From THE DEPARTMENT OF NEUROBIOLOGY CARE SCIENCES AND SOCIETY
Karolinska Institutet, Stockholm, Sweden

GESTATIONAL AGE AND SIZE AT BIRTH AND RISK OF ESOPHAGEAL INFLAMMATION AND CANCER

Lina Forssell

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“Avspänning och koncentration.”
Suzanne Sidenbladh

ABSTRACT

Background In a hypothesis generating study by my colleagues a 7-fold increase in the risk of esophageal adenocarcinoma (EAC) was found in a cohort of individuals born preterm or with a low birth weight. Preterm born individuals regurgitate more than term born infants, and infant gastroesophageal reflux disease (GERD) might continue into childhood and even adulthood. GERD, a major public health problem in adult westernized populations, is a risk factor for esophagitis, Barrett's esophagus (BE), and EAC. There are no previous studies assessing risk of inflammation, metaplasia, and cancer among adults in relation to perinatal characteristics.

Aims This thesis aims to explore the effect of gestational age and size at birth, on the risk of being diagnosed with esophagitis, BE or EAC later in life.

Patients and Methods We performed four population-based case-control studies. As cases we identified patients with endoscopy verified esophagitis, BE of intestinal metaplasia type, and EAC from the Swedish Cancer Register, the Patient Register and from two local Barrett Registers. Control individuals were randomly selected from the source population, and matched on age, sex and location of birth. We collected exposure data from birth records, including the variables gestational age, birth weight and length, and maternal diseases, among others. Using conditional logistic regression we modeled the risk of being a case based on exposure status, and calculated odds ratios (OR) and 95% confidence intervals (CI). A p value of 0.05 was considered statistically significant.

Results Compared to birth at term with adequate birth weight for gestational age, preterm birth and being SGA increased the risk of being diagnosed with esophagitis (OR 2.7, 95% CI 2.2-3.5 and OR 1.5, 95% CI 1.3-1.7, respectively), and even more so among those diagnosed before 10 years of age (OR 6.8, 95% CI 4.7-10.0 and OR 2.0, 95% CI 1.6-2.5, respectively). We found an increased risk of being diagnosed with BE among those born SGA and <3rd percentile (OR 3.0, 95% CI 1.4-6.4), as well as those in the 3rd to<10th percentile (OR 1.8, 95% CI 1.0-3.1). The risk of BE was also increased among those with a birth weight <2,500 grams (OR 8.2, 95% CI 2.8-23.9). The risk of EAC was increased by 13% per week preterm birth, compared to birth at term (OR 1.1, 95% CI 1.0-1.3). No effect of size at birth was seen for EAC, or for cardia adenocarcinoma and esophageal squamous cell carcinoma.

Conclusions Altogether, these data indicate that gestational age and size at birth are strongly associated with risk of esophagitis and BE later in life. Furthermore, the results

indicate that preterm birth is associated with a risk of EAC and cardia adenocarcinoma, but not esophageal squamous cell carcinoma.

LIST OF PUBLICATIONS

I. Akre O, Forssell L, Kaijser M, Norén-Nilsson I, Lagergren J, Nyrén O, Ekbom A. Perinatal risk factors for cancer of the esophagus and gastric cardia: a nested case-control study. *Cancer Epidemiology Biomarkers and Prevention* 2006;15(5), 867-871.

II. Forssell L, Cnattingius S, Bottai M, Lagergren J, Ekbom A, Akre O. Risk of esophagitis among individuals born preterm or small for gestational age. *Journal of Clinical Gastroenterology and Hepatology* 2012;10:1369-1375

III. Forssell L, Cnattingius S, Bottai M, Edstedt Bonamy A-K, Lagergren J, Agréus L, Akre O. Risk of Barrett's esophagus among individuals born preterm or small for gestational age. Submitted manuscript.

IV. Forssell L, Cnattingius S, Bottai M, Edstedt Bonamy A-K, Lagergren J, Agréus L, Akre O. Risk of esophageal adenocarcinoma among individuals born preterm or small for gestational age. Submitted manuscript.

CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS

BE	Barrett's esophagus. Specialized, intestinal columnar metaplasia in the lower part of the esophagus.
BMI	Body mass index
CAC	Cardia adenocarcinoma
CI	Confidence Interval
EAC	Esophageal adenocarcinoma
EGD	Esophagogastroduodenoscopy. Camera examination of the esophagus and stomach.
Endoscopy	Everyday term for EGD
ESCC	Esophageal squamous cell carcinoma
Esophagitis	Inflammation of the esophagus. In this work "esophagitis" exclusively denotes erosive esophagitis, ulcerations of the esophageal, squamous mucosa caused by GERD.
GER	Gastroesophageal reflux
GERD	Gastroesophageal reflux disease
Gestational age	Age at birth in weeks, from first day of last menstrual period.
ICD	International classification of diseases
KI	Konfidensintervall
LES	Lower esophageal sphincter
OR	Odds Ratio
PAD	Pathological anatomical diagnosis
PIN	Personal identity number (Personnummer)
Pys	Person years, a unit including number of individuals and time.
SCB	Statistiska Centralbyrån
SGA	Small for gestational age. A birth weight less than 2 standard deviations below the average for that gestational age.

1 INTRODUCTION

This journey started in January 1998 when I worked part time at the Clinical Epidemiology Unit to sponsor my season as a ski bum in the French Alps. I assisted in collecting birth record data for a cohort of preterm and low birth weight infants. The study found an unexpected 7-fold increase in risk of esophageal adenocarcinoma (EAC) in this cohort[1], and generated the hypothesis and research questions that are the foundation of this thesis project. Now in 2013, I am proud to present the results of some of the choices I made that winter.

The question that was raised was: why would there be an increased risk of EAC among individuals that were born preterm? Infants regurgitate frequently during their first year in life and preterm infants even more than term born infants. Gastroesophageal reflux in adults is a main risk factor for EAC. Is there a possible association, or was it a chance finding?

There are different physiological prerequisites in the upper gastrointestinal tract in infants compared to adults, the pattern of reflux is different. But infant reflux may in some individuals continue into childhood and even adulthood, thus giving this individual a prolonged exposure time to the refluxate. Not much is known of how the mucosa of the preterm infant handles refluxate, if it can be damaged even by 'normal' reflux. To address this research question in a more comprehensive fashion, we added the biologically relevant pre-stages of EAC to the narrative; erosive esophagitis and Barrett's esophagus (BE), and the plan for a full thesis was formed.

The main aim of this thesis is to elucidate if gestational age at birth or size at birth increases the risk of esophagitis, BE and EAC later in life.

2 BACKGROUND

2.1 EPIDEMIOLOGY OF PRETERM BIRTH AND SGA

2.1.1 Definitions of age and size at birth

At birth the infant's gestational age is calculated in completed weeks, and it is a measure of the duration of the pregnancy. Either it is calculated from the date of the first day of the last menstrual period, or by an ultrasound examination in early pregnancy (since the 1980's in Sweden)[2]. A pregnancy lasting 280 days or 40 completed weeks is the 'normal' duration of a pregnancy and a birth in week 37 to 42 is considered a term birth (Figure 1). Birth before 37 completed weeks is called preterm birth, before 32 weeks is very preterm, and before 28 weeks is extremely preterm[3].

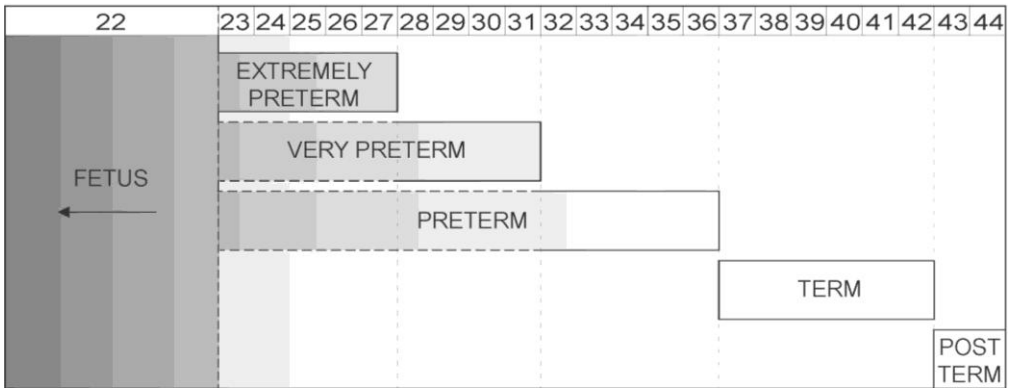

Figure 1 Definitions of gestational age, adapted from Tucker et. al 2004.

Regarding birth weight, WHO has defined low birth weight as less than 2,500 grams [4]. Most infants born preterm are also of low birth weight, but not all of them. By combining gestational age and birth weight, size at birth can be estimated. An infant can be of lower birth weight than expected for its age and thus be small for gestational age (SGA). The concept of SGA was first used in the 1950's [5], and today it is defined as having a birth weight for gestational age less than 2 standard deviations below the average weight for gestational age in a reference population, which is approximately equivalent to <3rd percentile [6]. SGA can also be defined as a weight for gestational age below the 10th or 5th percentile[7]. In this thesis we defined SGA as being either <3rd or <10th percentile of birth weight for gestational age. At the other extreme are infants born large for gestational age (>97th percentile), but most infants are born adequate for gestational age (AGA)[6]. Ponderal index (PI) is another measure of size sometimes used as an indication of asymmetrical weight for length in infants, to judge if an infant is fat

or thin. PI is calculated with the formula PI=100*(birth weight/birth length^3), and low values may indicate intra-uterine growth restriction of the fetus[8].

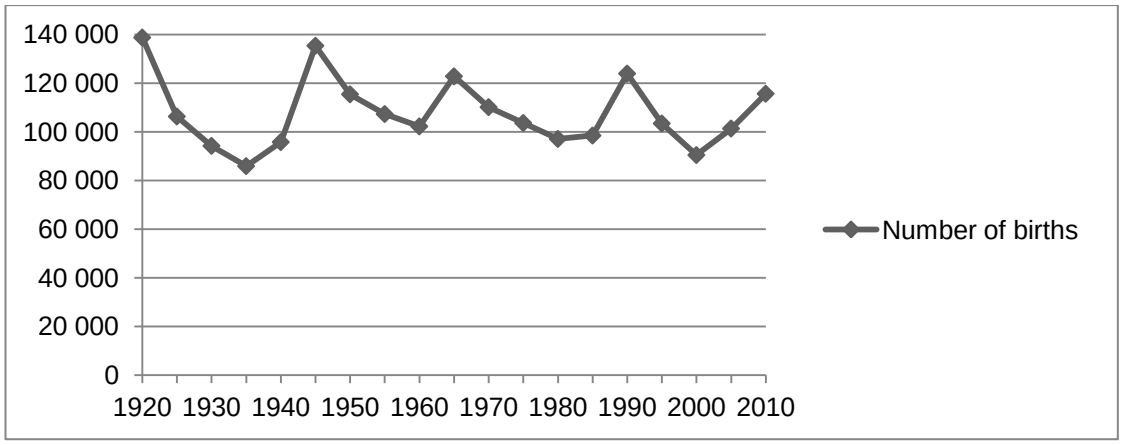

Figure 2 Total number of births annually in Sweden 1920-2010. Data from Statistics Sweden.

