in Sweden increased during the study period from 8.9 million to 9.9 million; birth rates were higher than death rates and immigration was larger than emigration (Figure 1 population size, SCB) (Figure 2 birth/death/migration, SCB).

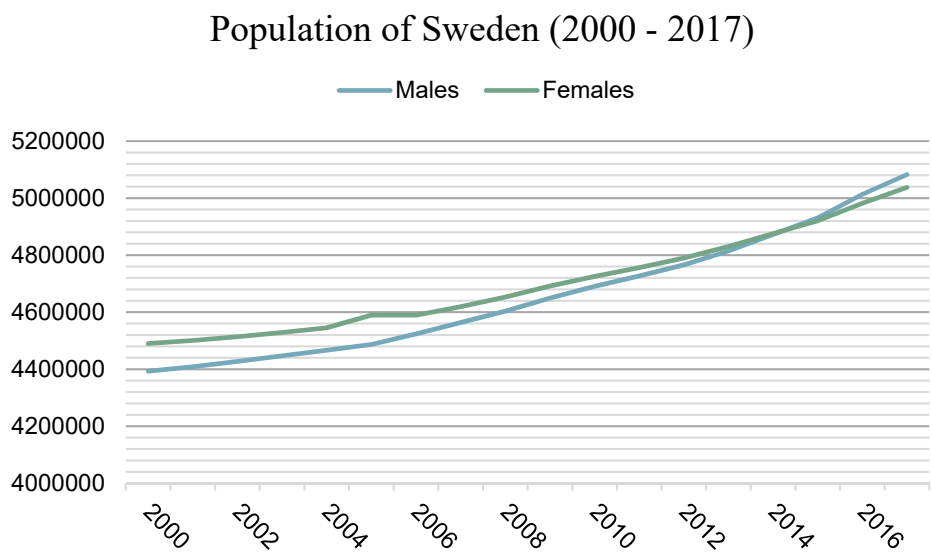


Figure 1. The Swedish population, 2000-2017.
There was a population growth in Sweden throughout the study period for both males and females. (Data from Statistics Sweden (115))

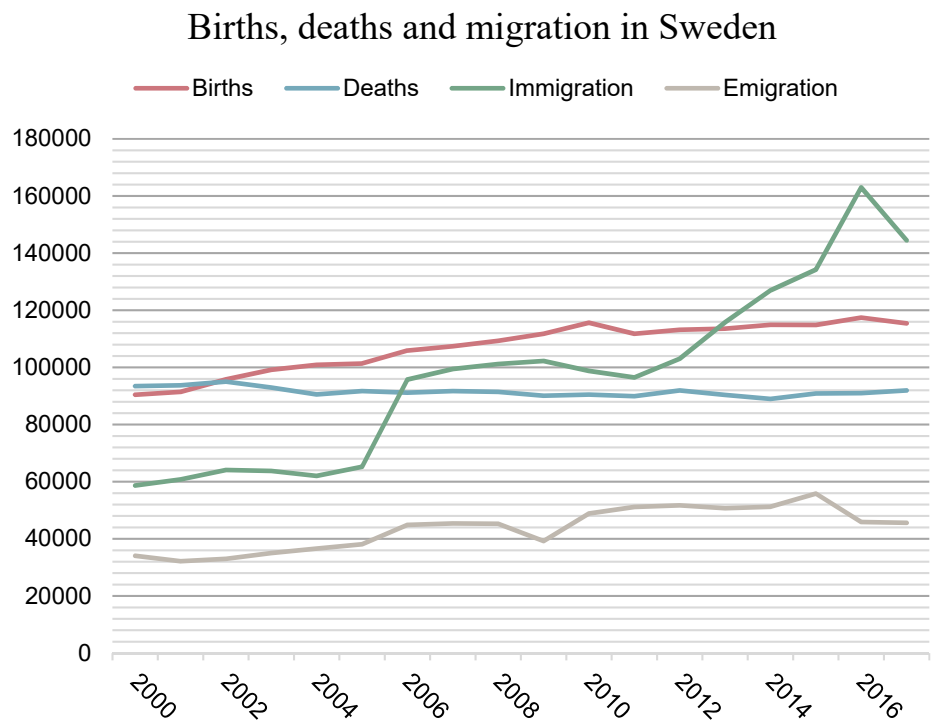


Figure 2. Annual number of births, deaths, immigrations and emigrations in the Swedish population, 2000-2017. (Data from Statistics Sweden (115))

Demography in Sweden

The Swedish population is currently about 10.2 million people.[20] Overall, the distribution of males and females is equal, except in the upper age strata where females are in the majority (Figure 3: SCB population pyramid). This relates to the gender difference in life expectancy: 80.7 years for men and 84.1 years for women in 2017, measured as the average age at death. The gender difference in life expectancy is lower than the European average of 6 years (2014) (116). There are no major variations in life expectancy between geographical regions within Sweden. Yet a gradient in life expectancy that follows the educational level can be detected (117). The fertility rate was 1.6-1.9 children per woman during the study period (1.8 child per woman in 2017). The under 5 mortality (years old) was 2.7 per 1000 live births in 2013, which is almost half that compared to the UK, and lower than all European countries except for Iceland and Andorra (118,119).

[20] SCB population statistics: 10,223,505 citizens, as at November 2018 (115).

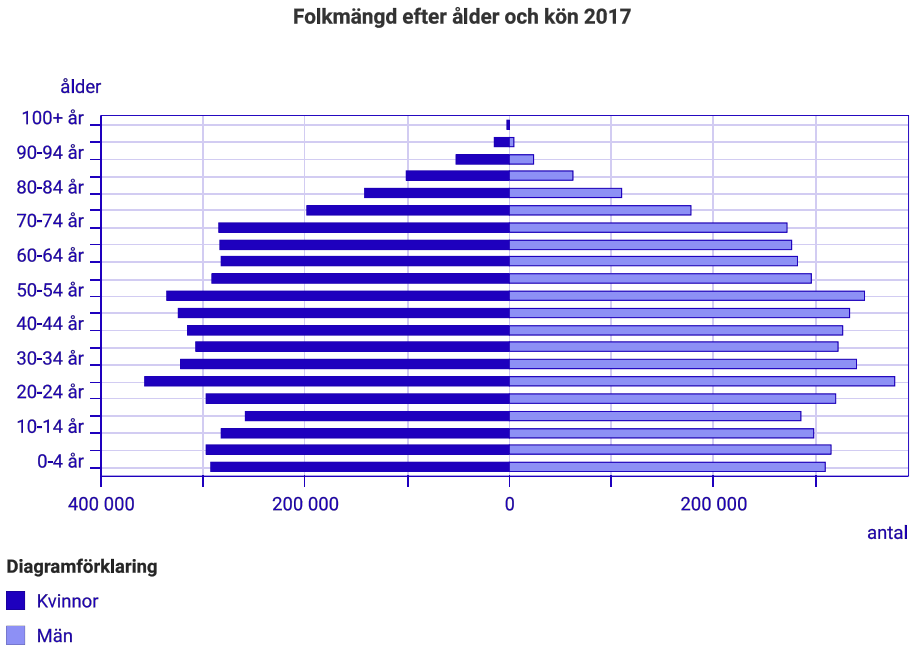


Figure 3. The population pyramid in Sweden.
The Swedish population in 2017, by gender and 5-year age groups. The population pyramid of Sweden takes the shape of a tower rather than a pyramid. (Source: Statistics Sweden (115), with permission to reprint)

Population at risk for disease

In this thesis, the study population was either:

1. *All people* eligible for seeking healthcare in any hospital or specialised outpatient clinic in Sweden between January 1, 2006 and December 31, 2013 (study I), or
2. *Any Swedish boy* (study II), or *any Swedish child* (study III and V), who was between 0-18 years of age during the study period (January 1, 2001 and December 31, 2014), or
3. *Any boy* born in Sweden between January 1, 2001 and December 31, 2014 (study IV).

With these definitions, the study population for each study could be readily identified in the population registers.[21]

In studies II-V, additional definitions of the study population were applied: children were excluded from the study population at the time of migration from Sweden or when the first outcome event occurred.

Considerations in epidemiological studies

In epidemiological research, it is crucial to define the population at risk of the particular event studied. This may not be as straightforward as expected, however. The Swedish population is suitable for epidemiological studies due to reliable information of the size and demographics, births, deaths and migration in the population.

All citizens have a unique personal identity number, and this makes it possible to trace individuals through the course of their life, from birth to death. The unique personal identity number also links individuals to various social, financial and health-related events in life, such as educational achievements, parental status, taxation and social security financial support, place of residence and migration, and health-related events.

The Swedish population is suitable for epidemiological studies when homogeneity of the study population is an advantage, such as the studies performed in this thesis. The access to education, social security and healthcare is high and distributed rather equally in the population. However, it is important to point out that the generalisability (also known as the external validity) of epidemiological studies performed in Sweden may be limited in some aspects. The socialised society and generally high standard in terms of income, education, social security and health in the population, is rather unique for Sweden (and a few other countries). Extrapolations to other countries, which may differ in demography or social determinants of health, must therefore be made with caution.

[21] To be correct, study I was an exception: the population at risk who sought medical care in Sweden was merely a proxy of the Swedish population at the time. Non-Swedish citizens may seek healthcare in Sweden during visits to the country, and therefore be eligible for inclusion.

Setting

The Swedish healthcare system

The Swedish healthcare system is a socially responsible system with an explicit public commitment to ensure the health of all citizens (4). Several of the indicators of health outcomes and quality of care are better than the OECD average, while health expenditure is only slightly above the OECD average (120). The healthcare governance is decentralised into 21 local governments (counties, regions or municipalities), and the national government is responsible for general healthcare policies. The state policies are outlined by the Ministry of Health and Social Affairs, and executed through the governmental agencies (4).

The current primary care model in Sweden originates from 1970. Primary care is responsible for most primary and secondary preventive healthcare for the population, and provides guidance to the right level of specialised care (121). Every third medical doctor with a specialist degree in Sweden possesses a degree in general medicine, which is rather low compared to other OECD countries. The continuous decrease in hospital beds during last decades, and the demographical changes with increasing number of ageing people have increased the need for primary healthcare dramatically (120). The burden of disease in the ageing population, along with the limited amount of specialists in general medicine, has drained financial and human resources from the primary care and increased the financial risks for the primary care units (122).

Specialised care in Sweden is mainly located to the approximately 70 public and six private hospitals, with most of them being dimensioned for acute care around the clock (4). In 2013, 44 hospitals in Sweden offered 24-hour services including the Bellwether procedures (emergency laparotomy, Caesarean section and open fracture repair) (123). There are seven university hospitals serving the six healthcare regions (Table 3). Besides providing tertiary care, they are centres for medical research and education. Unlike most countries in northern Europe, primary care in Sweden has no gate-keeping function, and citizens can choose to seek healthcare at the emergency department of their choice (120).

Child health care includes healthy child visits on a regular basis from birth until school age. The healthy child visits reach most of the paediatric population, with attendance being over 98% of children born in 2015 (124).

Despite the generally high standard of care and top scorings in public health indicators and various metrics of cost-efficiency in the healthcare system, there are areas with great potential of improvement. Patient satisfaction has been impaired by access problems to timely care, and by restricted continuity. Waiting times have

increased at all levels: in the emergency department, for the specialist clinics and for elective as well as emergency surgery. Doctor continuity in both primary care and specialised care has been reduced due to organisational shifts, but also due to legislation and restrictions in working hours.

Table 3. Healthcare regions and univeristy hospitals in Sweden

Healthcare region	University hospital	Location
Northern Healthcare Region	University Hospital of Umeå	Umeå
Uppsala-Örebro Healthcare Region	Uppsala University Hospital Örebro University Hospital	Uppsala Örebro
Stockholm Healthcare Region	Karolinska University Hospital[22]	Stockholm
South-eastern Healthcare Region	Linköping University Hospital	Linköping
Western Healthcare Region	Sahlgrenska University Hospital	Göteborg
Southern Healthcare Region	Skåne University Hospital[23]	Lund and Malmö

Health insurance and financial aspects of Swedish healthcare

All citizens in Sweden are covered by the tax-financed health insurance system. The national public health insurance includes primary care as well as specialised care throughout the course of life. The average total health expenditure was 5511 USD per capita (about 50,058 SEK) annually in 2017, of which 83.6% was publicly funded and 16.4% was user-financed, mainly through out-of-pocket fees (1). The expenditures accounts for 10.9% of the gross domestic product[24], which is just above the average of the OECD countries. Whereas adults contribute with a limited payment for healthcare visits and medications[25], the child health insurance is extensive, so that there are no direct out-of-pocket expenses related to health care visits, treatments or medications for children.

[22] : Karolinska University Hospital in Solna and Huddinge University Hospital were fused to form Karolinska University Hospital in 2004. They were both entitled University Hospitals and connected to the Karolinska Institute prior to the fusion. For simplicity, Karolinska University Hospital refers to both hospitals in this thesis. However, they are considered to be two separate entities in the geographical information system analyses of travel times in studies IV and V.

[23] Lund University Hospital and Malmö MAS University Hospital were both linked to Lund University, and fused to Skåne University Hospital in 2010. For simplicity, Skåne University Hospital refers to both hospitals in this thesis. However, they are considered to be two separate entities in the geographical information system analyses of travel times in studies IV and V

[24] GDP [Swedish: bruttonationalprodukt, BNP]

[25] The fee in the Skåne Region is currently (2018) limited to 1150 SEK (equals to 112 EUR) on an annual basis for healthcare visits, and varies slightly between counties. The national limit for expenses for prescribed medications is currently 2300 SEK (equals 225 EUR).

Public and private healthcare in Sweden

Most Swedish healthcare is still publicly owned and managed. However, in 2016 almost every second primary care unit in Sweden (42%), and two out of three in Stockholm (67%) were privately owned (122). Of the few privately owned hospitals, most offered non-emergency healthcare only; in 2016 St Görans Hospital in Stockholm was the only one that offered acute care.

Inpatient and outpatient care – what is the difference?

Specialised care is provided either as inpatient care or outpatient care. Inpatient care is always hospital-based in some form, and requires the patient to be admitted for healthcare or treatment, and ends with a discharge from the unit providing the care. Outpatient care and day surgery can be either hospital-based or provided at clinics separate from the hospital.

In the last decades, as a result of better and safer anaesthetic methods and technical advancements in surgical procedures, such as minimal-invasive techniques, the demand for perioperative care, post-surgical surveillance and pain management has decreased markedly. Therefore, increasing types of surgical procedures can now be performed as day surgery. This has led to reduced costs and more effective use of surgical resources, fewer societal costs, and also fewer obstacles for the patient in terms of pain and wound management, sick-leave and rehabilitation.

Data sources

The national registers in Sweden

As concluded in the OECD Review of Health Care Quality report (120):

> 'Sweden has an impressive track record around measuring and publishing indicators on the quality of care, both at provider level and at population level. In particular, a broad range of national quality registers have been developed covering defined diagnostic areas.'

The national registers of the total Swedish population provide an important piece of information for epidemiological research in Sweden, as the background population can be identified quite accurately. Size, demographics, geographical distribution and other characteristics of the Swedish population are available from the Register of the Total Population, provided by Statistics Sweden since 1968 and based on administrative data from the Swedish Taxation Agency (125). Statistics Sweden

provides several additional sources of information regarding social and financial activities and public intervention in the population. Therefore, migration status and place of birth, education, marital status and family composition, employment and profession, social security intervention and sick-leave, place of residence and income can be followed during the course of life at an individual level.

National registers

In this section, the national healthcare and population registers utilised in the thesis are described briefly. These registers form the foundation of the preformed studies.

The National Patient Register

The National Patient Register (NPR) is administered by the Swedish Board of Health and Welfare (Socialstyrelsen), and it is currently a register of all inpatient care and specialised outpatient care in both the public and private sectors. The register started in 1968, and in the early days coverage was very limited to a few counties. Since then, the register has expanded to cover all counties, and since 1987 it includes both somatic and psychiatric inpatient care. In the 1990s, day surgery was also reported to the register, and since 2001 all public and private specialised outpatient care and day surgery are obliged by law to report to the register. It has been estimated that since 1987 the coverage of inpatient care exceeds 99%, with 99% of diagnoses being reported correctly (126). The overall coverage of specialised outpatient care since 2004 was estimated to be 80%.[26] Missing data are mainly found in psychiatric care and private care providers. The register is limited to healthcare provided within the healthcare legislation, whereas other sectors (such as privately financed cosmetic care) do not report to the NPR. Primary care and school care are not reported to the NPR. The register collects information on every admission to inpatient care and every visit to outpatient care and day surgery, including primary and additional diagnoses, procedures, date of admission and discharge or visit, clinic, place of residence, and links these to the unique personal number of the patient.

The Swedish Prescription Register

The Swedish Prescription Register has been administered by the Swedish Board of Health and Welfare (Socialstyrelsen) since it began in July 2005. The register collects information on all pharmaceutical prescriptions within Sweden, and links

[26] The National Patient Register claims to have full coverage of outpatient visits in the public specialised healthcare since 2004. Visits to private caregivers account for nearly all the missing data.

the type of medication, date of prescription and date of delivery to the unique personal identity number.

The Swedish Cause of Death Register

The Swedish Cause of Death Register is a register of all deaths in Sweden, and the impressive history dates back to the Swedish parliament decision to collect cause of death statistics in 1749 (127). It was initially limited to deaths of particular public health interest, such as maternal and plague-related mortality. In 1911, when Statistics Sweden became responsible for the register, the register expanded and information on all deaths in the population was recorded. Thus, records include all deaths in Sweden since 1911, and the electronic part of the register dates back to 1952. In 1993, the Cause of Death register was transferred to the Swedish Board of Health and Welfare (Socialstyrelsen).

