Childhood overweight and pubertal timing as predictors of adult cancer in men

The BMI Epidemiology Study Gothenburg

Jimmy Célind

Department of Internal Medicine and Clinical nutrition
Institute of Medicine
Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

Supervisor
Jenny Kindblom, MD, Associate Professor

Co-supervisor
Claes Ohlsson, MD, Professor

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jimmy.celind@gu.se

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När inga ungar längre finns är allting slut
Vad är det då för mening om man står ut?
Visst har det blivit kaos i tidens lopp
Men så länge det finns ungar så finns det hopp
-C Vreeswijk

Till Frida, Jon, Arvid och Ingrid

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ABSTRACT

Background and Aim

Obesity is one of the leading causes of cancer globally. The importance of overweight in childhood for adult cancer risk, independent of overweight status in young adulthood is still unknown. Furthermore, how male pubertal timing influences the risk of prostate cancer has not been established. Birthweight has been associated with increased cancer risk. Short-term trends of increasing birthweights are established, but trends from before the initiation of the obesity epidemic are scarce. The aims of this thesis were to evaluate the importance of high body mass index (BMI) in childhood, independent of the subsequent BMI development during puberty, for colon and rectal cancer, hematologic malignancies and obesity-related cancer in late adulthood. Furthermore, we also sought to explore a possible link between pubertal timing and prostate cancer and to characterize the long-term trends of birthweight in boys before and during the obesity epidemic.

Methods

Projects I-IV used a cohort of men born 1945–61 who finished school in Gothenburg. Height and weight measurements were collected from School Health Care records and military conscription tests. The main exposure variables were body mass index (BMI) at 8 and 20 years of age, pubertal BMI change (the difference in BMI between 8 and 20 years of age), and age at peak height velocity (PHV), an objective marker of pubertal timing. Cancer outcomes were collected from national registers. In project V, we assessed the long-term birth weight trends of 46,548 boys born between 1946 and 2011.

Results

Overweight at age 8 was associated with an almost triple risk of colon cancer (HR 2.81, 95% CI 1.70–4.64) compared to normal weight at 8 years, when both groups had a pubertal BMI change above the median (paper I). For hematological malignancies, BMI at 8 years was significantly associated with increased risk of overall hematologic malignancy, and with increased risk of Non-Hodgkin Lymphoma (HR 1.14, 95% CI 1.00-1.30), but increased height at age 8 was linked to a higher risk of multiple myeloma (HR 1.31, 95% CI 1.03–1.67) (paper II). Boys with childhood overweight whose weight

normalized during puberty, but not boys with pubertal onset overweight, had substantially increased risk of obesity-related adult cancer (HR 1.38, 95% CI 1.04–1.78) compared with those with a normal body weight at both 8 and 20 years of age (paper III). We found a reduced risk of prostate cancer, and high-risk prostate cancer for individuals with late pubertal timing (HR 0.73 for Q5 vs Q2–4, 95% CI 0.54–0.96) (paper IV). For birthweight trends, three significant periodic fluctuations were identified; a decrease between 1950 and 1980, an increase between 1980 and 2000, and finally another decrease between 2000–2010, but the overall birthweight trends between 1950 and 2010 were stable (paper V).

Conclusions

These findings establish that onset of overweight in childhood is of specific importance for adult cancer development in men and demonstrate a reduced risk of prostate cancer and the clinically important high-risk or metastatic prostate cancer in individuals with late pubertal timing. The long-term birth weight trends are marginal and future studies should determine the associations between birthweight and cancer risk independent of childhood overweight.

SAMMANFATTNING PÅ SVENSKA

Bakgrund och Syfte

Trots att obesitas (fetma) är en av de viktigaste riskfaktorerna för cancer globalt, är de oberoende riskerna relaterade till uppkomst av övervikt under barndom och/eller pubertet ej klarlagda. Vidare har timing av pubertet visat sig vara kopplad till cancer i äggstockar, bröst och livmoderslemhinna hos kvinnor. Däremot finns väldigt få studier av sambandet mellan pubertetstiming och cancer hos män, och kopplingen mellan pubertetstid och prostatacancer är därför ej klarlagd. Även födelsevikt har kopplats till framtida cancerrisk. Trender för födelsevikter sedan 70-talet är etablerade, men studier på trender av födelsevikter på längre sikt är sällsynta. Syftet med denna avhandling är att kartlägga vikten av högt kroppsmasseindex (BMI) under barndom, oberoende av BMI-utveckling under efterföljande pubertet, för risken för colon och rektal cancer, blodcancer, och fetmarelaterad cancer i vuxen ålder. Dessutom att klargöra en tänkbar koppling mellan pubertetstiming och prostatacancer, samt att karaktärisera långtidsutvecklingen av födelsevikter hos pojkar även före fetmaepidemin. I framtida studier planerar vi också att studera betydelsen av födelsevikt, oberoende av BMI i barndom, för risk för cancer i vuxen ålder.

Metod

Projekt I-IV använde en kohort av män födda 1946–61 som avslutade sin skolgång i Göteborg. Vi samlade in längd och viktmätningar från arkiverade skolhälsovårds-journaler samt mönstringsdata och passregistret, för beräkning av BMI vid 8 och 20 års ålder, samt förändring av BMI under pubertet (mellan 8 och 20 års ålder). Genom längdmätningarna kan tidpunkten för maximal tillväxtspurt (peak height velocity), en objektiv pubertetsmarkör, beräknas och användas för att studera associationer mellan pubertetstiming och prostatacancer. Projekt V använde 46,548 pojkars födelsevikter mellan 1946–2011 för att utvärdera långtidsutvecklingen av födelsevikter hos pojkar.

Resultat

Pojkar med övervikt vid 8 års ålder, vars fortsatta BMI-utveckling mellan 8 och 20 års ålder är över medianen, har en nästan tredubblad risk för cancer i tjocktarmen (delarbete I). För gruppen hematologiska (blod-) maligniteter finns ett samband mellan högt BMI vid 8 år och Non-Hodgkin lymfom, medan längden vid 8 års ålder var kopplad till risken för multipelt myelom (delarbete II). Pojkar med övervikt vid 8 års ålder men som blivit normalviktiga till 20 års ålder har 38% kvarstående ökad risk för fetmarelaterad cancer (delarbete III). Sen pubertetsutveckling associerar med en reducerad risk för

prostatacancer, samt för de farligaste varianterna av prostatacancer (delarbete IV). Den övergripande födelseviktstrenden 1950–2010 var stabil, men periodiskt signifikanta förändringar observerades.

Slutsatser

Dessa resultat visar på en särskild betydelse av överviktsutveckling före 8 års ålder gällande risken för cancer i vuxen ålder, och slår fast att preventivt arbete för cancer i vuxen ålder bör initieras redan i barndomen. Sen pubertetstiming associeras med minskad risk för prostatacancer, och än mer uttalat för de kliniskt viktiga högrisk- eller metastaserad prostatacancer. Utvärderingar angående födelseviktstrender bör om möjligt innefatta kunskap om trender på längre sikt, och det behövs framtida studier som utvärderar kopplingen mellan födelsevikt och cancer oberoende av övervikt i barndom.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Celind J***, Ohlsson C*, Bygdell M, Nethander M, Kindblom JM. Childhood Body Mass Index Is Associated with Risk of Adult Colon Cancer in Men: An Association Modulated by Pubertal Change in Body Mass Index. *Cancer Epidemiol Biomarkers Prev* 2019; 28, 974–978.

II. **Celind J**, Ohlsson C, Bygdell M, Martikainen J, Lewerin C, Kindblom JM. Childhood body mass index is associated with the risk of adult hematologic malignancies in men — The best Gothenburg cohort.
Int. J. Cancer. 2020; 1–8

III. **Celind J**, Bygdell M, Martikainen J, Ohlsson C, Kindblom, J.M. Childhood overweight and risk of obesity-related adult cancer in men. *Submitted manuscript*

IV. **Celind J**, Bygdell M, Martikainen J, Styrke J, Damber JE, Kindblom JM, Ohlsson C. Timing of the pubertal growth spurt and the risk of prostate cancer. *Submitted manuscript*

V. **Celind J**, Hedlund M, Bygdell M, Sonden A, Elfvin A, Kindblom, J. M. Secular trends of birthweight in boys from 1950 to 2010. Pediatr Neonatol 2019; 60(5):543–548.

*shared first authorship

CONTENT

ABBREVIATIONS

ALL	Acute Lymphatic Leukemia
AML	Acute Myeloid Leukemia
BEST	BMI Epidemiology Study
BMI	Body Mass Index
BW	Birthweight
CDC	Centers for Disease Control and Prevention (USA)
CI	Confidence Interval
CLL	Chronic Lymphatic Leukemia
CVD	Cardiovascular Disease
DHEA	Dehydroepiandrosterone
DHEA-S	Dehydroepiandrosterone sulfate
DOHaD	Developmental Origin of Health and Disease
FSH	Follicle Stimulating Hormone
GH	Growth Hormone
GnRH	Gonadotropin Releasing Hormone
HR	Hazard Ratio
IARC	The International Agency for Research on Cancer
ICD	International Classification of Diseases
IGF-1	Insulin-Like Growth Factor 1
IL-6/18	Interleukin 6/18
IOTF	International Obesity Task Force
IPR	The Swedish National Inpatient Register
LH	Luteinizing Hormone
LISA	Longitudinal integrated database for health insurance and labor market studies

MBR	The Medical Birth Register
NPCR	The National Prostate Cancer Register
PHV	Peak Height Velocity
PIN	Personal Identity Number
SCR	The Swedish Cancer Register
SD	Standard Deviation
TNF	Tumor Necrosis Factor
WHO	World Health Organization

DEFINITIONS IN SHORT

Childhood overweight	BMI at 8 years of age >17.9 (CDC definition)
Young adult overweight	BMI at 20 years of age >25
Pubertal BMI change	The change in BMI between age 8 and 20 years. (BMI at 20 years of age minus BMI at 8 years of age)
Timing of PHV	The age of the highest growth velocity during puberty
Obesity-related cancer	The cancer forms where a high BMI is regarded a risk factor according to the International Agency for Cancer Research[1], complemented with the recent Lancet publication by Furer et al[2].
Standard Deviation	A standardized measure of the of the variation and dispersion of a variable in a population related to the mean, which is set at 0.

1 INTRODUCTION

The year 2000 was a milestone in human history. For the first time, there were more overweight than underweight people in the world[3]. From one point of view, this was a human accomplishment unprecedented in human history, as the search for energy and supply of food has been a limiting factor for human survival and development throughout our history. However, overweight and obesity are associated with morbidity and mortality from several diseases, such as cardiovascular disease (CVD), diabetes, and a range of cancers[1]. While the increased risk of CVD related to overweight and obesity is generally accepted, the associations with different forms of cancers are still being unraveled.

Moreover, obesity contributes not only to disease development but also to a substantial decrease in quality of life[4]. In 2015, excess weight accounted for four million deaths and 120 million disability-adjusted life years globally[5]. Although the global prevalence of childhood obesity has been lower than among adults, the increase rate of childhood obesity has outraced that of adult obesity in many countries, including China and India[5]. The obesity epidemic has further been suggested to induce an increase in birthweights globally, but trends of birthweights from the period before the obesity epidemic are mostly unknown.

The long-term health consequences of overweight and obesity during development (childhood and puberty) are largely unknown. In addition, it has not yet been elucidated whether the timing of developmental onset of elevated body mass index (BMI) is of importance. Nonetheless, the obesity epidemic has the potential to halt or even counteract a long era of progress in general health and life expectancy[6].

1.1 THE OBESITY EPIDEMIC

There is no exact beginning of the obesity epidemic. Historical records have shown that height and weight have increased progressively in developing countries, especially during the 19th century[7]. The incidence of obesity gradually increased during the last century as energy-dense food became abundant and populations in developed regions of the world approached their genetic height potential[7]. At some point, energy access on a population level exceeded the needs to reach the genetic height potential, so weight expansion became disproportionate to the height increase. Overweight turned into an epidemic. Although the diffuse start of the obesity epidemic shows large regional discrepancies, it is now a concern of pandemic proportions. The global prevalence of obesity tripled between 1975 and 2016[8], and by 2016 also obesity surpassed underweight in global prevalence[9].

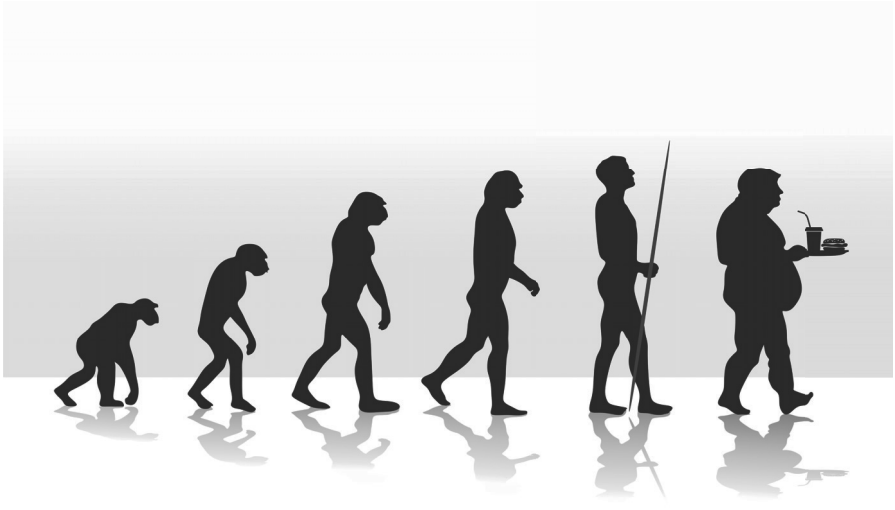


Figure 1. Satirical view of the human evolution, illustrating the development in height transcending to BMI acceleration. Published with the approval of Dreamstime.com.

In 2018, for the first time ever in Sweden, more adults (51%) were overweight or obese than normal or underweight[10]. Our research group recently showed that a significant increase in childhood BMI at eight years of age was present from the end of the seventies, compared to the mid-1950s[11]. Between 1954 and 2014, overweight among eight-year-old boys

quadrupled[11], although a recent small but significant decline has been observed[11].

Birthweight trends during the obesity epidemic

Birthweight is an accessible and established marker of health during the fetal period. Birthweight is strongly correlated with survival of the newborn, as well as a predictor of future health or disease[12-16] and even adult mortality[17]. This research area, which focuses on early life exposures and particularly the fetal period, and their association with adult disease, is called the Developmental Origin of Health and Disease (see Chapter 2.2). However, a causal implication of observed associations between birthweight and adult disease has been questioned[18]. As with the historical focus on sufficient nutrition after birth, health concerns regarding birthweights have primarily involved efforts to prevent low birthweight[19].

Two major shifts affecting birthweights during the 20th century

Around the millennium, as numerous developed countries reported increasing birthweights, health concerns for birthweight trends shifted towards the increase in birthweights[20-27]. The increase was linked to the coinciding weight increase in adult populations[28]. Nevertheless, smoking is the single most important determinant of decreased birthweight[29], even passive smoking has been linked to reduction of placental function[30]. Prevalence of smoking among women in the US increased after the World War II, and reached a peak around the mid-sixties[29]. In Sweden, smoking rates among women was halved from 1980 to 2000, and the decline was even more pronounced in pregnant women[29].

What is known of long-term birthweight trends?

Two studies that investigated birthweight trends in the USA and Denmark from the mid-1930s to the early 1980s demonstrated stable or slightly negative trends[31,32]. Since 1973, the Swedish Medical Birth Register has made available data on many perinatal variables from both mother and offspring for practically all births in Sweden[33]. However, data on birthweight trends in Sweden before 1973, as well as international studies of birthweight trends spanning the smoking as well as the obesity era, are largely missing.

1.2 BODY MASS INDEX

There are several ways to measure excess weight and total body fat. The most common methods are BMI, skinfold thickness, waist-hip ratio, hydrodensitometry (underwater weighing), waist circumference, dual-energy X-ray absorptiometry (DXA), bioimpedance analysis, imaging methods such as computed tomography (CT) and magnetic resonance imaging (MR).

The need to measure of excess weight originates from a desire to reliably identify individuals with excess fat mass as these individuals have an increased risk of associated diseases. BMI is the most widespread measure because it does not require special equipment or machines. Furthermore, because BMI is calculated using only height and weight measurements, it is possible to determine BMI retrospectively (i.e., from old measurements such as those recorded in school or military records).

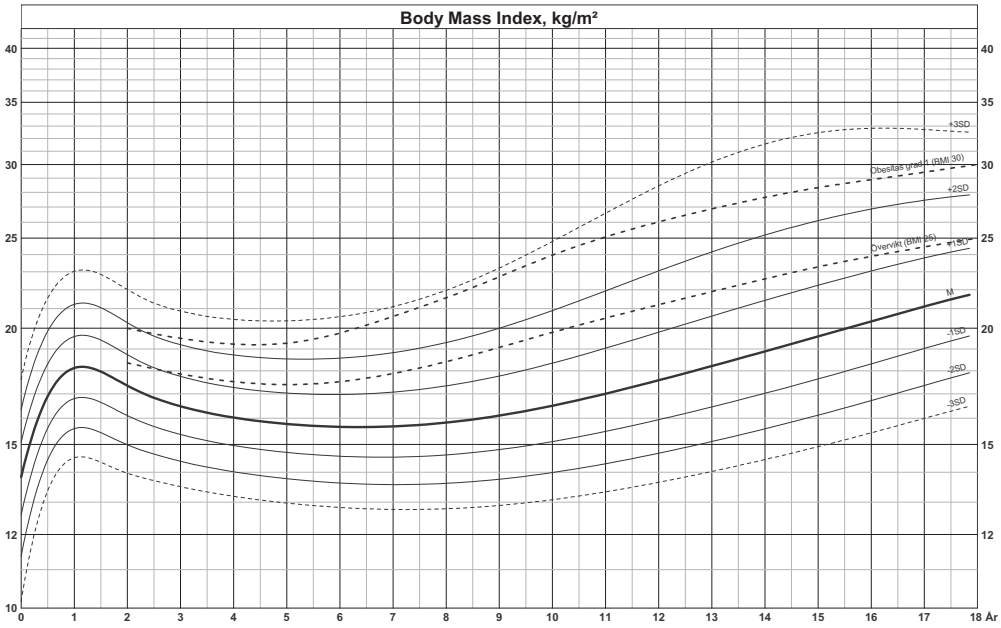


Figure 2. BMI growth chart for boys in Sweden. Dotted lines represent IOTF-cut-offs for overweight and obesity, extrapolated from adult definitions.