2.1.2 Incidence and survival

In Sweden the number of births per year has varied between 85 and 140 thousand since 1920 (Figure 2). Since the early 1970's, about 4-5% of the births annually are preterm births (Figure 3), and an additional 1% are very preterm births.[2] Globally the incidence of preterm birth varies over time and between countries, from 5-9% in many developed countries to almost 12% in the United States [9] and 16% in Zimbabwe[10]; the incidence is increasing in Brazil [11], decreasing since 2006 in the USA [9], and have been stable in Sweden since the early 1980's (Figure 3). Neonatal death rates have decreased during the past 20 years among all births (figure 3), and especially among those born preterm (data not shown)[2].

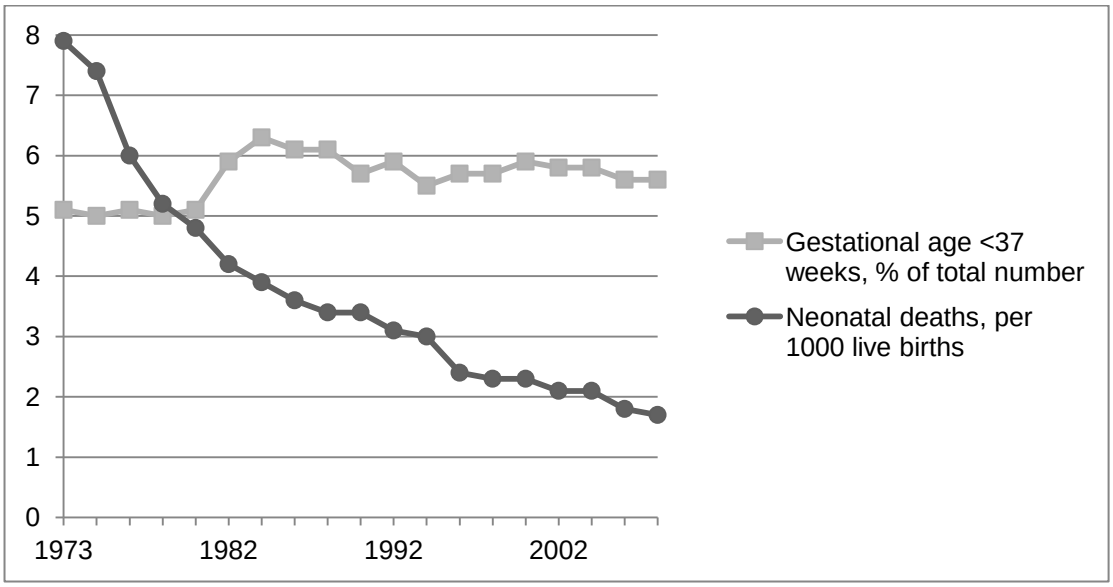

Figure 3 Annual percentage of births with gestational age <37 weeks and number of neonatal deaths per 1000 live births. Data from the National Board of Health and Welfare.

There is a scarcity of historical data on rates of preterm birth and neonatal survival, the Swedish Board of Health and Welfare only has statistics from 1973 and onward. A publication from 1914 states that approximately 1 in 10 Swedish infants died before 1 years of age, often from nutritional problems[12]. An historical cohort of infants born in Sweden 1925 to 1949 found that 3,361 out of approximately 250,000 infants (1.3%) were either born before 35 completed weeks of gestation or with a low birth weight (2,000 grams for girls or 2,100 grams for boys)[1]. In a study from a Chicago hospital following-up preterm and low birth weight infants born 1920 to 1950, approximately 83% survived to adulthood which is comparable to a death rate of 170 per 1000 live births [13].

Neonatal care of the preterm or 'small' infant has varied over the years. An active approach was advocated from late 19th century to the 1930's. From the 1940's to the mid 1960's was a period of well intended but not always successful interventions, especially in the USA. The preterm born infants were for example not fed but observed, for the first hours or even days of life, which affected both mortality and morbidity in a negative way[14, 15]. In Sweden in the 1950's, infants with a birth weight <2,500 grams were considered preterm and dysmature, in need of extra assistance with body temperature and feeding. Bottle fed infants were known to have more feeding- and gastrointestinal problems[16]. For most infants born after 32 weeks of gestation the survival and outcome is and has been almost as good as for infants born at term [17], but the outcome for male preterm infants is generally worse than for females[18].

2.1.3 Causes of preterm birth and SGA

Preterm birth is either elective, i.e. medically indicated (about 1/3) or spontaneous (about 2/3). The cause of preterm birth, whether induced or spontaneous, is unknown in most deliveries, but factors including inflammation or infection, placental ischemia, stress and hormones, all play roles in the process. The two most common causes of induced preterm birth are the maternal hypertensive disorder pre-eclampsia and intra-uterine growth restriction (IUGR), a condition of reduced growth velocity of the fetus caused by maternal malnutrition and placental malfunctioning[11, 19]. Additional maternal risk factors for preterm birth are low maternal age, low socioeconomic status, multiple previous pregnancies or preterm delivery, family history of preterm delivery and uterine or cervical abnormalities [20].

Among the causes of being born SGA is IUGR one of the most common, and the two are sometimes and wrongly interchanged. Additional causes and risk factors for SGA are maternal hypertensive disease with or without pre-eclampsia, genetic factors both in the mother and the fetus, chromosomal abnormalities like Down syndrome, and infections. The single most important risk factor is tobacco smoking, in a dose dependent way[7, 21].

2.1.4 Outcomes of preterm birth and SGA

A general statement is that the lower the gestational age is, the higher is the risk of morbidity and mortality associated with the prematurity[22, 23].

The gastrointestinal tract is quite immature until about 30 weeks of gestation, when most physiological- , digestive- and functional-parts are in place. Coordination of sucking, swallowing and breathing that is necessary for successful oral feeding, is possible from 34 weeks of gestational age[24]. Infants born before 35 weeks usually require assistance to keep up the homeostasis, i.e. they need help in regulating their body temperature, respiration, circulation and nutrition. They need to be fed with assistance, for example feeding through a nasogastric tube or parenteral feeding and often with supplementation of calories to the recommended feed human breast milk[15, 25]. It is common for preterm born infants to fail to grow as they would have if still in the womb. It is also more common with a late passage of the first meconium, feeding intolerance and constipation partly due to formula feeding in this population [23, 26, 27].

The bacterial colonization of the gut in the newborn infant, necessary for maturation of the gastrointestinal system and nutrient absorption, is delayed and somewhat abnormal

in the preterm infant. This is suggested to affect balance of the gastrointestinal system and increase the risk of diseases like necrotizing enterocolitis in this population[28, 29]. Medical problems affecting organ systems other than the gastrointestinal tract include an increased risk of cerebral hemorrhage leading to brain damages[30], infections, bronco-pulmonary dysplasia[31] and retinopathy of prematurity that can lead to blindness[32]. The long term consequences of prematurity can be of neurological-, somatic- and socioeconomic- character. Examples are cerebral palsy, hearing- or visual impairments, learning difficulties [17], diabetes mellitus, cardiovascular disease including hypertension [33], and low socioeconomic status [34].

The long term consequences of being born SGA includes an increased risk of psychosocial disadvantages and cognitive impairments[7], hypertension [33], ischemic heart disease [35], diabetes mellitus type 2 [36] and short stature if there is no catch-up growth in early childhood.

In conclusion, there are many causes of preterm birth and of SGA birth and the two conditions are often, but not always, present in the same infant. As the causes as well as the treatments are so differentiated, the resulting population of preterm and SGA individuals is heterogeneous. Gestational age at birth affects the health of the infant more than size at birth does, both in the short- and the long perspective. The severe cases of long-term morbidity caused by prematurity is mainly found in the very preterm (<32 weeks) and in the extremely low birth weight groups (<1000 grams), but the major part of the morbidity is accounted for by the moderately preterm population (33-38 weeks) as they are a larger group[34]. It is most likely that the association between gestational age at birth and morbidity, is a gradual process[22, 23, 37], and the majority of preterm born individuals do very well when they grow up.

2.2 ANATOMY AND PHYSIOLOGY OF THE ESOPHAGUS

2.2.1 Anatomy

The esophagus or the gullet is the organ of interest in this thesis. It is, roughly described, the muscular tube linking the mouth to the stomach (Figure 4). At birth it is 8-10 cm long, it doubles in length during the first years in life and is approximately 25 cm in adult individuals[38]. The upper third is composed of striated muscle, the lower 2/3 of smooth muscle and it is enervated by the cranial nerve X, the vagus nerve. The esophageal distal ending is located at the level of the diaphragm at birth, and sinks to a location approximately 3 cm below the diaphragm after a couple of years [39]. The entire esophagus, from the upper esophageal sphincter to the distal ending at the z-line, is

lined with a pale pink stratified, non-keratinized, squamous epithelium (Figure 6 A). There is mucus producing glands in the wall of the esophagus, for lubrication that facilitates swallowing [38].

In the lower end of the esophagus where it meets the stomach, is the lower esophageal sphincter (LES) located. It is a functional area with a higher pressure than in the parts of the esophagus above or below, not an anatomical structure. In resting state the esophagus is relaxed and collapsed, unlike the open structure in figure 4, and the LES is closing the passage between the esophagus and the stomach.

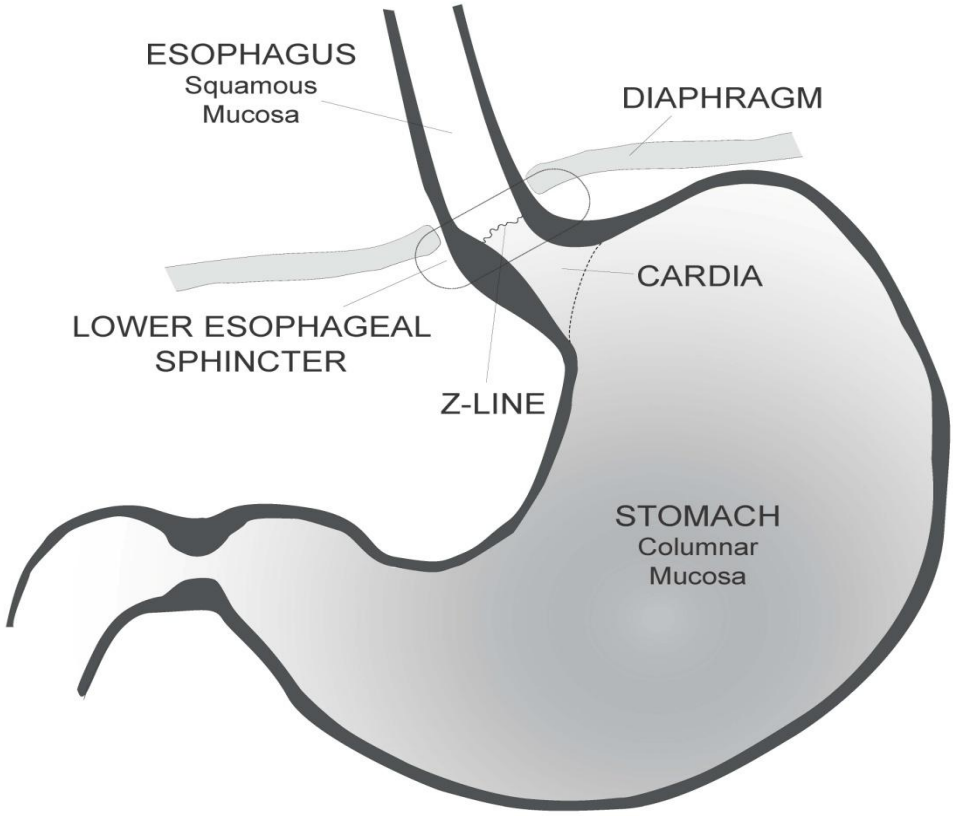

Figure 4 Anatomy of the distal esophagus and stomach, by T. Conaglen.