When a person in Sweden dies, the death must be confirmed immediately to the Swedish National Tax Agency, and the primary cause of death and underlying causes of death must be determined and reported to the Swedish Board of Health and Welfare within 3 weeks. This is usually done by the patient's physician or the last physician seeing the patient in life. Both the information from the Tax Agency and the causes of death from the physician are included in the register, along with the date and place of death, and linked to the unique personal identity number of the deceased individual. The register is considered virtually complete, and information about the underlying cause of death is reported in 96% of deaths (127).

The Population Register and the Total Population Register

These two registers are records of the Swedish population and include trajectories of life recorded on an individual level. The Population register is administered by the Swedish National Tax Agency and linked to the Total Population Register, which is administered by Statistics Sweden. Information about births, deaths, country of birth, domestic and international migration, child-parental relationships and family composition, are all linked to names and unique personal identity numbers of each individual. It is estimated that the coverage is 100% of all births and deaths and 95% of immigrations and 91% of emigrations are reported to the register (125). The Total Population Register is the source of several special registers provided by Statistics Sweden, including the Multi-generation Register, and the Sibling Register.

The Longitudinal Integration Database for Health Insurance and Labour market Studies (LISA)

The Longitudinal Integration Database for Health Insurance and Labour Martet Studies (Longitudinell Integrationsdatabas för Sjukförsäkrings- och Arbetsmarknadsstudier, LISA) is a longitudinal database administered by Statistics

Sweden. The database integrates information on several registers, including the Total Population Register, Income and Taxation Register (IoT, provided by Swedish National Tax Agency), Education Attainment Register (Utbildningsregistret, Statistics Sweden), Datalagret (The register of unemployed persons in Sweden, provided by the Swedish Public Employment Service -Arbetsförmedlingen), STORE-database by the Insurance agency (Försäkringskassan[27]), and several other sources of information. The LISA database provides longitudinal socioeconomic information on individuals in Sweden, including education, income, employment and work sector, social security benefits and sick-leave benefits.

Acquisition of healthcare data

The purpose and rationale to keep registers may vary, even if they are generally kept to provide accurate administrative information for the governance of Sweden, provide statistics on the population status or provide estimates of quality or effects from interventions by authorities and organisation, and for research purposes (128). Even if registers are run for purposes other than research, national registers are encouraged to facilitate research, as already collected and maintained data have great potential to contribute to knowledge gains, public health and economic growth of the country (128). Efforts to facilitate register-based research in Sweden, and the Nordic countries have been made on both the national (129) and international level (130).

To access healthcare and administrative data on the Swedish population from the national registers, formal application must be made to each authority responsible for the register. It must be stressed, however, as these registers contain multiple pieces of personal information on citizens, that can be directly or indirectly linked to individuals, they are considered highly sensitive and access is highly restricted (130). In line with the Helsinki Declaration (131), all acquisition of individual-level data for research purposes is subject to ethical vetting, and requires approval from one of the six regional Ethical Review Boards, or the Central Review Board (132).

[27] Försäkringskassan (the national Insurance agency), responsible for public health maintenance and social security has, to my knowledge, no official English translation.

Methods: studies I-V

This chapter briefly describes the methods applied in the included studies. Statistical tests used in this thesis for assessing differences between groups and estimating associations between exposures and outcomes are summarised in Table 4: Detailed descriptions are found in the method section of each study (appendix I-V), and complementary discussions on the applied methods are found in the Discussion chapter.

Table 4. Statistical tests applied in study I-V.

Application	Test
Testing differences in categorical variables	
between two groups	Chi2-test
	Fisher's exact test
Testing differences in continous variables	
between two groups	Student's t-test (parametric test)
	Wilcoxon rank-sum test (non-parametric test)
	Mann-Whitney U-test (similar to Wilcoxon rank-sum test)
between two groups or more	Kruskal-Wallis
Testing correlation between continous variables	Spearman rank correlation
Estimating exposure-outcome associations	
Outcome is continous	Linear regression
Outcome is a rate (events per unit of time)	Poisson regression
Outcome is binary	Logistic regression
Estimating differences in time-dependent variables	
Univariate analysis of time-to-event outcome	Log rank test
Analysis of time-to-event outcome, one or more variable	Cox regression

Study I

Study population, outcomes and independent variables

The design was a retrospective register study of healthcare provided by all public and private care givers in inpatient and specialised outpatient care in the Swedish healthcare system. Primary care was not eligible for inclusion. The study population was an open cohort of all citizens in Sweden, 2006-2013. The primary outcomes were occurrence of healthcare contacts and surgery during inpatient or outpatient care and day surgery. Secondary outcome was cause of admission or visit, as defined by the primary diagnosis. Independent variables were study year, age and gender. No exposure variable was assigned.

Statistics

Data on inpatient and outpatient care were grouped by age, gender, year, and primary diagnosis. Incidence of surgery was calculated by dividing the number of surgical procedures in each age- and gender-specific strata for each time-period, with the Swedish population in that specific strata, and reported as the annual number of operations per 100,000 population-years. Linear regression was used to estimate univariate time trends. Multivariate Poisson regression was used to estimate changes in incidence over time, with adjustment for demographical changes (age- and gender) in the background population, and the obtained incidence rate ratio was reported as percentages.

Study II

Study population, outcomes and independent variables

The design was an observational study based on longitudinal register data, and the study population was an open cohort of all boys born in Sweden, aged 0-18 years between 2001 and 2014. The main outcome was age of treatment for cryptorchidism in Swedish inpatient or specialised outpatient care. Secondary outcomes were age at cryptorchidism diagnosis, use of laparoscopy, outpatient surgery, and occurrence of surgical site infection or death within 30 days. Independent variables were birth characteristics (birth weight, birth week and intrauterine growth restriction), place of residence, hospital type, and year of treatment.

Statistics

Descriptive statistics were performed. The cumulative childhood prevalence, overall and per dependent variable, was calculated by dividing annual cases in each age group for each study year with the particular population at risk, and then calculating the mean incidence for each year of age across the study years. The sum of these age-specific mean incidences was presented as the cumulative prevalence of cryptorchidism. Differences between groups were tested with the Chi2-test for categorical variables and with the Mann-Whitney U-test or Kruskal-Wallis for two or more continuous variables, respectively. Trends over time were assessed with the Spearman rank correlation in continuous variables. Multiple imputation was applied to test for robustness of results.

Study III

Study population, outcomes and exposures

The design was an observational study based on longitudinal register data, and the study population was a cohort of all children in Sweden, 0-18 years of age, with a first episode of acute appendicitis in 2001-2014. The outcomes were length of stay in hospital, risk of postoperative infection, readmission or re-operation or death within 30 days, and the risk of small bowel obstruction requiring surgery during long-term follow-up (median follow-up 7.4 years). Exposure was type of appendicitis (classified as complicated or uncomplicated), and treatment modality (categorised as open, laparoscopic or converted appendectomy, drainage only, or non-surgical treatment). Independent variables were gender, age and study year.

Statistics

Descriptive statistics were performed. Univariate differences between groups were assessed using the Chi2 or Wilcoxon rank-sum test, and multivariable associations were presented as odds ratios obtained by logistic regression. Survival analysis was applied to length of hospital stay and long-term risk of small bowel obstruction, presenting univariate associations with Kaplan-Meier curves and log rank test, and multivariable associations using Cox regression estimates.

Study IV

Study population, outcome and exposures

The design was an observational study of longitudinal register data, consisting of two parts. All boys born in Sweden between 2001-2014 were included, and the main outcome was occurrence and age at treatment for cryptorchidism. In the first part of the study the exposure was the birth-related risk factors for cryptorchidism: prematurity, birth weight, size at birth and maternal age and smoking status. The exposure in the second part of the study was distance to the treating hospital, measured in minutes by car, and applied only to those treated for cryptorchidism (see Figure 4). Dependent variables were socioeconomic determinants of health, including parental education, employment and income. Independent variables were year of birth and place of residence.

Statistics

Kaplan-Meier curves, with follow-up from birth to day of surgery and censoring at 31 December 2014, presented the outcome by levels of each birth-related risk factor and the trend over time, and cumulative incidences were calculated. Univariate differences were assessed with the log rank test. Cox regression analysis was applied

to obtain multivariable estimates of associations, and overall contribution of each variable was assessed with the F-test and presented as p-values. In the second part of the analysis, where travel time was the exposure, an age cut-off of 3 years was chosen to assess probability of being treated by levels of travel time.

Study V

Study population, outcome and exposure

The design was an observational study of longitudinal register data, and the study population was a cohort of all children in Sweden with a first episode of appendicitis 2001-2014. The population at risk of being diagnosed with appendicitis in Swedish hospitals was estimated by identifying all Swedish children in the respective age- and gender strata for each year. Primary outcome was appendicitis severity (dichotomised as complicated or uncomplicated), and the exposure was distance to the treating hospital, measured in minutes by car (see Figure 4). Dependent variables were socioeconomic determinants of health, including education, employment and income. Independent variables were gender, year and age at diagnosis, place of residence and treating hospital.

Statistics

Primary outcome was calculated as new cases of appendicitis in each age and gender group for each year divided by the official population for each study year, and reported as incidence per 1000 person-years per age and gender. The corresponding mean incidences of appendicitis for each gender and age across the study years were calculated and the sum of these age-specific incidences up to 18 years of age were reported as the cumulative childhood incidence. Multivariate Poisson regression was used to estimate trends in incidence over time. The association between the exposure and the dependent variables, and the risk of complicated appendicitis were estimated with logistic regression, and overall contribution of obtained odds ratios was assessed with the F-test for categorical variables and presented as p-values. Trend in hospital caseload volume was estimated with linear regression.

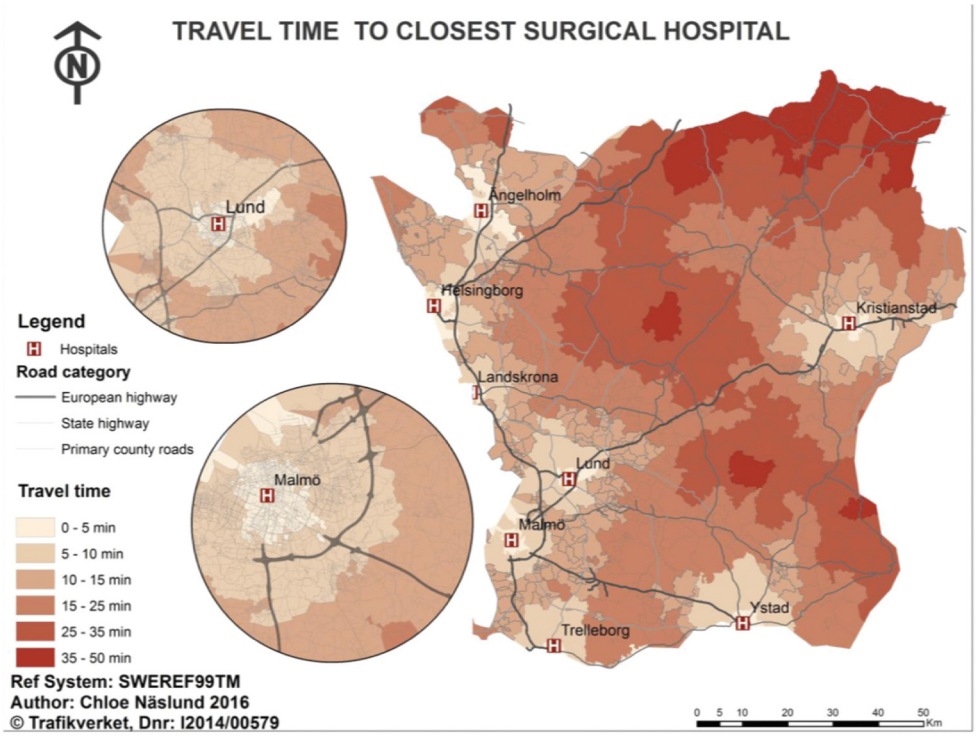


Figure 4. Estimated travel times by car to hospitals providing surgical services within Skåne county. Geographic Information System (GIS) methods were applied to estimate the distance in minutes to the nearest hospital, using the most time-eficient route by car, considering speed limitations, trafic lights, right-turns and left-turns, as they were at the year of interest. Based on annual data from the Swedish Road Database (Trafikverket) and the small area for market studies (SAMS-areas, Statistics Sweden). (Graphic by Chloe Näslund, with her kind permission to reprint)

Ethical considerations

Appropriate ethical permissions were obtained for the studies conducted in this thesis (Table 5).

Study I was based on aggregated data on admissions and operations performed per age and gender over the entire country. As no individual level data were accessed at any step in the analysis, and no indirect identification of study subjects was possible, ethical vetting was not applicable for this study (as advised by the ethical review board in Lund). The internal ethical review at the Swedish Board of Health and Welfare did not consider the aggregated dataset sensitive from an ethical point of view, as it did not differ substantially from the open datasets available on their web page (http://www.socialstyrelsen.se/statistik/statistikdatabas/).

In contrast, data in studies II-V were considered highly sensitive. The data consisted of multiple health-related information on an individual level, and linked individuals by time of birth, place of residence and place of treatment. The dataset used in studies IV and V contained individual-level healthcare information for all children in Sweden (or substantial proportions of them), and they were linked to longitudinal information on place of residence, parents' biometrics and health determinants over time.

Even if the data for study II-V were deidentified, and key-only accessible for the register holder for a maximum of 3 years, indirect identification of individual study subjects would be possible in theory. For data security reasons, storage of data, data management and statistical analyses were restricted to a secure server, accessed only by a limited number of researchers.

Table 5. Ethical Review Board approvals for studies I-V.

Study	Ethical Review Board	Comment
I Surgery in Sweden	Internal review board at Swedish Board of Health and Welfare	Aggregated data only. No formal vetting required.
II Cryptorchidism - outcome	Regional Review Board in Lund (diary number 2014/791)	Access to individual-level healthcare data approved
	Swedish Central Review Board in Stockholm (diary number Ö 19-2015)	Access to data on postoperative prescriptions and mortality approved.
	National Board of Health and Welfare (diary number 5.2.1-12821/015)	Access to medical birth data approved.
III Appendicitis - outcome	Regional Review Board in Lund (diary number 2014/792 and 2015/430)	Access to individual-level healthcare data and postoperative mortality approved
	Swedish Central Review Board in Stockholm (diary number Ö 18-2015)	Access to data on postoperative prescriptions approved.
IV Cryptrochidism - access	Regional Review Board in Lund (diary number 2014/791 and 2015/429)	Access to individual-level healthcare data approved
	Swedish Central Review Board in Stockholm (diary number Ö 19-2015)	Access to data on socioeconomic determinants and birth-related risk factors approved.
V Appendicitis - access	Regional Review Board in Lund (diary number 2014/792 and 2015/430)	Access to individual-level healthcare data approved
	Swedish Central Review Board in Stockholm (diary number Ö 18-2015)	Access to data on socioeconomic determinants approved.

Main findings

Study I

Surgery in Sweden

Of all inpatient healthcare in Sweden, both children and adults considered, 30.6% of admissions were related to surgery of any kind. As many as 8% of all healthcare contacts, and 27% of inpatient care in the paediatric population (0-19 years of age), resulted in surgery. There were large variations in surgical incidences in different age groups, with highest incidence rates seen in the elderly (Figure 5).

All ages considered, women had a 9.8% higher incidence rate of surgery than men (95% confidence interval 5.6 to 14.0%, $p<0.001$), and the difference was most pronounced in inpatient care.

The incidence rate of paediatric surgery increased for each year, so that in 2013, a minimum of 6784 operations were conducted per 100,000 children in the age 0-19 years [range 6784–8515 operations per 100,000 person-years] (Figure 6). In comparison, the incidence rate of surgery in adults (≥20 years of age) was estimated to be a minimum of 21,152 annual operations per 100,000 population [conservative estimate: 21,152 annual operations, and liberal estimate: 25,806 annual operations per 100,000 adults].

Most surgery was conducted in outpatient settings (day surgery), and this proportion increased over time. In 2013, at least two-thirds of all surgery in children and adults was conducted in outpatient settings (overall conservative estimate: 75.4%, liberal estimate: 66.9%).

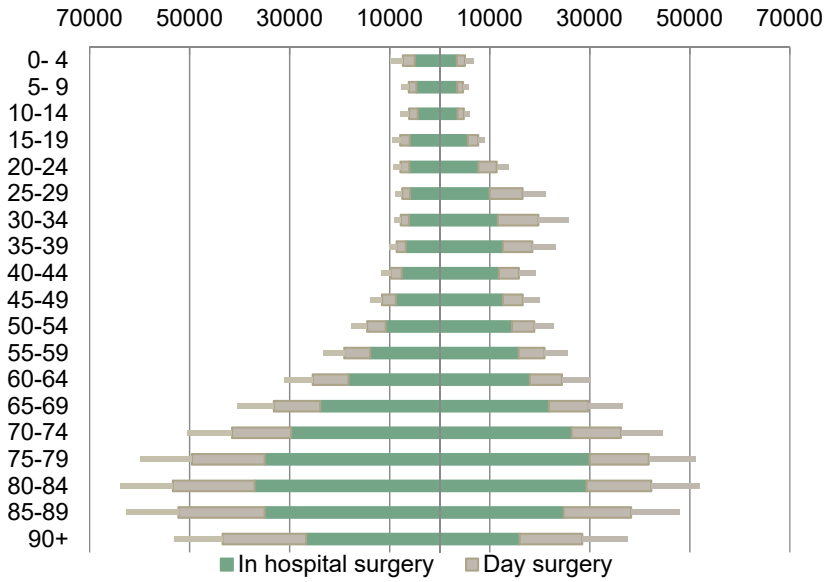


Figure 5. Incidence of inpatient and outpatient sugery among males (left) and females (right) in Sweden 2006-2013.

Incidence expressed per 5-year age group as annual number of major surgical procedures per 100,000 population. On average, individuals 75-89 years of age had almost one major operation every second year (conservative and liberal estimates for men: 53,390 to 63,970 operations per 100,000 person-years, and for women: 42,310 to 51,990 operations per 100,000 person-years).