The BMI-measure was invented by Adolph Quetelet in the 19th century, and was formerly called the Quetelet index[34]. Quetelet, a Belgian mathematician, discovered that an adult´s ideal weight (in kilograms) correlates with the adult´s squared height (in meters).

On an individual level, BMI is a meager measure of excess fat, since it does not distinguish a high BMI due to excess fat from a high BMI due to a large lean mass. In children, lean mass varies less than in adults[35], so BMI-defined overweight and obesity is a good measure of excess fat on a group level[36]. In the retrospective, population-based studies such as those presented in the current thesis, including childhood measurements of height and weight, BMI was the only available assessment of overweight and obesity.

1.3 DEFINING OVERWEIGHT AND OBESITY

In adults

Overweight and obesity are excess weight related to height, and BMI is the internationally used measure by which overweight and obesity is defined. With the exception of the specific Asian definitions, adult definitions of overweight and obesity are the same globally. The Asian cut-off limits for overweight and obesity are lower than the global ones (Table 1). In the year 2000 the Western Pacific Regional Office (WPRO) of the World Health Organization (WHO) proposed this specific Asian definition based on the fact that Asians in general have lower BMI, and that their body fat percentage and cardiovascular risk are higher at lower BMI-levels[37-39]. Because children of Asian ethnicity often have a body composition similar to the Asian adults[40], it has been argued that these children should be monitored by a different standard to avoid overestimation of underweight and underestimation of overweight[41].

In children and adolescents

For children and adolescents, overweight and obesity cut offs have also been controversial. As BMI varies with age during childhood and adolescence (Figure 2), the cut-offs for overweight and obesity must be age dependent. Internationally, different BMI classifications to determine childhood overweight and obesity are used; the WHO classification, the International Obesity Task Force (IOTF) classification, and the US Centers for Disease Control and Prevention (CDC) classification (Table 1).

Table 1. Definition of overweight and obesity at eight years of age and in adulthood according to the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and International Obesity Task Force (IOTF) classifications.

	Overweight	**Obesity**
At eight years of age		
WHO	17.4-19.7	>19.7
CDC	17.9-20.0	>20.0
IOTF	18.4-21.6	>21.6
Adult (WHO)	25-30	>30
Asian adult	23-25	>25

The different classifications are the result of different standards being used to represent different populations and views on how best to define overweight and obesity.

The WHO classification

In 1995, the WHO released a report of anthropometric measurement and interpretation, but it did not include a definition of overweight or obesity in children[19]. In adolescents, individuals with a BMI above the 85th percentile was considered "at risk of overweight" and should have their body fatness monitored, for example by testing skinfold thickness[19]. In the latest WHO report, produced by the Multicentre Growth Reference Study (MGRS) in 2006, the growth references were healthy child populations from Brazil, Ghana, India, Norway, Oman and the USA[42]. The children included in the WHO reference lived under conditions that would favor optimal growth (breastfeeding, transition to good diet, non-smoking mother, basic immunization, and access to health care). Unlike the CDC and IOTF standards, the WHO growth curves represent a desired standard rather than a descriptive representation of the reference population. Interestingly, the children in the WHO standards from different economic, cultural and hereditary backgrounds showed very similar growth patterns. In the 2006 WHO-reference, overweight was defined as above one standard deviation (SD, or z-score) of BMI, and obesity as above two SD of BMI. These definitions were based on the finding that +1 SD of BMI in their reference population was equivalent to an adult BMI of 25.4 in boys and 25.0 in girls, and the +2 z-score of BMI was equivalent to an adult BMI of 29.7 in both sexes (i.e., very close to the adult cut offs for overweight and obesity) (Table 1).

The CDC classification

In the USA, the CDC identified a need for growth curves that reflected growth of American children better than the WHO growth curves. The CDC, therefore, produced its own growth curves based on US national survey data between 1963 and 1994[43]. Their cut offs for overweight and obesity were also set at the 85th and 95th percentiles, but used their reference population´s distribution of BMI[43].

The IOTF classification

At the millennial shift, the IOTF set out to create a new international standard[44]. Their aim was to establish a commonly accepted international standard to enable comparisons between nations and a standard that would also relate to established adult definitions of overweight and obesity, in contrast to the existing arbitrary percentile-definitions of the WHO and the CDC. The IOTF used reference populations from six different countries that represent a mix of various economic and continental settings (Brazil, Great Britain, Hong Kong, the Netherlands, Singapore, and the United States).

Comparing classifications

With different internationally used standards for overweight and obesity during development, the prevalence will highly depend on the standard used. The CDC classification of overweight at eight years of age is somewhat lower than the IOTF classification[45]. A study from Canada showed that a mere change of the definition of obesity from the IOTF´s definition to the CDC´s definition could double the prevalence of childhood obesity[46]. This inconsistency underlines the need for international consensus concerning definitions of overweight and obesity, and, until this is accomplished, an awareness of which definition is used is important. The men included in the present cohort were children between the 1940s and 1960s, when childhood overweight and obesity was uncommon. To facilitate recognition for readers in the USA, the CDC definition of overweight and obesity was used in the present projects.

1.4 OVERWEIGHT AND ADULT DISEASE

There is an abundance of scientific evidence demonstrating associations between adult overweight and the risk of cardiovascular disease[47] and diabetes[48] and there is accumulating evidence for specific cancers[49-51]. However, the risk of adult disease related to overweight and obesity in childhood and during puberty is less studied. Some evidence suggests an association between a high BMI in childhood or adolescence and cardiovascular disease[52-56], while others found no such associations[57]. One study showed that BMI at 17 years of age was associated with CVD independent of BMI around 30 years of age[55]. Our research group has demonstrated that the pubertal BMI change, but not childhood BMI, was associated with increased risk of several cardiovascular outcomes such as CVD mortality, stroke, and heart failure[58-60].

While CVD includes a number of different conditions with a high degree of similarities regarding risk factors and disease mechanisms, the different types of cancers share some similar disease mechanisms but risk factors (carcinogenic stimuli) differ greatly between cancer types. However, common risk factors do exist. Smoking is a well-known risk factor for a variety of cancers[61]. Although certain cancer types are not associated with obesity, the importance of overweight and obesity for the risk of cancer is well-established for a range of cancer types, and for others, evidence is still accumulating[62]. As a result of the obesity epidemic, obesity has turned into one of the most important preventable risk factors of cancer globally[62,63].

1.5 CANCER OUTCOMES

Colon and rectal cancer

Combined, colorectal cancer is the third most common cancer globally, but arguments for a distinction between colon and rectal cancer are increasingly common[64-66]. Risk factors for colon and rectal cancer are similar, but not identical, and include adult obesity, diet (low-fiber, high calories, red meat, and alcohol increase risk), diabetes[67], inactivity, smoking, and inflammatory bowel disease (primarily ulcerative colitis)[68]. Risks related to unhealthy lifestyle tend to be higher for colon than rectal cancer[66]. Although the incidence of colon cancer in Sweden has increased, the rectal cancer incidence has been stable over the last decades[69].

Colon and rectal cancers primarily originate from adenomas (neoplastic polyps) in the colorectal tract, a slow development suggested to span over at

least 10 to 15 years[70]. Colon and rectal cancer are diseases of late life, as only 4-5% of those diagnosed with colon or rectal cancer are younger than 50 years, and more than 20% are above 80 years of age at diagnosis[69].

Hematological malignancies

Hematologic malignancies are a heterogenous group of cancers that stem from the blood forming cells (Figure 3). The three major groups of hematologic malignancies include leukemia, lymphoma and multiple myeloma, although classification of the hematologic malignancies is complex due to contrasts in historical morphologic traditions, emerging genetic knowledge, and clinical practice[71-73]. An overview of the hematologic malignancies is presented in Figure 3.

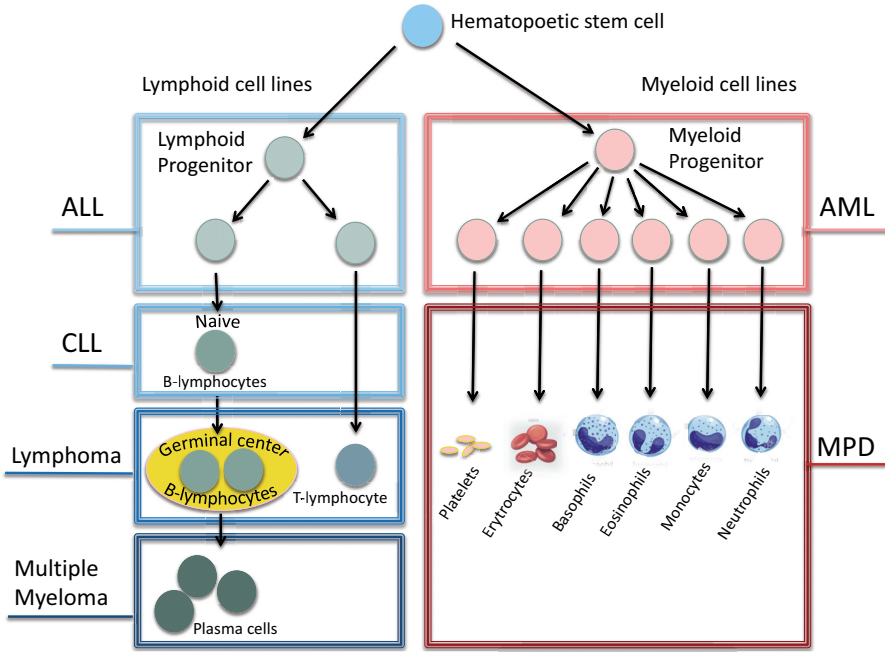


Figure 3. Overview of the hematologic malignancies including the cell lineage and developmental phase from where the various types of cancer originate. ALL=Acute Lymphatic Leukemia, AML=Acute Myeloid Leukemia, CLL=Chronic Lymphatic Leukemia, MPD=Myeloproliferative Disorders

The risk of hematologic malignancies increases with increasing age, and the other scarce known risk factors include adult obesity[74-76], male sex, some chemicals, and, for some types of lymphoma, viral infections.

Obesity-related cancer

The term "obesity-related" is used for cancers with sufficient evidence that excess weight is a risk factor for a cancer type[77]. The field of obesity-related cancer is yet expanding, and with accumulating evidence additional cancers will most likely be regarded as obesity-related. However, associations with obesity vary largely between cancer types. Some cancers have not shown any association and one of the most common cancer types, lung cancer, seems inversely associated (i.e., reduced risk with increasing BMI)[78], although the association is complicated[79].

The International Agency for Research on Cancer (IARC) is the specialized unit for research on cancer at the WHO. Their objective is to promote international collaboration in cancer research. The first IARC-report on the evidence of obesity-related cancer was released in 2002[80] and an update was released in 2016[1] (Table 2).

Among the first cancers linked to diet and excess weight were breast and colon cancer[81]. In the 2016 report, male breast cancer, fatal prostate cancer, and diffuse large B-cell lymphoma were on IARC´s list of cancers with a possible link to obesity, that is, the existing evidence needed additional corroboration. At present, oral cancer, leukemia, and lymphoma are among the next probable candidates to be included in the IARC´s list of obesity-related cancers[2,74-76].

Table 2. Cancers established as obesity-related according to the International Agency for Research on Cancer (IARC) in 2002 and 2016.

Year	Obesity-related cancer	Possible link
2002	Breast (postmenopausal) Colon Endometrium Kidney (renal cell) Esophagus (adenocarcinoma)	Thyroid
2016	Esophagus (adenocarcinoma) Gastric cardia Colon and Rectum Liver Gallbladder Pancreas Breast (postmenopausal) Corpus uteri Ovary Kidney (renal cell) Meningioma Thyroid Multiple myeloma	Male breast Prostate (fatal) Diffuse large B-cell lymphoma

Prostate cancer

The prostate gland is located below the urinary bladder, surrounding the urethra. The prostate gland produces fluid that protects and nourishes the sperm. At ejaculation, this fluid is squeezed into the urethra where it is expelled with sperm as semen. The highest growth rate of the prostate occurs during puberty, and the adult prostate is about the size of a walnut.

Prostate cancer is the most common cancer in men in developed countries, but in developing countries the incidence is lower[82] due to lower PSA-testing and shorter life expectancy. Prostate cancer is a disease of older men. In Sweden, the mean age at prostate cancer diagnosis is 70 years[83], and it is very rare in men younger than 40[84]. Known risk factors include diet, smoking, family history of prostate cancer, ethnicity and older age.

A majority of prostate cancers are slow growing and confined to the prostate, with a very good prognosis. The Swedish 10-year prostate cancer specific survival for low-risk cancers is above 95%, whereas for primary metastatic disease it is below 35%[85].

Prostate-specific antigen (PSA) was identified in 1966 in the search of antigens in human semen to use as forensic evidence in cases of rape[86]. In the 1980s, PSA was found to be a biomarker for prostate cancer, and was initially used to monitor diagnosed prostate cancers. The use of PSA for detection of prostate cancer started in the 1990s[87]. Although PSA screening can save lives[88], it has been controversial because it increases detection of primarily low-risk cancers, and is associated with morbidity related to overdiagnosis and overtreatment[89].

In 1941, Huggins and Hodges showed that prostate cancer responded to androgen deprivation[90]. Treatment of metastatic (and certain high-risk) prostate cancer includes androgen-deprivation therapy (ADT), which is not curative but does increase quality of life and survival[91]. After a median of two to three years of ADT, prostate cancer cells become castrate resistant. The mechanism is thought to relate to up-regulation of androgen sensitivity and self-sufficiency in androgen growth stimulating signals[91].

1.6 CARCINOGENESIS

The genetic code

Deoxyribonucleic acid (DNA) is the inherited program code of all known living organisms (not including RNA-viruses, viruses are generally not considered living organisms[92]). DNA is coded through combinations of the four nucleotides guanin (G), thymine (T), cytosine (C), and adenine (A). The DNA sequence is unique for every human, except for identical (homozygotic) twins. With a few exceptions, each cell in the body contains identical DNA code. Yet, somehow, the cells in the body display a vast variety of form and function. This variance is the result of epigenetic regulation, the mechanisms used to turn genes off and on. Epigenetic regulation includes inactivation of DNA-segments by tight packaging around protein complexes called *histones*, and tagging DNA for activation with methyl groups (methylation)[93]. The discovery that epigenetic variations sometimes is inherited has revolutionized the concept of a clear distinction between genetic inheritance and environmental influence[94]. Inherited epigenetic characteristics could explain some of the previously unexplained heritance in carcinogenesis[95]. Whether these mechanisms could apply to increased cancer risks related to lifestyle or obesity is yet to be elucidated.

Carcinogenesis

The transition of a normal, functional cell into an uncontrollable, potentially life-threatening cancer cell is called carcinogenesis. Carcinogenesis is a process which includes multiple DNA-altering steps, and often a long transition time.

Different stimuli can promote DNA-alterations by direct damage of DNA (e.g., ultraviolet light and chronic inflammation) and stimulation of proliferation and/or inhibition of cell control and programmed cell death (e.g., estrogen and IGF-1)[93]. Furthermore, epigenetic aberration through histone modification and increased or decreased methylation can enhance cancer promoting gene activity, or inhibit cancer controlling genes[93].

The multistage model of carcinogenesis

In 1954, Armitage and Doll presented the multistage model of carcinogenesis in the British Journal of Cancer, to explain the long latency period between carcinogenic exposure and manifest cancer[96]. The multistage model could explain previous findings that circumcision of Jewish newborns at the eighth day of life gave a near complete protection from penis cancer, but when performed in Muslim 14-year-old boys the protective effect was only partial, compared to countries where circumcision was not practiced[97].

This association has later been suggested to be at least partly attributed to phimosis[98].

The multistage model of carcinogenesis is thought to be a sequence of events that occur in a cell line (the cell and its clones), with years between the stages[96]. If a cell survives an initial genetic carcinogenic alteration, and the DNA-repair systems does not reconstruct the altered DNA code, it may result in loss of control of the cell. The cell proliferation could become more uncoordinated and autonomous. The proliferation of such cells leads to a cluster of disorderly and abnormal cells arranged in an abnormal structure, a state of pre-malignancy called dysplasia[99]. The dysplastic cells can either perish or proliferate, and can persist for years or even decades[100]. Dysplastic cells are often more susceptible to further genetic alteration due to insensitivity to controlling stimuli[101]. Eventually, an evolutionary developmental order can replace the normal surrounding control over the cells. The lesion then enters a mode of survival of the fittest. The cells most capable of self-sufficient proliferation and survival from defense systems proliferate more than the others, gaining an advantage[99]. Dysplasia turns into neoplasia. The proliferation of renegade cells becomes exponential.

In a modern approach, the multistage model of carcinogenesis has been simplified into three general steps[99]:

1. *Initiation*. Genetic or epigenetic change of a susceptible cell.
2. *Promotion*. Clonal expansion of initiated cells.
3. *Transformation*. Additional genetic or epigenetic change to one of the cloned initiated cells, turning it into a malignant cell.

The genes of carcinogenesis – the oncogenes

Certain genes that are of specific importance in carcinogenesis are called oncogenes. Typically, these genes are involved in cell proliferation and survival, or DNA-repair and programmed cell death (apoptosis)[102]. Inactivation or upregulation of oncogenes are often crucial steps of cancer development[102]. Important oncogenes include the Ras-genes and p53. The Ras-genes are tumor inducer genes that promote cell growth, differentiation and survival, and p53 is a tumor suppressor gene that regulates DNA-repair and apoptosis. Mutations in the Ras-genes are found in 20–25% of all human tumors, but up to 90% in specific tumors[103], and mutations of the p53-pathway are found in about 50% of human tumors[104].

Carcinogenic alterations of the cell

Carcinogenic development differs between cancer forms, and so does the exposures that stimulate carcinogenesis in different cells and organs. However, eight fundamental cellular characteristics are common, and has been illustrated in Figure 4.