2.2.2 Pathophysiology of reflux

The LES relaxes to allow passage of food, liquid or air. This transient relaxations of the LES is a necessary and 'normal' physiological function to let food in and excess air out, but at the same time facilitates reflux[40]. Gastroesophageal reflux (GER) represents the passage of contents from the stomach backwards up into the esophagus. There are many pathophysiological mechanisms causing or worsening GER, including a reduced production of saliva, increased number of transient relaxations of the LES, low resting pressure of the LES, hiatal hernia, increased intra-abdominal pressure (from overeating,

cough or obesity), slower emptying of the stomach or impaired neurological function of the esophagus[41]. Not only are the mechanisms of *how* GER arises important, but also *what* and *where*. The composition of the refluxing stomach contents (acidic gastric juice, digestive enzymes, food items, beverages, gas, or bile and pancreatic juices from the duodenum) as well as how high up in the esophagus the reflux reaches, affects the influence the reflux has on perceived symptoms and on what damage it can cause[42].

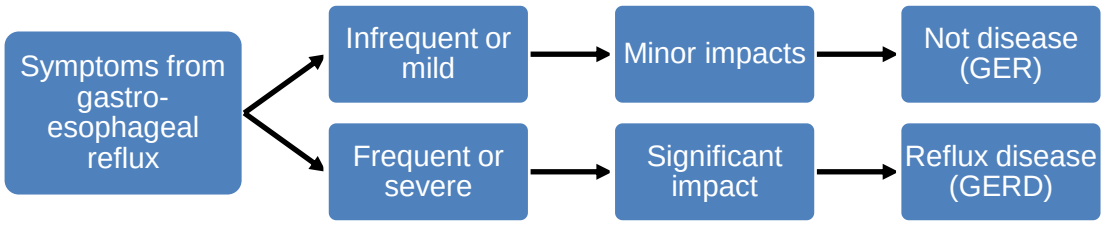

Figure 5. Classification of reflux symptoms according to severity. Modified from Dent et. al. 2005.

2.3 GASTROESOPHAGEAL REFLUX DISEASE IN ADULTS

The definition of gastroesophageal reflux disease (GERD) has been and still is debated and there is no gold standard for the diagnosis[43]. "Gastroesophageal reflux disease is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications" [44], and it is up to the patient to decide when it is "troublesome". GERD can be interpreted as an umbrella term, including severe symptomatic GER and the consequences of it, both esophageal manifestations and extra-esophageal manifestations. There is an overlap of the symptoms and signs of GERD with other upper gastrointestinal diseases; a patient can present with typical GERD symptoms without having visible signs of erosions at endoscopy, and patients can have esophagitis and be asymptomatic[43, 45, 46]. With reflux as a common denominator there is a likely development from esophagitis via Barrett's esophagus to adenocarcinoma[47], but the number of patients passing all these steps to EAC is very limited[48]. The risk of severe outcomes and complications of GERD increases with increasing frequency and duration of the GER, and not necessarily with the severity of the symptoms[49].

2.3.1 Gastroesophageal reflux disease

GERD is estimated to affect at least 1 in 5 adult individuals in the westernized world, and it is in spite of a 'simple' appearance a debilitating and costly disease. The major

symptoms according to 'The Montreal Definition and Classification of GERD' are heartburn, regurgitation, and retrosternal or epigastric pain[44]. Esophageal complications of GERD, which are the diagnoses and outcomes of interest in this thesis, include erosive esophagitis, strictures, metaplastic BE and EAC (Figure 6, A-D). Extra-esophageal manifestations of GERD are chronic cough, chronic laryngitis, dental enamel erosions and asthma, among others[50]. GERD leads to a lowered rating of the quality of life, comparable to the effect of chronic diseases like diabetes mellitus or arthritis[51, 52]. GERD is costly for the affected individual as well as for society, in terms of productivity loss at work and prescribed drugs[53, 54]. A recently published study showed that approximately 3-4% of all outpatient clinic visits in Sweden, were due to GERD[55].

Between 14% and 30% of the adult North American and European populations reports at least weekly reflux symptoms [56-59], and a recently published large population-based study from Norway reported a prevalence of up to 40% for any reflux symptoms [60]. There seems to be a geographical gradient in the prevalence of GERD [40] and it is less prevalent in Asia, where a recent review estimates that 10% of the population suffers from GERD [61]. GERD is most probably a chronic disease with a high prevalence and a low incidence[56, 62], meaning that not very many new patients are diagnosed each year, but those who have it are affected for a long time. There are indications of an increasing prevalence in most parts of the world during the past 30 years[60, 63], possibly at least in part due to the increasing number of obese people.

The main known risk factors for GERD are abdominal obesity and high body mass index (BMI)[40], heredity[64-66], tobacco smoking[40, 67] and hiatal hernia[50]. There is also an association between GERD and low socioeconomic status and being pregnant[68]. It is less clear whether overeating, coffee, alcohol or other dietary habits, like spicy food or a diet high in fat or low in vegetables, affects the risk of GERD, although these factors might evoke occasional episodes of reflux symptoms[40]. GERD is equally common in men and women, and it is increasing with age[58, 69]. Among patients with GERD examined with endoscopy, it is estimated that 60% have no signs of inflammation, i.e. non-erosive GERD, 30% have esophagitis and 10% have BE[48].

2.3.2 Esophagitis

Erosive esophagitis is the most common complication of GERD. Esophagitis, i.e. inflammation of the esophagus, can be of various types and origins; erosive esophagitis caused by GERD[50], eosinophilic esophagitis due to food allergy and/or atopy[70],

infectious or fungal esophagitis for example caused by Candida species, or erosive due to ingestion of lye or other corrosive agent[71]. Hereafter in this thesis the term "esophagitis" denotes exclusively erosive esophagitis caused by GERD (Figure 6A). Esophagitis is found in 11-15% of the general adult western population, and in approximately 25% of those reporting GERD symptoms[59, 72]. Among those diagnosed with esophagitis, 1 to 2 out of 3 individuals report having any reflux symptoms, and many esophagitis patients are thus asymptomatic[73].

Esophagitis is detected by endoscopy and is classified using the Los Angeles Classification system, in grades A to D depending on the length and circumference of the mucosal breaks[74]. A mucosal break is defined as "an area of slough or erythema with a sharp line of demarcation from the adjacent normal mucosa…"[43, 75] (Figure 6 A).

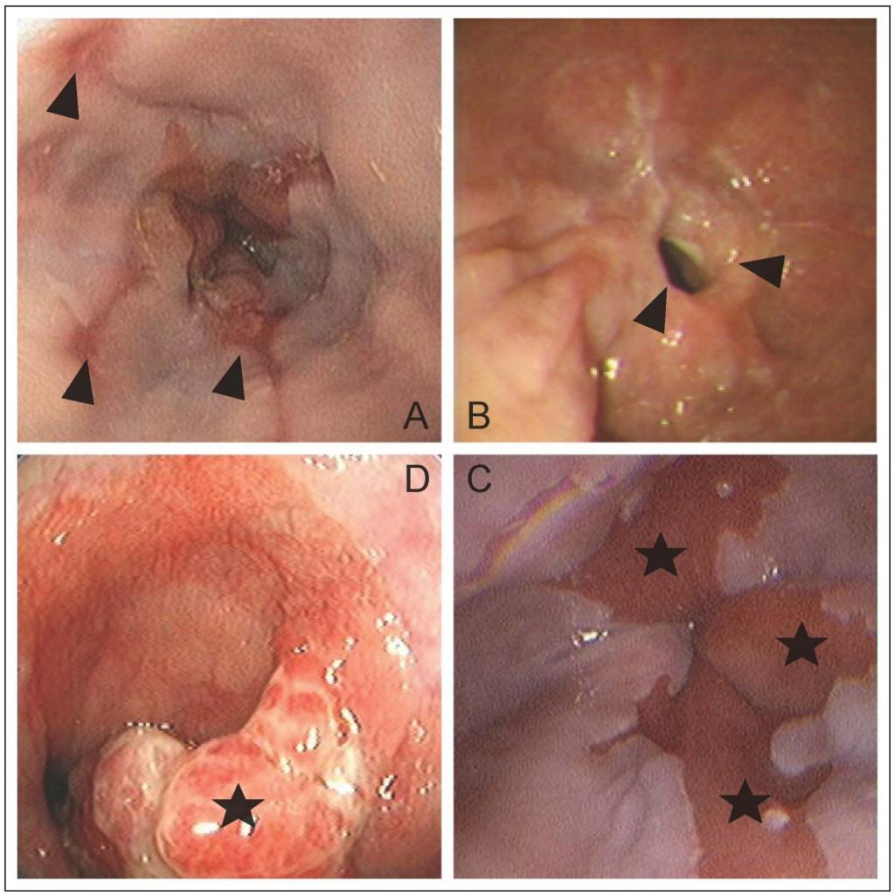

Figure 6 Endoscopic pictures of the esophagus, clockwise from top left. A: arrow heads show areas of erosive esophagitis surrounded by normal squamous epithelium; B arrow heads show a peptic stricture; C stars show areas of Barrett's esophagus; D star show adenocarcinoma. Pictures adapted with permission from P. Kahrilas, 2008.

2.3.3 Barrett's esophagus

Another complication of GERD is BE named after Norman Barrett, a surgeon working in London in the 1950's and who identified a "short esophagus". BE represents a metaplastic columnar mucosa replacing the native stratified squamous mucosa of the distal esophagus [76, 77](Figure 6 C), where metaplasia is the process of one mature cell type being replaced by another mature cell type. BE most likely develops as a protective response, i.e. the esophagitis heals through a metaplastic process with a cell type more resilient to the refluxate[78-80]. There are three histologic types of metaplasia where specialized columnar metaplasia of intestinal type, also called type 3, is the only type regarded as premalignant, with a potential to transform into adenocarcinoma[81]. Hereafter in this thesis 'BE' denotes specialized intestinal metaplasia i.e. BE type 3. There is a variation in the reported population prevalence of BE due to differences in indications and frequency of endoscopy, as well as varying diagnostic criteria and study populations in different studies[82]. A large population based study with endoscopy findings from healthy volunteers randomly sampled from the Swedish population, found BE in 1.6% of the adult general population[83]. It is found in 2.4% of primary care patients with dyspepsia [84], in 6.8% of a population referred for a colonoscopy [85] and in about 5-10% of those with severe reflux symptoms [78, 86, 87] of which an estimated 3-5% have long segment BE and 10-15% have short segment BE [79, 88].

Major risk factors for BE are severe GER of long duration and frequent eruptions, esophagitis, hiatal hernia, male gender, obesity and abdominal fat, old age and Caucasian ethnicity. Tobacco smoking and hereditary factors are also suggested to increase the risk of BE[49]. Alcohol consumption is not proven to be a risk factor, while infection with *Helicobacter pylori* (the gastric ulcer bug), consumption of non steroid anti-inflammatory drugs (NSAID's), wine consumption as well as "healthy" diets rich in vegetables and fruit are suggested as protective factors [49].