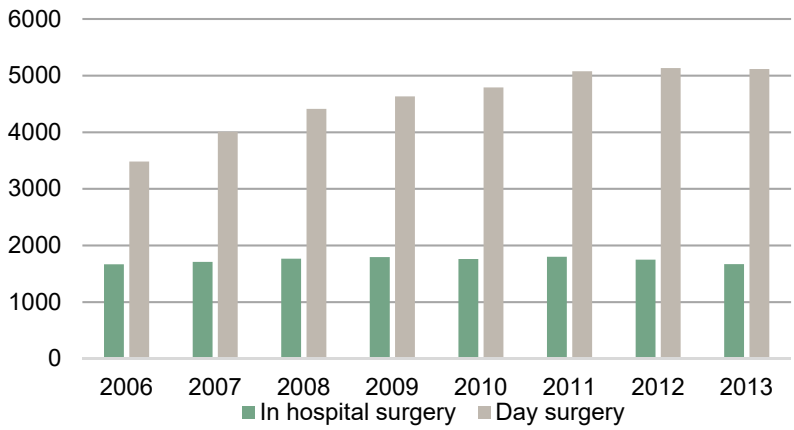


Figure 6. Incidence rate of major surgery in inpatient and outpatient care among children 0-19 years of age in Sweden, 2006-2013.

Incidence rate was expressed as the annual number of operations per 100,000 population in ages 0-19 years. The incidence rate among children was estimated to be 6320 annual operations per 100,000 persons on average during the 8-year study period [conservative to most liberal estimated range 6320–7890 per 100,000 person-years].

Study II

Cryptorchidism in Sweden – treatment and complications

1.8% (95% confidence interval 1.5-2.0%) of Swedish boys were diagnosed and treated for cryptorchidism by age 18, and the risk increased dramatically for those born prematurely, those with low birth weight, or small for gestational age.

The median age at treatment decreased from 6.2 (IQR 3.1-9.4) years in 2001 to 3.4 (IQR 1.5-7.6) years in 2014. Most children were treated first years in life, and a smaller peak in treatment were seen in early school age (Figure 7).

In 2014, the vast majority of all boys with cryptorchidism (94.1%, 95% confidence interval 92.7-95.6%) were older than 1 year of age at treatment, and there were considerable variations in treatment age in different counties (Figure 8).

Treatment age was lower in university hospitals than non-university hospitals (median age at surgery: 3.3 [IQR 1.6-7.5] years at university hospitals versus 5.6 [IQR 2.4-8.7] years at non-university hospitals, $p<0.001$), with a trend towards more surgery being referred to university hospitals ($p<0.001$) and more surgery being localised to outpatient settings (49% of cryptorchidism treatments were conducted as day surgery in 2001. The corresponding number in 2014 was 87%).

Complications were rare: surgical site infection rate was 1.4% (95% confidence interval 1.1-1.6%), and stable over time, with no geographical variation, and there were no deaths within 30 days.

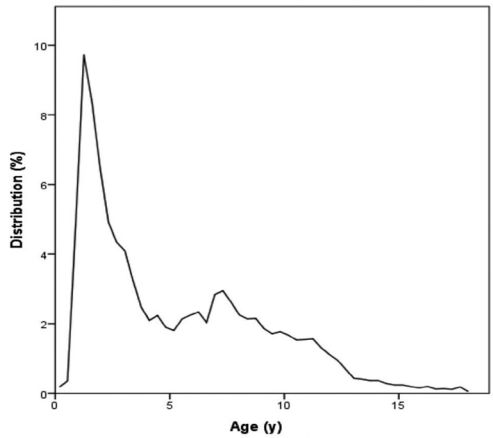


Figure 7. Distribution of age at cryptorchidism treatment in Sweden, 2001-2014.
Treatment age for Swedish boys up to 18 years of age. Most boys were treated early in life. A second peak was seen in early school age.

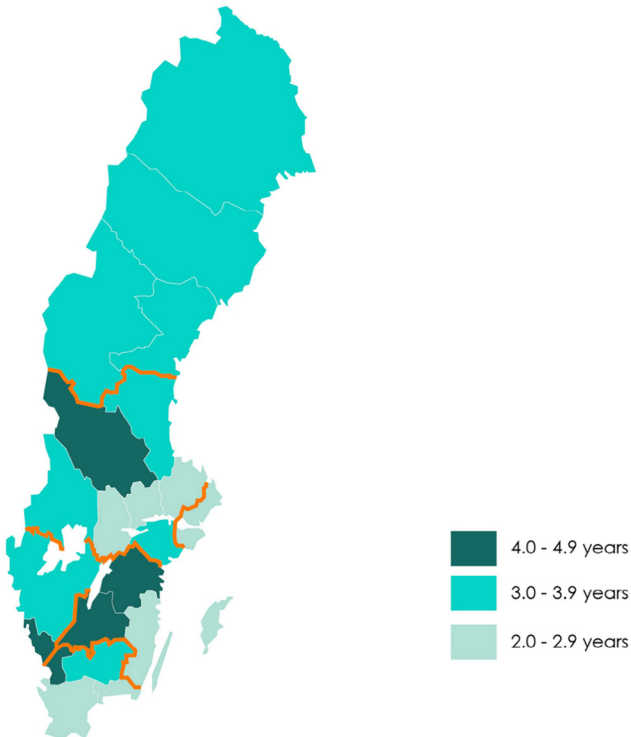


Figure 8. Median age at treatment for cryptorchidism in Sweden, 2001-2014.
The median age at treatment differed considerably for boys in Sweden, depending on the county of residence.

Study III

Paediatric appendicitis in Sweden – treatment and complications

Median hospitalisation was twice as long in complicated appendicitis compared to uncomplicated appendicitis, and the length of hospitalisation was also associated with the treatment modality (Figure 9).

Postoperative infections were more common following complicated appendicitis than uncomplicated disease (5.9% versus 2.3%, adjusted OR 2.64 [95% confidence interval 2.18-3.18], p<0.001).

Complicated appendicitis increased the 30-day risk of readmission (5.5% versus 1.2%, adjusted OR 4.75 [95% confidence interval 4.08-5.53], p<0.001) and additional abdominal surgery (2.2% versus 0.6%, p<0.001).

Complicated appendicitis increased the risk of small bowel obstruction requiring surgical intervention (Figure 10).

The use of laparoscopic appendectomy increased throughout the study period and was the preferred treatment modality by the end of the study period (Figure 11).

Laparoscopic appendectomies were associated with fewer postoperative infections compared to open appendectomy (2.0% versus 3.1%, adjusted for disease severity, age, gender and study year: OR 0.65 [95% confidence interval 0.54-0.79], p<0.001), and the risk increased after converted appendectomies (5.0%, adjusted OR 1.41 [95% confidence interval 1.02-1.95], p=0.04).

Laparoscopic appendectomy, compared to open appendectomy, reduced the risk of small bowel obstruction (Figure 12).

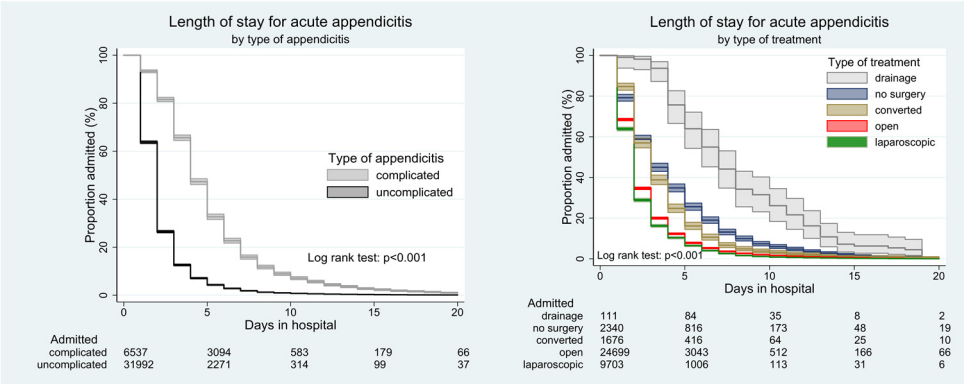


Figure 9. Length of stay in hospital at first episode of appendicitis among Swedish children, 2001-2014.
Left: Median hospitalisation was 2 [IQR 1-3] days of uncomplicated appendicitis, and 4 [IQR 3-6] days for complicated appendicitis. Right: Length of stay (with 95% confidence intervals) by treatment modality.

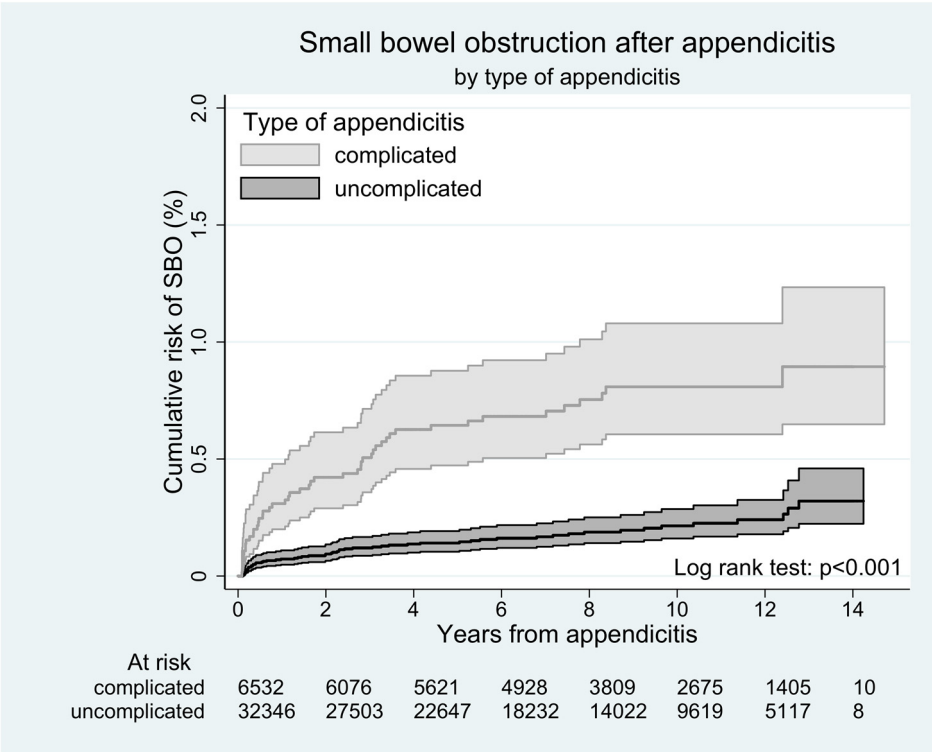


Figure 10. Cumulative risk of small bowel obstruction after paediatric appendicitis in Sweden, 2001-2014.
The risk of small bowel obstruction increased after complicated appendicitis (0.7% versus 0.2%, adjusted HR 3.89 [95% confidence interval 2.61-5.78], p<0.001).

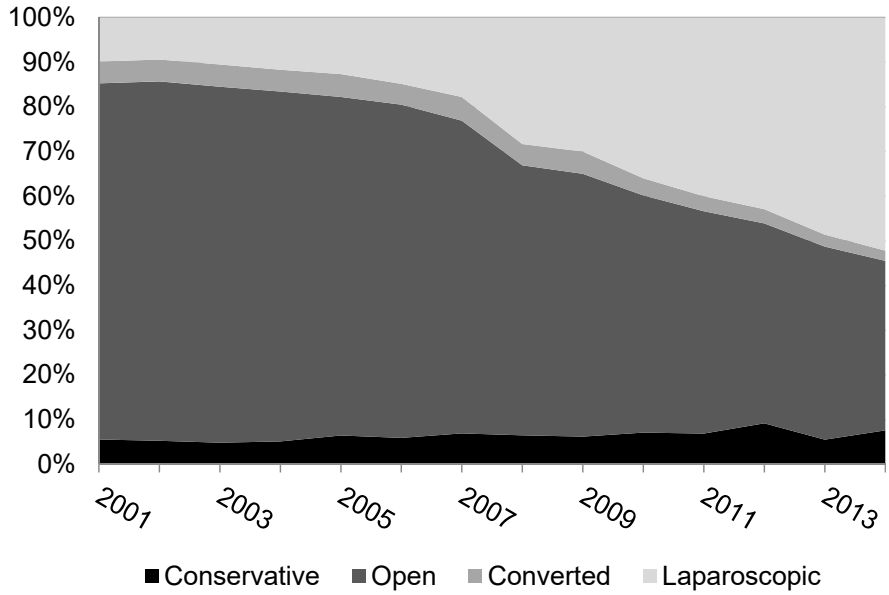


Figure 11. Treatment modality at first admission for paediatric appendicitis in Sweden 2001-2014.
Laparocsopic appendectomy increased from 10% in 2001 to 52% in 2014, and the conversion rates decreased by half, from 4.9% to 2.3%.

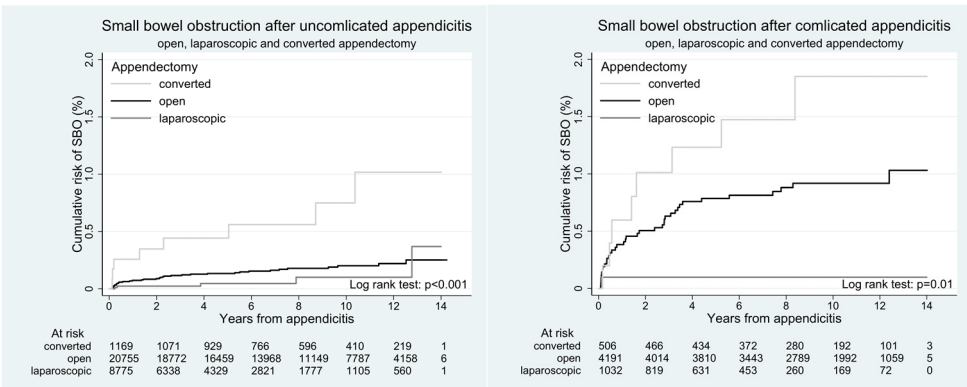


Figure 12. Cumulative risk of small bowel obstruction after paediatric appendicitis in Sweden.
The cumulative incidence of small bowel obstruction requiring surgical intervention was <0.1% after laparoscopic appendectomy and 0.3% after open appendectomy (HR after laparoscopic compared to open appendectomy 0.27 [95% confidence interval 0.11-0.63], p=0.002, adjusted for gender, age, year and appendicitis severity).

Study IV

Cryptorchidism –risk factors for disease and for treatment delay

Cumulative incidence of cryptorchidism up to 14 years of age was 1.4% (95% confidence interval 1.3-1.5%) (Figure 13).

Prematurity, birth weight and intrauterine growth restriction were all associated with the incidence of cryptorchidism (Figure 14, Kaplan Meier curves). However, maternal age (p=0.42) and maternal smoking during pregnancy (p=0.19) were not considered to be independent risk factors for the condition.

Each 30-minute increase in travel time to the treating hospital, adjusted for birth-related risk factors and potential socioeconomic confounders, was associated with a reduced probability of being treated at 3 years of age (adjusted HR 0.91 [95% confidence interval 0.88-0.95], p<0.001) (Figure 15).

The association between travel distance and age at treatment remained stable in all performed sensitivity analyses, and was robust to changes in classification of travel distance, to changes in age cut-off in the survival analysis and to the introduction of the Nordic Guidelines in 2007.

Figure 13. Cumulative incidence of cryptorchidism treated with surgery among Swedish boys born in 2001-2014.

Of 748,678 boys born, 7351 cases of cryptorchidism were identified and evaluated for timing of surgical treatment. The 2-year birth cohorts were followed in Swedish healthcare registers until December 31, 2014.

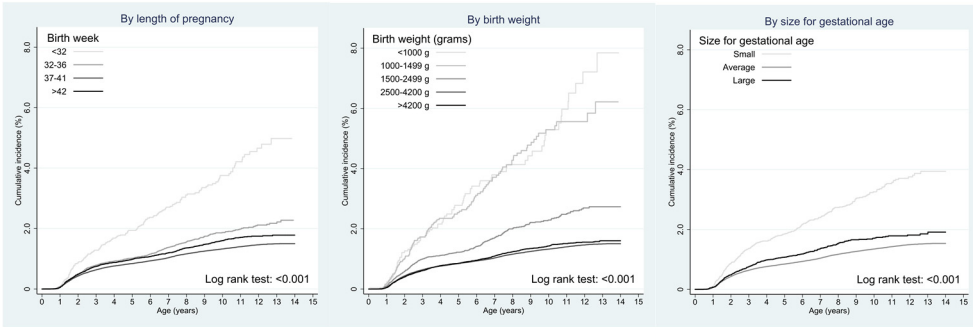


Figure 14. Birth-related risk factors for cryptorchidism in Swedish boys born in 2001-2014; pregnancy length (left), birth weight (centre) and size for gestational age (right).
The cumulative incidence among 748,678 boys, in percentages.

Treated for cryptorchidism at age 3 years	Timing of treatment Later Earlier	Hazard ratio (95% confidence interval)	P-value
Travel time to treating hospital			
By each 30-minute increase		0.91 (0.88 to 0.95)	<0.001
Education (years)			0.64
>12[a]		1	
10-12		0.97 (0.90 to 1.04)	
<10		0.99 (0.82 to 1.20)	
Employment			0.19
Yes[a]		1	
Unemployment		0.93 (0.84 to 1.03)	
Income (quintiles)			<0.001
Q5, highest income[a]		1	
Q4		0.88 (0.79 to 0.97)	
Q3		0.80 (0.72 to 0.89)	
Q2		0.90 (0.81 to 1.00)	
Q1, lowest income		0.82 (0.72 to 0.93)	
Financial support			0.02
No support[a]		1	
Support		0.85 (0.73 to 0.97)	
Parents born in Sweden			0.46
Two[a]		1	
One		1.06 (0.96 to 1.17)	
None		1.04 (0.93 to 1.16)	
	0.7		

[a] Reference category chosen as baseline in the regression analysis.