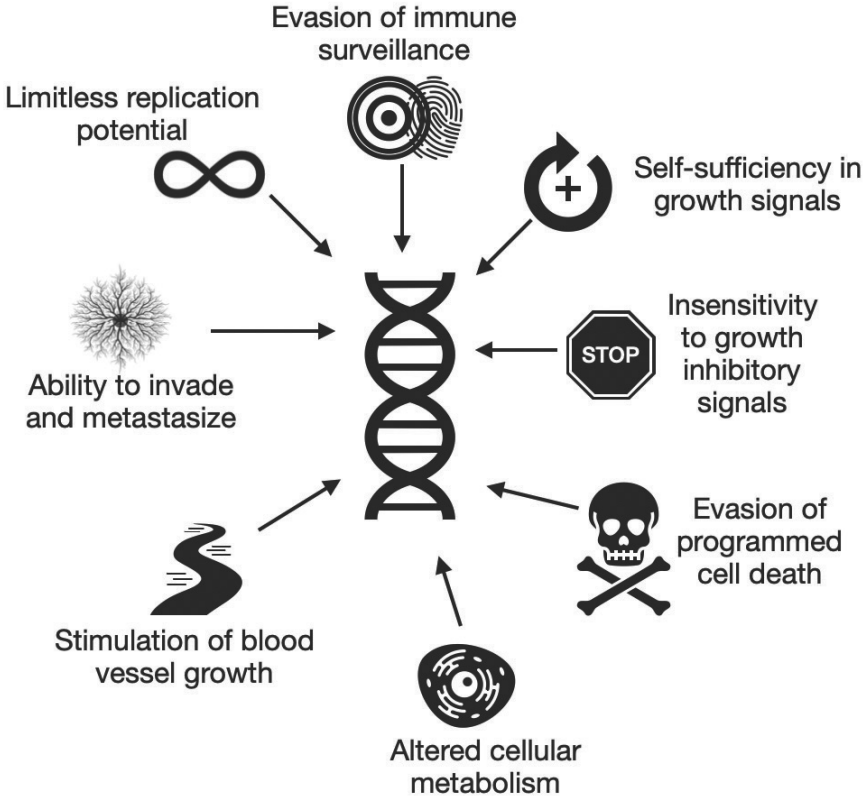


Figure 4. Schematic figure of the eight common characteristics in the transformation of a normal cell into an uncontrolled cancer cell. Although common for most cancer forms, the order of the changes may vary. Self-sufficiency in growth signals and insensitivity to growth inhibitory signals are early changes in many cancers, whereas the ability to invade and metastasize generally are late alterations. Adopted from Robbins Basic Pathophysiology[93].

Cancer prevention

Despite a common focus on environmental and hereditary risk factors in the public cancer discourse, only a third of the variation in cancer risk is attributable to these factors[105]. The majority of the variation in cancer risk is due to random mutations in stem cells during DNA-replication, bad luck to put it simply[106]. The lifetime risk of cancer in specific tissues has been shown to strongly correlate with the total number of stem cell divisions in the specific tissue´s normal maintenance[106]. Nevertheless, the WHO has proposed that avoidance of environmental risk factors and optimal cancer screening strategies to find and eliminate precancerous lesions has the potential to prevent 30-50% of all cancers[107].

1.7 POTENTIAL MECHANISMS

Obesity and cancer

The mechanisms behind the associations between obesity and cancer are not fully elucidated. Several plausible pathophysiologic mechanisms have been postulated, and most of them have been linked to obesity in adulthood. High BMI is probably associated with different malignancies through diverse and multifactorial mechanisms. The plausible mechanisms addressed here are listed below:

- Genetic instability
- Systemic and local inflammation
- Hyperinsulinemia
- Insulin-like growth factor 1(IGF-1) stimulation
- Adipokine aberrations
- Sex steroid effects
- Body size and the number of proliferating cells
- Local effects

Genetic instability

Carcinogenesis is a result of increased genomic instability[93]. Obesity can affect the genomic stability of cells, through obesogenic molecular changes[108]. These changes include lipid dysregulation, which causes oxidative stress, and subsequent DNA-damage. Impairment of DNA-repair and genotoxic effects have been associated with by-products of lipid degradation and obesity-related increase of bile acid metabolites[108]. In addition, obesity-induced epigenetic alterations/dysregulation has been proposed as a cause for obesity-induced genomic instability[108].

Interestingly, mutations in the RAS oncogenes were found in obese but not lean mouse models with hepatocellular cancer, indicating specific obesity-driven pathways of hepatocellular cancer pathways[109]. Furthermore, the altered lipid metabolism associated with obesity includes lipid peroxidation. By-products of obesity-induced lipid peroxidation, such as malondialdehyde (MDA), can increase DNA damage and impair DNA repair systems[108]. In vitro elevation of MDA levels in mammalian cells led to a 15-fold increase in the DNA mutation rate[110].

Systemic and local inflammation

Inflammation as an acute phenomenon is a physiologic response to infection, irritation or injury to the body. Chronic inflammation is a state of constant, low grade stress in the body associated with long term morbidity in affected tissue, such as in arthritis or atherosclerosis[111]. Obesity can induce a state of chronic systemic inflammation in adults as well as in children[111,112] as the result of excess and metabolically active adipose tissue.

The subcutaneous and visceral adipose tissue compartments are often considered separately. Of the two, visceral adipose tissue (VAT) is the more metabolically active and produces pro-inflammatory cytokines (adipokines) and certain acute phase reactants such as interleukin-18 (IL-18), as well as being involved in stimulation of the release of other acute phase reactants such as interleukin-6 (IL-6) and tumor necrosis factor (TNF)[113]. Macrophages could play an important role in obesity-related chronic inflammation, and macrophage infiltration is higher in VAT than in subcutaneous tissue[114].

Several diseases that induce chronic inflammation, are also known to increase the risk of future malignancy, for example inflammatory bowel disease, hepatitis, and *Helicobacter pylori* infection. Inflammation can have anti-carcinogenic or tumor promoting effects, depending on the composition of the inflammatory microenvironment[115]. Inflammation can promote tumor development through angiogenesis, growth stimulation, and by inducing genomic instability[116]. It has been suggested that up to 20% of human cancers can be related to chronic inflammation[117].

Hyperinsulinemia

Insulin is a hormone that is released from the beta cells in the pancreas as a response to increased levels of circulating glucose. Insulin enables glucose to enter cells by activating glucose transporters in the cell membranes[118]. Insulin also affects the intracellular environment by stimulating energy deposit, growth and proliferation[118]. Overweight and obesity is often

associated with elevated levels of free fatty acids, increased plasma triglyceride levels, TNF, and a low degree of physical activity[118,119]. These factors contribute to a lower affinity of insulin to insulin-receptors in target cells leading to a decreased intracellular insulin sensitivity, known as impaired glucose tolerance and insulin resistance[120]. The reduced uptake of glucose results in hyperglycemia in the blood. As a response to the hyperglycemia, the beta cells release more insulin and plasma insulin-levels are elevated[120]. There is some evidence that chronically elevated insulin-levels are associated with certain cancers[50]. The mechanisms include enhanced anti-apoptotic and growth-stimulative insulin effects of hyperinsulinemia[121]. Interestingly, Nobel Prize winner Otto Warburg demonstrated an altered glucose metabolism in cancer cells, that cancer cells exhibit higher demands of glucose supply[122]. This "Warburg effect" revealed how increased hyperglycemic exposure could favor the metabolism in carcinogenic cells[123]. In addition, hypoxia is one of the major limiting factors of neoplastic growth[93], and hyperglycemia has been shown to improve survival of cancer cells in hypoxic conditions[124]. Correspondingly, type II diabetes has been shown to be associated with a higher risk of cancer, independently of BMI-status[125], and among individuals with Type II diabetes, those treated with metformin have a significantly decreased risk of cancer diagnosis and death from cancer[126].

Insulin-like growth factor 1

Insulin-like growth factor-1 (IGF-1) is a peptide hormone mainly produced in the liver, but also in other tissues, primarily as a response to Growth Hormone (GH) stimulation. IGF-1 has been linked to carcinogenesis in a variety of cells through its anabolic effects. These proliferation-stimulating and apoptosis-inhibiting effects can help cancer cells evade programmed cell death, and to induce stronger proliferative effects in cancer cells where responses to growth-stimuli have been up-regulated[127]. IGF-1 receptors are often overexpressed in cancer cells[128], and in vitro studies have shown tumor progression with IGF-1 stimulation. Animal models have corroborated the role of IGF-1 in cancer development and progression[129]. Increased serum levels of IGF-1 have also been associated with increased risk of cancer mortality in men[130]. Overweight and states of overnutrition increase the sensitivity of the liver and other tissues to GH-stimulation[127]. However, the associations are complicated by the observational finding that both obese and undernourished individuals have lower levels of total IGF-1 in the serum. There is no clear, linear relationship between the degree of adiposity and circulating levels of IGF-1[131-133]. Instead, increased bioactivity of IGF-1 and upregulated insulin and IGF-1 receptors mediated by hyperinsulinemia

have been proposed to explain some of the mechanisms linking IGF-1 to cancer[129].

Adipokines

Fat cells, adipocytes, are active endocrine units that secrete adipocyte-derived cytokines called adipokines[114]. Adipokines include leptin and adiponectin, among others. Leptin is an adipokine that has a central role in the balance between hunger and satiety in the body[134]. Adipocytes release leptin in response to triglyceride storage, as a signal to the brain to regulate food intake. Leptin-deficient mice and humans display hyperphagia, decreased energy expenditure and early onset excessive obesity[135]. Individuals with obesity display increased levels of circulating leptin as a consequence of adipose tissue expansion. A proposed link between leptin and cancer is based on the metabolic effects of leptin, and that leptin acts as a growth factor on certain organs, including vascular endothelium and smooth muscle, important for tumor growth[136-138]. Leptin also exerts pro-inflammatory effects through the ability to stimulate TNF and IL-6 release from monocytes[114], and therefore it is a possible mediator of inflammatory carcinogenesis.

Another adipokine is adiponectin[114]. Adiponectin levels in both plasma and adipocytes are decreased in obese individuals[114]. Adiponectin has anti-inflammatory and beneficial metabolic effects, and has been shown to increase insulin sensitivity and modulate macrophage function in an inflammation-controlling manner in mice[114]. In addition, adiponectin-deficient mice have been shown to display a reduced capacity to clear apoptotic cells in the peritoneal cavity, leading to increased risk of systemic inflammation. Plasma adiponectin levels in humans are negatively correlated with C-reactive protein levels[139].

Sex steroids

Sex steroids, including estrogens, androgens and progesterone, are vital for normal human development and physiology. Different types of studies have demonstrated increased risk of breast cancer in women related to increased estrogen stimulation, both from exogenous estrogen (such as contraceptives and estrogen replacement therapy) and serum estradiol concentrations[140]. The risk of cancer development in the endometrium has also been shown to increase with the use of estrogen replacement therapy, alone, and with cyclic progesterone[141]. Effects on cellular differentiation, proliferation and induction of apoptosis are plausible mechanisms[50]. Adipose tissue produces aromatase, which metabolizes androgenic precursors into estrogens[50].

Adipose tissue also inhibits the production of sex hormone binding globulin (SHBG), leading to increased free, bioactive estrogens in plasma[142]. Both total and free levels of estradiol are increased in obese men[50]. Together, these effects of obesity on sex hormones could contribute to a higher risk of some cancers, as have been shown for breast and endometrium cancer in women, but estrogen has also been suggested to be involved in the risk of lung cancer[143]. Male androgen stimulation, such as testosterone, has been implicated in the risk of prostate cancer[91], but obesity is inversely associated with testosterone levels in men[144]. Therefore, obesity in men is associated with decreased concentrations of both total and free testosterone in the blood[144]. A sex steroid-mediated link between obesity and cancer in the male cohort of the present projects could be mediated through increased estrogen exposure, lower testosterone levels, or secondary effects of a deranged sex steroid balance.

Body size and the number of proliferating cells

Several studies have found an association between height and adult cancer[145-149]. One hypothesis to explain this association is that factors contributing to tall stature during development (nutritional, genetic, and hormonal) could be associated with increased risk of adult cancer. Another proposed hypothesis is that increased height is associated with an increased number of proliferating cells. Tomasetti et al hypothesize that variation in cancer risk among tissues is explained by the number of stem cell divisions in the tissue[106]. Accordingly, an increase of proliferating cells could lead to an increased risk of acquired mutations and therefore potentially affect the risk of cancer development.

Local effects for specific cancers

Lastly, local obesity-induced carcinogenic stimuli could increase organ-specific risk of cancer[121]. These local obesity-induced stimuli include dysbiosis in the colorectum, reflux in the esophagus, non-alcoholic steatohepatitis in the liver, gallstones and cholecystitis in the gallbladder, and bone marrow adipocyte expansion in the bone marrow[121,150].

Pubertal timing and prostate cancer

Sex steroids have anabolic effects, and the link to cancer development has been explored and debated, but is well-established for certain cancers. Because puberty initiates the exposure to sex steroids, pubertal timing has been of interest for specific cancers. In women, pubertal timing is associated with risk of breast, ovarian, and endometrial cancer[151-153].

For prostate cancer development and progression, the importance of androgen stimulation is no longer debatable[91]. The efficiency of anti-androgen treatment for prostate cancer has fueled hypotheses regarding androgen-stimulation of various types, i.e., testosterone replacement therapy, total serum testosterone levels, and pubertal timing, as risk factors for prostate cancer. However, because pubertal timing in men is difficult to determine retrospectively, the risk related to pubertal timing is still unknown.

Pubertal proliferation of the prostate gland

Puberty represents a period of rapid growth and development of the prostate gland, when oncogenic mechanisms leading to the first steps toward cancer may occur[84]. During puberty the prostate gland increases its volume from about 3-4 grams to nearly 20 grams (Figure 5).

Interestingly, one study found low grade neoplasia in the prostates of 9% of examined males in their 20s, suggesting that the initiating events of prostate cancer could occur decades before a diagnosis[154]. The genetic doubling time of some prostate cancers, together with the average size and number of cancer cells in a prostate cancer lesion at diagnosis, and the mean age at diagnosis suggest that some prostate cancers probably arise during puberty[155].

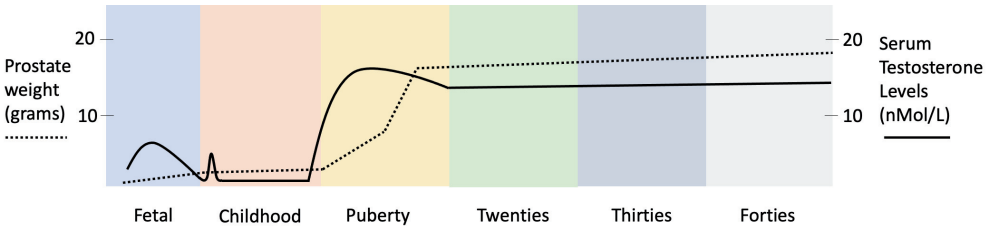


Figure 5. Schematic overview of the development of the prostate and the testosterone levels in men during the first decades of life[84,156].

Sex steroid exposure

Despite intensive investigations, a conclusive association between testosterone levels and prostate cancer has not been found[157]. A Mendelian Randomization study found that genetic determinants of bioactive, but not total, testosterone was associated with increased risk of prostate cancer[158].

Another study found positive associations for ratios of testosterone to estradiol levels among Caucasian men (but not African-American men)[159]. One hypothesis, called the saturation model, states that the cumulative time with exposure to androgen stimulation above a certain threshold is related to prostate cancer risk[160].

1.8 CHILDHOOD AND PUBERTY

The process of turning a single fertilized cell into a reproductive adult human being is complicated. This remarkable process includes a range of distinct physiologic stages: the embryological stage, the fetal stage, infancy, childhood, and finally puberty. Each stage involves unique physiological circumstances and physical transitions. For the projects in the present thesis, we used birthweight as a marker of fetal growth, and the accumulated height and BMI at eight years of age to represent both infancy and childhood. Pubertal timing is represented by age at peak height velocity, and the specific BMI development during puberty is represented by pubertal BMI change.

Infancy and childhood

Childhood can be defined in various ways. Some include the period between birth and puberty, although others categorize infancy as a distinct period. The transition from childhood to puberty comes with distinct changes of the body. These apparent physical changes mark the end of childhood and the start of puberty. However, as the transition from infancy to childhood lacks distinct physical changes, this shift is somewhat arbitrarily set, most often at either one or two years of age. From a perspective of growth, a delimiter at two years of age is a more appropriate choice[161,162] (Figure 7), although Karlberg modelled growth during infancy between 0-3 years in his ICP-model[163] (Chapter 3.2). To exemplify the intense growth rate in infancy, the mean growth rate during the first year of life is 25 cm/year[161], and human children acquire about half of their final height at the age of two years[164].

As the infant enters childhood hormonal regulators become more important for growth[161] (Figure 6). The hormonal regulators of growth during childhood are primarily GH, IGF-1, and the thyroid hormones[161]. The growth rate in childhood is about 6-8 cm per year, but the growth rate slowly decreases after the intense and rapidly decelerating growth of the infancy period[164] (Figure 6).