At endoscopy, BE is diagnosed by visible changes of the mucosa and is confirmed by histological examination of biopsy specimens showing intestinal metaplasia. In 1998 BE was suggested to be classified and described as either long segment BE (≥3 cm) or short segment BE (<3 cm) but the clinical importance of this classification is debated[79, 89]. In 2006 an international working group presented the 'Prague C & M Criteria' for grading of circumference and maximal height of the BE lesions[90]. The histopathology of BE can be classified as non-dysplastic, low-grade dysplasia or high-grade dysplasia, where high-grade dysplasia has the highest potential to become malignant[79].

2.3.4 Esophageal adenocarcinoma

Esophageal cancer is among the top-10 most common cancers [91, 92], and accounts for almost 6% of all cancer deaths globally [93]. There are two histologic types of esophageal cancer, squamous cell carcinoma and adenocarcinoma (Figure 6D). They differ in their etiology, but share methods of diagnosis, treatment and prognosis.

The symptoms of EAC are initially GERD symptoms, and later in the process dysphagia, odynophagia (difficulties and pain at swallowing, respectively) and weight loss can appear. The tumor grows in an infiltrative and 'patchy' way, it metastasizes early and most patients seek help at a late stage, which influences the prognosis and results in a poor 5-year survival rate[81, 94]. From the 1950's until 2008 the 5-year survival rate has increased from 3-4% to almost 16%, which still is clearly lower than almost all other tumor types[94-96]. Before the 1970's EAC was rare but has since the late 1980's increased in incidence, especially in the developed world in a drastic way. For example, the incidence in the white male American population 1974-1976 was $0.7/10^5$/person years (pys), for the period 1992-1994 it was $3.2/10^5$/pys[97], and increased to $5.69/10^5$/pys in 2000-2004[98]. In Denmark 1970 to 1991 the age- and sex-adjusted incidence rose from $0.3/10^5$/pys to $2.3/10^5$/pys[99]. The actual number of affected patients is low compared to other tumors like breast cancer ($135/10^5$/pys in USA) or lung cancer in American men ($85/10^5$/pys), but the increase is high[94]. What causes the increase, as well as the geographical gradient of it, remains unexplained [100]. Nowadays EAC is the most common type of esophageal cancer in many countries in the developed world [93]. In Sweden there were 210 new cases of EAC in 2010 (Figure 7).

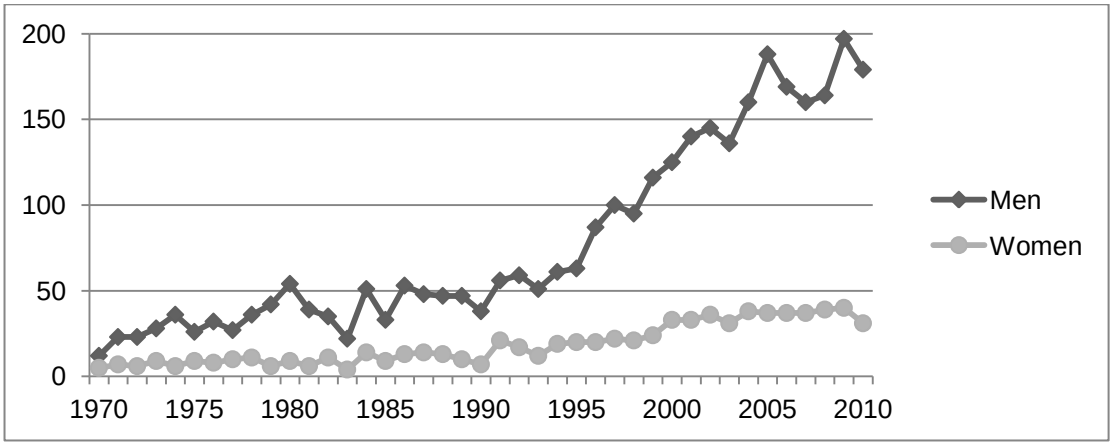

Figure 7 Number of cases of EAC per year in Sweden 1970-2010. Data from the National Board of Health and Welfare.

EAC is most common in developed countries with a westernized lifestyle, and the typical patient is a male of Caucasian origin, 65 years of age or older and with a long history of GERD. Like most types of cancer EAC is a multifactorial disease, but there are a number of known risk factors like gastroesophageal reflux disease [101] with or without hiatal hernia [102], BE [47, 99], high BMI [103]and more specifically abdominal obesity [104]and low socioeconomic status [105]. Tobacco smoking is a moderate risk factor for EAC, while alcohol consumption does not contribute to the etiology of this tumor[106, 107]. Low dietary intake of fruit and vegetables is followed by an increased risk of EAC, while other dietary factors like intake of fat and meat have been studied but without conclusive results [93]. The male predominance estimated to be 4-9:1 is unexplained [100], and studies of the effects of estrogen exposure have not given answers as to why there is such an imbalance [108-110]. Breastfeeding has however recently been established as a protective factor in women[111]. Infection with *Helicobacter pylori* has been reported to be a protective factor[112, 113]. Nowadays populations of developed countries are infected to a much lesser extent than earlier and also compared to less developed countries, which is reflected in lowered rates of cancer in the stomach[94]. By which mechanism the protection by *H. pylori* works remains to be elucidated[113].

Although less than 5% of EAC patients were previously diagnosed with BE[99, 114], BE increases the risk of EAC 30 to 125 times compared to a very low risk in the general population (Figure 7) [115, 116]. A meta-analysis combining the results from 51 studies estimate the incidence of EAC in BE patients being 6/1000/pys of follow up (95% CI 4.7-8.4/1000 pys), equal to a rate of transition in 0.6% annually[116]. Other, smaller studies estimated this number to be as high as 3.5% annually[117, 118], or 6% if there is high-grade dysplasia present[115]. BE transforms to EAC twice as often in men than in women, something that is reflected in the skewed male to female ratio of EAC[119]. The incidence of BE appears to be rising, and this is suggested to partially explain the rising incidence of EAC[120-122]. Up to 40% of EAC patients claim they never experienced GERD symptoms[101].

2.4 GASTROESOPHAGEAL REFLUX DISEASE IN INFANTS AND CHILDREN

2.4.1 In infants

It is a known phenomenon that infants regurgitate and throw up. Infant GER is commonly considered effortless, and it is usually classified as physiological. It is considered pathological only when associated with severe symptoms or complications.

In infants as well as in adults described above, is it when the LES relaxes that gastric content can enter the esophagus[123]. Infants have differences in the anatomy as compared to adults, increasing the likelihood of GER. Their esophagus is shorter, the area of the LES is smaller and it is not located below the diaphragm, which reduces the efficiency of the sphincter[39, 124]. Furthermore, they ingest fluids equivalent to 14 liters/24 h for an adult and they have a slumped sitting position or are laying down[125, 126]. Infants have the same enzymatic composition and pH in the stomach as adults, pH drops to <2 within hours of birth for infants as young as 24 weeks[125, 127, 128]. It is likely the acidity of the refluxate that defines the symptoms[123, 126].

Physiologic GER is found in almost all infants before 3 months of age, in 40-65% of healthy infants before one year of age and is outgrown by 18 months of age in most infants[125, 129]. Pediatric gastroenterologists distinguish the otherwise healthy 'happy spitter' from infants with GERD. It is known that infant GERD can lead to feeding problems in early childhood[130], but not much is known of the long term consequences of infant GERD.

Symptoms of GERD in infants include inadequate weight gain or even weight loss, crying, irritability or arching backwards during or after feeding or excessive vomiting[124]. It has been suggested that GERD causes extra-esophageal consequences like apnea and respiratory diseases, but the evidence are conflicting[131].

It is estimated that 1 in 300 infants have GERD [132] and that 6-7% of infants come to medical attention during their first year in life because of GERD [125]. Risk factors include use of nasogastric feeding tubes [133], very low birth weight [125], neurological impairments, esophageal malformations [132], exposure to tobacco smoke [124] and preterm birth [134, 135]. In preterm born infants three factors may add to the risk of GERD; the hypotonic state of their muscles, a reduced oropharyngeal capacity of clearance of refluxate and a lack of peristaltic movements to clear refluxate from the esophagus [125, 136]. In general, the smaller or more premature the infant is and the more complicating factors or diseases there are, the bigger is the risk of infant GERD[134, 137, 138].

2.4.2 In children

Older children also have GERD. The prevalence ranges from 2% to 20% in otherwise healthy children[139, 140], and possibly up to 27% in former preterm children[141].

Children can have esophagitis and BE as well, but the true prevalence is unknown. It is most likely lower than in the adult population[142], but the definitions have varied over time and between studies[142, 143]. There are even some rare cases of EAC described in

children[144]. The prevalence of esophagitis in the general pediatric population is estimated to be 0.5-5%[38, 145, 146], and 40-83% in children with GERD [147-149].
The prevalence of BE in the general pediatric population is estimated to be <0.02%[150], 0.12-4.8% in children with GERD[140, 151], and the incidence is possibly rising[152].
In conclusion, the pathophysiological consequences of infant GER is debated[126], and the long term effects of infant or childhood GER are not known[129]. GERD is most likely a chronic disease with childhood onset that wax and wane over the years, and that continues into adulthood[125, 153-155].

2.5 CLINICAL ASPECTS OF GERD

2.5.1 Histopathology of GERD

2.5.1.1 Inflammation to metaplasia

The transition from esophagitis to EAC progresses via a 'metaplasia-dysplasia-carcinoma' process, and chronic GER is the driving force in the development[47]. The histopathological signs of inflammation are elongated vascular papillae in the mucosa, increased height of the growth zone, basal cell hyperplasia, dilated intercellular spaces and infiltrating immunological cells[48]. The chronic inflammation releases a number of inflammatory mediators, which causes cell transformation through different mechanisms[47].
Esophagitis and erosions heal with the original squamous cell type in most cases, and it is not known why the erosion heal with metaplastic columnar cells i.e. BE in some individuals. The progenitor cell of BE is not know and it is hypothesized that stem cells in the basal layers of the esophageal mucosa are involved. When the stem cell become exposed to refluxate and chronic inflammation a transforming process starts, resulting in the metaplastic change of cell type to a type more adapted to refluxate [82, 156-159].

2.5.1.2 Dysplasia to cancer

With continuing inflammation and reflux, some or at least one metaplastic BE cell continue to develop mutations, and becomes dysplastic. Whether the length or grade of dysplasia is important is debated, and it is almost impossible to predict the speed of this transition and in whom it will take place[160].
There are a number of important mutations in the development from dysplastic BE to EAC, but the exact pathway is not known[161]. First the cell cycle regulating gene *p16* is damaged, followed by an upregulation of cyclin D1 and E, which triggers a state of

growth autonomy in the cell. By additional damage to the *p53* gene the cell does not respond to stop signals nor induce apoptosis, and the cell continues its journey towards immortality. These factors, together with growth self-sufficiency, the ability of angiogenesis and ability to metastasize, are the hallmarks of a cancer cell[162, 163].
No biomarker is found that can predict the progression from metaplasia to dysplasia and cancer, and high-grade dysplasia is the best 'warning sign' of this process there is today[47, 164].