Figure 15. Multivariable estimates of association between travel time by car to the treating hospital and the probability of being treated at 3 years of age among all boys treated for cryptorchidism in Sweden 2001 and 2011 (minimum 3 years of follow-up).
Estimated associations between all dependent variables included in the multivariable Cox regressoin model. The model was adjusted for study year and stratified by county of residence.

Study V

Paediatric appendicitis – Cumulative incidence and risk factors for complicated disease

The incidence of appendicitis up to 18 years of age was 2.5% (Figure 16). Complicated appendicitis accounted for 17% of all cases of paediatric appendicitis [95% confidence interval 16.6 to 17.4%], with no gender differences (Figure 17). The risk of complicated disease peaked in the youngest children, and decreased by age.

The caseload volume of paediatric appendicitis in the seven university hospitals remained unchanged between 2001 and 2014. The number of non-university hospitals providing treatment for paediatric appendicitis decreased from 54 to 44 hospitals during the study period, and the median annual caseload volume decreased from 35 [IQR 19 to 59] to 24 [7 to 39] (B=-0.77 [95% confidence interval -1.19 to -0.35], p<0.001).

There was no evidence of a linear association between travel time to hospital by car and the risk of complicated appendicitis in Swedish children (adjusted for age, gender, place of treatment, year and socioeconomic variables: OR 1.00 [95% confidence interval 0.96 to 1.05], per 30-minute increase in travel time, p=0.93) (Figure 18).

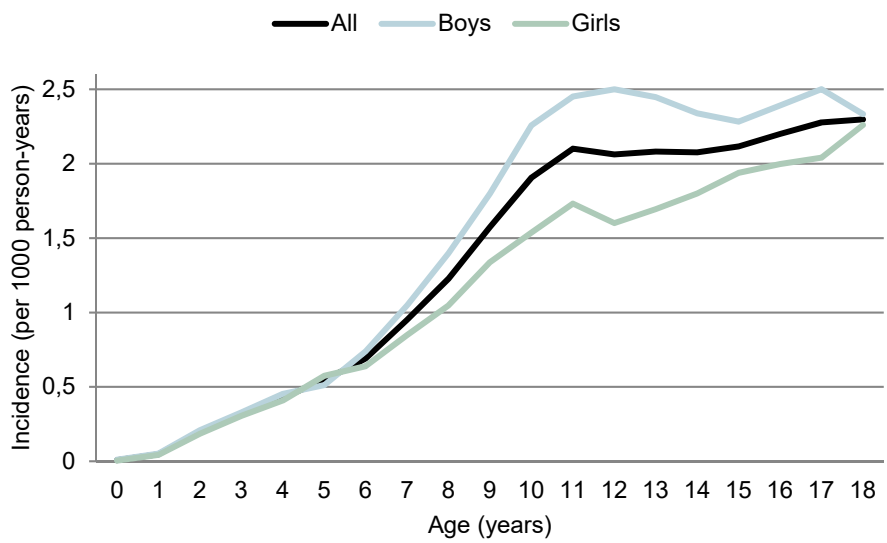


Figure 16. Age-specific incidence of appendicitis in Swedish children 0-18 years of age, 2001-2014. Adjusted for age and study year, boys had 27% [95% confidence interval 25-30%]) higher incidence than girls (p<0.001).

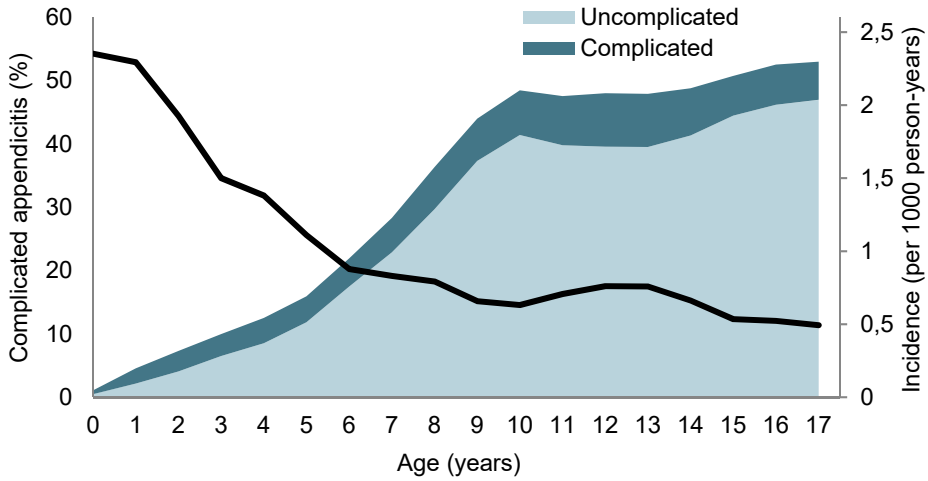


Figure 17. Uncomplicated and complicated paediatric appendicitis in Swedish children 0-18 years of age, 2001-2014.
Left axis (black line): Complicated appendicitis as a proportion of all cases of paediatric appendicitis. Right axis: Age-specific incidence of uncomplicated and complicated appendicitis in age 0-18 years.

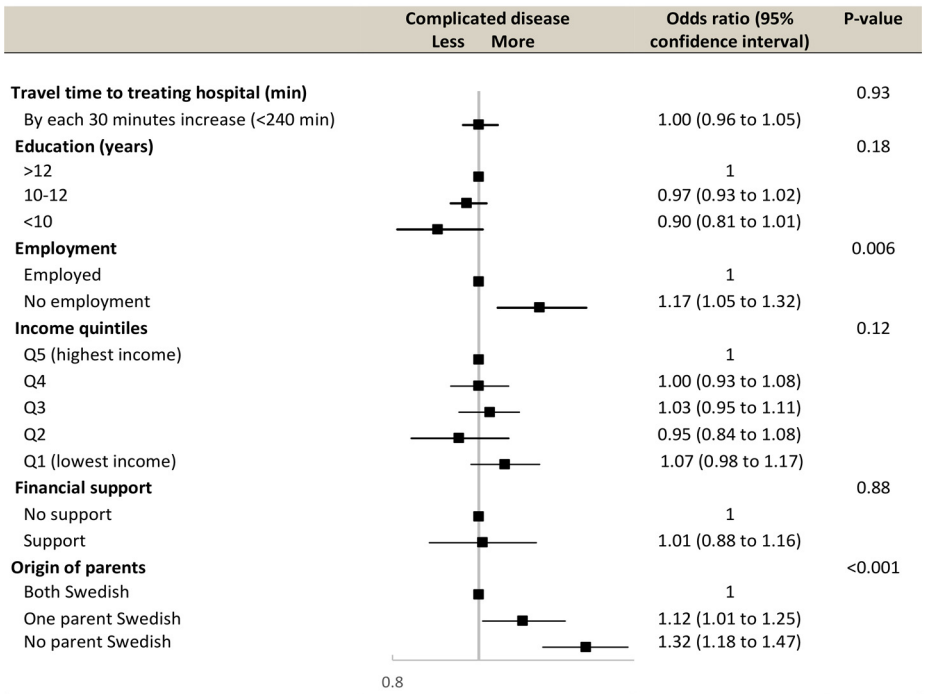


Figure 18. Multivariable effect estimates of travel time to treating hospital on the risk of complicated appendicitis in Swedish children 0-18 years of age, 2001-2014.
Model stratified by county of treatment and adjusted for socioeconomic determinants, age and year.

Discussion

Incidence, outcome and access of paediatric surgery

In this thesis, three aspects of surgery and public health have been targeted for the paediatric population in Sweden:

1) The *incidence* of surgical care for children has been placed in relation to the entire population.
2) Disease-specific *incidences* and *outcomes,* in terms of surgical-related risks, have been analysed for one congenital condition (cryptorchidism, requiring non-emergency surgical care), and one acute condition (appendicitis, requiring emergency surgical care).
3) *Access* to paediatric surgery has been evaluated by estimating geographical and socioeconomic risk factors for delayed surgical treatment or disease progression, respectively, in one elective and one emergency paediatric condition.

In summary, the studies presented in this thesis suggest that:

a) The need for surgery on a population level was even greater than previous estimations had indicated.
b) Surgery affected 1 in 20 children every year of childhood on average, and 1 in 4 hospitalised children underwent surgical procedures.
c) One in 55 boys was treated for cryptorchidism, and 1 in 40 children was treated for appendicitis. Overall, the surgery-related risks for these two conditions were low.
d) The risk of morbidity after appendicitis increased substantially after complicated appendicitis, with more postoperative infections, readmissions and reoperations, and higher risk of later small bowel obstruction.
e) There was an access gradient to timely treatment for cryptorchidism by increasing distance to treatment facility. Such a gradient was not seen in paediatric appendicitis.

Methodological considerations and limitations

The studies performed in this thesis all have their associated strengths and limitations that affect the validity and generalisability of the results. These considerations need to be addressed in order to interpret the results correctly and draw balanced and sound conclusions. This chapter provides a general discussion on these aspects, with special regard to methodology and suitability of the chosen study designs.

Validity of data sources

The five studies in this thesis are based on longitudinal data, collected from national healthcare and administrative registers. Data in these registers were longitudinally collected; the data points were collected in chronological order and the complete trajectory of each individual's course of life was not known at the time of inclusion in the registers.[28] In terms of coverage and accuracy, these registers are excellent and highly reliable sources of information.

The Register of the Total Population is considered to provide virtually complete coverage of births and deaths in Sweden (127). The Medical Birth Register includes all births in Sweden with few exceptions, and with very few missing data for birth characteristics and maternal risk factors (Table 6). The National Inpatient Register covers close to 100% of inpatient care and 85% (2007) of specialised outpatient care and day surgery, and >99% of primary diagnosis are reported to the register correctly (133,134). Dates of admission and discharge from hospital care or dates of visits to outpatient clinics are highly accurate. Nonetheless, even if overall coverage is good in most registers, parts of them may be incomplete and missing data can be a real problem for some variables.[29]

The accuracy in the administrative registers is expected to be high, as the registers are based on the taxation authorities and public services reports, including the public-funded education system and social services. Nonetheless, under-reporting of incomes and other financial assets must be expected to some extent and unemployment may be voluntary and not always captured by the authorities. Consequently, the true validity of the administrative registers is unknown.

[28] The inclusion in the Swedish Cause of Death register being an exception, as this *de facto* defines a completed life trajectory.

[29] The variable indicating 'date of surgery' in the National Patient Register was only available for a minority of inpatient care for appendicitis in children, and the anaesthetic codes were virtually not registered in these patients (unpublished data).

Data coverage is related to incitements to systematically fulfil reports and conduct registrations. Even if the reporting of surgical procedures in outpatient care has been mandatory by law since 2001, the coverage was progressively increasing initially and reached 85% by 2006. On the other hand, incitements such as financial and other benefits may promote rigorous reporting, particularly if economic profit is to achieved.

Table 6. Data coverage of birth characteristics and maternal risk factors in the Medical Birth Register.
All registered male births in Sweden 2001-2014 (n=728,678).

MBR variable	Data records in MBR	Missing data, n (%)
Births	748,678	-
Birth weight (grams)	747,240	1438 (0.2)
Size for gestational week	748,678	0
Length of pregnancy	748,363	315 (<0.1%)
Maternal age	748,674	4 (<0.1%)
Maternal smoking status	701,616	47,062 (6.3%)

To what extent the considerable increase in outpatient care, seen in study I, can be explained by shifts in reporting propensity is not known.

Register studies come with inherent limitation in granularity. In studies IV and V, parental education is categorised as attendance to compulsory school only (<10 years of studies), high school education (10-12 years of studies), or higher education (>12 years of studies). These categories were chosen in the studies, as they reflect levels of formal education for most people in Sweden, but do not necessarily capture all forms of education or skills. There may also be some miss-classification as only completions of educations are registered, and people may have attended longer educations than indicated in the registers.

Misclassification of data may introduce a serious threat to validity in the geographic information system (GIS) analysis of estimated travel times to the treating hospital (study IV and V). In the GIS analysis, the estimated travel times by car from the population centroid[30] of each SAMS area[31] to the geo-coordinates of the treating

[30] Children 0-18 years of age defined the population in each area, and the centroid was calculated as this population density centre.

[31] Small Area for Market Studies (SAMS) is a system of rather small geographical areas, defined by the Statistics Sweden and used since 1994, that allows the analysis of demographical and socioeconomic distribution in the population with a rather high geographical granularity. There are just over 9200 defined SAMS areas in Sweden, with 80% of the areas covering 500-4000 inhabitants and an average of 1000 inhabitants. The system provides rather high granularity (there are 128 SAMS areas in Stockholm City) but has been criticised for large variations (Gothenburg has 876 SAMS on a similar area, and Surahammar 33 SAMS). The SAMS areas are to be replaced by the Demographic Statistical Areas (DeSO, Demografiska statistsikområden), a new

hospital were calculated, using the road net as it was in the year of the diagnosis, considering speed limits, stop signals and turns as they were then. This estimation is expected to be rather accurate under the assumption that the child lived at the registered address at the moment of diagnosis. If this assumption is not fulfilled, the GIS analysis will be invalid.

It is all about definitions

Incidence of surgery

Register content needs to reflect the reality in order to be useful, and when interpreting register-based studies, it is important to understand to what extent this is fulfilled. The studies in this thesis are all sensitive to misclassification, and to interpretation errors.

In study I, major surgery was defined as any procedure listed in chapter A-Q of the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (NSCP) version 1.16 (135). This definition of surgery excluded procedures listed in Table 7 from the analysis, yet there may be specific procedures found in chapter A-Q that occasionally, or never, should be considered as major surgery by most physicians.

Table 7. Definition of major surgery and exclusion of other surgical and investigative procedures in study I. As defined by the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (NSCP) version 1.16 .

NOMESCO NSCP version 1.16 Chapter(135)	**Description of procedures**	**Major surgery in study I**
Chapter A-Q	Disease-sepcific or organ-specific invasive procedures	Yes, analysed for primary outcome
Chapter T	Superficial incisions Excisions Punctures Needle aspirations Needle biopsies	No, reported separately.
Chapter U	Endoscopies	No, reported separately
Chapter X	Radiological investigations	No, reported separately
Chapter Y	Procedures related to transplant of organs or tissue	No, reported separately

Outcome and access of paediatric surgery

Cryptorchidism and appendicitis are defined by their specific ICD-10 codes. In studies III and V, acute appendicitis was classified by disease severity as either

system for geographical analyses; the DeSO, containing 5985 areas of rather equal population sizes but less geographical granularity (149).

complicated or uncomplicated (Table 8). In study III, levels of appendicitis severity were assigned as the *exposure,* and in study V, they represented the *outcome*. Grading of appendicitis severity from ICD-codes is not straightforward, however. Both these studies are therefore sensitive to misclassification of several reasons, outlined in Table 9. In this context, a validation of the clinical subtypes of appendicitis by their respective ICD-10 codes would be valuable to assess the correlation between the diagnostic code and the severity of disease. However, such validation would require access to medical records.

Table 8. The categorisation of appendicits severity in study III and V ws based on ICD-10 codes.
The Swedish version of ICD-10 was revised in 2010, and the classification and coding of appendicitis changed from being based on radiological, perioperative or pahtological findings, such as abscess or perforation of the appendix, to clinical findings, such as abcence of peritonitis, localised or generalised peritonitis.

Appendicitis type	ICD-10 (2001-2009)	ICD-10 (2010-2014)
Complicated	K35.0 (with generalized peritonitis) K35.1 (with abscess)	K35.2 (with generalised peritonitis)
Uncomplicated	K35.9-K37.9 (other forms of appendicitis)	K35.8-K37.9 (other forms of appendicitis)

In studies II and III, the risks of surgical site infections were studied. Estimations of postoperative infection rates in register-based research are highly dependent on the definition of a postoperative infection, and how well these are captured in the registers. In study III, the postoperative infection rate was 5.9% in complicated appendicitis, and 2.3% in uncomplicated appendicitis. These are reasonable rates when compared to some register-based studies of paediatric appendicitis (136). However, in studies where wider definitions of surgical site infections were used, or with active follow-up in medical chart records and telephone questionnaires, much higher rates have been reported: 20-30% for complicated appendicitis and 5% for uncomplicated appendicitis (136–139).

In this thesis, the definition of surgical site infections included patients who had either a registered diagnostic code of infection related to surgery (ICD-10 code T81.4) within 30 days from discharge from any hospital or specialised outpatient clinic, or a prescription within Sweden of any of the antibiotics used for surgical site infections within 30 days of discharge. This definition is likely to capture most surgical site infections of clinical significance (i.e. severe enough to render clinical follow-up at a specialised clinic, or treatment with antibiotics, or a re-admission to the hospital). However, this definition excludes cases where patients were able to treat the infection by themselves, or with the aid of primary care, and where no antibiotics were prescribed.

Finally, as complicated appendicitis is more likely to be treated with antibiotics to prevent abdominal complications related to appendicitis perforation, it is possible

that the rates of surgical site infection following complicated appendicitis have been underestimated to some extent.

Table 9. Sources of misclassification of appendicitis subtypes in the National Patient Register.
Potential explanations for variations in accuracy of diagnosis, and hypothesised direction of the error.

Source of misclassification	Likely direction of error	Rational
Judgement errors by the surgeon	Any	Ignorance of symptoms or findings, or over-interpretations of symptoms and findings may cause individual cases to be misclassified as more (or less) complicated than motivated.
Reporting bias	Towards more complicated disese	Individual surgeons may systematically report more severe disease than motivated by the symptoms.
	Any	Local traditions of describing symptoms or applying diagnostic codes may systematically bias the classification of complicated disease in some clinics.
Coding errors	Any	Stress, ignorance or lack of interest in proper coding by the surgeon. Ignorance or mishaps by the clinical administrator when reporting clinical data to the register.
Changes in classification of appendicitis subtypes	Towards less complicated disease	The revision of the Swedish version of ICD-10 in 2010 introduced appendicitis with local peritonitis as a subtype, and appendicitis with abscess was removed as an subtype of appendicitis. Most surgeons would consider appendicitis with an abscess as a complicated subtype, whereas local peritonitis is not necessarily complicated. Thus, the change in coding caused a systematic reduction of appendicitis cases being classified as complicated in the registers.