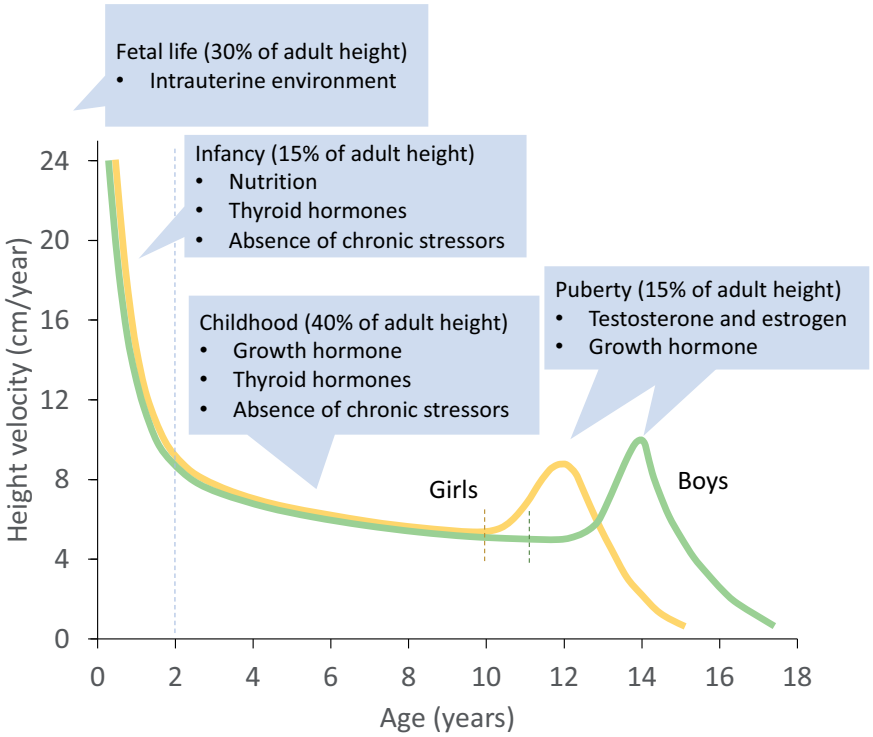


Figure 6. Overview of the height velocity during the developmental growth phases and the important growth promoters during each phase. Genetic heritage is important in all phases. Green line represents average male growth velocity, and yellow line average female growth velocity. Dotted lines mark transitions between infancy and childhood, and childhood and puberty (earlier in girls). The pubertal growth spurt (and the peak height velocity) comes earlier in puberty in girls than in boys.

BMI also changes with the human developmental periods (Figure 2). After the accelerated growth during infancy, BMI slowly declines in childhood, reaching a lifetime nadir at around six years of age when the mean BMI in boys is below 16 kg/m^2 (Figure 2)[165]. The low BMI of the child at this age is not solely a result of a low fat-percentage, it is also the result of altered body proportions. Due to an unproportionate growth of extremities compared to the trunk and head, a larger proportion of the total height at this age consists of the legs, which are less dense than the trunk and head (Figure 7).

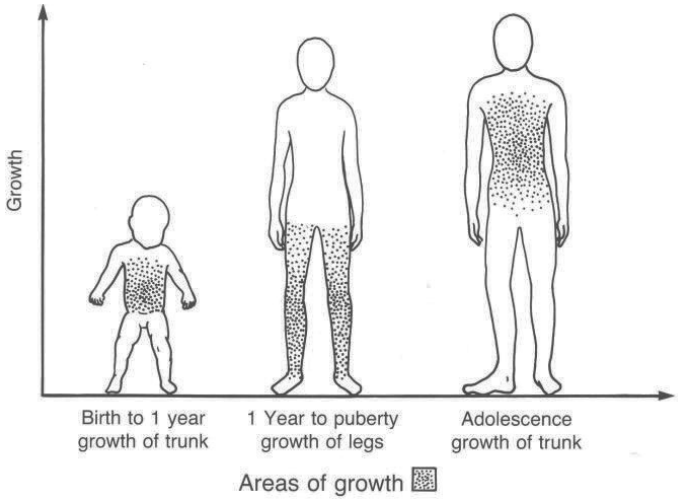


Figure 7. Schematic figure of the main growth of body segments during the physiologic ages. The proportion of the total height from different body segments is different at different ages. The pubertal growth spurt starts with enlargement of feet and hands, followed by arms and legs, and lastly the trunk/spine follows. Adopted with permission from www.coachr.org

Adiposity rebound

The BMI nadir between three and seven years of age marks an inflection point where the BMI decrease becomes a BMI increase (Figure 2). This change is called *adiposity rebound* (AR) after the initial article by Rolland-Cachera et al where age at AR was suggested to be a predictor of later overweight[165]. Early AR has been shown to be associated with adult overweight and obesity[166], and increased fat mass index (fat mass[kg]/height[m]^2)[167] independently of BMI level at AR[168]. AR has also been shown to be associated with markers of the metabolic syndrome in adults[169]. Interestingly, individuals with early AR have average or low BMI before the AR[170]. However, Cole showed that AR reflects either a normal growth pattern of children with higher BMI or a general BMI centile crossing during the childhood period, thus challenging the notion of AR as a critical period and explaining why early AR is predictive of future overweight[171]. Cole suggested BMI centile crossing as a more direct measure of the underlying drive to subsequent fatness[171]. He later acknowledged AR as a significant developmental marker, analogous to pubertal timing or bone age[172]. Consistent with this perspective, early AR has been shown to be associated with early pubertal timing in men[168]. In the present projects,

height and weight measurements for the preschool age have not been detailed enough to assess age at AR.

Adrenarche

Parallel to the pubertal process of the gonads, another hormonal organ pair, the adrenals, are also activated and initiate changes such as acne and pubic hair development. Pubarche, initiation of pubic hair development, is caused by increased androgen production from the adrenal glands[173]. Adrenarche, raise in adrenal androgen hormone production starts at around six years of age, a few years before puberty, but signs of adrenarche are most often not apparent until signs of puberty are also present[173]. Table 3 briefly lists the characteristics of adrenarche and gonadarche (puberty).

Table 3. Overview of adrenarche and gonadarche in boys.

	Adrenarche	**Gonadarche**
Hormonal axis	Hypothalamus, adrenal	Hypothalamus, pituitary, gonad
Initiation	Unknown	Reactivation of pulsatile secretion of GnRH from hypothalamus
Hormones	Androgen hormones (androstenedione, DHEA, DHEA-S)	GnRH LH FSH Sex steroids (testosterone, estrogen, and variants)
Physical changes	Skin oil, acne, pubic hair growth	Testicular and genital development, facial hair growth, voice change, skeletal maturation
Timing	Start 6-8 years of age, peak at early 20s	start at 9–14 years of age, duration 4-5 years

Adrenarche and gonadarche are the two hormonally controlled events responsible for the physical changes during adolescence.

Puberty

Puberty is characterized by a series of physical changes, through which the individual transitions from child to adult with reproductive ability. The

pubertal transformation is controlled by the hypothalamus-pituitary-gonadal (HPG) hormonal axis[174] (male gonads are the testes and female gonads are the ovaries). The HPG hormonal axis is developed and temporarily active during the fetal and neonatal stages in humans, but is inactive during the childhood[174]. It is not entirely clear what triggers the reactivation of the system in time for puberty, but dietary and nutritional factors seem to be at least partly involved[175,176]. During the pubertal reactivation of the HPG-axis, pulsatile secretion of gonadotropin releasing hormone (GnRH) from the hypothalamus induces the pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH), that in turn stimulates the gonads to produce sex steroids (primarily testosterone in men)[177]. The process of the "awakening" of the gonads, the initiation of puberty, is called gonadarche[177]. The series of pubertal events usually follow a specific order (Figure 8), starting with testicular enlargement in boys[178].

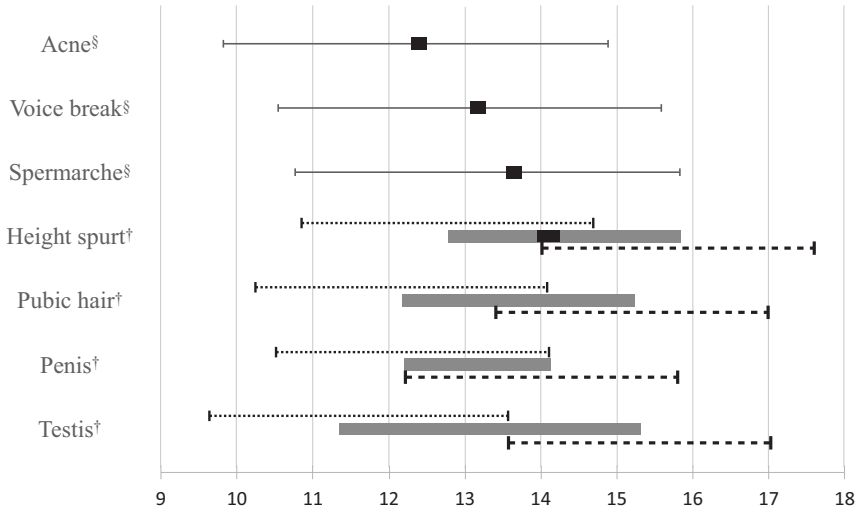


Figure 8. Simplified figure of the pubertal series of events in boys. Black rectangles represent the mean age at the debut of immediate events (for height spurt the black rectangle represents the age at peak height velocity). Solid bars represent the period during which 95% of individuals have attained the event. Grey areas represent the mean duration of an event. The small dotted bars above grey areas are the ages when the changes are initiated in most individuals. The large dotted line below the grey areas are the ages when most individuals reach the mature state of the event. †Based on WA Marshall and JM Tanner, Variations in the pattern of pubertal timing in boys[179]. §Based on Brix et al, Timing of puberty in boys and girls: A population-based study[180].

Pubertal stages – the Tanner stages

Assessment of boys' pubertal status in the clinical setting is performed through Tanner staging, after Dr James Tanner, who together with Dr W.A. Marshall created the Tanner stages of puberty[179]. The Tanner stages categorize pubertal development into five stages, where 1 indicates prepubertal stage and 5 the fully maturated stage. The first sign of pubertal development in boys is attainment of a testicular volume ≥3-4 ml[178,181]. Tanner staging in boys includes measurement of testicular volume with an orchidometer (Figure 9), along with evaluation of skin of the scrotum, growth of the penis and development pubic hair[179].

Figure 9. The orchidometer. The orchidometer is an instrument used to measure testicular volume and thereby pubertal development in boys. The volume (in milliliters) is written on the side of each testicular model. The volume of the testis is approximated by comparing the testis between the fingers of one hand and the orchidometer model of the corresponding size in the other.

Clinical assessment of pubertal status through individual evaluation of pubic hair growth, penis or breast development, and testicular volume in a study setting is time consuming, only possible in prospective studies, and requires pediatric expertise. Clinical assessment can also breach the integrity of the child or adolescent. For studies of adult cancer, the long latency period between puberty and the middle- to old age when cancer incidence increases, makes studies with prospective assessments of pubertal status practically impossible to carry out. Therefore, studies of pubertal timing and adult cancer are mainly restricted to retrospective assessment of pubertal timing. In girls, menarche serves as a distinct pubertal marker, and the timing of menarche can be recalled with some accuracy. In boys, the absence of distinct pubertal changes makes recalled estimates uncertain, so studies on the association between male pubertal timing and the risk of cancer are scarce[182].

Peak height velocity

During puberty, growth velocity rapidly increases, driven by the activation of the HPG hormonal axis[174]. This pubertal height spurt is characterized by a swift acceleration followed by a steep deceleration and eventual cessation of growth. As a result, the average boy increases his height by 25-30 cm during puberty[161]. The highest growth velocity during this period is called the peak height velocity (PHV)[183]. For boys, the height velocity increases from 6-8 cm/year during the prepubertal years, to about 11 cm/year at peak height velocity[183] (Figure 6). In boys, the PHV often occurs at around 14 years, about two years after the initiation of puberty[161]. Recently, we demonstrated a secular trend of pubertal timing in boys of 1.5 months earlier age at PHV per decade increase in birth year was demonstrated, a trend only partially explained by increasing BMI[184].

1.9 CHILDHOOD OVERWEIGHT AND ADULT CANCER

Challenges in studies of early life exposure

The link between excess body weight in childhood and adult cancer is less studied than the link between adult excess body weight and cancer. However, some studies do exist and have shown that for many of the obesity-related cancer types, not only adult overweight but also overweight in childhood is associated with increased risk of cancer in adulthood[185,186]. These studies are challenging to perform because they require several BMI measurements during development and a very long follow-up. However, because overweight and obesity show a high degree of tracking from childhood to adulthood[166,187,188], adjustment for adult BMI is needed to determine the independent risk of childhood overweight for adult cancer. Unfortunately, studies with BMI measured in both childhood and adulthood, that have a long enough follow-up to assess adult cancer risk, are scarce.

The turbulent puberty

Onset and duration of puberty varies between individuals, and pubertal development greatly alter body composition[189]. Males increase their lean and skeletal mass as well as total BMI during puberty, and also body proportions and fat distribution change within the pubertal years[189]. Despite this well-known physiologic phenomenon, existing studies rarely take into account that childhood and puberty are distinct phases[185]. Rather, BMI is often measured at an age where some individuals will be pre-pubertal and

others in the middle of the pubertal changes of body composition[186,190]. Others have reported adolescent associations at an age where some individuals are in the middle of puberty and others post-pubertal[52]. The use of BMI during pubertal ages, without adjustment for pubertal status, introduces a risk of bias of the analyses related to the effect of puberty on BMI.

1.10 KNOWLEDGE GAPS

At present, early life exposures and their potential influence on later cancer risk, alone or in combination with other environmental and genetic factors, are largely unknown[191]. The knowledge gaps are mainly due to methodological challenges related to long latency periods between exposure and outcome. These challenges limit access to, and validity and reliability of, the early life exposures in studies. The studies that have been performed are generally limited by short periods of follow-up, insufficient power[192], the use of varied definitions of childhood[190], or the use of self-reported information on early life exposures, information that is prone to recall bias[193].

Furthermore, most studies that investigate early life BMI and adult cancer rely on only one measurement of BMI[2,186,194], or have been unable to separate childhood from young adult exposure[185]. Because of the high degree of tracking of high BMI between ages, association with a single BMI measurement cannot distinguish from a tracked association to high BMI at another age. High BMI in adulthood is an established risk factor for many cancers. The independent risk related to BMI in specific early life ages requires BMI measurements from at least two different ages and a long follow-up.

There is a link between prostate cancer and androgen hormone activity, but due to lack of distinguished objective markers, the pubertal timing in boys is difficult to assess. This is especially true in retrospective studies and for outcomes with long latency periods, such as prostate cancer. The link has been probed through recalled proxies of pubertal timing[195-197]. Therefore, the independent roles of BMI at different stages of development for the risk of adult cancer, and the influence of pubertal timing on prostate cancer risk have yet to be determined.

Birthweight has been associated with risk of adult cancer[14,185] and cancer mortality[17], but most studies do not adjust for childhood BMI. Furthermore,

studies that focus on birthweight trends are generally based on data from the 1970s and onwards, and have reported of increasing birthweights. The increasing birthweight trends have been associated with the obesity epidemic and decreased smoking prevalence. Long-term trends of birthweight before the 1970s are not fully elucidated.

2 AIM

This thesis has three overall aims:

1. To determine the inter-relative roles of excess weight in childhood and puberty for the risk of colon and rectal cancer, hematological cancer, and obesity-related cancer in adulthood.

2. To explore male pubertal timing as a risk factor for future prostate cancer.

3. To describe the long-term changes of birthweights in boys, including the decades before the initiation of the Swedish Medical Birth Register.

3 SCIENTIFIC ORIENTATION

Before we dive into the methodology, a brief orientation of scientific research will ease the digestion.

3.1 STUDY DESIGN

Scientific studies are either *observational* or *experimental* (Figure 10). In the observational study, the gathered information is based on observation of the state of things or associations without interference from the researcher. In the experimental study, a change is introduced by the researcher and in a controlled form for some or all of the objects of interest. The purpose is to determine what effect the introduced change, or experiment, has on the studied objects.

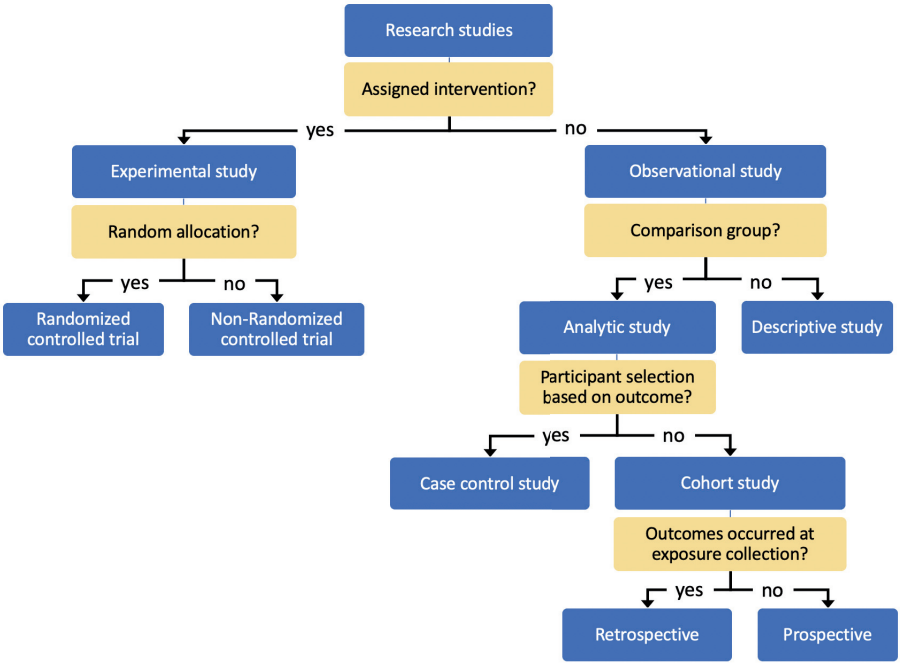


Figure 10. Schematic overview of study designs.

The advantages of experimental studies include a controlled introduction of an exposure and better control over mediators and confounders, resulting in a better possibility to determine causal relationships. However, experimental studies on humans are not feasible to carry out when the exposure is dangerous, when the exposure is not possible to allocate (e.g., pubertal timing), or when there are long latency periods between exposure and outcome. Although only experimental studies are designed to determine causal relationship, almost all present knowledge of determinants of human health and disease have originated from observational studies.

Observational studies

There are two kinds of observational studies: descriptive and analytical. Descriptive studies describe the nature of something, whereas analytical studies use the observed information to calculate associations, correlations and risks through statistical analyses. Observational studies that follow a defined group of people are called cohort studies. The strengths of observational cohort studies include the possibility to study the following:

- associations with long latency periods,
- large numbers of people,
- several outcomes, and
- hazardous exposures not ethical to inflict on humans.

During these circumstances, experimental studies might not be feasible, and observational cohort studies might be the best available study design. The negative aspects of observational cohort studies include the inability to determine causal relationships, i.e., observational studies cannot for certain determine that a specific outcome is caused by the exposure studied. The causal predicament of observational cohort studies originates from the uncertainty whether there might be other factors affecting the outcome than the one studied. A factor that influences both the exposure (the independent variable) and the outcome (the dependent variable) in a study is called a *confounder*.