2.5.2 Diagnostic tools

A person experiencing symptoms from the upper gastrointestinal tract, like reflux, heartburn or pain when swallowing, most probably makes an appointment with a doctor. The doctor evaluates the symptoms in the light of the medical history of the patient, taking into account risk factors, a clinical examination and perhaps also some laboratory tests. Unless the patient presents with alarm symptoms (bloody stool or vomiting, weight loss, severe pain) indicating a severe disease and possibly cancer, the most common start for the help seeking patient is the 'test-and-treat' strategy.
Treatment with an antacid medication is evaluated after a couple of weeks; symptom relief gives the diagnosis GERD *ex juvantibus*. Questionnaires quantifying symptoms or quality of life are valuable tools, and are also used in children[165]. The symptom based diagnosis have a sensitivity and specificity of 65-70%[46, 166, 167].
To add objectivity to the diagnostic process, an esophagogastroduodenoscopy (EGD) can be performed. During this camera examination of the esophagus, stomach and duodenum, signs of inflammation, erosions, hernias or cancer can be visualized and biopsies taken. The number of biopsies, the method used and the pattern of where they are taken depends on what the mucosal lesions looks like and the suspected diagnosis[81, 168-170]. The final diagnosis is most often made on the basis of the histopathology. EGD is a method of high specificity and low sensitivity as many of the patients with GERD have no visible erosions[59, 171].
With no erosions to examine histopathologically, esophageal impedance monitoring visualizing abnormal patterns of peristalsis in the esophagus, or a pH monitoring can be performed. The impedance measurement is thought to be more informative than the mere pH measurement[172, 173].
When EAC is diagnosed an esophageal ultrasound can be used to examine the invasiveness or depth of the tumor, and a PET-CT examination (a combination of a

computer tomography and a positron emission tomography with radioactivity labeled molecule) to search for metastases.

2.5.3 Treatment of GERD in adults

The initial treatment for GERD is lifestyle changes like weight loss, smoking cessation or avoidance of certain foods; the level of evidence for this is low [174]. The next step is antacid drugs, substances that either neutralizes the acidity of the stomach or prevents acid secretion and thus reduces the symptoms. Examples are proton pump inhibitors (PPI's), histamine-2 receptor antagonists (H2RA) and buffering salts. The effect of PPI's on symptom relief, healing of esophagitis and on rated quality of life is better than what is reported for H2-blockers [174]. In severe cases where antacids do not give enough symptom relief, surgery is an option. The procedure called fundoplication has been performed since the 1950's, and has a well documented effect on symptoms[174].
BE lesions can either be ablated or resected, the latter technique allows further histopathological examination of the lesion[170]. There is a variety of ablative techniques all aimed at destruction of the tissue by adding energy; the method used depends on the traditions and experiences at the clinic, and on the condition and state of the patient. After ablation and together with PPI treatment, the mucosa can heal and regenerate native squamous cells[170].
'Buried metaplasia' is a debated concept after ablation of BE, where some metaplastic cells survive under the healing layer of squamous cells and these cells might continue to transform without being readily detected[82]. For this reason there is an ongoing debate whether doctors should "wait or ablate" if they find a BE in a patient, and the existing guidelines on the topic differ between countries[116, 170, 175]. Yet, no treatment of BE has proved to reduce the rate of transition to, or mortality from EAC[115, 161]. Screening for BE in patients with GERD is not recommended; but once BE is detected, surveillance is recommended depending on histopathology.
The treatment of EAC consists of neoadjuvant chemo- and/or radiotherapy and surgery[81]. There is no evidence that aggressive anti reflux therapy in early GERD stages, later reduces the number of deaths from EAC[79].

2.5.4 Treatment of GERD in children

Treatment of GERD in infants and children is similar to what is described above for adults[143, 176]. The 'test-and-treat' strategy is most commonly used[177]. Unlike the adult recommendations, there are a number of lifestyle changes proven to result in less

troublesome reflux, namely to thicken the feed, rule out cow milk allergy and to let the infant rest in a prone or right lateral position after feeding [178, 179]. PPI's are used in infants, in spite of the fact that no PPI substance has been approved in this population[176]. In children that do not respond to medical treatment, fundoplication is an option[180].

3 AIMS AND OBJECTIVES

Due to a development in the care of pregnant women and their offspring, the number of preterm born and SGA infants surviving to adulthood is increasing. Preterm born infants have more GER than infants born at term, possibly prolonging the exposure of their esophagus to refluxate. Not much is known of the effects of preterm or SGA birth on gastrointestinal health later in life. Symptomatic reflux is a common complaint in many populations among adults as well as among children, and GERD is most likely a chronic disease with childhood onset. GERD is a risk factor for esophagitis, BE and EAC, where EAC is a deadly tumor type with an unexplained and rapid increase in incidence. In a hypothesis generating study, an increased risk of EAC was found in a cohort of infants born preterm and with low birth weight. Therefore, our aim with this thesis project is to answer the following questions:

1) Is gestational age or size at birth associated with an increased risk of esophagitis later in life?

2) Is gestational age or size at birth associated with an increased risk of BE later in life?

3) Is gestational age or size at birth associated with an increased risk of EAC later in life?

4 MATERIALS AND METHODS

All four studies in this thesis are population based case-control studies. For each study we chose a group of individuals with a pre-defined outcome, a diagnosis of interest; these individuals were the cases. We collected information on the exposure from the birth records at different hospitals, or from a register. We chose the control individuals for each case in a pre-defined manner, collected their exposure data and finally made sure that they were alive at the date of the respective cases diagnosis. Sweden is a country with a long and robust tradition of archiving, and has excellent sources of data for epidemiological research.

4.1 METHODOLOGICAL CONSIDERATIONS

4.1.1 Case-control design

The case-control design has been a part of the epidemiological toolbox since the 1950's and it was initially developed for etiologic studies of cancer. Its validity has been and is debated as it is a method that requires careful handling, in spite of its simple and straightforward appearance. The case-control design has been developed and improved over the years, and it is now a method used in diagnostic and prognostic as well as etiologic research [181]. With a case-control design it is possible to study multiple exposure variables, it is useful for rare outcomes and for situations where there is a long latency between exposure and outcome. It is also an efficient study design both in terms of time and money[181].

4.1.2 Control selection and matching in case-control studies

The control group is selected to represent the non-diseased part of the source population. Ideally the controls are a random sample from the source population so that their likelihood of becoming a control does not depend on their exposure status. We selected controls at the same point in time as the cases (density sampling)[182, 183]. Matching is a method of balancing cases and controls with respect to certain characteristics. For example, in a study with a male dominance among the cases, randomly chosen controls will probably not reflect this skewed sex distribution, but be normally distributed (50% males, 50% females). This results in male cases without male controls and an abundance of female controls. Matching handles the imbalance and increases the efficiency and statistical power of the study. Matching on a variable makes it impossible to assess it as an explanatory variable, because the proportion of

exposed is set by the design.[183]. In our studies we matched on sex and age due to a known skewed distribution of these factors for the outcomes of interest. We also matched for location of birth for practical reasons, and it might hypothetically have lead to an equal distribution of some background exposures.

4.1.3 Follow-up of controls

Having identified all the cases and controls and their exposure data, what was left was to make sure the controls were alive at the time of their respective cases diagnosis. If not, the prerequisites stated above are not valid. From a place of birth, a mother's name and perhaps a name of the newborn control individual, we traced the individuals through parish archives and the Register of the Total Population. The fastest way to do this is by using the micro film copies of all parish books located in the depot of the National Archive in Arninge, Stockholm, and the web page Ratsit.com which contains selected but sufficient data from the Register of the Total Population.

4.2 DATA SOURCES FOR COLLECTING CASES AND CONTROLS

The personal identity number (PIN) is assigned to all Swedish citizens at birth or immigration since 1947. The PIN is a unique 10 digit identifier used in most contacts with the health care system and authorities. By using the PIN we were able to retrieve archived medical records and link information from the different archives. The PIN is a valid identifier, less than 0.5% of assigned PIN's have been subject to change over the years[184].

4.2.1 The Cancer Register

From the Cancer Register we identified the cases included in studies I and IV. Initiated in 1958, this register contains data on all incident cancer cases in Sweden, by histological type, location and stage. Clinicians, pathologists and cytologists must by law report findings to the regional oncologic registers, which in turn reports to the National Cancer Register. Due to its robust and mandatory reporting system, it is 98% complete regarding esophageal cancer[109].

4.2.2 The Swedish Patient Register

From the Patient Register we identified the cases included in study II. The register is organized using the PIN, and contains data on hospitalizations, diagnosis at discharge and surgical procedures. The register was initiated in 1964 by the National Board of

Health and Welfare, a governmental agency within the Ministry of Health and Social affairs, and has nationwide coverage since 1987. Since 2001 are hospital outpatient visits included as well[185]. Diagnoses are coded using the International Classification of Disease (ICD) version 8 in 1969 to1986, ICD-9 in 1987 to 1996 and ICD-10 from 1997 and onward. Surgical procedures are coded using the Swedish versions of the NOMESCO Classification of Surgical Procedures version 1.9, 'Surgical procedures 6th ed.' in 1963 to 1996 and 'Classification of surgical procedures 1997' from 1997 and onwards.

4.2.3 The Barrett registers

The cases to study III were retrieved from two local Barrett's registers at Ersta Hospital Stockholm and Kalmar County Hospital. The registers contain name, PIN, BE segment length and year of diagnosis for the patients.

4.2.4 The Register of the Total Population

This register provided us with information on the cases parents name and birth date, and name and correct identity of the controls at follow-up. The Register of the Total Population is part of the official statistical body of the Swedish population. Organized around the PIN, it contains demographic information on place of birth, sex, age, civil status, date of migration or immigration and death, among other things. It is kept by Statistics Sweden (Statistiska Centralbyrån, SCB) and is continuously updated by the local tax authorities of the National Tax Agency, and finally to SCB. From this register we obtained information regarding the place of birth of the cases (births until 1947) or the place of maternal residency at time of birth (from 1948 and onward), the name of the mother and father of the case and their date of birth. We also used it to trace the control individuals. Larger sets of data are accessible with an ethical permit and by file, or you can access the data one individual at a time by phone or on the web. With this information the next step was to search for information regarding the actual location of the birth; only individuals born in hospitals have a traceable birth record, and this was done at the parishes.

4.2.5 The Parish registers

The information we gathered from these registers was location of birth for cases, and identity of controls at follow-up. The Swedish parishes have since the 17th century been obliged to keep records of all births, marriages and deaths within their population,

among other variables. These registers were not only used by the church, but also as a means for the state to keep census of the population and enroll soldiers for the army[184]. The predecessor of Statistics Sweden was created by a decision by King Fredrik 1st in 1749[186]. In 1991 the responsibility for the information in these population registers was taken over by the tax authorities, resulting in the Register of the Total Population. The original parish books are no longer kept at the parishes, but in the eight Regional state archives (Landsarkiv) where they are accessible to the public in their original format, on microfilm or as scanned computerized copies. Based on the place of birth, we searched the books in the corresponding parish until finding the 'right' mother and her offspring.

4.2.6 The Medical Birth Register

The Medical Birth Register contains information from delivery wards on almost all live births in Sweden since 1973[2], and was our source of controls to study II. The selection of variables in the register has been updated several times since the start. It contains information about maternal variables such as age, parity and civil status; birth characteristics such as mode of delivery; and child characteristics such as birth weight, gestational age and diseases in the neonatal period. The register is kept by the National Board of Health and Welfare.

4.3 STUDY POPULATIONS

4.3.1 Study I and IV

By combining the pathological anatomical diagnosis (PAD) code of the histopathological type of cancer, with the ICD code indicating the location of the tumor, we could extract exact eligible cases from the Cancer Register. We collected all incident cases of esophageal adenocarcinoma (PAD 094, 096; ICD-9 150), cardia adenocarcinoma (PAD 094, 096; ICD-9 151.0) and esophageal squamous cell carcinoma (PAD 144, 146; ICD-9 150) diagnosed 1994 to 1997 for inclusion in study I, and those diagnosed 1998 to 2004 for study II. Controls were chosen as the three live born infants of the same sex, following the delivery of the case at the same maternity ward. Twins and infants with severe congenital malformations were excluded. The study base was individuals born in hospitals all over Sweden 1912 to 1985, and that were alive in Sweden in 2004.