Study design suitable for the questions asked?

Observational studies of longitudinal register data

The five studies presented in this thesis share common properties: all are register-based, observational studies of longitudinal data. It is worth pointing out that the data were collected prospectively, so that individuals in the cohorts were followed longitudinally in the registers, from the time of inclusion to the event of interest, censoring or death. Yet, the study designs impose limitations and even if trends and associations can be estimated quite accurately, it is not possible to derive causal relationships in these studies, and reported incidences are to be considered estimates.

Calculations of incidence rates

Incidence rate is, as mentioned previously, the number of events in a designated population per person and unit of time. In this thesis, estimates of incidence have been derived using various methods and accuracy:

a) In study I, incidences of major surgery were estimated in an open cohort of an entire population.

b) In studies II and V, the incidences of treatment for cryptorchidism and appendicitis, respectively, were estimated in an open national cohort of children.

c) In study III, the cumulative incidence of small bowel obstruction was estimated with survival analysis in a cohort of children treated with appendectomy, with prospective follow-up in the national healthcare register.

d) In study IV, the cumulative incidence of treatment for cryptorchidism was estimated using survival analysis in a total population of boys, with prospective follow-up in the national healthcare register.

The accuracy of incidence calculations is the product of the accuracy in recorded events and to what extent the population at risk is defined properly. These aspects need to be considered when incidences are interpreted.

In study I, the minimum number of events recorded in the register may rather accurately reflect the reality in the surgical clinics reporting to the register, yet some healthcare providers did not report at all and thus the true incidence would be higher than estimated. Furthermore, the background population was an open cohort of Swedes, and individual level data were not available, and none-Swedish citizens visiting the country were at risk of seeking medical care as well. Thus, the population at risk was not well defined, and the Swedish population was merely a proxy for the true population at risk in study I.

In studies II and study V, the definition of the population at risk was again slightly problematic due to the non-individual data of the background population. In these two studies, however, the error was reduced as only Swedish-born children were eligible for inclusion and outcome.

Unlike studies I, II and V, estimations of incidences in studies III and IV, were highly reliable. The exact population at risk was known from the start of follow-up and throughout the study periods, and the outcomes were likely to be captured in the registers.

It is worth pointing out that the method chosen in studies II and V allowed for calculation of cumulative incidence until 18 years of age, but the estimates were not completely accurate. In contrast, the method chosen for incidence analysis in studies III and IV is highly accurate, but limited in the sense that full follow-up is required during the entire study period for incidence calculations. The cumulative incidence in studies III and IV could therefore only be reported up to the age equal to the length of the study period (i.e. 14 years of age, from the beginning of 2001 to the end of 2014).

Observational studies and causality

In study III, the estimated associations between laparoscopic appendectomy and fewer surgical site infections, and also reduced risk of small bowel obstruction, was of particular interest. Yet, it is not possible to determine if the observed association represents a causal relationship. Even if the association seems plausible and there was a temporal association between the exposure (which was the treatment modality), and the outcome (which was the risk of adverse events during follow-up), and even if several possible confounders were controlled for in the analysis, other factors not captured in the registers may still explain this observed association. The surgeon's decision of treatment modality (for example open versus laparoscopic appendectomy) is not random, in general. There may have been a systematic skewness in this decision, so that children with milder symptoms were more likely to be treated with laparoscopic appendectomy, whereas more worrying cases, in terms of comorbidities or symptoms, were chosen for open appendectomy to reduce perioperative risks.[32] Furthermore, as the propensity for postoperative follow-up may be higher after open appendectomy or converted procedures, than after laparoscopic procedures, there may be a *selection bias*[33] in which cases are clinically evaluated for surgical site infections.

Randomised trial – a costly dream in epidemiology

To avoid selection bias, the preferred study design to capture outcomes such as postoperative risks by treatment modality, would be a randomised trial where eligible cases for any of the treatment modalities of interest were assigned one of the treatment modalities in a randomised pattern, and followed for complications. Given the low expected rates of adverse outcomes, a randomised study for this research question would require inclusion of a large cohort of children, which is a costly and time-demanding process.

Selection bias, confounding and sensitivity analyses

There are several threats to the internal validity in the studies presented in the thesis. The study designs, being observational in nature, and the data sources, being registers rather than first-hand information or journal transcripts, open up for different sources of bias and confounding.

In this section, the validity of the results reported in this thesis will be discussed, and the following potential sources of bias and confounding will be addressed:

[32] This systematic skewness is commonly referred to as *confounding by indication*. We return to this term later in the chapter.

[33] Selection bias will be discussed later in this chapter.

a) Selection bias is a common and serious threat to the validity in all observational epidemiological studies and may cause the observed study sample to differ systematically from the background population in important aspects. The risk is considerable in cohort studies, but also to some extent in total population studies.[34]

b) Reporting bias is relevant in all register studies, even if the risk may be reduced in registers with prospective inclusion and follow up as compared to retrospectively collected datasets.

c) Misclassification of variables may systematically skew the data in registers. Both reporting bias and misclassification are especially relevant in cases where the data collection has dual purposes, such as quality comparisons, or financial benefits linked to the registration of data.

d) Confounding may arise when there is a propensity for one particular exposure among patients who exhibit certain characteristics (such as a risk factor, that may not be captured properly in the data), and when this exposure is also associated with the outcome.[35] This includes *confounding by indication* (in several aspects closely related to selection bias), and *unmeasured confounding*.

Risk of selection bias, reporting bias and misclassification in studies II-V

Selection bias can be introduced at multiple levels in observational epidemiological studies. Even a representative study cohort, such as a total population, may still be subject to selection bias on other levels. It is possible that some groups of individuals (for example an individual possessing a certain risk characteristic, a beneficial background or whatever) systematically are selected for more interventions or screened for more outcomes. Consequently, selection bias may have skewed the results of postoperative adverse events in study III (see also the discussion on *Observational studies and causality* above).

Selection bias may also have skewed the results in study IV, in which the age at treatment was assessed by levels of the distance to the hospital. Travel distance to the hospital could only be estimated accurately for those children who de facto had the treatment. Therefore, the cohort analysed for this outcome included only those children who successfully manged to receive medical attention for correct diagnosis and treatment. It is possible that some cryptorchid children actually remained undiagnosed throughout the study period, and if these children differed

[34] What is to be considered a total population may be up for debate and is usually sensitive to the research question and the intended application of the results.

[35] Confounding is by definition the occurrence of an independent risk factor for the outcome, that has a systematically imbalanced distribution in the studied exposure groups (150).

systematically from those receiving medical attention (such as living relatively close to the hospital, or living in a relatively wealthy family), a selection bias may have been introduced that potentially could explain away to the observed associations of travel distance and income on the age at surgery.

Reporting bias is commonly referred to when some events are more likely to be reported than others. Reporting bias may have been present in the coding process of appendicitis severity (studies III and V), either by the physician responsible for the coding, or influenced by local clinical routines. This reporting bias may have caused misclassification of appendicitis severity in the National Patient Register. If more severe types of appendicitis were reported systematically following open or converted appendectomy (to motivate the more invasive procedures), we would in fact expect the results to be biased towards fewer adverse events following open or converted appendectomies.

Risk of confounding of results in study III-V

Confounding by indication may have skewed the results in study III, so that the association between treatment modality and risk of postoperative adverse events became inflated. As mentioned earlier in this chapter, the decision of suitable treatment modality for the appendicitis is made for each individual rather than at random, yet gradients in appendicitis severity are not easily captured by the register data. A systematic propensity towards laparoscopic appendectomy in suitable cases without risk factors, and towards open appendectomy in cases with comorbidities, previous history of abdominal surgery or other factors that increase the general risks, may explain some of the observed associations.

Related to confounding by indication, unmeasured confounding is a relevant source of error in observational studies (Text box 9). In this context, unmeasured confounding relates to hypothetical remaining factors that may explain away part of, or the entire observed association between the exposure and the outcome. In studies III and V, we were not able to adjust for comorbidities and other risk factors that have been shown or suggested to impact the probability of timely treatment or risk for more complicated disease.[36]

In the GIS analyses (studies IV and V), we were not able to adjust for the fact that some children may have been referred further away to a paediatric surgery centre to receive timely (i.e. early) treatment, and consequently these children were classified as living far from the treating hospital. This may explain the (unadjusted)

[36] The few known or suggested risk factors for complicated paediatric appendicitis include the radiological or perioperative finding of faecalith (a solid faecal concrement causing obstruction in the appendiceal lumen), whereas co-morbidity of IgE-mediated allergies, and a history of prior healthcare visits indicating connectivity to the healthcare system have been associated with lower complication rates (86,103).

observation that the treatment age among those with longest distance to the hospital was equal or even more optimal, than for those living close to the treating hospital (Figure 19).

Text box 9

Unmeasured confounding and the use of E-value

Causality can generally not be claimed from observational studies, even when a temporal association are found. The reason is that observational studies are vulnerable to various forms of bias (of which selection bias may be the most serious threat to validity in general) and confounding; Even if multiple relevant variables have been adjusted for, there may be residual explanations for an association that have not been captured by the included variables in the data. The term *unmeasured confounding* is used for unknown, and more or less plausible factors, that influences both the exposure and the outcome, and may explain away some or all of an association in observational studies.

There are methods to assess how sensitive an observed association is to unmeasured confounding. The calculation of the E-value provides such a measure.(Vanderweele, 2017) Even if the true size and the direction is unknown for a particular unmeasured confounder, the E-value method estimates how much such a confounder would need to be associated with the exposure and the outcome, to explain away the observed main association. It is worth to point out that the method assumes the presence of only one unmeasured confounder, and that it is associated equally to both the exposure and the outcome, even if this is a simplification of reality in most cases.

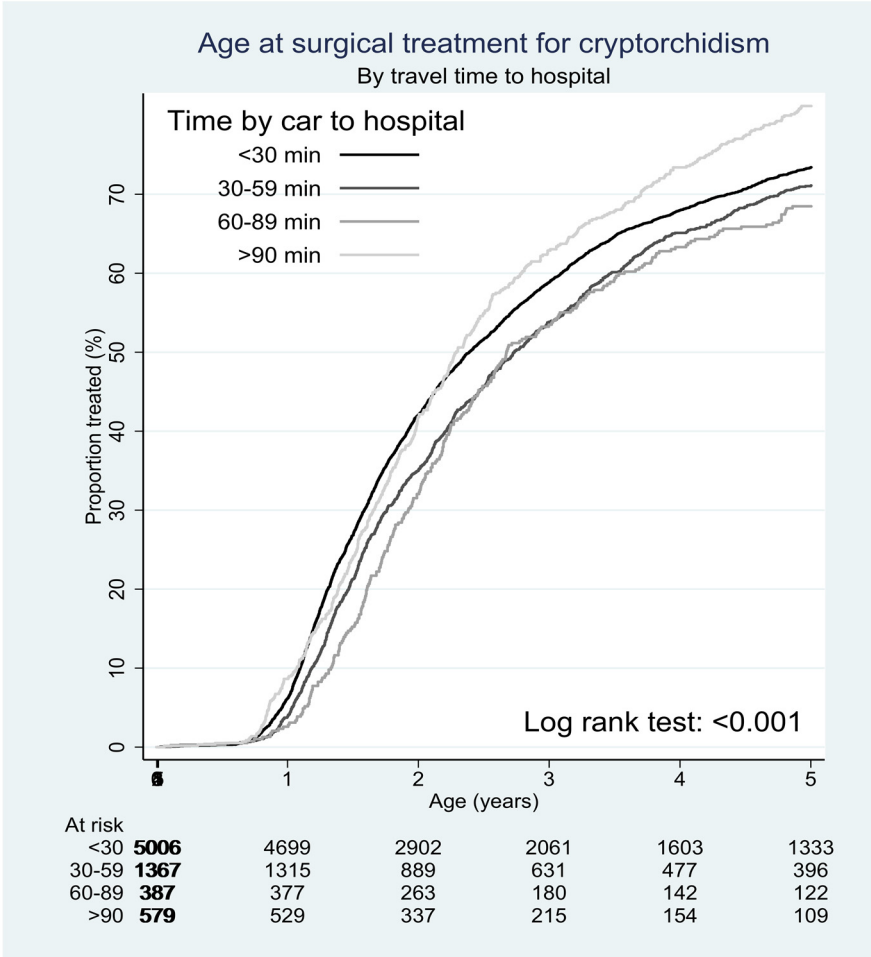


Figure 19. Travel time to the hospital and the probability of having been treated for cryptorchidism.
Swedish boys treated for cryptorchidism (2001-2009), with a minimum of 5 years' follow-up.

An interesting observation in study V, which may as well be attributed to an unmeasured confounder, was the finding of a non-linear association between travel time to the treating hospital and the risk of complicated appendicitis in children. As previously presented in the *Result* chapter, the primary multivariable logistic regression analysis suggested no dose-response association (linear trend) in the risk by levels of travel distance. However, in the sensitivity analyses, where the categories of 30-minute intervals in travel time to hospital were considered categorical (nominal scale) rather than ordered categorical (ordinal scale), the multivariable estimates indicated an increased risk for those children living approximately half an hour from hospital, as compared to those living less than 30 minutes, or more than 1 hour, from the hospital (Figure 20A). These results were

even more granularly reviled when travel time was categorised in quintiles instead of fixed intervals (Figure 20B). It is possible that this non-linear trend would be explained by an unmeasured risk factor for complicated appendicitis, that is geographically unequally distributed in the population. The results in Figures 20A and 20B suggest that this yet unknown risk factor (perhaps just not captured in our data?) for complicated appendicitis would be most abundant in the population living 10 minutes to 60 minutes from the hospital.

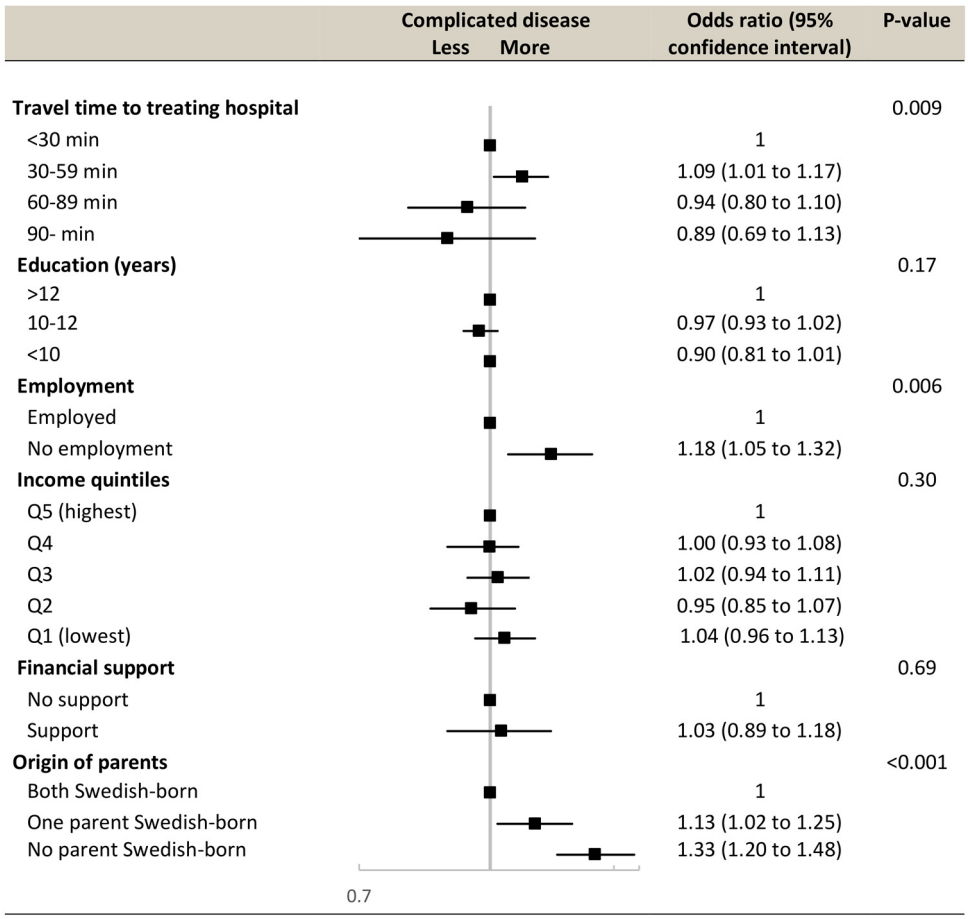
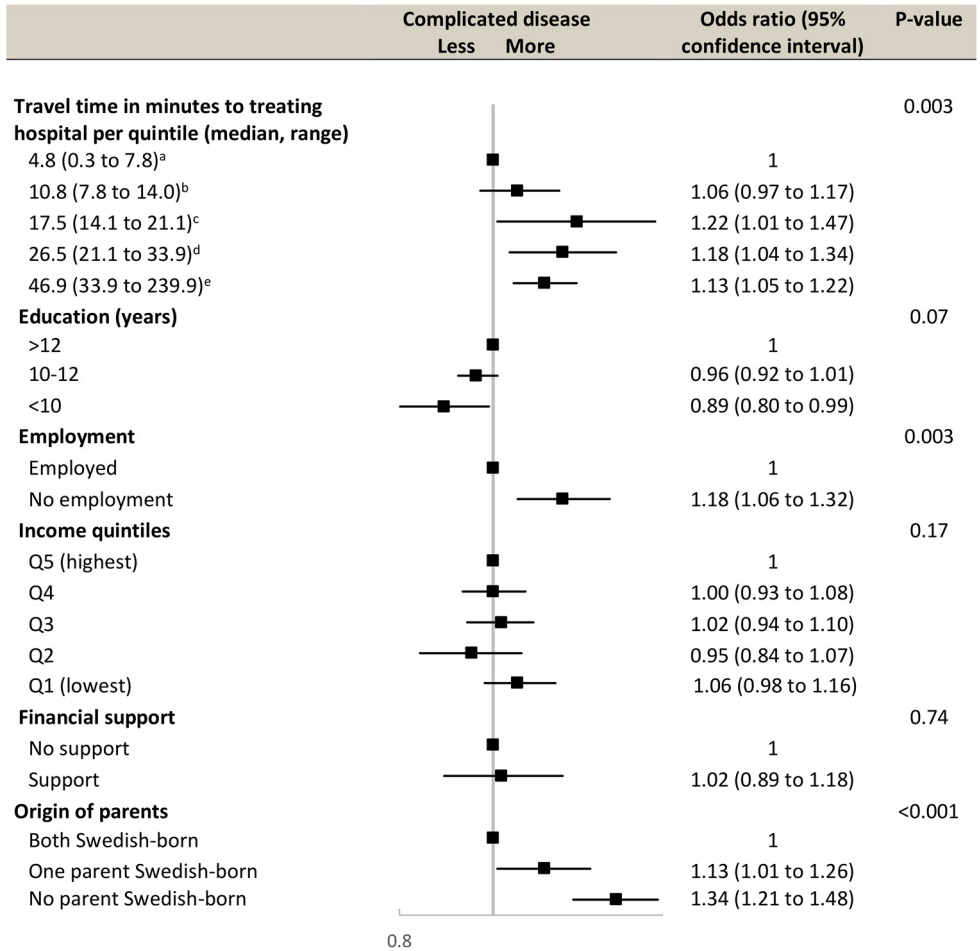


Figure 20A. Sensitivity analysis with travel time as 30-minute categories. Association between travel time to the treating hospital and the risk of complicatred appendicitis in Swedish children, 2001-2014.
Multivariable logistic regression model with socioeconomic determinants of health in the model as dependent variables. Model adjusted for age, gender and year, and clustered by county of treatment.