If unaccounted for, a confounder can give a false impression of a direct relationship between an exposure and an outcome (Figure 11). In observational cohort studies, efforts are made to adjust for all possible confounders, but they are limited by the eternal possibility of unknown confounders, i.e., residual confounding.

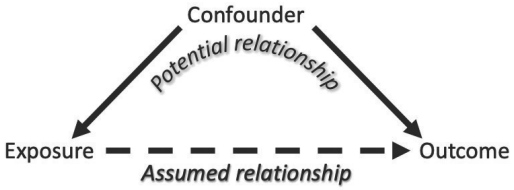


Figure 11. The assumed (direct) relationship between an exposure and an outcome is how we often visualize a theoretical association. A confounder affects both exposure and outcome and has the potential to be the driver of the assumed relationship.

An example of residual confounding was discovered in a study published 1999 in the eminent journal *Nature*, concluding that children who slept in lighted rooms at night as infants were much more likely to be diagnosed with myopia (short-sightedness) later in childhood[198]. The authors speculated that the night light might negatively affect the development of the eyes. The next year, another research group tried to replicate the results, but instead showed that the first group had missed an important confounder, namely the hereditary risk of myopia[199]. Parents with myopia were more prone to leave the light on in their infant children´s sleeping room and more prone to have children with myopia.

Furthermore, observational cohort studies can either be retrospective or prospective. In retrospective studies, information is gathered after an outcome, so information of the exposure(s) and potential confounders and mediators are collected retrospectively. This design enables long observational periods between exposure and outcome, but often results in missing data of exposure and/or potential confounders. In prospective observational cohort studies, collection of information of exposures and other informations is initiated before an outcome. Hence, participants are followed prospectively, in real time. This design enables good opportunity to gather data on exposures and potential confounders, but is less suited for studies with long observation periods.

3.2 RESEARCH HIERARCHY

Because scientific studies often produce contradicting conclusions, evaluating evidence is an important part of scientific research. This is especially important when scientific evidence is to be translated into clinical practice or for the general community. In the evaluation of scientific evidence, the research hierarchy provides a framework for the level of uncertainty associated with different types of evidence (Figure 12). It states that, if the methods and study design are appropriate, the systematic review provides more conclusive evidence than the randomized controlled trial (RCT), results from a RCT is more reliable than results from an observational study, evidence from observational studies outweighs the expert opinion, and if no other evidence is available, the expert opinion is more trustworthy than anecdotal experience (Figure 12). However, research conclusions are primarily determined by adequate study design and validity, no matter where in the hierarchy. This is why a well-designed observational study can outweigh a flawed RCT.

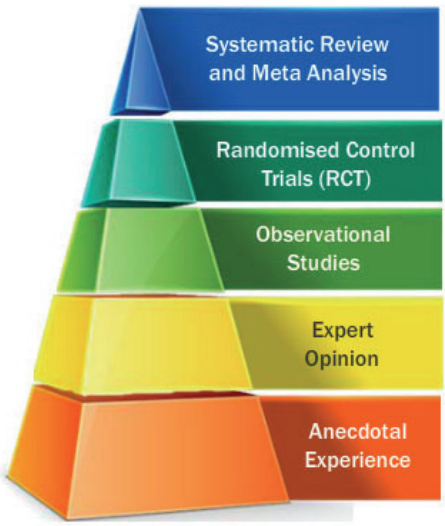


Figure 12. Research hierarchy.

3.3 EPIDEMIOLOGY

Epidemiology is the research area for studies of distribution and determinants of health and disease in a population. Epidemiologic studies can be of both observational or experimental design[200]. A special area of epidemiology focuses on accumulation of exposures throughout life, with certain attention to early life exposures. This epidemiologic area is known as life course epidemiology. Professor David Barker is the founder of life course epidemiology, and the research field of Developmental Origins of Health and Disease (DOHaD). He discovered that children born with low birthweight with a subsequent catch-up growth, had a marked increased risk of type II diabetes, hypertension and coronary heart disease as adults[201,202]. Barker hypothesized that certain growth patterns, such as intrauterine growth suppression during the critical fetal period followed by catch up growth during childhood, leads to a life-long altering of metabolic programming, which is associated with increased risk of certain diseases. The fundamental premise of life course epidemiology is that individuals do not suddenly catch cardiovascular disease or cancer in adulthood. Rather, they essentially grow into the diseases that will be manifested in late adulthood.

4 SUBJECTS AND METHODS

4.1 COHORTS

The BEST Gothenburg cohort includes height and weight measurements from child health care, school health care, conscription and passport registers for men and women born between 1920 and 2012 who finished school in Gothenburg city. Importantly, as Sweden has mandatory school attendance and the 99% compliance with school health care[203], the cohort can be regarded as population-based. The work process of the BEST Gothenburg is illustrated in Figure 13.

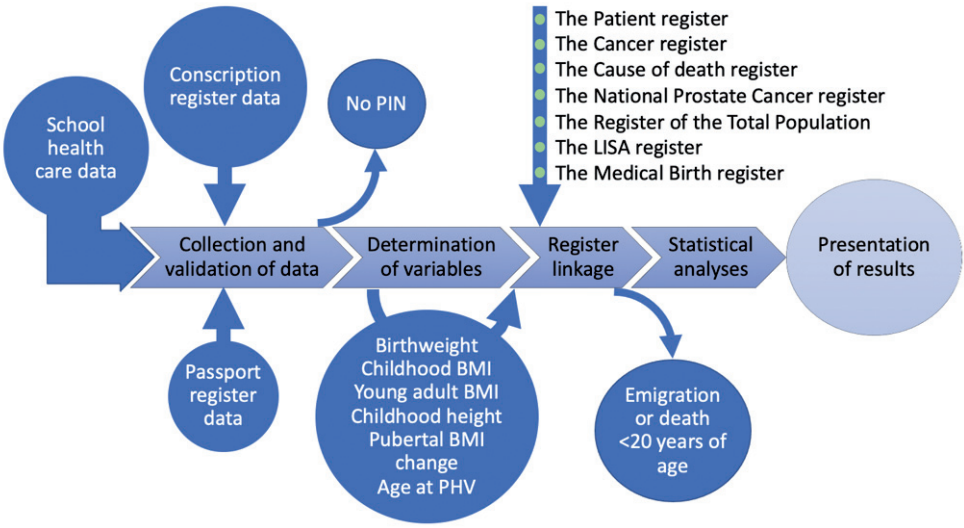


Figure 13. Overview of the work process of BMI Epidemiology Study Gothenburg.

The initial process of the data collection has led to a first BEST-cohort that consists of all men born between 1945 and 1961 (N=50,020). The exclusion criteria included not having a complete PIN, or death or emigration before 20 years of age. After these exclusions, 37,762 individuals had enough height and weight measurements recorded in both childhood and young adulthood to estimate BMI at eight and 20 years of age.

Projects I–III are based on this population. Small differences in the number of included individuals in the three projects are due to variations in the disease-specific exclusion criteria, i.e., exclusion of those with site-specific

or any cancer before start of follow-up. In project IV, we also excluded individuals without sufficient height measurements to estimate PHV. In project V, boys with a PIN and information of birthweight in the BEST cohort were included. To avoid trends related to immigration changes in the population, only boys born in Sweden with both parents born in Sweden were included (1946–2006). To ensure maximum power in the important earliest period of the study, all birth years between 1946 and 1961 were included, and thereafter samples were included for the available birthweights in the BEST cohort of every fifth year from 1966 to 2006. The 2011 birth cohort had not yet started school when data for the study were collected, so birthweights for 2011 were collected from the Sahlgrenska University Hospital birth records, which covers the same geographical area as the school health care. Information of country of birth of the parents was not available in the hospital records. To facilitate comparison, birth cohorts were harmonized in decade cohorts (representing each decade).

4.2 SCHOOL HEALTH CARE DATA

inspired by initiatives in Germany, Swedish school health care was initiated in higher educational institutions (läroverk) already during the middle of the 19th century[204]. In 1890, Gothenburg was first city to introduce school health care in the obligatory public schools. In the early 20th century, in addition to general health examinations, public vaccination programs became one of the core functions of school health care[204].

In 1943, public school health care started to be funded by the government, just as the school health care in higher educational institutions had been for almost 50 years. The requirement for government funding was that the school health care was available for all pupils, and that it included both school nurses and physicians. At the same time, common national school health records that followed the child during his or her school period were introduced.

School health care records were archived in the school where the pupil finished school[203,204]. In Gothenburg, however, the school health care records were centrally archived in the Archives of the City of Gothenburg and Region Västra Götaland (Regionarkivet) after a decision by a former head of the archives, Jan Frisk. Frisk saw the potential for the school health care records to be excellent research material (as told by personal communication with Bo Thalén, a former director of the archives).

After the reorganization of the school health care system in Sweden in the middle of the 1940s, compliance with School Health Care (SHC) improved every year, and in 1952 school nurses were present in all schools throughout the country and 98.5% of all pupils nationwide were covered[205]. Therefore, the Swedish school health care system was population-based by the 1950s, and height and weight measurements were performed in a standardized manner by health care professionals.

4.3 DETERMINATION OF VARIABLES

Birthweight

Birthweights for included individuals were collected from the following sources, listed in order of priority:

1. the Medical Birth Register (years 1976-2006)
2. School health care records (1946-1971)
3. the Sahlgrenska University Hospital (2011)

Birthweights were registered in grams. The correlation between birthweights from the MBR and the school health care records was high for individuals with birthweights in both sources (Pearson´s $r = 0.98$, $p < 0.001$).

Childhood and young adult BMI

BMI at age eight (childhood) and at age 20 (young adulthood) were estimated using all paired height and weight measurements in the period between 6.5 and 9.5 years of age and 17.5 to 22 years of age, respectively. All measurements within these age intervals were then used to construct a linear regression model and the data for individual participants were adjusted along the childhood or young adulthood regression line to obtain BMI at eight respectively 20 years of age, i.e., the age-dependent change was assumed to follow the slope of the fitted models and BMI at age 8/20 years were estimated using the slope of the fitted model. For individuals with more than one BMI measurement between 6.5 and 9.5 years of age, the mean of the BMI estimations at eight years was used; a similar approach was used for repeated BMI measurements at ages 17.5–22.0 years.

Pubertal BMI change

The BMI development through puberty was defined as the difference between BMI at 20 years of age and BMI at eight years of age. Puberty has a great impact on BMI development, and pubertal timing and course varies between individuals[189]. We therefore chose to define the pubertal period with a rather wide time window in order to avoid the confounding effect of puberty on BMI. Hence, the time between eight and 20 years included not only the complete pubertal period but also time periods of varying length before and after puberty

Between the age of eight and twenty, the normal development includes an increase in BMI. Therefore most, but not all, individuals have a pubertal BMI change that is positive.

We observed and described that childhood BMI correlates only marginally with pubertal BMI change (Pearson's $r = 0.06$)[58] indicating that these two variables contribute separate information as risk markers for future illness. BMI at young adult age thus is the sum of BMI at eight years and the pubertal BMI change.

Age at Peak Height Velocity – a marker of pubertal timing

The gold standard to determine the pubertal timing of an individual is prospective, regular evaluations of the Tanner stages. However, using Tanner staging requires a great deal of resource, challenges the integrity of the study subject, and does not work well for large epidemiologic studies. In addition, retrospective studies that assess pubertal timing using Tanner staging is not possible unless such data were originally included in the resource material.

Using height measurements, the age at PHV can be estimated retrospectively and used as an objective assessment of pubertal timing. To estimate the age at PHV, it is necessary to convert height measurements into a continuous growth curve of height development. Karlberg found that the human growth phases can be modelled into mathematic functions, and created the Infancy-Childhood-Puberty (ICP) model[206] (Figure 14).

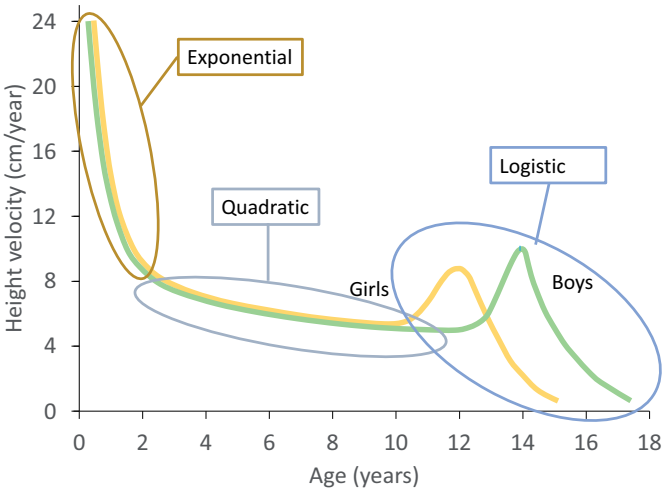


Figure 14. Schematic figure of the mathematical functions of human growth according to the Infancy-Childhood-Puberty-model by Karlberg[206].

In the present studies, we used a modified Infancy-Childhood-Puberty model for individual curve fitting of height measurements for all included subjects. The model was fitted by minimizing the sum of squares by using a modified of the Levenberg-Marquardt algorithm and including tests controlling for convergence. For all individuals with sufficient height measurements, age at PHV was estimated using this algorithm. A good model fit was further confirmed through visual inspection of all curves (Figure 15).

Menarche in women is a distinct event, and is a quite reliable as a marker for pubertal timing[207,208]. In men however, there is no such determining, distinct event reflecting pubertal timing. Therefore, assessment of pubertal timing in men is a challenge both prospectively and retrospectively.

The fastest longitudinal growth in humans after the infancy period occurs during the growth spurt of puberty. The highest growth velocity during the pubertal growth spurt is called Peak Height Velocity (PHV). In boys, the timing of PHV is around two years after the start of puberty[178]. Therefore, the timing of PHV can be used as an objective marker of pubertal timing, as it is assessable retrospectively when enough height measurements are available.

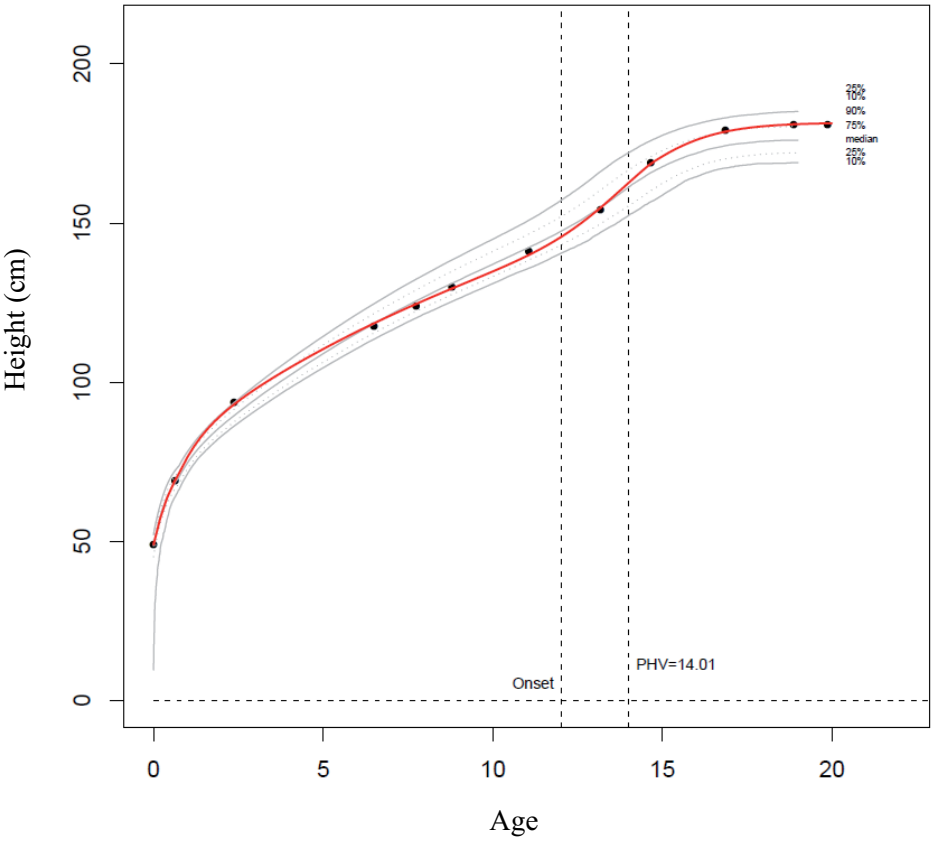


Figure 15. Example of a fitted growth curve and estimation of PHV in the BEST-projects by using a modified Infancy-Childhood-Puberty model for human growth.

4.4 OUTCOMES

The International Classification of Diseases (ICD) is a classification system managed by the WHO to facilitate common international definitions of diseases. The history of the ICD dates back to the 19th century, and was based on a topographic classification, i.e., diseases were classified according to the primary organ and localization where they caused sickness[209]. However, as cell biology and genetics knowledge increased, a topographic classification of cancer was sometimes inadequate. Therefore, an alternative ICD-Oncology classification (ICDO) has been developed that classifies cancer not just according to site (topography) but also according to morphology. The current ICDO-version is ICDO3. Classification of outcomes are listed in Table 4.

In paper I, colon and rectal cancer were separated to allow individual analyses. In paper II and III, classification of Diffuse Large B-Cell Lymphoma (paper II) and esophageal adenocarcinoma (paper III) was performed according to morphologic sub-types when topographic ICD classifications were inappropriate.

The classification of obesity-related cancer (paper III) was more inclusive than the definition in the 2016 report from IARC[1]. The associations between obesity and cancer are still not fully elucidated (Table 2), and new evidence is continuously added. Obesity-related cancer associations also differ between men and women. The 2016 IARC-report is an aggregate of the risk for men and women combined. Thus, a relevant and updated classification of obesity-related cancer in men for paper III required a fitting of the IARC definition. Five additional cancers (oral, male breast, lymphoma, leukemia, and malignant melanoma), where the recent and extremely well-powered Israeli conscription study demonstrated increased obesity-related risk in men, were added to the IARC-definition[2,75,210].

