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perspectives on prevention

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RAPID INFANT WEIGHT GAIN AND CHILDHOOD OVERWEIGHT AND OBESITY

PERSPECTIVES ON PREVENTION

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PhD Dissertation
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List of papers

The PhD thesis is based on the following scientific papers:

Study I   Rotevatn TA., Melendez-Torres GJ., Overgaard C., Peven K., Hyldgaard Nilsen J., Bøggild H., & Høstgaard AMB. (2019) Understanding rapid infant weight gain prevention: a systematic review of quantitative and qualitative evidence. *European Journal of Public Health*. pii: ckz140

Study II   Rotevatn TA., Overgaard C., Melendez-Torres GJ., Mortensen RN., Ullits LR., Høstgaard AMB., Torp-Pedersen C., & Bøggild H. (2019) Infancy weight gain, parental socioeconomic position, and childhood overweight and obesity: a Danish register-based cohort study. *BMC Public Health*. 19(1):1209

Study III   Rotevatn TA., Mortensen RN., Ullits LR., Torp-Pedersen C., Overgaard C., Høstgaard AMB., & Bøggild H. Early-life childhood obesity risk prediction: A Danish register-based cohort study exploring the predictive value of infancy weight gain. *(In preparation)*.

English Summary

Childhood overweight and obesity continues to be a significant public health problem due to its consequences on physical and psychosocial health of individuals. Obesity in childhood is often transferred into adulthood, why early prevention is key. The first 1.000 days of life, from conception to the child is two years of age, may be a crucial period for prevention, as numerous risk factors for overweight and obesity may operate during this period. One of these risk factors is rapid infant weight gain, which is associated with a considerable increase in later overweight and obesity risk. However, gaps in knowledge in relation to rapid infant weight gain prevention exist. This thesis sets out to address these gaps by developing further knowledge on to whom, when and how rapid infant weight gain prevention should be performed in order to prevent childhood overweight and obesity.

The thesis is based on three individual studies and an additional analysis. Through Study I, a systematic review collating quantitative and qualitative evidence on rapid infant weight gain prevention, it was discovered that preventive interventions generate small but statistically significant short-term effects on infancy weight gain. However, little evidence on longer-termed effects on overweight and obesity seem to exist. A range of barriers and enhancers for rapid infant weight gain prevention were also identified, which altogether highlighted that the intervention context, including parents, health professionals as well as the organisational and political environment, are important to take into account in order to enhance intervention effectiveness and success.

Study II, a register-based cohort study, showed that the risk of childhood overweight and obesity after rapid infant weight gain did not differ across socioeconomic position, although this was hypothesised. Applying rapid infant weight gain prevention as a strategy to prevent childhood overweight and obesity can thus be equally valuable for all socioeconomic groups. However, the additional analyses investigating risk differences across infant size at birth indicate that children born large for gestational age have a statistically significantly increased risks of developing childhood overweight and obesity if they also experience rapid infant weight gain. Results from these analyses thus suggest that children born large for gestational age pose a special risk group in need for rapid infant weight gain prevention.

Study III, another register-based cohort study, showed that infancy weight gain information can be important predictor for an early-life obesity risk prediction model, as inclusion of this predictor enhanced model ability to discriminate between children with and without obesity and to classify high and low-risk children correctly. This also increased model sensitivity although the sensitivity rate remained at a low level.

This thesis shows that the research field of rapid infant weight gain prevention is complex and under development. Overall, there exists a lack in comparable experimental evidence, especially in evidence considering long-term effects on childhood overweight and obesity. Based on the current evidence base, it is not yet possible to develop firm guidelines on how rapid infant weight gain prevention is best carried out. Despite this, the thesis contributes with new knowledge on who, when and how rapid infant weight gain prevention should be performed, as well as it presents suggestions for further research that can support the development of this field of research.

Dansk Resume

Overvægt og svær overvægt hos børn er fortsat et betydeligt folkesundhedsmæssigt problem på grund af dets konsekvenser for den enkeltes fysiske og psykiske helbred. Svær overvægt i barndommen overføres ofte til voksenlivet hvorfor tidlig forebyggelse er vigtigt. Barnets første 1.000 dage, fra undfangelse til barnet er to år gammelt, kan være en afgørende periode for forebyggelse, da adskillige risikofaktorer for overvægt og fedme kan være på spil i denne periode. En af disse risikofaktorer er hurtig vægtstigning i spædbarnsalderen, da denne risikofaktor er forbundet med en betydelig forhøjet risiko for at udvikle overvægt og svær overvægt i barndommen. Der mangler dog viden omkring forebyggelse af hurtig vægtstigning i spædbarnsalderen, hvorfor denne afhandling tager sigte på at udvikle yderligere viden om til hvem, hvornår og hvordan denne type forebyggelse skal udføres for at forhindre overvægt og svær overvægt hos børn.