In order to explain away the entire observed association between travel time and the risk of complicated appendicitis (i.e. an adjusted odds ratio of 1.18 [95% confidence interval 1.04 to 1.34] for distances in the interval of 21 to 34 minutes by car to the hospital, see Figure 20B), the derived E-value suggests that this unknown factor would need to be associated with both the travel time to the hospital and disease severity with a odds ratio of 1.6-fold each (and 1.2-fold for the 95% confidence interval) (140).



[a] Q1, [b] Q2, [c] Q3, [d] Q4, [e] Q5

Figure 20B. Sensitivity analysis with travel time in minutes categorised as quintiles. Association between travel time to the treating hospital and the risk of complicated appendicitis in Swedish children, 2001-2014.
Multivariable logistic regression model with socioeconomic determinants of health in the model as dependent variables. Model adjusted for age, gender and year, and clustered by county of treatment.

Whether this unknown risk factor or unmeasured confounder would be medical or socioeconomic in nature, remains to be clarified. Baxter et al suggested higher connectivity to healthcare services as a protective factor in a large cohort of privately insured children in the USA (86). However, no such association was seen in a cohort study of all paediatric appendectomies in our tertiary paediatric surgery centre in Lund (103).

Sensitivity analyses

To test robustness of results in the presented studies in this thesis, several sensitivity analyses have been performed.

a) Subgroup analyses have been performed (study IV) to test robustness to changes in the setting or classification frames; the introduction of new clinical guidelines for treatment of cryptorchidism in 2007 had a dramatic impact on the median age at treatment (as observed in study II). Therefore, a sensitivity analysis of robustness of results to this organisational shift was performed in study IV and the results indicated that the multivariable association between travel time and the probability of being treated at 3 years of age remained stable despite this shift.

b) Subgroup analyses have been performed (study III and V) to test robustness to the changes in the coding of appendicitis subtypes in the ICD-10 revision in 2010.

c) Multiple imputation analyses have been performed (study II) to assess whether missing data were likely to impact the results.

d) Multiple sensitivity analyses were performed (study IV and V) to test robustness in results to changes in classification of social determinants of health. The estimated associations between travel time and the risk of complicated appendicitis, and treatment age at cryptorchidism, respectively, were stable to changes and granularity in the classification of:

    i. Education (to six categories instead of three),

    ii. Parental migration status (to five categories instead of three) and

    iii. Categorisation of age (continuously, 3-year or 5-year age intervals).

e) Multiple sensitivity analyses were performed (studies IV and V) to test robustness in results to changes in classification of the exposure (travel time to hospital was categorised in 30-minute intervals, in quintiles and as a continuous variable) and changes in the cut-off age for treatment in the

survival analysis (censoring at 2 years, 3 years and 5 years of age). The results remained largely stable.[37]

Generalisability – the external validity

The studies presented in this thesis may be rather accurate reflections of healthcare provided for children in Sweden. However, as indicated in the introduction and background, population characteristics, societal structures and healthcare provision in Sweden differs in several aspects from other countries. This needs to be considered when results from these studies are interpreted, and extrapolations to other populations and different settings must be made with great caution.

Few countries in the world offer universal healthcare free of charge for their children, and this affects the generalisability of the results from the studies on incidence of surgery (study I) as well as on access to timely care (studies IV and V). The relative high incidence of surgery found in the Swedish population may not be confirmed in countries where healthcare is limited or expensive for some groups of the population, such as the elderly or those outside the labour market. Complication rates reported in healthcare registers may be sensitive to costs for seeking care, and also to expectations of provided care to some extent. Timely treatment and effects of travel distance are expected to be more differentiated in healthcare systems where the financial barriers are higher.

Beyond the aims

The research questions addressed in this thesis concerns general and specialised surgical care for children and relates to the local and regional organisation and distribution of surgical facilities in Sweden. However, this thesis does not claim to address the organisation and distribution of highly specialised paediatric surgery that is eligible for national centralisation, as defined by the Swedish Board of Health and Welfare and includes rare congenital anomalies such as congenital diaphragmatic hernias, oesophageal atresia and advanced anorectal and genito-urinary malformations (7). Nor does this thesis address advanced paediatric surgical care in conditions requiring multi-disciplinary approach to a large extent, such as neonatal surgery and paediatric oncology.

[37] Of particular interest, however, was the estimated association between travel time and risk of complicated appendicitis (study V) when travel time was categorised by quintiles. See discussion earlier in this chapter, and Figures 20A+B.

It is beyond the aims of this thesis to address centralisation in terms of minimum critical annual exposure to surgical procedures (case-load volumes) to maintain and transfer competence at a healthcare provider level or organisational level.

Significance

Putting pieces together

The overall aim of this thesis was to frame paediatric surgical care in Sweden in terms of *incidence* of all types of surgery in children, treatment *outcomes* and timely *access* to surgical care.

In summary the obtained results from the conducted studies suggested that paediatric surgery affected 1 in 20 children every year on average, throughout childhood. The incidence of any major surgery for children was at least 6784 operations per 100,000 person-years [range 6784 to 8515], and the incidence reached 21,152 operations per 100,000 person-years for adults [range 21,152 to 25,806].

The results suggested that surgery in outpatient settings provided a considerable contribution of the national volume of surgery in the Swedish population for both children and adults.

In the case of cryptorchidism, the most common genital anomaly in boys, only a fraction of all boys with the diagnosis were treated before 1 year of age. This was remarkably low, considering the known risks of future testicular malignancies and reduced fertility, and the explicit recommendations of early treatment in the current guidelines.

One in 55 Swedish boys (1.4%) were diagnosed and treated for cryptorchidism up to 14 years of age, and at 18 years of age, approximately 1.8% were treated. Even if the treatment age varied largely within the country, the overall surgical-related risks appeared low, with no regional variations; virtually no mortality was observed and a 1.4% risk of surgical site infection after the surgery was detected.

In the case of appendicitis, the most common cause of emergency abdominal surgery in children, approximately 1 in 40 Swedish children (2.5%) have had the condition during childhood, and 1 in 235 children had experienced a severe form of appendicitis. Even if the general risk for complications were low, those children with complicated appendicitis faced twice as many postoperative infections and a many-fold increase in risk of readmission during the first month after surgery.

Furthermore, they also faced a many-fold increase in the risk of surgery due to small bowel obstruction later on.

Postoperative risks were not only related to the appendicitis severity; also type of operative treatment seemed related to the risk of complications. Even if the validity of these results was less certain, as they were vulnerable to confounding, a strong association was detected between treatment modality in appendicitis and the immediate as well as the later risk for complications, so that fewer complications were seen after laparoscopic appendectomies compared to open appendectomies.

Finally, the results presented in this thesis suggested that children with a long distance to the surgical facility that provided the treatment were treated later for cryptorchidism. This finding was also stable when multiple risk factors and potential social determinants were adjusted for. No such clear association was found in paediatric appendicitis.

Implications for future measures of surgery

The transition from hospital-delivered surgical care to outpatient clinics and day surgery provision has revolutionised the Swedish healthcare system in slow motion. Yet, the extent of this transition has been unclear. As previous estimates of surgical output on population level are almost exclusively based on inpatient (i.e. hospital-based) care, we hypothesised that the proposed annual basic surgical demands of 5000 operations per 100,000 population were severely underestimated, and the demand for surgical care during childhood was previously not known. As presented in this thesis, estimations of the surgical output in the Swedish population were significantly greater than expected, mainly due to the inclusion of day surgery in this analysis.

The Swedish population has a different demography, and the healthcare system is also rather unique, as compared to many other countries. These two circumstances may explain the relatively high incidences of surgery observed in Sweden. Nonetheless, the results indicated large variations in surgical incidence between males and females in different age groups. The specific incidences per age and gender are of particular interest, as these can be used for derivation of population need in countries with similar healthcare systems and disease panorama, and form the basis in projections of population surgical needs in countries where the demography is changing.

In summary, the main conclusion from study I is that surgery provided in outpatient settings needs to be included in estimations of national output of surgery.

Implications for paediatric surgery in Sweden

Results presented in this thesis suggest that complicated appendicitis in children increases the risk of serious complications such as surgical site infection and later surgery for small bowel obstruction. Even if efforts to provide timely and accurate diagnosis and treatment are warranted to avoid disease progression, no modifiable factor in particular has been identified that can prevent the risk of more severe appendicitis disease in children.

There has been a trend during the last two decades towards more centralised, or regionalised, surgical treatment for paediatric appendicitis. The use of laparoscopy in the treatment of paediatric appendicitis has increased concomitantly. Even if Sweden has been relatively slow to introduce minimal-invasive techniques in paediatric appendicitis, as compared to other countries (141–144), laparoscopic appendectomy accounted for more than half of paediatric appendicitis treatments since 2014 and is now the most common treatment modality. The finding of a rather strong association between laparoscopic appendectomy and fewer postoperative complications is therefore of particular interest, as open appendectomy is still a relatively common treatment modality. It might be possible to reduce the postoperative risks further by advocating laparoscopic appendectomy as the first choice of treatment for children. Therefore, further clinical studies on the beneficial effects of laparoscopic appendectomy in children, as compared to open appendectomy, are encouraged.

In the case of cryptorchidism, the results presented in this thesis (study IV) suggest that geographic access to healthcare matters; children with a longer distance to the surgical facility that provided the treatment were at an increased risk of having their treatment later, as compared to children with a shorter distance to the treatment. If distance to the surgical facility is a factor for timely cryptorchidism treatment in children, this needs to be considered in future planning of paediatric surgical care on a regional and national level.

It is worth to point out that the evidence for geographic access being a determinant of optimal treatment in cryptorchidism, as presented in this thesis, is not sufficient to draw firm conclusions. Causality between distance to hospital and treatment delay cannot be claimed, as outlined in the *Discussion* chapter. Also, avoiding extrapolations to other diagnoses and other settings are paramount, as associations found in the case of cryptorchidism does not necessarily translate well to other settings.

Nonetheless, very little evidence is available, and to my knowledge, no study has thoroughly and convincingly either confirmed nor rejected the hypothesis that geographic distance determines the probability of timely treatment in the case of elective or emergency paediatric surgery. Therefore, the true value of the results

presented in this thesis remains unclear. They need to be discussed, scrutinized and questioned in the light of further evidence. In the meantime, a humble acknowledgement of the lack of evidence when it comes to overall beneficial effects of centralizing surgical care may be appropriate.

Svensk sammanfattning

Kirurgi och folkhälsa handlar om hur kirurgi bidrar till god hälsa i befolkningen, och berör frågor som *var*, *när* och *hur* kirurgisk vård bäst *organiseras* och *utförs* för att uppnå störst nytta. Detta avhandlingsarbete ägnas åt att studera just hur dessa frågor besvaras för barn i Sverige, med avsikten att förstå förutsättningarna för kirurgisk vård av svenska barn.

Syfte

Det övergripande syftet med detta avhandlingsarbete är att

1) beskriva omfattningen av kirurgisk vård av barn ur ett nationellt perspektiv,
2) beskriva förekomst och behandling av vanliga barnsjukdomar som kräver planerad respektive akut kirurgisk vård, samt de risker som den kirurgiska behandlingen kan medföra,
3) beskriva hur organisatoriska riskfaktorer kan inverka på barns tillgång till optimal kirurgisk vård

Studie I

Studien sätter barnkirurgin i relation till övrig kirurgisk vård i Sverige. All sjukvård som producerats på svenska sjukhus, specialistmottagningar och inom dagkirurgin under åren 2006-2013 analyserades och volymen av kirurgi hos barn och vuxna dokumenterades. Incidensen av kirurgiska operationer i hela den svenska befolkningen beräknades för kvinnor och män i olika åldrar. Resultaten visade att 8% av alla pediatriska sjukvårdskontakter (0-19 år), och 27% av pediatriska slutenvårdstillfällen, inkluderade någon form av kirurgi. Incidensen ökade varje år, och beräknades år 2013 till minst 6784 operationer årligen per 100,000 barn i åldrarna 0-19 år. Motsvarande siffra i den vuxna populationen var 21,152 operationer årligen per 100,000. I genomsnitt opererades 1 av 20 barn varje år under uppväxten, medan i genomsnitt varannan 75-80-åringar opererades årligen. Dagkirurgin stod för minst två tredjedelar av all kirurgi år 2013 (intervall 67- 75%). Kvinnor, alla åldrar inkluderade, erhöll i genomsnitt 10% mer kirurgi än män. Studien visade att beräkningar av kirurgiska behov på befolkningsnivå bör ta hänsyn även till dagkirurgisk vård för att vara rättvisande. Tidigare beräkningar har underskattat behoven av kirurgi på populationsnivå och är således ej applicerbara

på ett höginkomstland som Sverige med en relativt åldrad befolkning och god tillgång till kirurgi och väl utbyggd dagkirurgisk vård.

Studie II

Kryptorkism (testikel som inte har utvecklats till korrekt läge) bör enligt gällande riktlinjer opereras före 12 månaders ålder, eller så snart därefter som möjligt. I studien beskrivs omfattningen, förutsättningarna och riskerna vid planerad kirurgi av kryptorkism hos svenska pojkar under åren 2001-2014. Förekomsten av kryptorkism beräknades i olika riskgrupper, och åldern vid kirurgi kartlades i olika delar av landet. Förekomst av laparoskopisk (”titthålskirurgisk”) behandling och dagkirurgi kartlades och risken för postoperativa komplikationer beräknades. Resultaten visar att en av 55 svenska pojkar (1.8%) opererades för kryptorkism före 18 års ålder, och att de flesta som opereras (94.1%) är äldre än 12 månader vid operationen, med betydande geografiska skillnader i operationsålder. Riskerna med operationen är dock små oberoende av vart man opereras, med låg förekomst av sårinfektion (1.4%), utan några registrerade dödsfall inom 30 dagar efter operationen.

Studie III

Blindtarmsinflammation är en av de vanligaste orsakerna till akut bukkirurgi hos barn, och barn har relativt stor risk att drabbas av mer komplicerad blindtarmsinflammation (”sprucken blindtarm”) än vuxna. Även om tidigare mindre studier har visat hur det går efter behandling av blindtarmsinflammation hos barn så saknas det kunskap hur behandlingen utförs på nationell nivå, och det är oklart hur risken påverkas av sjukdomens svårighetsgrad samt om risken kan relateras till valet av behandlingsmetod. I studien inkluderades alla barn med blindtarmsinflammation i Sverige 2001-2014 (n=38,939) och grupperades efter blindtarmsinflammationens svårighetsgrad och efter vilken behandling som gavs. Resultaten visade att den genomsnittliga vårdtiden fördubblades vid komplicerad blindtarmsinflammation, och även om riskerna generellt är små så ökade risken markant för sårinfektion, återinläggning och ny bukoperation inom 30 dagar. Dessutom sågs en tydligt ökad risk för tarmvred hos de med mer komplicerad blindtarmsinflammation. Valet av operationsmetod visade sig kunna relateras till risken för sårinfektion och risken för tarmvred; färre komplikationer sågs efter laparoskopisk (”titthåls-kirurgisk”) teknik än vid öppen operationsteknik, och fler komplikationer sågs när en laparoskopisk operation konverterades till en öppen operation.

Studie IV

Studie IV syftade dels till att så exakt som möjligt beskriva hur vanligt kryptorkism är hos svenska barn, och hur kända riskfaktorer påverkade förekomsten, och dels till att analysera om avståndet till sjukhuset inverkade på möjligheten till optimal behandling. I studien inkluderades alla pojkar som föddes i Sverige 2001-2014 (n=748,678). Barnen grupperades utifrån kända riskfaktorer (graviditetslängd, födelsevikt och storlek för åldern, samt utifrån moderns ålder och rökvanor under graviditeten). Socioekonomiska förhållanden dokumenterades. Operationsålder dokumenterades för de som fick kryptorkism (n=7351), och analyserades med överlevnadsanalys. Avståndet till sjukhus beräknades för de barn som blev opererade. Resultaten visade att en av (1.4%) av alla svenska pojkar blev opererade för kryptorkism före 15 års ålder, med markant ökad risk hos förtidigt födda eller de med låg födelsevikt. När avståndet till sjukhus ökade, ökade också risken för försenad behandling, hänsyn tagen till socioekonomiska riskfaktorer (per 30-minuters ökning, justerat för socioekonomiska riskfaktorer; HR 0.91 [0.88-0.95], $p<0.001$). Låg inkomst ($p<0.001$) och arbetslöshet ($p=0.02$) uppvisade samband med risken för sen behandling.