Table 4. Classifications of cancer outcomes in projects I-IV according to ICD.

Paper: Outcome	**ICD10**	**ICD9/8**
I: Colon cancer	C18	153
I: Rectal cancer	C19–20	154.01–11
II: Hematologic malignancies	C81–C96, D46.6, D46.7, D46.9	200–209, 239.9, 287.2
Leukemia	C87, C89, C91.0, C91.2, C91.7, C91.8, C91.9, C92, C93.0, C93.1, C93.2–C93.6, C93.7, C93.8, C93.9, C94, C95, C96, D46.6, D46.7, D46.9	204.00, 204.90, 205, 206, 207.00, 207.10, 207.28, 207.99, 208, 209, 239.9, 287.2
Lymphoma	C81–C86, C88, C91.1, C91.3, C91.4, C91.5, C91.6	200–202, 204.15
Multiple Myeloma	C90	203
III: Obesity-related cancer	C00-C14, C15†, C16.0, C18, C19-C21, C22, C23-24, C25, C43, C50, C64, C70, C73, C81-C88, C90, C91-96	140-149, 150†, 151.0, 153, 154, 155, 156, 157, 172, 175, 189.0, 192.1, 192.3, 193, 200-202, 203, 204-208
IV: Prostate cancer	C61	185

†*Esophageal adenocarcinoma, sub-classified through ICDO3/SNOMED morphology codes (8140–8141, 8143–8145, 8190–8231, 8260–8263, 8310, 8410, 8480–8490, 8559–8561, 8570–8574, 8576).*

4.5 REGISTER LINKAGE

Registers can be important resources for acquiring large and population-based information intended for research and for follow-up of health care outcomes, as they provide an inexpensive and efficient way to collect data. As a result of foresightedness and the personal identity number, Sweden was early to build good premises for population-based registers.

Swedish Inpatient Register

Initiated in 1964, the Swedish Inpatient Register (IPR) is part of the Swedish National Patient Register (NPR), which contains diagnoses from both inpatient and outpatient care. The diagnoses in the NPR registers are based on the topographic ICD-system. The IPR, sometimes called the Hospital Discharge Register, is basically a register of diagnoses from hospital care. Initially, not all Swedish counties started reporting data to the IPR at the same time, and also within counties it was a timely process to get all clinics to report all diagnoses to the register. In 1987, 23 years after the initiation, it became mandatory for hospitals in Sweden to report all inpatient diagnoses to the IPR. As a result, full national coverage (i.e., all inpatient diagnoses were reported to the IPR) was accomplished[211]. In Gothenburg, where the cohort of the present project finished school, full coverage was established in 1972 and onwards, when the oldest subjects in the present cohort were 26 years old[212].

Cause of Death Register

The Swedish state started recording population-based data on causes of death already in 1751, but until 1911 only diagnoses of certain interest, such as plague and maternal deaths, were collected[213]. Since 1911, all causes of death have been included. Records from 1952 and onwards in the Cause of Death Register has been made available to researchers electronically.

Unlike other Swedish registers, the Cause of Death Register uses the International Classification of diseases system (ICD) rather than the Swedish version to classify cause of death. This is a result of international efforts to facilitate comparisons of causes of death between countries. The discrepancy with other Swedish registers primarily affects diagnoses of ICD9, where the fourth position in the Swedish ICD version uses a letter rather than a number. The registration sent to the cause of death register states (1) the direct cause of death, (2) the eventual diagnoses in the chain of events that led to the direct cause of death, and (3) the underlying diagnosis that initiated the chain of events that led to the direct cause of death[5].

Before 1991, a death certificate stating the underlying cause of death was legally required for burial, and even after this legal demand was removed, the coverage of the cause of death register is almost 100%[213] (in 2015 it was 99.1%[214]). However, in 2015 2.7% of the causes of death were insufficiently specified (with unspecific diagnoses), a problem that, for example, can arise in the elderly with multiple chronic diseases where the exact cause of death is difficult to determine[214]. The register is managed by the National Board of Health and Welfare, although until 1993 it was the responsibility of Statistics Sweden.

Swedish Cancer Register

The Swedish Cancer Register (SCR) was established in 1958, and is managed by the National Board of Health and Welfare. The SCR includes all primary cancer diagnoses, and information of cancers in the register is based on histologic examination from operation/autopsy, cytologic analyses, operation without histologic examination, or clinical or radiological examination. Reporting to the cancer register is compulsory, and includes the topographic classification of the ICD system (the International Statistical Classification of Diseases and Related Health Problems), and the morphologic classification according to the ICDO/SNOMED system, when available, which distinguishes tumor cell type[215].

National Prostate Cancer Register

N|P|C|R Nationella prostatacancerregistret

The National Prostate Cancer Register (NPCR) is a Swedish quality register for the collection of detailed information of prostate cancer characteristics and management, including data not available in the cancer register. The main purpose of the NPCR is to promote good and equal prostate cancer care, regardless of age or residential region. In 1987, the first regional prostate cancer register was initiated in the southeast health care region of Sweden, and during the 1990s, the other regions in Sweden followed with initiation of local registers. By 1998, all health care regions had regional prostate cancer registers, and these were merged into the NPCR. The NPCR has a 98% coverage of prostate cancer diagnoses, compared to the obligatory Swedish Cancer Register[216], and the quality of data is high[217].

Medical Birth Register

The Medical Birth Register (MBR) was launched in 1973 and contains perinatal data of pregnancies, births and newborns. More than 99% of all deliveries in Sweden take place in a hospital, but the MBR cover the few home births as well. All hospitals are obliged to provide data to the MBR[25],

and the information includes previous pregnancies, smoking, birth clinic, gestational age, analgetic drugs, birth procedure, diagnoses in mother and child, and operations, as well as the sex of the child, birthweight, length, and head circumference, and the condition at birth[25].

Register validation

Using register data is an efficient way to collect data for research, and enables large and, in Sweden, nationwide population-based studies. The disadvantages of register data include the secondary nature of the data, meaning that the data was not collected for a specific study, and could therefore be incomplete in regards of information needed in the study. Any population-based register with high data density (large amount of information on included individuals) will encounter issues of missing data. Individuals might not want to share high integrity personal information, but also incomplete reporting and unavailable information all lead to missing data. The efficacy of using of register data depends on the quality of the register. The quality of a register can be evaluated in three dimensions[218]:

1. **Comparability**. Consistency in classification and coding, adherence to international consensus that enables comparison between populations and time periods.
2. **Completeness**. The extent to which
    a. all incident cases of a disease are identified in the register, and
    b. all target populations are covered by the register.
3. **Accuracy** (validity). The proportion of cases in the register with a given characteristic that truly have that attribute.

An additional fourth dimension of evaluation, timeliness**,** is sometimes mentioned. Timeliness is the measure of how quickly new cases are registered to the register. Poor timeliness correlates to a high risk of incomplete recent data in the register. Timeliness can be viewed as a subgroup of the completeness of the register.

Evaluation of a register requires some other source of data to compare with, and the validity of the evaluation, of course, relies on the completeness and accuracy of the reference data source[219]. Examples of alternative data sources are (1) other reference source (i.e., laboratory records), (2) medical records, or (3) another database[219]. The accuracy can be measured as positive predictive value (PPV), i.e., the proportion of individuals diagnosed in the register who are also diagnosed in the reference source. The

completeness is often evaluated as sensitivity, i.e., the proportion of diagnosed individuals in the reference who are also diagnosed in the register[211].

By linking growth data to national registers from the National Board of Health and Welfare and the Statistics Sweden, we were able to link growth patterns during childhood and puberty with cancer outcomes in adulthood, adjusting for important parameters such as educational level and country of birth.

For the specific outcomes of the studies in this thesis, cancer diagnoses in projects I–III were collected from the IPR and the Cause of Death Register. The SCR was used only as a complement to classify DLBCL in paper II and to separate adenocarcinoma from squamous cell carcinoma of the esophagus in paper III. The overall completeness of the IPR is excellent, >99% of hospital discharges are registered here[211]. The accuracy, measured as PPV, averages between 85–95%, but varies significantly between groups of diagnoses. Evaluations of the IPR have rarely included cancer outcomes[211], although an assessment of prostate cancer found that 83% of the diagnoses in the NPCR were also registered in the IPR[211]. In the included studies, we restricted outcomes to primary diagnoses in the IPR, and to underlying causes of death in the Cause of Death Register, which has been shown to increase accuracy (PPV)[211]. Furthermore, for diagnoses of diseases treated in outpatient care, the sensitivity in the IPR is reduced[211]. Nonetheless, very few of the cancer outcomes in projects I–III would have been diagnosed and treated exclusively in an outpatient setting. Contrarily, the cancer diagnoses of projects I–III are often diagnosed and/or treated in specialized units, which further tends to increase sensitivity and PPV.

For the outcome in project IV, we used the NPCR to collect the prostate cancer diagnoses, and in an evaluation using the SCR as reference, the completeness of the NPCR was shown to be high (sensitivity of 98%)[217].

In project V, we complemented the school health care data with data from the MBR, where available. The MBR covers 98.6% of all infants born in Sweden, and 97-99% of all Swedish citizens registered at Statistics Sweden[25,220]. The most recent quality control from 2003 showed that completeness was good although somewhat varying, only 0.32% of all infants lacked birthweight, and 30% of mothers had missing information on pre-pregnancy weight[220]. Overall, however, data in the MBR have been assessed as accurate[221].

4.6 STATISTICAL ANALYSES

For included studies, a p-value < 0.05 was interpreted as statistically significant.

Parametric tests and Log-transformation

Statistical models to test associations can be either parametric or non-parametric, and the distinction has to do with variables being either normally distributed (for parametric testing) or non-normally distributed (for non-parametric testing). Statistics that can handle both parametric and non-parametric variables, such as Cox regression, are called semi-parametric[222]. To express outcomes for a variable per standard deviation (SD), a normal distribution of the variable is assumed. Because BMI is not a normally distributed variable, childhood and young adult BMI were log-transformed for the statistical analyses.

Comparisons between groups

To compare differences between groups for normally distributed, continuous variables, Students *t*-test was used. Continuous variables not normally distributed were tested using Mann-Whitney. Dichotomous variables were tested with chi-square test. In project V, linear regression was used to assess periodic changes, and logistic regression was used to compare rates of high, low, or very low birthweight between birth cohorts.

Association analyses

Cox proportional hazards regression is a statistical analysis that assess event rates (hazard ratios, HR). Time to event-analyses, such as HR, have the advantage of using more of the available information than odds (OR) and risk ratio´s (RR), since OR and RR take into account *if* an event occurred, whereas HR also relates to the timing of occurred events. In studies of associations between exposures and outcomes, especially studies where follow-up time is long, time-to-event analyses are preferable. In the present studies, where the outcomes are cancer, it matters whether the outcome occurred one year after the exposure, or 50 years after the exposure. HR is also advantageous for studies where follow-up differs between participants, i.e., when recruitment of participants occurs over a long period, whereas the end of follow-up is a fixed date. In the present studies we used Cox proportional hazards regression in SPSS (versions 24 to 27) to estimate HR.

In paper II, we used a stepwise model selection (backward conditional stepwise Cox regression) for our combined risk analyses to assess which

model, i.e., which set of included variables, that best approximates the risk related to the outcome of interest. A backward stepwise model selection starts with all available variables included in the model. That is, one variable at a time is dropped, and the variable dropped is the one that contributed least to the model fit[223]. For each step, the model fit is calculated through Akaike information criterion (AIC) or Bayesian information criterion (BIC). The procedure stops when the model does not improve by dropping another variable, or when only one variable remains[223]. Finally, the best model fit, i.e., the model with the lowest AIC or BIC, is presented.

The main assumption of the Cox proportional hazards regression is proportional hazards of the studied exposure variables for the outcome of interest during the time of follow-up. That is, the association between the exposure and the outcome must not change over time. Whether the hazards are proportional (in time) or not was tested by a goodness of fit-test and visual inspection of the Schoenfeld residual plots.

Another problem that can arise with analyses of hazards is competing risk. Competing risks can occur if the exposure (e.g., BMI) is associated with an increased risk of another cause of loss to follow-up (e.g., CVD mortality). This loss to follow-up could introduce a bias as there will be fewer remaining study participants in one of the exposure groups. In the present studies including hazard analyses (paper I–IV), cumulative incidence plots were used to assess potential competing risks.

Non-linear associations were assessed with the inclusion of a quadratic term (the variable of interest multiplied by itself) in the Cox regression model. A significant quadratic term meant the association was non-linear. Interaction between variables included in the Cox regression models was tested by inclusion of an interaction term in the model. The interaction term included the variables of interest multiplied by each other. In paper I, the significant interaction term was handled by stratification of the cohort according to the variable of least interest for the outcome (pubertal BMI change).

5 RESULTS

5.1 Paper I. Childhood Body Mass Index is associated with risk of adult colon cancer in men – an association modulated by pubertal change in Body Mass Index

In paper I we explored associations between childhood BMI (eight years of age), pubertal BMI change, and colon and rectal cancer in adulthood. We followed 37,663 men from 20 years of age, and during the 1.4 million years of follow-up 257 cases of colon cancer and 159 cases of rectal cancer were diagnosed.

Childhood BMI, but not pubertal BMI change, was associated with colon cancer. No significant associations were found for rectal cancer. Due to significant interaction between childhood BMI and pubertal BMI change for the risk of colon cancer, combined analyses were stratified according to the median of pubertal BMI change.

The main finding was that individuals with overweight at eight years, with an additional pubertal BMI increase above the median, had a nearly threefold risk of colon cancer in adulthood (Figure 16). This finding indicates that, on a population level, the increased risk of colon cancer associated with childhood overweight is modifiable during puberty.

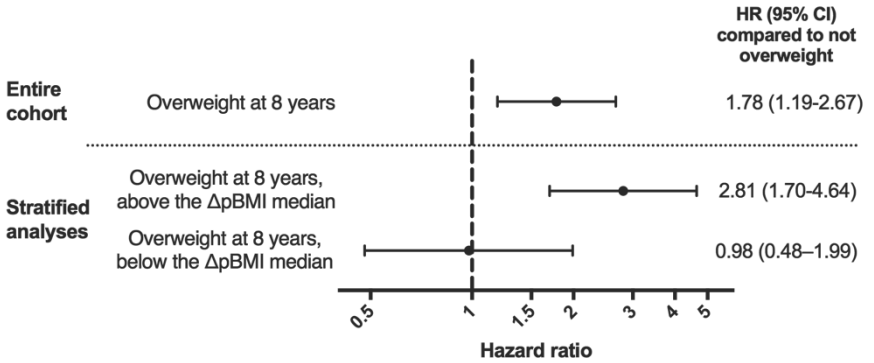


Figure 16. Adjusted hazard ratio for colon cancer in overweight compared to normal weight boys (at eight years of age), stratified according to the median of pubertal BMI change, N=18,832 above and N=18,831 below the median of pubertal BMI change. ΔpBMI=pubertal BMI change

Results Paper I

- BMI at 8, but not puberal BMI change, was associated with colon cancer
- For boys with a pubertal BMI progression above the median, those with overweight at 8 years had an almost 3-fold risk of colon cancer compared with those with normal weight
- In the group with a pubertal BMI progression below the median, no increased risk of colon cancer was found for those overweight at 8 years compared to normal weight

5.2 Paper II. Childhood Body Mass Index is associated with the risk of adult hematologic malignancies in men – the BEST Gothenburg cohort

In paper II, we examined the associations between BMI and height during development and hematologic malignancies and sub-groups. A total of 37,669 men were followed from 20 years of age. During the 1.5 million years of follow-up, 459 cases of hematologic malignancy (HM) were diagnosed. HM is a diverse group of diseases, and sub-groups were analyzed in exploratory analyses.

Overall, childhood BMI but not pubertal BMI change was associated with adult HM (HR 1.11, 95% CI 1.02–1.23), though results varied between subgroups. Non-Hodgkin Lymphoma (HR 1.14, 95% CI 1.00-1.30) and its largest subgroup Diffuse Large B-Cell Lymphoma (HR 1.31, 95% CI 1.03–1.67) was associated with childhood BMI, whereas multiple myeloma was associated with childhood height (HR 1.30, 95% CI 1.04–1.64), but not pubertal height change.

The main finding was that developmental anthropometric associations with adult HM originated from childhood and not puberty. The association between childhood height and multiple myeloma could facilitate insights of pathogenetic mechanisms, and since modifiable risk factors for HM are scarce, prevention depends on detecting the critical windows of opportunity for intervention.

Results Paper II

- BMI at 8 years, but not pubertal BMI change, was associated with overall hematologic malignancies
- For lymphoma and the sub-group Diffuse Large B-Cell Lymphoma, BMI at 8 years was associated with increased risk
- For multiple myeloma, height at 8 years was associated with increased risk

Table 5. Hazard ratios (HR) for the association between childhood BMI, childhood height and subgroups of hematologic malignancies.

	Separate analyses		Combined analyses	
	Childhood BMI HR (95% CI) per SD increase	**Childhood height** HR (95% CI) per SD increase	**Childhood BMI** HR (95% CI) per SD increase	**Childhood height** HR (95% CI) per SD increase
Lymphoma (n=288)	1.09 (0.97-1.22)	1.04 (0.93-1.17)		
Hodgkin Lymphoma (n=35)	0.79 (0.55-1.13)	1.01 (0.73-1.41)		
Chronic Lymphatic Leukemia (n=41)	1.07 (0.79-1.44)	1.25 (0.92-1.71)		
Non-Hodgkin Lymphoma (n=212)	**1.14 (1.00-1.29)**	1.01 (0.88-1.16)	**1.14 (1.00-1.30)**	
DLBCL (n=51)	**1.31 (1.03-1.67)**	0.90 (0.68-1.18)	**1.31 (1.03-1.67)**	
Multiple Myeloma (n=75)	1.15 (0.93-1.43)	**1.30 (1.04-1.64)**		**1.31 (1.05-1.65)**
Leukemia (n=96)†	1.15 (0.95-1.39)	1.07 (0.88-1.31)		
Acute Myeloic leukemia (n=66)	1.05 (0.83-1.34)	1.08 (0.84-1.37)		

Separate and combined analyses for BMI and height in childhood. Combined analyses of HRs were calculated for significant associations using conditional stepwise Cox proportional hazards regression, only the remaining significant variable is shown in the table. [a]Includes acute myeloid leukemia, acute lymphatic leukemia (n = 11), and other leukemia (n = 19). The groups of acute lymphatic leukemia and other leukemia were too small to analyze. DLBCL = Diffuse Large B-Cell Lymphoma.