4.3.2 Study II

Everyone in the Patient Register diagnosed with esophagitis (ICD-8 and -9: 530B, -C and 530.94; ICD-10: K20 and K21.0) after an endoscopic examination (Surgical Procedures 6th edition 288, 448; Surgical Procedures 1997 edition UJC02, UJC05, UJC12, UJC15, UJD02, UJD05), and who had retrievable birth data from the Medical Birth Register were included as cases. 5 controls per case were selected from the Medical Birth Register, of the same sex and age and born in the same county. This study was a case-control study, nested within the population of everyone born in Sweden and included in the Medical Birth Register from 1973 and onward. The data set was provided by the National Board of Health and Welfare.

4.3.3 Study III

Any patient with GERD symptoms referred to Ersta Hospital, Stockholm 1992-2007 or to Kalmar County Hospital 1986-2006, and who following an EGD with biopsies was diagnosed with specialized, intestinal metaplasia was included in the register. Of all registered cases of BE, only those who had a retrievable birth record were eligible as cases in our study. Controls were chosen as in study I and IV. The study population was born between 1921 and 1983 in hospitals all over Sweden, but mainly in the greater Stockholm region and Kalmar County.

4.4 STATISTICAL CONSIDERATIONS

4.4.1 Statistical models

We used conditional logistic regression models to calculate odds ratios (OR) as the measure of effect with 95% confidence intervals (CI). In study IV we additionally used a non-linear polynomial modeling approach, a spline, to allow the data to depart from a non-linear relation. With multiple logistic regression one can model the relationship between a dependent variable ‘x’ and one or more explanatory variables ‘y1’, ’y2’, ‘y3’ etc., and thereby adjust for confounding factors. This means that we built the statistical models including the variables in our a priori hypothesis, as well as some potential confounding factors. Our models had to be conditional logistic models, due to the matching of cases and controls. All data was analyzed using Stata IC11 or Stata IC12, Stata Corp, College Station, Texas, USA.

4.4.2 Interaction and effect-measure modification

Interaction is present when the effect measure (in this thesis OR) of one variable, varies across values or strata of another explanatory variable. Biological interaction occurs when two factors are part of the same causal pathway to disease. In practice such interaction becomes evident when the joint effect of two factors deviates from what would be expected under the assumption of no interaction. The judgment on interaction is dependent on whether the scale is additive or multiplicative. Using logistic regression models like we did throughout this thesis, implies that any statistical test of homogeneity evaluates deviation from the multiplicative scale. For example; no difference in OR between two strata, meaning no effect-measure modification on the multiplicative scale, implies a heterogeneity of risk differences on the additive scale[183, 187, 188].

We examined statistical interaction by stratification and by introducing an interaction term (z1*z3) into the regression models. We decided which variables to stratify for a priori based on biologic reasoning and plausibility[181].

In study I we examined potential interaction between gestational age and age at diagnosis, hypothesizing that the effect of neonatal factors might be stronger earlier in life. In study II we stratified by age at diagnosis for the same reason as in study I, and also by sex thinking there might be a difference between the sexes. We also examined interaction between gestational age and SGA. In study III we stratified by BE segment length for explorative reasons. In studies I and IV we stratified the analysis by the 3 tumor types knowing that they have different locations, etiologies and risk factors.

4.5 ETHICAL CONSIDERATIONS

We had ethical permits for all four studies from the Regional Ethical Review Board, Stockholm. Medical records and information in parish archives younger than 75 years is protected by secrecy and we had additional permits from the archives and registers that were used for data collection, to access the data.

In none of our studies did we have informed consent from the study participants. In our applications for ethical permits we argued that any breach on the personal integrity that comes from medical record- and data handling and subsequent analysis is small, smaller than it would be to locate all study participants and inform them about our hypotheses and request for their consent to collect the data. Moreover, a majority of the case patients of esophageal cancer were deceased at the time of the studies. All data

was de-identified after the initial identification and data collection. Data was analyzed and presented on group level and it was thus impossible to trace information back to single individuals. We believe that the value of our results is of greater good, than the potential harm we have done by collecting data from medical records of unknowing individuals.

5 RESULTS

This is a summary of the results. For a complete presentation, please see the individual studies at the end of the thesis.

5.1 GESTATIONAL AGE AND SIZE AT BIRTH AND RISK OF ESOPHAGITIS (STUDY II)

Of the 7,358 cases and the 34,094 controls included in study II, there was an overrepresentation of preterm birth, low birth weight or SGA among the cases. Being born very preterm (≤32 completed weeks) as compared to being born at term, increased the risk of esophagitis later in life almost 3-fold (OR 2.7, 95% CI 2.2-3.5), irrespective of age at diagnosis. When we stratified by age at diagnosis (Table 1) and sex (data not shown), different risk patterns appeared. The risk was highest among those diagnosed before 10 years of age and being born very preterm (Table 1). Being born very preterm and male gave an almost 10-fold risk increase (OR 9.9, 95% CI 5.9-16.5) in those diagnosed before 10 years of age, compared to being born very preterm and female which gave a 3-fold risk increase (OR 3.4, 95% CI 1.8-6.4).

Table 1 Gestational age and birth weight for gestational age and risk of esophagitis at different ages.

	Age at diagnosis of esophagitis OR* (95 % CI)		
	≤ 9 years	10–19 years	≥ 20 years
Number of cases/controls	1,907/8,808	1,587/7,138	3,759/17,029
Gestational age			
≤32 weeks	6.8 (4.7–10.0)	2.1 (1.2–3.7)	1.0 (0.6–1.6)
33–36 weeks	1.8 (1.4–2.1)	1.4 (1.1–1.8)	1.1 (0.9–1.3)
37–41 weeks	1.0 (referent)	1.0 (referent)	1.0 (referent)
≥42 weeks	1.1 (0.9-1.3)	1.3 (1.0–1.5)	0.9 (0.8–1.1)
Birth weight for gestational age			
SGA	2.0 (1.6–2.5)	1.5 (1.1–1.9)	1.3 (1.1–1.5)
AGA	1 (referent)	1 (referent)	1 (referent)
LGA	1.1 (0.8–1.4)	1.0 (0.8–1.4)	0.8 (0.6–1.0)

*Model includes gestational age, birth weight for gestational age, maternal age and birth order.
AGA, adequate for gestational age; LGA, large for gestational age.

Being born SGA as compared to adequate for gestational age (AGA) was associated with a risk increase of 50% independently of age at diagnosis (OR 1.5, 95% CI 1.3-

1.7). The effect of SGA was stronger among those diagnosed before 10 years of age, as compared to older ages at diagnosis (Table 1). Among those diagnosed before 10 years of age the effect of SGA was stronger among females than males.

The combination of being born preterm and SGA was associated with an OR of 7.4 (95% CI 4.0-13.9), but we found no statistically significant interaction between the two variables (p for homogeneity of ORs = 0.13).

Neither maternal smoking nor BMI in early pregnancy or the family's socioeconomic status confounded the risk estimates.

5.2 GESTATIONAL AGE AND SIZE AT BIRTH AND RISK OF BE (STUDY III)

Among 331 cases and 852 controls, the male to female ratio was 2.3 to 1. Being born with a birth weight of less than 2500 grams, as compared to a 'normal' birth weight of 3000-3999 grams, was associated with an 8-fold risk increase (OR 8.2, 95% CI 2.8-23.9) (Table 2).

Table 2 Odds ratios for the diagnosis of BE and birth weight, gestational age and a combination of the two.

	Number cases/controls	Crude OR (95% CI)	Adjusted[ϕ] OR (95% CI)
Birth weight			
<2500 grams	16/12	4.4 (1.9–10.1)	8.2 (2.8–23.9)
2500–2999 grams	40/93	1.1 (0.8–1.7)	1.4 (0.9–2.2)
3000–3999 grams	222/594	1.0 (referent)	1.0 (referent)
≥4000 grams	53/153	0.9 (0.7–1.3)	0.9 (0.6–1.4)
Gestational age[†]			
<37 weeks	19/44	1.2 (0.7–2.2)	1.2 (0.7–2.3)
37–41 weeks	265/687	1.0 (referent)	1.0 (referent)
≥42 weeks	39/103	1.0 (0.7–1.5)	0.9 (0.5–1.4)
Birth weight for gestational age			
<3^{d} percentile	16/20	2.5 (1.2–5.0)	3.0 (1.4–6.4)
3rd to <10th percentile	29/52	1.5 (0.9–2.5)	1.8 (1.0–3.1)
10th to <25th percentile	47/118	1.1 (0.8–1.7)	1.3 (0.9–2.0)
25th to 75th percentile	150/413	1.0 (referent)	1.0 (referent)
>75th to 90th percentile	51/116	1.2 (0.8–1.7)	1.1 (0.7–1.8)
>90th to 97th percentile	15/83	0.5 (0.3–0.9)	0.5 (0.3–1.0)
>97th percentile	15/31	1.4 (0.7–2.7)	1.6 (0.8–3.4)

ϕ Model including birth weight or birth weight for gestational age, and gestational age, parity, maternal age, socioeconomic status and mode of delivery.

† Gestational age is adjusted for birth weight for gestational age, parity, maternal age, socioeconomic status and mode of delivery.

Being born SGA (<3rd percentile) and moderately SGA (3rd to <10th percentile), increased the risk of BE almost 3-fold and 2-fold, respectively (Table 2). Analyzing the categories of birth weight for gestational age as a continuous variable, each stepwise increase in category resulted in OR 0.8 (95% CI 0.7-0.9, p for trend = 0.003). This can be interpreted as a protective effect of almost 17% per group from the smallest to the largest. The effect of being SGA was stronger among those with long segment BE as compared to those with short segment BE (OR 2.7, 95% CI 1.1-6.6 and OR 1.7, 95% CI 0.6-4.3, respectively) but the point estimates were not significantly heterogeneous (p for interaction = 0.63).

5.3 GESTATIONAL AGE AT BIRTH AND RISK OF EAC

The results from the two studies with EAC as the main outcome point in the same direction; gestational age at birth seems to affect the risk of EAC development later in life. There was a non-significant trend in both studies of increasing risk of EAC with decreasing gestational age.

5.3.1 Study I

In study I there were 67 cases of EAC, 93 cases of cardia adenocarcinoma and 50 cases of esophageal squamous cell carcinoma, and a total of 474 matched controls. Gestational age ≤38 weeks and risk of EAC was associated with an OR of 1.2 (95% CI 0.5-2.7). No associations were found between relative birth weight for gestational age and risk of EAC. Gestational age ≤38 weeks was associated with a slight increase in risk of cardia adenocarcinoma (OR 1.3, 95% CI 0.7-2.4) and there was a statistically significant trend of a protective effect with increasing gestational age (p-value = 0.001). No association was evident between gestational age or relative birth weight, and subsequent risk of esophageal squamous cell carcinoma.