Studie V

Blindtarmsinflammation är en akut bukåkomma som snabbt kan utvecklas till ett allvarligt tillstånd om inte rätt behandling sätts in i tid. Operation är den vanligaste behandlingen. Studie V syftade dels till att beräkna hur vanligt förekommande blindtarmsinflammation är hos svenska barn, och dels till att analysera om avståndet till sjukhuset uppvisade samband med blindtarmsinflammationens svårighetsgrad. I studien inkluderades alla barn med blindtarmsinflammation i Sverige 2001-2014 (n=38,939). De grupperades efter blindtarmsinflammationens svårighetsgrad, och avståndet från bostadsområdet till sjukhuset beräknades. Bakgrundspopulationen för incidens-beräkningen inhämtades från befolkningsregistret. Resultaten visade att blindtarmsinflammation var mycket ovanligt före skolåldern, men desto vanligare senare under uppväxten och att 1 av 40 barn (2.5%) i Sverige drabbas av blindtarmsinflammation före 18 års ålder. En av sex blindtarmsinflammationer hos barn (17%) var av mer allvarlig art, med en tydligt ökad risk hos de yngre barnen, men utan skillnader mellan könen. Under studieperioden reducerades antalet sjukhus som behandlade blindtarmsinflammation hos barn, och en relativt större andel av barnen skickades till universitetssjukhusen för behandling. Däremot sågs inget övertygande samband talande för att ökat avstånd till sjukhuset påverkade blindtarmsinflammationens svårighetsgrad, när hänsyn togs till övriga riskfaktorer och familjens socioekonomiska bakgrund.

Betydelse

Kirurgisk vård utgör en betydande komponent av barnsjukvården, då motsvarande 1 av 20 barn genomgår någon form av kirurgi varje år fram till vuxen ålder, och drygt var fjärde barn som vårdas på sjukhus genomgår någon form av kirurgiskt ingrepp. Generellt sett förefaller kirurgi hos barn vara behäftat med låga risker för komplikationer. Däremot är det förvånansvärt få pojkar som opereras i tid för kryptorkism, trots att operationen inte är akut och kan planeras med relativt god framförhållning.

Vid akut blindtarmsinflammation hos barn ökar risken för komplikationer markant vid svårare former av blindtarmsinflammation. Likaså förefaller risken till viss del vara sammanlänkad med valet av operationsmetod, så att laparoskopisk operation medför färre sårinfektioner och lägre risk för tarmvred senare. Då bara hälften av operationerna utförs med laparoskopisk teknik i nuläget, kan det finnas vinster med att välja laparoskopisk operation i första hand. Nyttan av laparoskopisk blindtarmsoperation behöver dock först bekräftas även i kliniska studier.

Resultaten antyder att geografiskt avstånd till sjukhus har betydelse för operationsåldern vid behandling av kryptorkism. Om detta samband kan bekräftas, har det betydelse för hur barnkirurgisk vård bör organiseras i framtiden, för att nå ut till befolkningen och förebygga avståndseffekter på den kirurgiska vårdkvaliteten.

Sammanfattningsvis visas i avhandlingsarbetet hur förekomsten av kirurgi för barn och unga ser ut i Sverige, och vilka risker som kan ses vid planerad respektive akut kirurgi på barn. Avhandlingen har även visat på hur medicinska och geografiska faktorer samspelar i risken för sjuklighet och optimal behandling.

Acknowledgements

First, I would like to thank my large family; my fantastic brothers, *Henrik*, *Olof* and *Petter*, and sisters, *Sofia* and *Sara*, for always being there. Mum and dad, for everything you have done for me, and for every Sunday dinner where we all have the chance to be gathered. *Bozena* and *Julia*, for the endless support to our little family in everyday life and *Bogumil* for being you (and for quite some Warka). The *Bonnor* family for always making us feel so welcome, and for teaching how to live the good life and drink champagne.

Cilla, without your and *Petters'* endless support with Philip, this would have been quite impossible.

Associate professor, senior consultant in paediatric surgery Lars Hagander, I remember very well the first time you somehow teased me into the idea of doing a PhD, but I don't remember *how* you did it; just one week earlier, I had told my father and Martiné that research was not for me. From that day, you have guided me, slowly and firmly, through every part of my research training as well as clinical situation in a humble way, tirelessly, constantly gazing far beyond my horizon. When I thought I was done with something, you made me realize I hadn't really started yet. And you managed to be there all the way through, always.

Professor Jonas Björk, you have been the solid rock throughout this PhD. The more I learned and the more experience I got, the more I have appreciated your guidance and advices. Thank you for your tireless efforts to enlighten me, and for the opportunity to attend the SINGS graduate school.

Olle Kristell, my dearest friend, you have always been there when I need you the most. Forgive me for all the other days.

Surgery and Public Health (SurPH), and all those affiliated to this small but growing institution, thank you. Located in the magnificent Hagander residence at Östervångsvägen in Lund, SurPH has provided a unique platform for ideas and inspiration. Inspiring fellows including *Hampus Holmer*, *Anton Jarnheimer*, *Adam Lantz*, *Martin Salö*, *Sanna Bergbrant*, *Niclas Rudolfsson* among meny more, thank you for giving me this.

The *Hagander* family, thank you for always being so warm and open to me and other of Lars (more or) less geeky PhD-students who invades your house (or the beautiful seaside holiday house) every now and then ☺ .

Senior consultant Torbjörn Backman, former head of the department of paediatric surgery in Lund, thank you for endless support and clinical mentoring throughout my residency, for showing me how to act in tough clinical situations, how to think during easy and tough surgery, and how to run faster and further than I have ever done.

Senior consultant Magnus Anderberg, head of the department for paediatric surgery in Lund, thank you for your support throughout the residency. I now look forward to the years to come. And *former head of the department, Cristina Clementsson Kockum*, for signing me up for paediatric surgery in the first place, that was a true turning point for me.

All the paediatric surgeons supporting me throughout my training, the core of the paediatric surgery profession as I know it, thank you *Anna Börjesson*, *Pernilla Stenström*, *Kristine Hagelsteen*, *Gunnar Westbacke*, *Einar Arnbjörnsson*, *Morten Vigen* and *Hans Winberg*.

Special thanks to all the residents and former residents at the department of paediatric surgery in Lund, for all we have gone through and done together throughout these years; *Christina Graneli*, *Ann Nozohoor Ekmark*, *Mette Hambraeus*, *Emma Grottling*, *Helena Arnadottir* and *Louise Toft*. You have all been very helpful and kind to allow for research and pleasure every now and then. There are more years to come!

Martin Salö, consultant in paediatric surgery, PhD, always a few steps ahead. I admire you for your inspiring and joyful way of doing all these serious stuffs you manage so well. Thank you for your help during this PhD, I look forward to many years at your side.

I would like to acknowledge the national *Swedish Interdisciplinary Graduate School in register-based research* (SINGS graduate school), fully financed by the Swedish Research Council, which have provided me extraordinary opportunities to advance my knowledge and see the beauty in register-based research and epidemiology. In addition, the *ST-ALF* grant has been the absolute relief that made this PhD possible.

Anton Jarnheimer, Sanna Bergbrant, Andreas Persson, Saurabh Saluja, John Rose, Louise Olsson, John Meara, thank you for your efforts and support. Anders Näsman, thank you for being an inspiration to me.

Last – and thereby most important – I want to thank my beloved *little family*: my son *Philip* for his absolutely wonderful habit to sneak in to my office early in the morning. He climbs up in my knee and gives me a few moments of beauty, so nothing else matters for the rest of that day. And *Martiné*, the beautiful mother of my son, who have so incredibly much patience with the slightly disorganised and confused part of me, who reminds me that life is larger than the hospital, and from whom I have had all the support I needed to manage this (most of the days, anyhow). What would I be without you?

Erik Omling and Philip. An early morning in their office, discussing something really important.
Erik Omling, consultant in paediatric surgery, holds a position at the Department of Paediatric Surgery, Skåne Univerity Hospital, Lund

References

1. OECD. Health spending (indicator). 2019.
2. Regeringskansliet. Strategi för en god och mer jämlik vård. 2012.
3. Socialdepartementet. Kommittedirektiv - En kommission för jämlik hälsa. 2015.
4. Anell A, Glenngård AH, Merkur S. Health Systems in Transition - Sweden Health system review. Health Syst Transit. 2012;14(5):187.
5. Lundström NR, Berggren H, Björkhem G, Jögi P, Sunnegårdh J. Centralization of pediatric heart surgery in Sweden. Pediatr Cardiol. 2000;21(4):353–7.
6. Socialstyrelsen (The National Board of Health and Welfare). Socialstyrelsens beslut om tillstånd att bedriva rikssjukvård inom Hjärtkirurgi för barn och ungdomar. 2008.
7. Socialstyrelsen. Avancerad barn- och ungdomskirurgi som rikssjukvård: Defintionsutredning. 2016;51.
8. Socialstyrelsen. Avancerad barn- och ungdomskirurgi som rikssjukvård. 2017;(December).
9. Rosén M. Träning ger färdighet. Koncentrera vården för patientens bästa. 2015.
10. Sandberg E. Dokument innifrån: Den stora sjukhusstriden. Swedish Television; 2018.
11. Troëng T, Haglund U. Underlaget i Måns Roséns utredning motiverar inte slutsatserna. Dagens Medicin. 29 December 2015.
12. Steering board SKF. Svensk Kirugisk Förening Statement. Sweden; 2018.
13. Farmer PE, Kim JY. Surgery and global health: A view from beyond the OR. World J Surg. 2008;32(4):533–6.
14. WHO. A Global Initiative for Emergency and Essential Surgical Care (GIEESC). 2005.
15. World Health Organization, WHO. Strengthening emergency and essential surgical care and anaesthesia as a component of universal health coverage Report by the Secretariat. Provisional agenda item 51. 2014;2002(May):16–8.
16. Holmer H, Lantz A, Kunjumen T, Finlayson S, Hoyler M, Siyam A, et al. Global distribution of surgeons, anaesthesiologists, and obstetricians. Lancet Glob Heal. 2015;3(S2):S9–11.

17. Debas T. Haile, Richard Gosselin, Colin McCord et al. Surgery. In: Jamison TL, Breman JG, Measham AR et al (Eds). Disease control priorities in developing countries 2nd edition. In: Oxford University Press, New York, pp 1245–1261. 2006.

18. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006;3(11):2011–30.

19. Grimes CE, Henry JA, Maraka J, Mkandawire NC, Cotton M. Cost-effectiveness of surgery in low- and middle-income countries: A systematic review. World J Surg. 2014;38(1):252–63.

20. Grimes CE, Holmer H, Maraka J, Ayana B, Hansen L, Lavy CBD. Cost-effectiveness of club-foot treatment in low-income and middle-income countries by the Ponseti method. BMJ Glob Heal. 2016;1: e000023.

21. Chao TE, Sharma K, Mandigo M, Hagander L, Resch SC, Weiser TG, et al. Cost-effectiveness of surgery and its policy implications for global health: A systematic review and analysis. Lancet Glob Heal. 2014;2:e334–45.

22. Meara JG, Leather AJM, Hagander L, Alkire BC, Alonso N, Ameh EA, et al. Global Surgery 2030: Evidence and solutions for achieving health, welfare, and economic development. Lancet. 2015;386(9993):569–624.

23. WHO. WHO Global Reference List of 100 Core Health Indicators. 2018.

24. World Bank. World Development Indicators 2016. 2016.

25. Debas HT, Gosselin R, Mccord C. Chapter 67 Surgery. 2004;1245–59.

26. Rose J, Weiser TG, Hider P, Wilson L, Gruen RL, Bickler SW. Estimated need for surgery worldwide based on prevalence of diseases: A modelling strategy for the WHO Global Health Estimate. Lancet Glob Health. 2015;3(S2):S13–20.

27. Hider P, Wilson L, Rose J, Weiser TG, Gruen R, Bickler SW. The role of facility-based surgical services in addressing the national burden of disease in New Zealand: An index of surgical incidence based on country-specific disease prevalence. Surg (United States). 2015;158(1):44–54.

28. Weiser TG, Haynes AB, Molina G, Lipsitz SR, Esquivel MM, Uribe-Leitz T, et al. Size and distribution of the global volume of surgery in 2012. Bull World Health Organ. 2016;94(3):201–209F.

29. Holmer H, Bekele A, Hagander L, Harrison EM, Kamali P, Ng-Kamstra JS, et al. Evaluating the collection, comparability and findings of six global surgery indicators. Br J Surg. 2019;106:e138–50.

30. Bickler S, Ozgediz D, Gosselin R, Weiser T, Spiegel D, Hsia R, et al. Key concepts for estimating the burden of surgical conditions and the unmet need for surgical care. World J Surg. 2010;34(3):374–80.

31. Gupta S, Ranjit A, Shrestha R, Wong EG, Robinson WC, Shrestha S, et al. Surgical needs of Nepal: Pilot study of population based survey in Pokhara, Nepal. World J Surg. 2014;38(12):3041–6.

32. Rose J, Chang DC, Weiser TG, Kassebaum NJ, Bickler SW. The role of surgery in global health: Analysis of United States inpatient procedure frequency by condition using the global burden of disease 2010 framework. PLoS One. 2014;9(2).

33. Jarnheimer A, Kantor G, Bickler S, Farmer P, Hagander L. Frequency of surgery and hospital admissions for communicable diseases in a high- and middle-income setting. Br J Surg. 2015;102(9):1142–9.

34. Indicators O. Health at a Glance 2017. 2017.

35. OECD. OECD (2019), Hospital beds (indicator). 2019.

36. Luft HS, Bunker JP, Enthoven AC. Should Operations Be Regionalized? The empirical relation between surgical volume and mortality. N Engl J Med. 1979;301(25):1364-9.

37. Aquina CT, Probst CP, Becerra AZ, Iannuzzi JC, Kelly KN, Hensley BJ, et al. High volume improves outcomes: The argument for centralization of rectal cancer surgery. Surg (United States). 2016;159(3):736–48.

38. Urbach DR. Pledging to elimiate low-volume surgery. N Engl J Med. 2015;373(15):1388–90.

39. Waag KL, Loff S, Zahn K, Ali M, Hien S, Kratz M, et al. Congenital diaphragmatic hernia: a modern day approach. Semin Pediatr Surg. 2008;17(4):244–54.

40. van der Zee DC, Tytgat SHA, van Herwaarden MYA. Esophageal atresia and tracheo-esophageal fistula. Semin Pediatr Surg. 2017;26(2):67–71.

41. Durkin N, Davenport M. Centralization of pediatric surgical procedures in the United Kingdom. Eur J Pediatr Surg. 2017;27:416–21.

42. Wijnen M. Centralization of pediatric surgery in the Netherlands. Eur J Pediatr Surg. 2017;27:407–9.

43. Pintér A, Vajda P. Centralization of pediatric surgery in Hungary. Eur J Pediatr Surg. 2017;27:429–30.

44. Pakarinen M, Björkland K, Qvist N, Wester T. Centralizing pediatric surgery in nordic countries: a role model for Europe? Eur J Pediatr Surg. 2017;27:395–8.

45. Stitzenberg KB, Sigurdson ER, Egleston BL, Starkey RB, Meropol NJ. Centralization of cancer surgery: Implications for patient access to optimal care. J Clin Oncol. 2009;27(28):4671–8.

46. The Herniasurge Group, Simons MP, Smietanski M, Bonjer HJ, Bittner R, Miserez M, et al. International guidelines for groin hernia management. Hernia. 2018;22(1):1-165.

47. Borenstein SH, To T, Wajja A, Langer JC. Effect of subspecialty training and volume on outcome after pediatric inguinal hernia repair. Journal of Pediatric Surgery. 2005;40(1):75-80.

48. Bisgaard T, Kehlet H, Oehlenschlager J, Rosenberg J. Acceptable nationwide outcome after paediatric inguinal hernia repair. Hernia. 2014;18(3):325-31.

49. Evans C, Van Woerden HC. The effect of surgical training and hospital characteristics on patient outcomes after pediatric surgery: A systematic review. J Pediatr Surg. 2011;46(11):2119–27.

50. Heyns CF, Hutson JM. Pediatric Urology: Review article. Historical review of theories on testicular descent. J Urol. 1995;153:754–67.

51. Costa WS, Sampaio FJB, Favorito LA, Cardoso LEM. Testicular migration: Remodeling of connective tissue and muscle cells in human gubernaculum testis. J Urol. 2002;167:2171–6.

52. Virtanen HE, Toppari J. Epidemiology and pathogenesis of cryptorchidism. Hum Reprod Update. 2008;14:49–58.

53. Holcomb GW, Murphy JP, Ostlie DJ, Eds. Aschcraft's Pediatric Surgery. 6th ed. Elsevier Inc.; 2014.

54. Berkowitz, Gertrud S, Lapinski, Robert H, Dolgin, Stephen E, Gazella, Jacqueline G, Bodian, Carol A, Holzman, Ian R. Prevalence and natural history of cryptorchidism. Pediatrics. 1993;92(1):44-9.

55. Boisen KA, Kaleva M, Main KM, Virtanen HE, Haavisto AM, Schmidt IM, et al. Difference in prevalence of congenital cryptorchidism in infants between two Nordic countries. Lancet. 2004;363(9417):1264–9.

56. Sijstermans K, Hack WWM, Meijer RW, Voort-Doedens LMV Der. The frequency of undescended testis from birth to adulthood: A review. Int J Androl. 2008;31(1):1–11.