5.3 Paper III. Childhood overweight and risk of obesity-related adult cancer in men

In paper III, the risk of overweight at eight years, independent of overweight status at 20 years of age, for of obesity-related cancer incidence and mortality was investigated.

In the included 35,665 men with information on overweight status at both eight and 20 years of age, and a proxy for socioeconomic status, 1,562 cases and 449 deaths from obesity-related cancer occurred during follow-up. Our main finding was a direct association between childhood overweight and obesity-related adult cancer incidence and mortality, independent of young adult overweight status.

Importantly, boys with childhood overweight that normalized during puberty, but not boys with pubertal onset overweight, had substantially increased risk of obesity-related adult cancer compared with men who had normal body weight both at eight and 20 years of age (Table 3, paper III).

Results Paper III

- Boys who where overweight at both 8 and 20 years showed the highest risk of obesity-related cancer
- Boys with overweight at 8 years and normal weight at 20 years of age demonstrated significantly increased risk of obesity-related cancer in adulthood compared to those normal weight at both occasions
- Normal weight at 8 years and overweight at 20 years of age was not associated with an increased risk of obesity-related cancer in adulthood

5.4 Paper IV. Timing of the pubertal growth spurt and prostate cancer

In paper IV, we explored associations between pubertal timing and prostate cancer. We used the BEST step 1 cohort including the men with sufficient height measurements to calculate age at peak height velocity (N=31,971). 1,759 cases of prostate cancer, and 449 cases of high-risk or metastatic prostate cancer occurred during follow-up starting at 20 years of age.

We found a non-linear association for age at peak height velocity and prostate cancer ($p < 0.05$ for the quadratic term for age at peak height velocity). The highest quintile (representing the 20% of the individuals with the latest pubertal timing) had a significantly lower number of prostate cancer cases, compared to quintile 2–4 ($p < 0.01$), whereas quintile 1 was not significantly separated from quintiles 2–4 ($p = 0.5$). Therefore, the non-linear association was driven by the highest quintile of age at PHV. In our analyses, age at PHV was stratified into quintile 1, quintile 2–4 (reference), and quintile 5. The highest quintile showed a protective effect for prostate cancer, HR 0.83, 95% CI 0.73-0.94, and for high-risk or metastatic prostate cancer, HR 0.73, 95% CI 0.54-0.96, compared to quintile 2–4.

We found a lower risk of high-risk or metastatic prostate cancer in the latest quintile of age at PHV compared to quintiles 2-4. Interestingly, in exploratory analyses with *follow-up* starting at age at PHV instead of at 20 years of age, we did not find any differences in risk of prostate cancer, or high-risk or metastatic prostate cancer, between quintile 5 and 2-4.

Results Paper IV

- Late pubertal timing, represented by quintile 5 of age at PHV, was associated with decreased risk of prostate cancer, including high-risk and metastatic prostate cancer
- In exploratory analyses where the follow up started at age at PHV of each individual, we found no differences in risk of prostate cancer between late pubertal timing and the average reference group
- This indicates that the duration of sex steroid exposure determines the risk of prostate cancer related to pubertal timing

5.5 Paper V. Secular trends of birthweight in boys from 1950 to 2010

Paper V addresses trends in birthweight from the time of increased smoking in women through the obesity epidemic to the present. This study included 46,548 birthweights from boys were recorded between the mid-1940s and 2011, categorized into seven-decade birth cohorts (Figure 17). The mean birthweight during the period was 3,580 grams, and the standard deviation was 562 grams. The highest mean birthweight was 3,612 grams (birth cohort 2000), and the lowest mean birthweight 3,537 grams (birth cohort 1980).

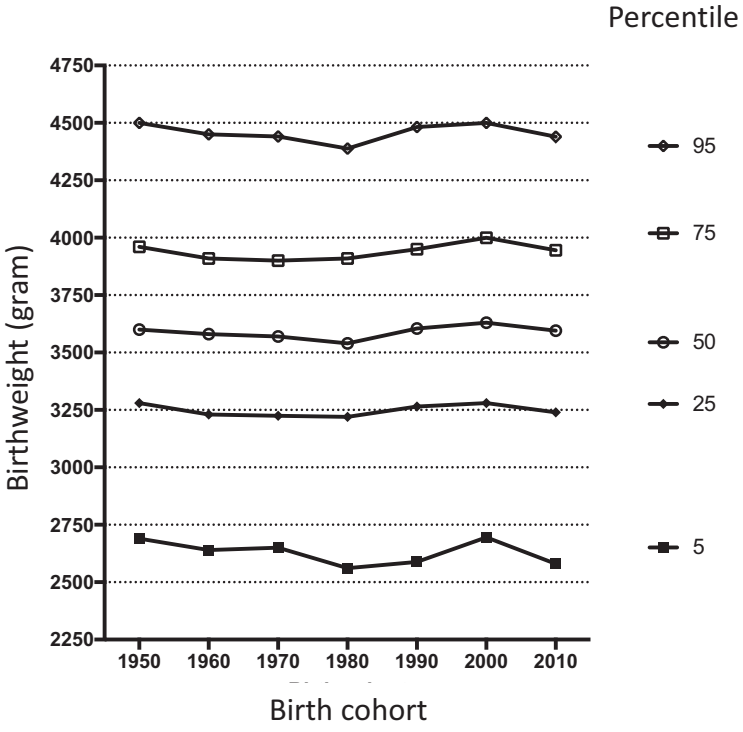
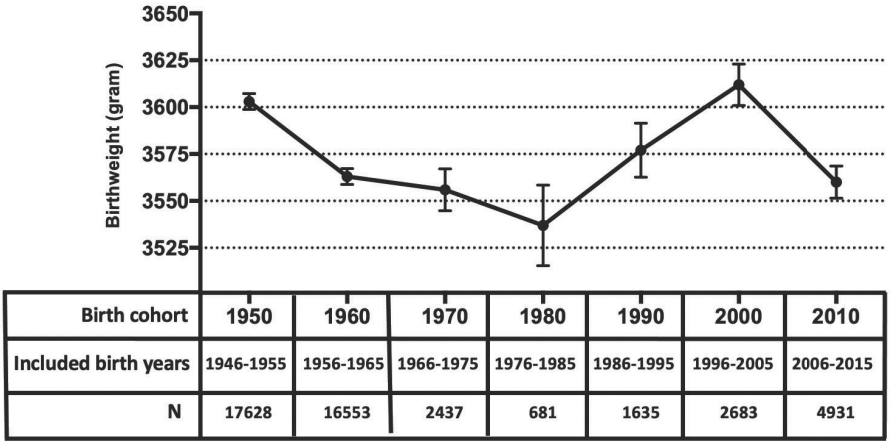


Figure 17. Distribution of birthweights in between 1950 and 2010.

The overall trend of birthweights was stable during the period (Figure 17). Three statistically significant periodical sub-trends were identified, a decrease between 1950–1980 (–66 grams, ß for trend –2.9 gram/year, $p < 0.001$), an increase between 1980–2000 (+75 gram, ß for trend +3.7

gram/year, p = 0.001), and a decrease between 2000–2010 (-42 gram, ß for trend -5.2 gram/year, p < 0.001) (Figure 18).



Birth cohort	1950	1960	1970	1980	1990	2000	2010
Included birth years	1946-1955	1956-1965	1966-1975	1976-1985	1986-1995	1996-2005	2006-2015
N	17628	16553	2437	681	1635	2683	4931

Figure 18. Trend of mean birthweight (standard error of the mean) from 1950–2010.

Results Paper V

- The overall trend of birthweights between 1950 and 2010 were stable.
- Periodic sub-trends were identified, a decrease between 1950–1980, an increase between 1980–2000, and a decrease between 2000–2010

6 DISCUSSION

The present projects have shown that onset of overweight in childhood was associated with increased risk of adult colon cancer, an association modulated by the pubertal BMI change. Childhood onset of overweight, but not pubertal BMI change, was associated also with hematologic malignancies and obesity-related cancer in men. In addition, the observed association between pubertal timing and prostate cancer was directly related to the duration of the latency time between the pubertal timing and the prostate cancer diagnosis. The long-term trends of male birthweights were stable.

6.1 METHODOLOGICAL CONSIDERATIONS

Choosing appropriate study design is crucial for the validity of a scientific study, and the best design relates to what you want to study. In projects I–IV, we aimed to study associations between pubertal timing and high BMI during development, and certain cancers in adulthood. Since high BMI is associated with significant morbidity and mortality, an experimental study where individuals were allocated to such exposure (high BMI) would not be feasible for ethical reasons. Correspondingly, a random allocation of individuals to different pubertal timing would be neither practical nor ethical. The use of animal models would be an alternative for studies of exposure from high BMI. However, it is plausible that animals and humans are different regarding mechanisms linked to high BMI (hormonal and metabolic regulation, diet, and physical activity). Furthermore, such studies would be limited by the fact that specific cancers are uncommon, and therefore would require large numbers of animals for adequate power, or methods to induce certain cancer types. Therefore, generalization of results to humans with “naturally” occurring cancer could be limited.

The long induction time between childhood and late adult cancer development makes prospective studies impractical. In the Nordic countries, early obligatory public school health care and foresighted archiving of records has generated unique opportunities for retrospective collection of potential exposures from long ago. Therefore, for the present scientific questions, retrospective observational studies are preferable when available, and reliability of the conclusions are determined by the internal and external validity and power of the studies.

Internal validity

Internal validity is the concept of how well a study is conducted, how well a study measures what it is set out to measure, and how well it eliminates possible alterative explanations for a finding. Studies with high internal validity will come to the same results if repeated. Table 6 lists threats to internal validity, and brief comments on the significance of each threat in the present studies.

Table 6. Threats to the internal validity of studies, and brief comments regarding their relevance in the present studies.

Threats	**In the present studies**
Misclassification Exposure or outcome	Classifications of exposures and outcomes are internationally established, except in paper III, where outcome-classification was based on up-to-date evidence and the sex of the cohort.
Selection bias Study participants are selected in a biased manner	Cohorts for projects I-IV were population-based, which eliminates risk of selection bias. Although selection bias cannot be ruled out in project V, where different sources for birthweights were used, and the 2011 birthweights were selected from hospital birth records rather than school health care, the hospital records covered the same geographical area as the school health care, and the accordance to the MBR does not lend support to significant selection bias (Figure 3, paper V).
Information bias Systematic differences in collection, recall, recording or handling of information. Missing data is an example of information bias.	Exposures and outcomes were registered in a prospective manner by trained professionals, reducing risk of systematic collection and recording bias. Objectively measured exposures and outcomes reduced the risk of information bias through recall. Due to the age of the exposure data and the secondary nature, missing data are unavoidable. Therefore, bias due to missing data cannot be ruled out.
Unadjusted confounders	Possible residual confounders in projects I–IV were smoking, diet, physical exercise, and BMI in later adulthood, and in project V, gestational age, maternal smoking, multiple birth, maternal weight and weight gain during pregnancy.
Loss to follow-up People lost to follow-up often have things in common that could bias results	Through high-quality registers, there were practically no losses to follow-up.

External validity

External validity is related to the extent to which conclusions from a study are generalizable:

1. to populations outside the study population
2. to settings outside the study setting
3. to periods other than the studied periods
4. to situations other than the study situation

Scientific studies often have to mediate between good external or internal validity. An increased internal validity often comes at the expense of external validity. The more controlled the study, the less generalizable to "real world" circumstances and vice versa. The more a study explores "real world" occurrences, the harder to control for all possible confounders and weaknesses. A common strategy to address these shortcomings is to first conduct a study with high internal validity to determine an association and secondly perform a study with high external validity to establish generalizability of the observed association.

The cohorts of the present studies were recruited from centrally archived records from school health care in Gothenburg. The school health care at the time of school start for the oldest members of the cohort already included 98.5% of all pupils, as we consider this a population-based cohort. In an analysis of the representativity of the cohort, we used the conscription register to compare BMI at 20 years of age in excluded individuals with those included, and found no significant difference between the two groups (included subjects mean BMI 21.13, SD 2.53 kg/m^2, and excluded subjects 21.15, 2.57, not significant using Students t-test).

The study population consists primarily of Caucasian men born during the 16 years following the World War II, when overweight was a sign of privilege in the wealthy. Today, in developed countries such as Sweden, overweight is increasingly turning into a problem for individuals in lower socioeconomic groups. Therefore, associations observed in the present cohort might be different in contemporary populations. However, the plausible mechanisms related to genetics, metabolism, and endocrine changes of overweight do not vary with socioeconomic status, nor from one generation to the next. Furthermore, associations between childhood overweight and adult cancer in women, in ethnicities other than Caucasian, and in populations living in rural areas or in developing countries have not been explored, and might differ from the ones observed in the present studies.

Power

In scientific research statistical power is the ability, or strength, to detect an actual difference between groups. The inability to detect an existing difference is called a type II-error. Statistical power ranges from 0 to 1, and increasing statistical power reduces the probability of type II-error. Statistical power improves when the number of included participants increases (the sample size), when effect size increases, when the variability of studied variables decreases (if continuous), and when the level of significance decreases. The level of significance is the statistical risk of obtaining a result by chance that states a difference when there is no real difference, i.e., making a type I-error. The level of significance is commonly set at 0.05, meaning that one in 20 analyses where no actual effect is present will result in an erroneous statistically significant effect by chance.

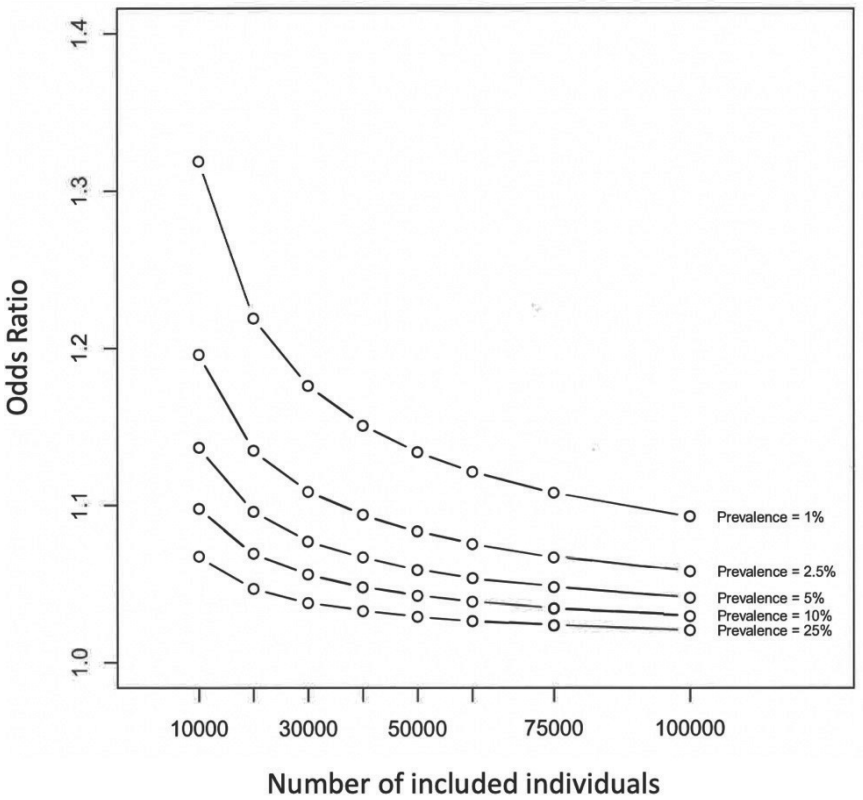


Figure 19. Power calculations of the BEST-project for a statistical power of 80% and p = 0.05 to identify relations between the effect sizes in Odds Ratio (y-axis), the size of the study populations (x-axis), and the prevalence of a studied disease as illustrated by the different curves.

Planning a research study should include calculations of the statistical power to estimate what size of difference the study will be able to detect with a given number of participants or to state the number of included participants needed to detect a specified difference between groups. The power calculations for projects I-IV are demonstrated in Figure 19.

Precision and Accuracy

Precision is related to the variability in the set of measurements used, in other words the degree to which repeated measurements under unchanged conditions give the same results. Good precision is related to low occurrence of random errors and to the size of the sample (Figure 20). Accuracy is the ability to achieve a correct result.

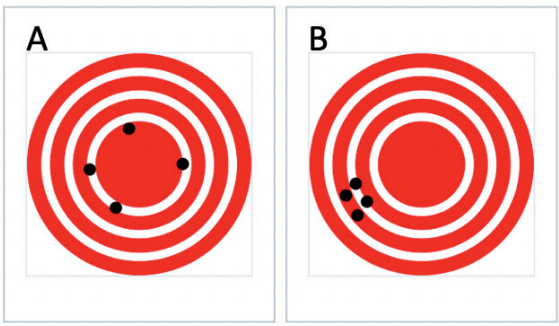


Figure 20. Examples of accuracy and precision. A) Random errors result in high variability and low precision. Accuracy is good. B) Systematic errors result in low accuracy, but low variability result in high precision. Note that an increase of random errors does not relate to good accuracy per se, and that systematic errors are not markers of low variability.

The sample sizes in the present studies are large, which reduces the variability and the sensitivity to random errors. To eliminate random and systematic errors, the exposure data have further been extensively quality checked during data collection and derivation of variables.

Gender aspects

The aims with the BMI Epidemiology Study Gothenburg include studies of BMI in childhood and young adulthood. Young adult BMI has been accessible primarily through the conscription register. Until recently, conscription has been mandatory for Swedish men, but not women.

Therefore, information regarding young adulthood has been easier to attain in men. This is the reason the initial studies from the BEST cohort have included only men.

When knowledge of diseases and trends of determinants for health are unknown for an excluded half of the population, it represents a larger problem of equality. Evidence has shown that there are significant sex-based differences in some, but not all, BMI-related diseases[224], and that conclusions from studies of men are not necessarily generalizable to women[225].