5.3.2 Study IV

In study IV there were 240 cases of EAC, 237 cases of cardia adenocarcinoma, 257 cases of esophageal squamous cell carcinoma, and a total of 1799 matched controls. Gestational age <37 weeks and risk of EAC was associated with an OR of 1.9 (95% CI 1.0-3.6). Modeling gestational age as a continuous variable was associated with a 13% increased risk per week earlier birth than birth at term (OR 1.1, 95% CI 1.0-1.2), equal

to a risk increase of 40% per month of prematurity. There was no evident association between gestational age and any of the other two tumor types.
No association was evident between birth weight for gestational age or ponderal index, and any of the three tumor types studied.

6 DISCUSSION

6.1 METHODOLOGICAL CONSIDERATIONS

6.1.1 Study design

We chose to do case-control studies as we deemed it the only feasible design. A randomized clinical trial would be impossible and unethical as you cannot randomize or induce the exposures preterm birth and SGA, nor can you randomize or induce pregnant women to preterm delivery by some intervention. Moreover, following-up a cohort of newborns, both term and preterm, until they are diagnosed with the outcome of interest many years later would be virtually impracticable.

All our studies can be said to be nested case-control studies as we had strict definitions as of the source population. In this way we were certain that the controls came from the same source population, and the same study base, that gave rise to the cases.

6.1.2 Internal validity

Internal validity is a description of whether the study at hand has succeeded in showing what it set out to show. There are two principally different threats to the internal validity of a study, systematic error also known as bias (selection bias, information bias, confounding etc.) and random error (the effect of chance variability).

6.1.2.1 Confounding

Confounding is a type of bias that confuses or distorts the results of a study. A confounder is a variable that is linked to the exposure as well as the outcome, but it is not an intermediate in the causal pathway[181]. A confounder is taken care of by adjusting for it in the analysis.

Possible confounders in our studies are for example BMI, tobacco smoking status, socioeconomic status, co-morbidities and level of symptoms of GERD. We did not have information on any of these factors, as we only had access to our cases diagnosis and exposure data from the birth records of cases and controls. It is likely that these variables above are intermediate factors in the causal pathway from preterm or SGA birth to inflammation and cancer of the esophagus, and thus not confounding factors. We can only speculate as to how this lack of information affects our results.

6.1.2.2 Detection bias

Detection bias arises when an outcome is more commonly found in one group compared to another, due to extra attention paid to that group. In study II for example,

we cannot completely exclude the possibility that preterm born or SGA individuals are seen by their doctor more often than infants born at term, and for that reason more often diagnosed with esophagitis. This is discussed in depth in the article. For the remaining studies there are no obvious reasons for any detection bias.

6.1.2.3 Selection bias

Selection bias occurs when there is distortion in the process of selecting study subjects or from factors influencing the participation in a study, resulting in a different relation between exposure and outcome in those *in* the study and those *not* in the study[183]. In a case-control study, the selection of controls is the key to avoid selection bias.

In our studies, cases were extracted from registers with regional or nationwide coverage. Anyone with the disease of interest ought to have had similar chance of ending up in the register and hence be an eligible case in our studies. Controls were selected among individuals born in the same hospitals as the cases, which ought to have affected neither exposure status nor outcome. These factors minimize the risk of selection bias in our studies.

A special type of selection bias is survivor bias[183]. Most likely did many of the exposed individuals (preterm born or SGA) born in the early 20th century, die before reaching adulthood when they would possibly have become eligible as study subjects. This leads to, together with life itself, that the effects of early life exposures often diminish with time i.e. older age of the study subjects. What was the reason for the survivors staying alive? We can only speculate of a kind of survival advantage perhaps in line with 'survival of the fittest'.

6.1.2.4 Information bias

Information bias, also called misclassification, arises when the measurement of exposure or outcome is dependent on other variables, or on errors in the measurement of other variables. Misclassification can be differential or non-differential, depending on whether the measurement error is equally distributed among the cases and controls or not. Non-differential misclassification mainly makes the comparison groups more alike and thus dilutes the association between the exposure and outcome, resulting in a bias towards the null. The effect of differential misclassification can either enhance or diminish an existing effect, or create a non-existing effect[181, 183].

6.1.2.4.1 Misclassification of exposure

The risk of misclassification of birth weight is very low, while the risk of misclassification of gestational age is considerably larger. The mother estimated the date of her last menstrual period, and gestational age was calculated from that date. It is possible that mothers misremembered, had bleedings in early pregnancy that were mistaken for menses, or that she purposely gave a forward-dated date to avoid having a child out of wedlock. This potential misclassification ought to be non-differential and independent, and if anything lead to a larger number of LGA infants. All exposure data was entered into the medical records prospectively, thus virtually precluding the risk of differential misclassification.

6.1.2.4.2 Misclassification of disease

For study I and IV cases were recruited from the Cancer Register that is 98% complete and there are unlikely any false negative cases of EAC in the population[109]. In study II cases were recruited from the Patient Register, and we validated the esophagitis diagnosis to be 95% accurate[189]. The prevalence of esophagitis in the population is estimated to 10%[59], and the resulting bias from this group of false negatives among the controls will influence the result towards the null[183]. Cases for study III were all confirmed by histopathology as being intestinal metaplasia, giving the registers a high specificity. The incidence of BE in the populations is estimated to be 1.6%[83], resulting in a small amount of false negative individuals among the controls and a low risk of misclassification bias.

6.1.2.5 Random errors

Any study result may be caused by chance or random error, and there are two types of random error. Type I or α error leads to an erroneous rejection of a 'true' null hypothesis and results in a false positive conclusion. The α-level or significance level is often set to 0.05. A Type II or β error leads to failure to reject a 'false' null hypothesis, and a false negative conclusion. The value of β is decided in advance, and is used in the power calculation to decide the sample size. By increasing the size of a study the statistical power and precision of a study is increased, thus reducing the risk of random error. With increasing sample size comes decreasing width of the confidence interval and smaller p-value, as indications of precision. The α and the β values are related to one another and the levels of them needs to be set with this in mind, as well as which statistical model is being used and the plausibility of the hypothesis tested.

In study I and IV the sample sizes were rather small resulting in confidence intervals including 1 and p-values>0.05, and a low statistical power. In studies II and III the sample sizes were larger, leading to less wide CI's and statistically significant p-values.

6.1.3 Generalizability

Generalizability or external validity, is the concept of whether results can be generalized to another population than the one specified in the study. This is a key concept in research, based on biological plausibility, with practical as well as economical aspects[181, 183]. Generalizability depends mainly on the internal validity of a study, and on the population used; do differences between populations change the results?

Our studies had sound internal validity and were population-based, restricted to individuals born in Sweden. Sweden is a country with high quality health care that is equally accessible for all, and with an infant mortality rate that has been lowered over the years. These facts might hamper generalizability to populations with higher infant mortality, or to birth cohorts within Sweden with better infant survival. It might also be difficult to generalize our results to populations with different access to health care.

6.2 POSSIBLE BIOLOGICAL MECHANISMS

From epidemiologic findings it is difficult to draw conclusions about biological mechanisms or causal pathways. Biological inference stems mainly from experimental research. Here we present some speculations regarding possible mechanisms, linking gestational age and size at birth to the esophageal health of the adult individual.

6.2.1.1 Preterm born are prone to cancer?

The hypothesis generating cohort study showed that apart from testicular cancer, breast cancer and EAC, there were no other tumor types that were overrepresented in that cohort of preterm and low birth weight infants (unpublished data)[190]. To our knowledge there are no other studies indicating a generally increased risk of cancer among preterm born individuals.

6.2.1.2 The Barker hypothesis

Also called the thrifty phenotype hypothesis, it was first presented by D. Barker in 1992 based on his work in the late 1980's and early 1990's[191, 192]. He suggested that intra-uterine growth restriction, the most common cause for low birth weight and SGA, leads

to adaptations in the fetus to a nutrient deprived environment. Once the fetus is born, these adaptations lead to chronic diseases like the metabolic syndrome, cardiovascular diseases and diabetes mellitus[193]. That the metabolic syndrome can lead to obesity is known, and also that obesity is a risk factor for GERD. The exposed cases in our studies could have been obese to a larger extent than the non-exposed cases[194], and obesity could thus be a link in the causal pathway between preterm birth or SGA and GERD related complications.

6.2.1.3 Pyloric stenosis

This is a condition that causes severe vomiting in infants due to a hypertrophy of the pyloric sphincter, at the outlet of the stomach. There is a clear male predominance and it is also more common among preterm born and SGA infants[195]. Among infants born preterm, male infants are in general more vulnerable than female[18]. Can this indicate an increased vulnerability also in the gastrointestinal tract of male preterm born infants?

6.2.1.4 Damages from stress?

Not all preterm infants end up in an intensive care unit after birth, but some do. It is common in adults and children in intensive care units to present with gastrointestinal bleeding and lesions due to stress[196, 197]. Although most of these stress induced lesions heal in a few days[198], they could perhaps affect the esophageal mucosa in the long term as well.

6.2.1.5 Feeding tubes

Most infants need assisted feeding before they reach a gestational age of 34 weeks. In Sweden nasogastric tubes have been used for feeding since late 1940's (Personal communication: Anna-Karin Edstedt Bonamy November 2012). It has been showed that nasogastric tubes placed with its tip inside the stomach increases the incidence of GERD in a preterm population[133].

6.3 FINDINGS & IMPLICATIONS

The data in this thesis suggests that gestational age and size at birth matters for the esophageal health later in life. The findings in the four studies are not entirely consistent as the exposure variable resulting in an increased risk varied between

preterm birth, SGA and low birth weight. Furthermore, we lack data to evaluate the possible pathologic mechanisms behind the associations, and we can only speculate regarding any potential causal links. Knowing the long term effect of prematurity and SGA on other organ systems in the body, it is not impossible to imagine a negative effect on the gastrointestinal tract as well.

We speculate that the most plausible biological mechanism that links preterm birth to esophageal inflammation, metaplasia and cancer later in life is GER. Either the association is mediated through an extended period of exposure to reflux as it starts earlier in the preterm infant, or because the refluxate is more toxic to the preterm or SGA infant's esophageal mucosa than it is to a mucosa in an infant born at term. There is a study showing symptomatic esophagitis becoming asymptomatic without treatment but with remaining pathology in the mucosa[199]. This could indicate that pathology might arise early in life and continue to exist but asymptomatic.

The clinical implications of our results could include an increased awareness of that the effects of gestational age and size at birth possibly continues into adulthood, and this especially with regard to individuals presenting with GERD symptoms. But I would like to suggest some further studies to elucidate the biological mechanisms, before any preventive or treatment suggestions can be made.

6.4 SUGGESTIONS FOR FUTURE RESEARCH

Future studies could focus on:

- What does the esophageal mucosa of preterm infants actually look like? It could be an explorative case report of infants born preterm or it could be designed as a case-control study looking at esophageal biopsies from preterm compared to term born infants. Furthermore, it would be very interesting to examine biopsies from preterm individuals with GERD, compared to biopsies from term born infants with GERD. Are there histopathological differences between the groups?
- Could the findings on esophagitis be repeated in 10 years time, when most infants with GERD probably will have been treated with antacids during the neonatal period?
- Is there an increased risk of other gastrointestinal diseases in adulthood among individuals born preterm or SGA, like inflammatory bowel disease or Celiac Disease? This could be explored in a case-control study.

- What is the actual mechanism behind the association between preterm birth and inflammation of the esophagus? This needs to be studied at a molecular level; perhaps genetic studies, and most likely experimental studies of animal models. Knowledge of the potential mechanisms could enable early detection of precancerous lesions, and potentially development of prophylactic strategies.