57. Acerini CL, Miles HL, Dunger DB, Ong KK, Hughes IA. The descriptive epidemiology of congenital and acquired cryptorchidism in a UK infant cohort. Arch Dis Child. 2009;94(11):868–72.

58. Hamza AF, Elrahim M, Elnagar O, Maaty SA, Bassiouny IE, Jehannin B. Testicular descent: When to interfere? Eur J Pediatr Surg. 2001;11(3):173-6.

59. Wenzler DL, Bloom DA, Park JM. What is the rate of spontaneous testicular descent in infants with cryptorchidism? J Urol. 2004;171:849–51.

60. Cortes D, Kjellberg EM, Breddam M, Thorup J. The true incidence of cryptorchidism in Denmark. J Urol. 2008;179(1):314-8.

61. Schneuer FJ, Holland AJA, Pereira G, Jamieson S, Bower C, Nassar N. Age at surgery and outcomes of an undescended testis. Pediatrics. 2016;137(2):e20152768–e20152768.

62. Jensen MS, Olsen LH, Thulstrup AM, Bonde JP, Olsen J, Henriksen TB. Age at cryptorchidism diagnosis and orchiopexy in Denmark: A population based study of 508,964 boys born from 1995 to 2009. J Urol. 2011;186(4 Suppl.):1595–600.

63. Husmann DA, Levy JB. Current concepts in the pathophysiology of testicular undescent. Urology. 1995;46(2):267–76.

64. Singh R, Hamada A., Bukavina L, Agarwal A. Physical deformities relevant to male infertility. Nat Rev Urol. 2012;9(3):156-74.

65. Arendt LH, Ramlau-Hansen CH, Lindhard MS, Henriksen TB, Olsen J, Yu Y, et al. Maternal overweight and obesity and genital anomalies in male offspring: a population-based Swedish cohort study. Paediatr Perinat Epidemiol. 2017;31(4):317–27.

66. Kjersgaard C, Arendt LH, Ernst A, Lindhard MS, Olsen J, Henriksen TB, et al. Lifestyle in pregnancy and cryptorchidism in sons: A study within two large Danish birth cohorts. Clin Epidemiol. 2018;10:311–22.

67. Martin Ritzén E, Bergh A, Bjerknes R, Christiansen P, Cortes D, Haugen SE, et al. Nordic consensus on treatment of undescended testes. Acta Paediatr Int J Paediatr. 2007;96(5):638–43.

68. Kolon TF, Herndon CDA, Baker LA, Baskin LS, Baxter CG, Cheng EY, et al. Evaluation and treatment of cryptorchidism: AUA guideline. J Urol. 2014;192(2):337–45.

69. Gerharz E, Hoebeke P, Kocvara R, Nijman JM, Stein R. EAU guidelines of pediatric urology. Urology. 2013;291–303.

70. Spitz L, Coran AG. Operative pediatric surgery. 6th ed. Spitz L, Coran AG, Eds. London: Hodder Arnold; 2006.

71. Lindgren BW, Franco I, Blick S, Levitt SB, Brock WA, Palmer LS, et al. Laparoscopic Fowler-Stephens orchiopexy for the high abdominal testis. J Urol. 1999;162:990–4.

72. Engeler DS, Hösli PO, John H, Bannwart F, Sulser T, Amin MB, et al. Early orchiopexy: Prepubertal intratubular germ cell neoplasia and fertility outcome. Urology. 2000;56(1):144-8.

73. Lee PA, Coughlin MT. Fertility after bilateral cryptorchidism. Evaluation by paternity, hormone, and semen data. In: Horm Res. 2001;55(1):28-32.

74. Hadziselimovic F, Herzog B. The importance of both an early orchidopexy and germ cell maturation for fertility. Lancet. 2001;358(9288):1156-7.

75. Hadziselimovic F, Höcht B, Herzog B, Buser MW. Infertility in cryptorchidism is linked to the stage of germ cell development at orchidopexy. Horm Res. 2007;68(1):46-52.

76. Pettersson A, Richiardi L, Nordenskjold A, Kaijser M, Akre O. Age at surgery for undescended testis and risk of testicular cancer. N Engl J Med. 2007;256:1835–41.

77. Wagner-Mahler K, Kurzenne JY, Delattre I, Bérard E, Mas JC, Bornebush L, et al. Prospective study on the prevalence and associated risk factors of cryptorchidism in 6246 newborn boys from Nice area, France. Int J Androl. 2011;34(5 Part 2):499–510.

78. Savoie KB, Bachier-Rodriguez M, Schurtz E, Tolley EA, Giel D, Feliz A. Health disparities in the appropriate management of cryptorchidism. J Pediatr. 2017;185:187–192.e1.

79. Bayne AP, Alonzo DG, Hsieh MH, Roth DR. Impact of anatomical and socioeconomic factors on timing of urological consultation for boys with cryptorchidism. J Urol. 2011;186(4 SUPPL.):1601–5.

80. Hougaard KS, Larsen AD, Hannerz H, Andersen AMN, Jørgensen KT, Toft GV, et al. Socio-occupational class, region of birth and maternal age: Influence on time to detection of cryptorchidism (undescended testes): A Danish nationwide register study. BMC Urol. 2014;14(1).23.

81. Braveman P, Schaaf VM, Egerter S, Bennett T, Schecter W. Insurance-related differences in the risk of ruptured appendix. N Engl J Med. 1994;331(7):444-9.

82. Gadomski A, Jenkins P. Ruptured appendicitis among children as an indicator of access to care. Health Serv Res. 2001;36(1 Pt 1):129–42.

83. Toole BSJO, Karamanoukian HL, Allen JE, Caw MG, Toole DO, Azizkhan RG, et al. Insurance-related differences in the presentation of pediatric appendicitis. J Pediatr Surg. 1996;31(8):1032–4.

84. Ponsky TA, Huang ZJ, Kittle K, Eichelberger MR, Gilbert JC, Brody F, et al. Hospital- and patient-level characteristics and the risk of appendiceal rupture and negative appendectomy in children. JAMA. 2004;292(16):1977–82.

85. Scott JW, Rose JA, Tsai TC, Zogg CK, Shrime M, Sommer BD, et al. Impact of insurance coverage expansion on access to care: rates of acute appendicitis perforation among young adults. Med Care. 2015;54(9):818-26.

86. Baxter K, Nguyen H, Wulkan M, Raval M. Association of health care utilization with rates of perforated appendicitis in children 18 years or younger. JAMA Surg. 2018;153(6):544–50.

87. Andersson RE, Olaison G, Tysk C, Ekbom A. Appendectomy is followed by increased risk of Crohn's disease. Gastroenterology. 2003;124:40–6.

88. Frisch M, Pedersen BV., Andersson REA. Appendicitis, mesenteric lymphadenitis, and subsequent risk of ulcerative colitis: cohort studies in Sweden and Denmark. BMJ. 2009;338:b716.

89. Shepherd JA. Acute appendicitis: a historical survey. Lancet. 1954;267(6833):299–302.

90. Guthery SL, Hutchings C, Dean JM, Hoff C. National estimates of hospital utilization by children with gastrointestinal disorders: Analysis of the 1997 kids' inpatient database. J Pediatr. 2004;144:589–94.

91. Flum DR, Morris A, Koepsell T, Dellinger EP. Has misdiagnosis of appendicitis decreased over time? JAMA. 2012;286(14):1748.

92. Addiss DG, Shaffer N, Fowler BS, Tauxe R V. The epidemiology of appendicitis and appendectomy in the united states. Am J Epidemiol. 1990;132(5):910-25.

93. Andersson R, Hugander A, Thulin A, Nystrom PO, Olaison G. Indications for operation in suspected appendicitis and incidence of perforation. BMJ. 1994;308(6921):107.

94. Almström M, Svensson JF, Svenningsson A, Hagel E, Wester T. Population-based cohort study on the epidemiology of acute appendicitis in children in Sweden in 1987 – 2013. 2018;142–50.

95. Lin KB, Lai KR, Yang NP, Chan CL, Liu YH, Pan RH, et al. Epidemiology and socioeconomic features of appendicitis in Taiwan: A 12-year population-based study. World J Emerg Surg. 2015;10(1):1–13.

96. Kang JY, Hoare J, Majeed A, Williamson RCN, Maxwell JD. Decline in admission rates for acute appendicitis in England. Br J Surg. 2003;90(12):1586–92.

97. Livingston EH, Woodward WA, Sarosi GA, Haley RW. Disconnect between incidence of nonperforated and perforated appendicitis: Implications for pathophysiology and management. Ann Surg. 2007;245(6):886–92.

98. Aarabi S, Sidhwa F, Riehle KJ, Chen Q, Mooney DP. Pediatric appendicitis in New England: Epidemiology and outcomes. J Pediatr Surg. 2011;46(6):1106–14.

99. Ferris M, Quan S, Kaplan BS, Molodecky N, Ball CG, Chernoff GW, et al. The global incidence of appendicitis. Ann Surg. 2017;266(2):237–41.

100. Terlinder J, Andersson RE. Incidence of appendicitis according to region of origin in first-and second-generation immigrants and adoptees in Sweden. A cohort follow-up study. Scand J Gastroenterol. 2016;51(1):111–20.

101. Curran TJ, Muenchow SK. The treatment of complicated appendicitis in children using peritoneal drainage: Results from a public hospital. J Pediatr Surg. 1993;28(2):204–8.

102. Alaedeen DI, Cook M, Chwals WJ. Appendiceal fecalith is associated with early perforation in pediatric patients. J Pediatr Surg. 2008;43:889–92.

103. Salö M, Gudjonsdottir J, Omling E, Hagander L, Stenström P. Association of IgE-mediated allergy with risk of complicated appendicitis in a pediatric population. JAMA Pediatrics. 2018;172(10):943-948.

104. Temple CL, Huchcroft SA, Temple WJ. The natural history of appendicitis in adults: A prospective study. Ann Surg. 1995;221(3):278–81.

105. Kim M, Kim SJ, Cho HJ. Effect of surgical timing and outcomes for appendicitis severity. Ann Surg Treat Res. 2016;91(2):85.

106. Bickell NA, Aufses AH, Rojas M, Bodian C. How time affects the risk of rupture in appendicitis. J Am Coll Surg. 2006;202(3):401–6.

107. Andersson RE. Does delay of diagnosis and treatment in appendicitis cause perforation? World J Surg. 2016;40(6):1315–7.

108. Almström M, Svensson JF, Patkova B, Svenningsson A, Wester T. In-hospital surgical delay does not increase the risk for perforated appendicitis in children. Ann Surg. 2017;265(3):616–21.

109. Serres SK, Cameron DB, Glass CC, Graham DA, Zurakowski D, Karki M, et al. Time to appendectomy and risk of complicated appendicitis and adverse outcomes in children. JAMA Pediatr. 2017;171(8):740–6.

110. Smink DS, Fishman SJ, Kleinman K, Finkelstein JA. Effects of race, insurance status, and hospital volume on perforated appendicitis in children. Pediatrics. 2005;115(4):920–5.

111. Bratu I, Martens PJ, Leslie WD, Dik N, Chateau D, Katz A. Pediatric appendicitis rupture rate: disparities despite universal health care. J Pediatr Surg. 2008;43(11):1964–9.

112. Penfold RB, Chisolm DJ, Nwomeh BC, Kelleher KJ. Geographic disparities in the risk of perforated appendicitis among children in Ohio: 2001-2003. Int J Health Geogr. 2008;7:1–9.

113. Hernandez MC, Finnesgaard E, Aho JM, Kong VY, Bruce JL, Polites SF, et al. Appendicitis: rural patient status is associated with increased duration of prehospital symptoms and worse outcomes in high- and low-middle-income countries. World J Surg. 2018;42(6):1573–80.

114. Andersson RE. Diagnoskodningen bör vara entydig och konsekvent. 2015;112(12):600–1.

115. Statistiska centralbyrån (Statistics Sweden). Finding Statistics [Hitta statistik] [Internet]. Available from: https://www.scb.se/en/finding-statistics/ [accessed 4 February 2019]

116. Statistiska Centralbyrån. Demografiska rapporter - livslängden i Sverige 2011-2015. 2016.

117. Statistiska centralbyrån (Statistics Sweden). Skilda världar? Det demografiskt delade Sverige. 2018.

118. Zylbersztejn A, Gilbert R, Hjern A, Wijlaars L, Hardelid P. Child mortality in England compared with Sweden: a birth cohort study. Lancet. 2018;391(10134):2008–18.

119. Wang H, Liddell CA, Coates MM, Mooney MD, Levitz CE, Schumacher AE, et al. Global, regional, and national levels of neonatal, infant, and under-5 mortality during 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384:957–79.

120. OECD. OECD Reviews of Health Care Quality. 2015.

121. Anell A. The Public–Private Pendulum — Patient choice and equity in sweden. N Engl J Med. 2015;372(1):1-4.

122. Konkurrensverket. Konkurrensen i Sverige 2018. 2018.

123. Ng-Kamstra JS, Raykar NP, Lin Y, Mukhopadhyay S, Saluja S, Yorlets R, et al. Data for the sustainable development of surgical systems : A global collaboration. 2015;(September):46.

124. Folkhäslomyndigheten. Vaccinationsstatisik BHV 2018. 2018.

125. Ludvigsson JF, Almqvist C, Bonamy AKE, Ljung R, Michaëlsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol. 2016;31(2):125–36.

126. Kvalitet och innehåll i patientregistret. Centrum. 2007;1997–2007.

127. Brooke HL, Talbäck M, Hörnblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. Eur J Epidemiol. 2017;32(9):765–73.

128. Westerberg B. Unik kunskap genom registerforskning. 2014.

129. The Swedish Research Council [Vetenskapsårdet]. Registerforskning.se [Internet]. 2018 [cited 2019 Jan 14]. Available from: https://www.registerforskning.se/en/ [accessed 4 February 2019].

130. Organisation for Economic Cooperation and Development. OECD Principles and guidelines for access to research data from public funding. Data Sci J. 2007;6:23.

131. World Medical Association. WMA Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. 2013;107(6):1–8.

132. The Minsitry of Education and Cultrual Affairs. SFS 2003:460. The Act concerning the Ethical Review of Research Involving Humans. 2003 p. 11.

133. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11(1):450.

134. Socialstyrelsen. Kodningskvalitet i patientregistret Ett nytt verktyg för att mäta kvalitet. 2013;55.

135. Nordic Medico-Statistical Committee. NOMESCO Classification of Surgical Procedures (NCSP), version 1.16. 2010;1–295.

136. Anandalwar SP, Cameron DB, Graham DA, Melvin P, Dunlap JL, Kashtan M, et al. Association of intraoperative findings with outcomes and resource use in children with complicated appendicitis. JAMA Surg. 2018;153(11):1021–7.

137. Humes DJ, Simpson J. Acute appendicitis. BMJ. 2006;333(7567):530–4.

138. Blakely ML, Williams R, Dassinger MS, Eubanks JW, Fischer P, Huang EY, et al. Early vs interval appendectomy for children with perforated appendicitis. Arch Surg. 2011;146(6):660–5.

139. Putnam LR, Ostovar-Kermani TG, Le Blanc A, Anderson KT, Holzmann-Pazgal G, Lally KP, et al. Surgical site infection reporting: more than meets the agar. J Pediatr Surg. 2017;52(1):156–60.

140. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med. 2017;167(4):268-74.

141. Gasior AC, St. Peter SD, Knott EM, Hall M, Ostlie DJ, Snyder CL. National trends in approach and outcomes with appendicitis in children. J Pediatr Surg. 2012;47:2264–7.

142. Dingemann J, Metzelder M, Szavay P. Current status of laparoscopic appendectomy in children: A nation wide survey in Germany. Eur J Pediatr Surg. 2013;23(3):226–33.

143. Drake TM, Camilleri-Brennan J, Tabiri S, Fergusson SJ, Spence R, Fitzgerald JEF, et al. Laparoscopy in management of appendicitis in high-, middle-, and low-income countries: a multicenter, prospective, cohort study. Surg Endosc Other Interv Tech. 2018;32:3450–66.

144. Gomes CA, Abu-Zidan FM, Sartelli M, Coccolini F, Ansaloni L, Baiocchi GL, et al. Management of appendicitis globally based on income of countries (MAGIC) Study. World J Surg. 2018;42:3903–10.

145. Rubér M, Berg A, Ekerfelt C, Olaison G, Andersson RE. Different cytokine profiles in patients with a history of gangrenous or phlegmonous appendicitis. Clin Exp Immunol. 2006;143(1):117–124.

146. Rubér M, Andersson M, Petersson BF, Olaison G, Andersson RE, Ekerfelt C. Systemic Th17-like cytokine pattern in gangrenous appendicitis but not in phlegmonous appendicitis. Surgery. 2010;147(3):366–72.

147. Lund DP, Murphy EU. Management of perforated appendicitis in children: A decade of aggressive treatment. J Pediatr Surg. 1994;29(8):1130–4.

148. Lee SL, Islam S, Cassidy LD, Abdullah F, Arca MJ. Antibiotics and appendicitis in the pediatric population: An American Pediatric Surgical Association Outcomes and Clinical Trials Committee Systematic Review. J Pediatr Surg. 2010;45:2181–5.

149. Statistiska centralbyrån (Statistics Sweden). Demografiska statistikområden Ny regional indelning under kommunnivå. Available on web page: https://www.registerforskning.se/wp-content/uploads/2018/10/StefanSvanstrom_SCB.pdf [accessed 6 Februrary 2019].

150. Cook JA, Ranstam J. Statistical models and confounding adjustment. Br J Surg. 2017;104(6):786–7.

OTTENBY, ÖLAND

Printed by Media-Tryck, Lund 2019 NORDIC SWAN ECOLABEL 3041 0903

LUND UNIVERSITY

FACULTY OF MEDICINE

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2019:21
ISBN 978-91-7619-750-9
ISSN 1652-8220