We have been working on the female part of the cohort, where other sources of information on exposures need to be scouted, and different models for growth curve algorithms, pre-pubertal BMI, and peak height velocity are developed. Our aim is to complete our population-based approach with studies of women in the near future.

Ethical considerations

All collection of personal data is accompanied with a risk of intrusion of the personal integrity. The basis of all medical research on humans is the consent of included individuals. This has been an important rule in the scientific community since the crimes against humanity by the Nazi's during the 1930s and 1940s. However, in certain cases where the risk for the individual is considered insignificant and the general benefit large, the principle of consent can be waived by the ethical committees. This is often the case in large register studies, as in the present ones, where results are only presented on a group level without any possibility to identify individuals.

In these cases, requiring consent would result in massive dropouts and require large resources for administration, making many research projects unfeasible. Therefore, research questions would go unanswered. For some of these population-based register studies, where research questions with importance for populational health can be explored that would otherwise remain unknown, it can be more unethical not to go through with a study than to carry it out without consent. All studies in this thesis were approved by the Regional Ethics Review Board.

6.2 PAPER-SPECIFIC DISCUSSION

Paper I. Colon and rectal cancer demonstrated significant differences regarding the risk related to BMI during development, in line with evidence arguing for a distinction between them[66]. BMI at eight years of age was associated with risk of colon cancer, whereas pubertal BMI change was not. Interestingly, the observed association was conditioned by a subsequent BMI increase above the median during puberty. For children overweight at eight years with a pubertal BMI change below the median there was no increased risk compared to normal weight peers (at eight years). This implicates that childhood could be a sensitive period for colon cancer risk, and puberty a potent modulator of an eventual risk acquired during childhood.

Paper II. In this paper, we found large discrepancies regarding risks related to BMI and height in childhood for the hematologic malignancies. This is in congruence with the research field, where the sub-groups of hematologic malignancies most often are regarded separately. These discrepancies indicate differences in pathologic mechanisms. In our results, childhood was the period of importance for all three main groups of hematologic malignancies (lymphoma, multiple myeloma, and leukemia), even though sub-group analyses were somewhat underpowered and results for leukemia were not statistically significant. We found that both childhood BMI and childhood height seemed to be of importance for our outcomes. Since height is used in the calculation of BMI, height and BMI at the same age are variables that have overlapping information. Therefore, in paper II, we used backward conditional stepwise cox regression to assess the best model fit for the combined analyses of childhood BMI and childhood height for the risk of the sub-groups of hematologic malignancies. Height at eight years was associated with an increased risk of multiple myeloma, while BMI was associated with an increased risk of Non-Hodgkin Lymphoma and DLBCL. Possible underlying mechanisms to explain these associations and the divergent results include that high BMI triggers growth and proliferation-stimulating mechanism, such as insulin and IGF-1, but also chronic inflammation and adipokine aberration that all could induce carcinogenic transformation. Height is largely stimulated by growth hormone/IGF-1 stimulation (Figure 6, page 23), and the differences in associations could be explained by various sensitivity in different types of hematological malignancies to these different types of stimuli.

Paper III. In this study the highest risk for obesity-related cancer was found in individuals with overweight at both eight and 20 years of age, which is reasonable considering the nature of the outcome. In regards of eventual differences between the timing of onset of overweight, onset during childhood was crucial for risk generation in our study. Onset of overweight during puberty (between eight and 20 years of age) did not associate with an increased risk of obesity-related cancer, and onset of overweight in childhood was associated with an increased risk that persisted even when overweight was reversed into normal weight by the age of 20 years. Of course, confounding by potential relapse of overweight in later adulthood could not be ruled out in the present study, but reasonably, overweight at 20 years of age would correlate better with later adult overweight than overweight at eight years of age. The absence of an association for the group with overweight at 20 years of age suggests that confounding by later adult overweight does not explain the observed association for childhood overweight. Speculations of underlying mechanisms includes metabolic programming during childhood that persist through life, initiation of pre-carcinogenic steps during the growth-intense childhood phase, or that life-long habits of diet and physical activity could be cemented during childhood rather than during puberty.

Paper IV. This was the first observational study to explore associations between objectively assessed pubertal timing and prostate cancer risk. We could corroborate previous findings from recalled pubertal timing of an association, and demonstrate an association also with a clinically relevant high-risk or metastatic prostate cancer definition. The assumed relation between pubertal timing and prostate cancer has been thought to relate either to a phenotype of high androgen-stimulation that would stimulate earlier puberty and increased risk of prostate cancer, or that early puberty results in longer accumulated life-time exposure to post-pubertal levels of androgens. We could demonstrate that the association was related to the duration of time after the pubertal timing.

Paper V. Alarming and numerous reports of increasing birthweights from the initiation of the obesity epidemic to the 1990s or early 2000 have been published. We found that the sub-trend during that period was increasing also in our cohort, but decreasing sub-trends preceded and followed, resulting in a stable overall trend of birthweights from 1950–2010 in a large cohort from Gothenburg. Although different sources were used, accordance to the National MBR was good (r=0.98, Figure 3, paper V), where data were overlapping, indicating that our cohort is representative for the population.

The power of the study was concentrated to the previous unknown period before the start of the MBR.

The recent decline in birthweights, shown in our data and in the MBR, has not been described for Sweden before (nor has it received the same wide attention as the previous increase where it has been demonstrated), but is established in the USA, where increased use of induced labor and planned cesarian section is thought to be the cause[226].

6.3 EARLY LIFE EXPOSURE AND RISK OF ADULT CANCER

Mechanistic models of associations

There are several plausible approaches of how exposure, such as high BMI, in early life can influence the future risk of an outcome, such as cancer. One alternative is the **critical period** model, which assumes that there is a critical period, a window of opportunity, for the exposure to affect the outcome. When the critical period has passed, the exposure no longer has the ability to affect the outcome. A well-known example of a critical period association is the Thalidomide catastrophe in the late 1950s and early 1960s[227]. Thalidomide was a drug used to control morning sickness during pregnancy that turned out to cause severe malformations in the embryo only if the embryo was exposed between day 20 and 36 after fertilization. After day 36 Thalidomide exposure has not been associated with harmful effects for the embryo. The drug is still used the for a range of conditions in adults, such as multiple myeloma and leprosy[227]. In the critical period hypothesis, the exposure might require some sort of effect modifier to activate an increased risk of the outcome (Figure 21).

Another resembling model is the **sensitive period** model, where exposure does not affect the outcome exclusively during the specific period. Rather, during the sensitive period, individuals are more vulnerable to certain exposures compared to during other time points. The sensitive period model is a combination of the critical period model and the cumulative period model.

Both the critical and the sensitive period models are often illustrated by a specific developmental period, but other initiators of critical or sensitive periods such as infections, inflammatory activation, dietary changes, drug treatment and physical inactivity are plausible (Figure 21).

The model of certain periods with increased sensitivity to carcinogenic exposure is supported by the finding that variations in cancer risk among tissues can be explained by the number of stem cell divisions[106]. Because the number of stem cell divisions in a tissue during a life time is not constant, periods of highly intensive stem cell divisions, such as during proliferative growth, would logically be periods of higher sensitivity to carcinogenic exposure.

The **cumulative effect** theory stipulates that repeated exposure increase cancer risk, but the additive risk is equivalent regardless of during what period the exposure is acquired. Both the **additive effect** and the **trigger effect** hypotheses assumes that several different exposures are required to cause cancer, either in a sequential order as in the trigger effect theory, or in any order such as the additive effect theory[191].

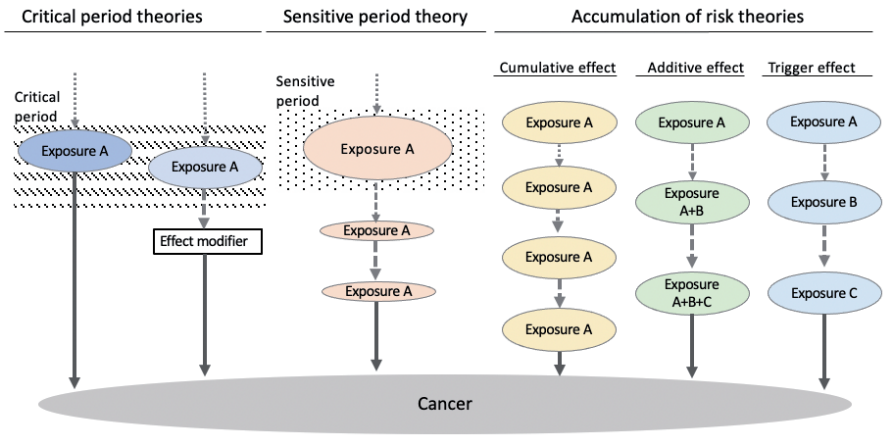


Figure 21. Early life exposure and adult cancer risk. Schematic overview of hypotheses on how exposure in early life could influence cancer development in adulthood. Adopted from Clarke et al[191].

In paper I, the association between childhood BMI and colon cancer was modified through pubertal BMI change, but for NHL only childhood BMI showed an association, without interaction through pubertal BMI change. This exemplifies that early life exposure probably affects adult cancer risk in different ways for different cancers.

The use of BMI as a risk factor

Excess weight, in the form of elevated BMI, could increase the risk of future cancer in several different ways. Consider a hypothetical BMI-curve, with some BMI-accelerations and decelerations (Figure 22A). It is plausible that the highest attained BMI-status (*Peak BMI*) induces an increased risk of future disease (Figure 22B). This is probably the most widely used model in scientific studies[185].

Another possibility is that the cumulative time above a BMI-threshold (*Accumulated time*) determine the future risk (Figure 22C). In the *BMI-accelerations* model, the accumulated accelerations in BMI, i.e., the sum of the BMI centile crossings, serve as the exposure that triggers an increased risk (Figure 22D). This theory proposes that a person could attain increased risk of future disease without ever being overweight by pronounced "catch up-growth" or frequent weight pendling[77]. The theories of the developmental origin of health and disease started with observations by Barker that centile crossing (BMI-acceleration), from low birthweight to normal or overweight in later childhood/adolescence, was associated with increased risk of adult disease[201,202].

The *Area under the curve*-model uses the sum of the area under the curve as risk marker (Figure 22E). This model takes into account both the extent of the excess weight, and the accumulated time with high BMI. The use of this model in scientific research requires data intense BMI-measurements, and is seldom used.

The *sensitive/critical period* (addressed in Figure 21, and Figure 22F), the individual is more vulnerable to the exposure during the specific period. The sensitive/critical period model can be combined with the other theories.

These theories exemplify possible ways of how high BMI could act as a risk marker or generator of disease. The theories demonstrate how a variable of BMI-exposure should be adapted to the plausible mechanism of risk triggering. The most accurate perspective is probably a combination of models, where separate mechanisms are of importance for different diseases.

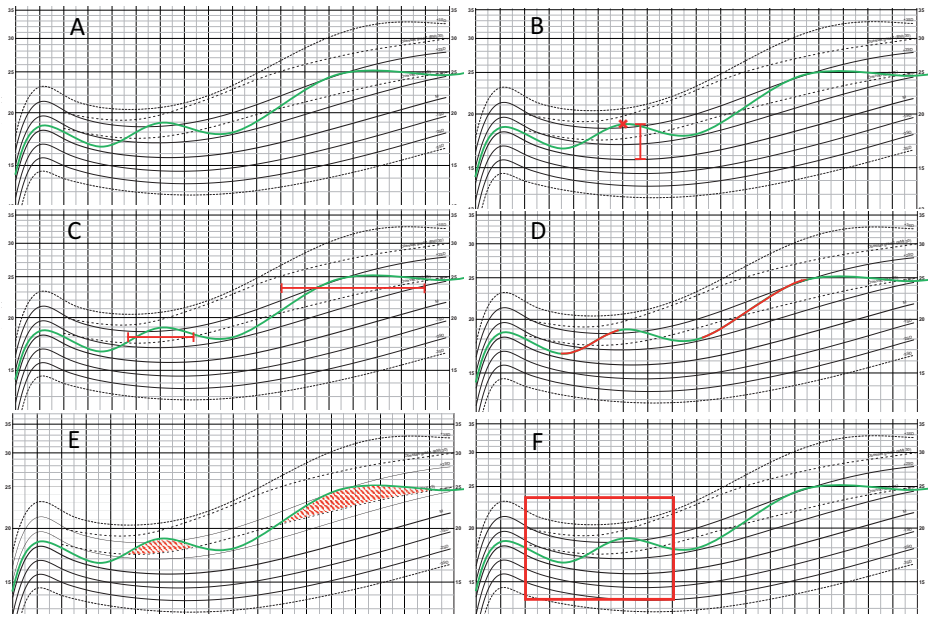


Figure 24. BMI risk factor models. Theories of how excess weight might affect future risk of disease.
A. A hypothetical BMI-curve.
*B. **Peak BMI**. The highest attained (standardized) BMI-value is the BMI-measure associated with increased risk.*
*C. **Accumulative time**. The total accumulated time above a BMI-threshold is what induces increased risk[77,228].*
*D. **BMI accelerations**. The sum of BMI-accelerations, upward centile crossing, is the risk inducer.*
*E. **Area under the curve**. The sum of the area under the curve above a certain threshold induces risk.*
*F. **The sensitive/critical period**. During a specific period, vulnerability to excess weight is increased.*

6.4 IMPLICATIONS AND CLINICAL SIGNIFICANCE

BMI is an important prognostic marker of health and disease and its importance will increase in the upcoming generations[5]. Despite the available knowledge, efforts to prevent overweight and obesity in Sweden and in the international community are arbitrary and insufficient. We are still in the initial phase of the obesity epidemic regarding insight and management, but also consequences. In support of an inevitable acceptance of the grave health consequences of the obesity epidemic, these studies contribute further evidence of a plausible initiation of disease mechanisms already in pre-pubertal children.

We have previously found an association between pubertal BMI change and CVD. In the present project we explored associations between childhood BMI and pubertal timing and different cancer forms, and found that childhood BMI is important for certain cancers, and that pubertal timing is associated with prostate cancer. Interestingly, our results demonstrate different associations for separate cancers, and even more contrasting associations when compared with CVD.

For CVD we have found higher risk estimates for individuals with a pubertal onset of overweight, than for individuals overweight at both childhood and young adulthood[58]. For obesity-related cancer risk, individuals overweight at eight years but normal weight at 20 still demonstrated significantly increased risk. Thus, adult risks of CVD and cancer are not merely a product of accumulation of exposures, but rather that the timing of onset of overweight is of certain importance. These findings support a sensitive period model for both CVD and cancer, and warrant further exploration of exposure to BMI-centile crossing as a risk factor for cancer and CVD.

Our results indicate that prevention of adult cancer should start already in childhood.

7 CONCLUSIONS

In the present projects, childhood onset of overweight seems to be of certain importance for cancer development, and that pubertal onset is indicated to be of lesser importance, contrary to our previous findings regarding CVD. Pubertal timing has been implicated to be associated with prostate cancer, an association corroborated in our study (project IV), and in our cohort, the association was directly related to the duration of time after the pubertal timing. Our results of stable long-term birthweight-trends show that rational conclusions of periodic changes in birthweight deserve a long time-perspective.

Childhood overweight and obesity need to be addressed with severity. At present, there is an inequity regarding resources for preventive work and medical care of childhood overweight and obesity are widely diverse between regions in Sweden. All available evidence demonstrates that high BMI during development is a serious factor of ill health. Comparable health consequences in our children from other exposures, e.g., cigarette or alcohol consumption, that were supplied by parents or bought in the school-adjacent liquor or cigarette store during school recess, would not be accepted.

A history of insufficient energy access has primed us to crave and conserve energy. Abundant dietary energy supplies in modern societies have made some of our survival mechanisms obsolete, and even harmful. Although results from preventive efforts of childhood obesity often have been discouraging, authorities can and should not resign on childhood obesity as a preventable health risk. Hopefully, the present thesis can further encourage decisionmakers to prioritize intensified efforts.

8 FUTURE PERSPECTIVES

These findings need to be corroborated by future studies. Studies of associations in women are of course crucial for a population-based approach to prevention, for pathophysiological understanding of developmental overweight as a risk factor for cancer, and for a conclusive perspective of birthweight trends.

We observed a BMI-related sensitive period between birth and eight years of age for the risk of adult cancer. Studies that would deepen knowledge in this area could include:

1. Studies dense with growth data to separate associations of peak BMI models from acceleration- and total exposure time-models for overweight and obesity. Specifically, the use of BMI change-variables, i.e., standardized change in BMI between 0–2, 2–8 and 8–20 years of age, to determine the role of timing of onset of overweight/obesity for the risk of adult cancer.

2. Studies with the ability to separate childhood overweight from risks related to inactivity and diet.

3. Studies of risks related to adult life BMI development in relation to risks specifically from developmental BMI.

4. Studies to evaluate the independent associations between birthweight and cancer risk.

5. Lastly, and perhaps most important, studies to determine the preventive measures to halt and counteract the present BMI-development in young children.

9 RELATED PUBLICATIONS NOT INCLUDED IN THE THESIS

I. **Celind, J**, Södermark, L, Hjalmarson, O. Adherence to treatment guidelines for acute otitis media in children. The necessity of an effective strategy of guideline implementation. Int J Pediatr Otorhinolaryngol 2014; 78(7):1128-32.

II. Bygdell, M, Ohlsson, C, **Celind, J**, Saternus, J, Sonden, A, Kindblom, J. M. The rise and the recent decline of childhood obesity in Swedish boys: the BEST cohort. Int J Obes 2017; 41(5):807-812.

III. Kindblom, J. M, Bygdell, M, Sonden, A, **Celind, J**, Rosengren, A, Ohlsson, C. BMI change during puberty and the risk of heart failure. J Intern Med 2018; 283(6):558-567.

IV. Bygdell, M, Kindblom, J. M, **Celind, J**, Nethander, M, Ohlsson, C. Childhood BMI is inversely associated with pubertal timing in normal-weight but not overweight boys. Am J Clin Nutr 2018; 108(6):1259-1263.

V. Ohlsson, C, Bygdell, M, **Celind, J**, Sonden, A, Tidblad, A, Savendahl, L, Kindblom, J. M. Secular Trends in Pubertal Growth Acceleration in Swedish Boys Born From 1947 to 1996. JAMA Pediatr 2019; 173(9):860-865.

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