7 CONCLUSIONS

In this work we have explored a hypothesis divided into three research questions, by performing four separate studies. This is to our knowledge the first time that gestational age and size at birth are evaluated as possible risk factors for esophageal inflammation, metaplasia and adenocarcinoma later in life. From our work we conclude that:

1) Being born preterm and being born small for gestational age might increase the risk of being diagnosed with esophagitis later in life.

2) The association between preterm birth and being born small for gestational age and risk of esophagitis was strongest among those diagnosed before 10 years of age.

3) Being small for gestational age at birth or having a birth weight below 2,500 grams might increase the risk of being diagnosed with BE as an adult, while no such effect was seen for gestational age alone.

4) Gestational age at birth might influence the risk of EAC and also cardia adenocarcinoma as an adult. Our results indicate a dose-response relation between gestational age at birth and risk of EAC, with an increasing risk per week earlier birth as compared to birth at term.

5) No association was evident in our material for age or size at birth and risk of esophageal squamous cell carcinoma later in life.

8 POPULÄRVETENSKAPLIG SAMMANFATTNING

8.1 SYFTE

I den här avhandlingen har vi försökt besvara frågan om för tidig födsel eller att vara liten för tiden vid födseln, kan påverka risken att drabbas av inflammation, cellomvandling eller körtelcancer i matstrupen som vuxen.

8.2 BAKGRUND

8.2.1.1 Historik och förklaringsmodell

Idén bakom avhandlingens fyra delarbeten föddes ur en studie baserad på en stor grupp individer som var födda för tidigt eller med låg födelsevikt. Gruppen följdes till vuxen ålder, då man fann en 7-faldigt ökad risk för körtelcancer i matstrupen (EAC). EAC är en tumörform där förekomsten ökar oförklarligt i många länder, och sura uppstötningar är den största riskfaktorn. De som föds för tidigt har mer sura uppstötningar än barn födda i fullgången tid, och förklaringsmodellen var att de tar större skada av uppstötningarna och därför får mer cancer som vuxna. Förstadier till EAC är inflammation och cellförändringar i matstrupen, och vi valde att studera även dessa sjukdomar för att få till en ’röd tråd’ i avhandlingen.

8.2.1.2 Tidig födsel och liten för tiden

I Sverige föds varje år ca 80-140,000 barn (Figur 2), varav 5-6% föds för tidigt (Figur 3). Data från år tidigare än 1973 är osäkra, då inget offentlig medicinskt register över födslar fanns före dess. Spädbarnsdödligheten har sjunkit drastiskt sedan seklets början, pga. förbättrad mödra-, förlossnings-, och neonatalvård. För tidig födsel är att födas innan vecka 37 (Figur 1). Bland orsakerna till att födas för tidigt finns inflammation och sjukdomar hos mamman eller fostret, och missbildningar. Födelsevikt för tiden är ett mått på barnets tillväxt, de flesta spädbarn har en adekvat vikt för tiden (AGA) och ca 3% föds liten för tiden (SGA). Att vara för tidigt född kan innebära att man även är SGA, men det måste inte vara så. Bland orsakerna till att födas SGA är kromosomavvikelser hos fostret, att mamman röker eller är undernärd, samt dåligt blodflöde och funktion i moderkakan. Majoriteten av de för tidigt födda eller SGA födda klarar sig till vuxen ålder utan några fysiska men.

8.2.1.3 GERD

Reflux av maginnehåll upp i halsen eller munnen är vanligt i den vuxna befolkningen, men även hos barn. Det är när övre magmunnen (lower esophageal sphincter, Figur 4) slappnar av som mat passerar ner och luft eller vätska kan passera upp. Har man uttalade besvär som t.ex. halsbränna, smärta bakom bröstbenet eller sur smak i munnen så kallas det för gastroesofagal refluxsjukdom (GERD), ca 15-40% av den vuxna befolkningen i västvärlden lider av detta. Efter en längre tid med GERD kan det uppstå inflammation i matstrupen, detta kallas esofagit och finns hos ca 10-15% av vuxna i västvärlden, oavsett om de har symtom eller inte (Figur 6A). Hos vissa individer med GERD kan utvecklingen fortsätta till Barretts esofagus (BE). BE innebär att cellerna i matstrupen har förändrats och bytt både utseende och funktion, som en anpassning till den sura miljön med reflux (Figur 6C). Slutligen kan BE hos ett fåtal individer, man vet inte hos vilka eller varför, fortsätta att förändras och tillslut omvandlas till EAC (Figur 6D). Cancerceller kan växa till ohämmat, de uppvisar respektlöshet mot sin omgivning och har möjlighet att skapa egna blodkärl. EAC drabbar ca 200 personer per år i Sverige (Figur 7), fler män än kvinnor drabbas och endast 15% av dem lever 5 år efter diagnosen. Kända riskfaktorer för GERD är manligt kön, hög ålder, bukfetma, rökning och ärftlighet. GERD är en riskfaktor och gemensam nämnare för esofagit, BE och EAC. Antalet upptäckta fall av esofagit, BE och EAC ökar i västvärlden och har gjort så de senaste 40 åren. Ingen har hittills kunnat förklara vad denna ökning beror på. Barn som är födda för tidigt har mer reflux än barn födda i fullgången tid. GERD finns även bland barn, i en utsträckning som troligen är lägre än hos vuxna. GERD är troligen en kronisk sjukdom som startar i barndomen, och sedan ger symtom i perioder, och fortsätter upp i vuxen ålder.

8.3 PATIENTER OCH METODER

Samma studiedesign är använd i alla fyra delarbeten, som är s.k. fall-kontroll studier. Riskfaktorerna, eller exponeringarna, har varit liknande i alla delarbeten; ålder vid födseln räknad från datum för sista mens (gestationsålder), vikt vid födseln och ett mått på storlek vid födseln. Sjukdomen, eller utfallet, och därmed definitionen av vem som blir fall har varit olika; esofagit, BE och EAC. Fallen jämförs mot kontroller, som är personer från samma population som gav upphov till fallen. Vilka som blir fall, hur man samlar in fall och kontroller, och vilka exponeringar man undersöker väljs innan studien startar. Vi hade 3 eller 5 kontroller per fall, och i alla delarbeten var

kontrollerna matchade "sin" fallperson för ålder, kön och födelseort, vilket betyder att dessa variabler hade samma värde hos fall och kontroll.

Delstudie I och IV: Fallen kom från Cancer Registret. Alla i Sverige som fått diagnosen EAC, körtelcancer i cardia (Figur 4) och skivepitelcancer i matstrupen 1994-1997 och som hade en förlossningsjournal ingick i studie I, och på motsvarande sätt 1998-2004 för studie IV. Information om födelseålder och vikt mm, hämtades ur förlossningsjournalen. Som kontrollpersoner valdes 3 matchade individer som föddes efter fallet och skrevs ut levande från sjukhuset.

Delstudie II: Alla individer med diagnosen esofagit i Patientregistret 1973 – 2007 och som även fanns med i Medicinska Födelseregistret (MFR) utgjorde fall i studien. 5 matchade kontroller per fall plockades slumpmässigt ur MFR.

Delstudie III: Fallen utgjordes av individer som fått diagnosen BE åren 1986-2006 på Kalmar Länssjukhus och 1992-2007 på Ersta Sjukhus, Stockholm. Endast de individer där vi kunde hitta en förlossningsjournal ingick som fall i studien. Som kontroller valdes 3 matchade individer som föddes efter fallet och skrevs ut levande från sjukhuset.

I alla studier har vi analyserat data med konditionell logistisk regression och beräknat odds kvot (OR) och 95% konfidens intervall (KI). Mjukvaran heter STATA IC 11 och IC 12, från StataCorp, College station, Texas, USA.

8.4 RESULTAT

Delstudie I: I denna studie inkluderades 67 fall av EAC, 93 fall av körtelcancer i cardia, 50 fall av skivepitelcancer i matstrupen samt 474 kontroller. Vi fann ingen uppenbar riskökning för EAC av varken låg gestationsålder eller av låg relativ vikt vid födseln (jämförbart med SGA). Vi fann ett omvänt samband mellan gestationsålder och risken för körtelcancer i cardia, dvs. att vara född med en gestationsålder ≥41 veckor kan ha en skyddande effekt. Vi fann inget samband mellan gestationsålder eller vikt vid födseln och skivepitelcancer i matstrupen.

Delstudie II: 7,358 fall och 34,094 kontroller inkluderades i studien. Vi fann en 7-faldigt ökad risk hos barn födda före vecka 32 och en 2-faldigt ökad risk hos de som var SGA, för att diagnosticeras med esofagit innan 10 års ålder (OR 6.8, 95% KI 4.7-10.0 respektive OR 2.0, 95% KI 1.6-2.5). Då vi analyserade hela studiepopulationen oberoende av ålder vid diagnos, fann vi en knappt 3-faldigt ökad risk bland de som var födda före vecka 32 och en 50% ökad risk hos de som var SGA (OR 2.7, 95% KI 2.2-3.5 respektive OR1.5, 95% KI 1.3-1.7).

Delstudie III: 331 fall och 852 kontroller inkluderades i studien. Vi fann att SGA var associerat med en 3-faldigt ökad risk (OR 3.0, 95% KI 1.4-6.4) och de som vägde 2,500 gram eller mindre vid födelsen hade en 8-faldigt ökad risk att diagnosticerad med BE som vuxna (OR 8.2, 95% KI 2.8-23.9). För variabeln gestationsålder sågs ingen koppling till BE.
Delstudie IV: I denna studie inkluderades 240 fall av EAC, 237 fall av körtelcancer i cardia, 257 fall av skivepitelcancer i matstrupen samt 1799 kontroller. För varje vecka tidigare födsel än i fullgången tid (40 veckor) ökade risken för EAC med 13% (OR 1.1, 95% KI 1.0-1.3), eller ca 40% riskökning per månad för tidig födsel. Inget statistiskt signifikant samband sågs mellan gestationsålder och körtelcancer i cardia eller skivepitelcancer. Vi fann inte någon association mellan SGA eller risk för EAC, körtelcancer i cardia eller skivepitelcancer.

8.5 SLUTSATSER

Våra studier har visat att gestationsålder och storlek vid födelsen kan påverka risken för inflammation, cellförändringar och körtelcancer i matstrupen senare i livet. Vår hypotes är att denna riskökning kan vara orsakad av GERD, då de för tidigt födda barnen har mer reflux under sitt första år i livet, och eventuellt även senare också. Vi föreslår som förklaringsmodell hur reflux kan skada, att det antingen sker genom att cellerna är omogna och blir skadade av att utsättas för reflux, eller att de utsätts för en längre tid av reflux då den börjar tidigare i livet, än jämförelsegruppen individer födda i fullgången tid.
Våra studier visar ett samband på populationsnivå, och säger inte någonting om risken för den enskilda individen. Vidare så är sambandet statistiskt, och vi kan endast spekulera om de biologiska mekanismerna som kunde förklara fynden. Utöver GERD finns det troligen fler verksamma faktorer i orsakskedjan.
Styrkan med våra studier är att de är genomförda på ett metodologiskt och statistiskt korrekt vis, egentligen på det enda vis dessa samband kan undersökas. Förhoppningsvis kan resultaten föra med sig en ökad medvetenhet hos läkare om att gestationsålder och storlek vid födseln spelar roll även senare i livet, och att extra uppmärksamhet riktas mot individer som fötts för tidigt eller SGA som i vuxen ålder har besvär av GERD.

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