Afhandlingen baseres på tre individuelle studier og en ekstra analyse. Gennem Studie I, en systematisk oversigtsartikel baseret på eksisterende kvantitative og kvalitative studier omkring forebyggelse af hurtig vægtstigning i spædbarnsalderen, blev det kendt, at eksisterende forebyggende interventioner genererer små men statistiske signifikante effekter på spædbørns vægtstigning på kort sigt. Dog eksisterer der ikke meget evidens omkring de længerevarende effekter på overvægt og svær overvægt. En række barrierer og muligheder for forebyggelse af hurtig vægtstigning i spædbarnsalderen blev også identificeret igennem studiet, hvilket understregede at interventionskonteksten, herunder forældre, sundhedspersonale såvel som det organisatoriske og politiske miljø, er vigtigt at tage i betragtning for at fremme interventioners effekt og succes.

Studie II, en registerbaseret kohorteundersøgelse, viste, at risikoen for overvægt og svær overvægt hos børn efter hurtig vægtstigning i spædbarnsalderen ikke var forskellig på tværs af socioøkonomiske positioner, skønt denne hypotese var antaget. Forebyggelse af hurtig vægtstigning i spædbarnsalderen som en strategi til at forhindre overvægt og svær overvægt hos børn kan derfor være lige så værdifuld for alle socioøkonomiske grupper. Imidlertid indikerer de ekstra analyser, der undersøger risikoforskelle på tværs af spædbørnsstørrelse ved fødslen, at børn, der er født store i forhold til gestationsalder, har en statistisk signifikant øget risiko for at udvikle overvægt og svær overvægt i barndommen, hvis de også oplever hurtig vægtstigning i

spædbarnsalderen. Disse resultater tyder derfor på, at børn født store for gestationsalder udgør en særlig risikogruppe med behov for forebyggelse af hurtig vægtstigning i spædbarnsalderen.

Studie III, en anden registerbaseret kohorteundersøgelse, viste, at information om spædbørns vægtøgning kan være vigtig prædiktor for en prædiktionsmodel der tidligt i barnets liv forudsiger risiko for svær overvægt senere i barndommen, da inklusion af denne prædiktor forbedrede modellens evne til at skelne mellem børn med og uden svær overvægt og til at korrekt klassificere børn med høj vs. lav risiko for svær overvægt. Inkludering af denne information øgede også modellens sensitivitet selv om sensitivitetsniveauet forblev på et lavt niveau.

Denne afhandling viser, at forskningsområdet for forebyggelse af hurtig vægtstigning i spædbarnsalderen er komplekst og under udvikling. Generelt mangler der sammenlignelig evidens omkring eksperimentel forskning, især når det gælder evidens der tager interventioners langtidsvirkninger på overvægt og svær overvægt i barndommen i betragtning. Baseret på den eksisterende evidens er det endnu ikke muligt at udvikle klare retningslinjer for, hvordan forebyggelse af hurtig vægtstigning i spædbarnsalderen bedst udføres. På trods af dette bidrager afhandlingen med ny viden om til hvem, hvornår og hvordan denne type forebyggelse kan udføres, såvel som den præsenterer forslag til videre forskning, der kan understøtte udviklingen af dette forskningsområde.

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List of Abbreviations

AGA   Appropriate-for-gestational age

AUC   The area under the receiver operating characteristic curve

BMI   Body Mass Index

CDB   The Children's Database

CI   Confidence interval

COO   Childhood overweight and obesity

CPR   Civil Personal Register

LGA   Large-for-gestational age

OR   Odds ratio

RCT   Randomised controlled trial

RERI   Relative Excess Risk due to Interaction

RIWG   Rapid Infant Weight Gain

SEP   Socioeconomic position

WAZ   Weight-for-age z-score

WHO   World Health Organization

WIC   The Special Supplemental Nutrition Program for Women, Infants, and Children

1   Introduction

1.1   The complex problem of childhood overweight and obesity

The previous increase in prevalence of childhood overweight and obesity (COO) tends to level off in many high-income countries including Denmark (Morgen et al., 2013; NCD Risk Factor Collaboration (NCD-RisC), 2017; Rokholm, Baker, & Sørensen, 2010). However, more than 9% of Danish children are still classified with overweight and 3% with obesity when reaching school-age (Sundhedsdatastyrelsen, 2019). Even though the Danish prevalence of COO are low in a European perspective (WHO Regional Office for Europe, 2018), a large number of children are still at risk of developing physiological, psychological and social consequences due to their weight. Compared to normal-weight children, children with overweight and obesity are at higher risk of cardiometabolic diseases, asthma, poor dental health and mortality (Pulgarón, 2013; Reilly & Kelly, 2011). These children are also in greater risk of having poorer academic performance, of receiving disability pension or of experiencing stigmatization and bullying that in turn may lower one's self-esteem and confidence (Reilly & Kelly, 2011; Sahoo et al., 2015).

The prevalence of COO varies across population groups (WHO Regional Office for Europe, 2018). Children from families with lower compared to higher socioeconomic position (SEP) are more likely to develop overweight or obesity, which result in a social gradient in several European high-income countries (Lissner et al., 2016), including Denmark (Magnusson et al., 2014; Pedersen, Aarestrup, Pearson, & Baker, 2016). This social gradient demonstrate the complexity of COO, as it indicate that characteristics and factors related to parent education, income or occupation are of great importance for the development of this problem (Solar & Irwin, 2010). By now, this complexity has been widely acknowledged, why it is assumed that several child, parental, social and environmental factors simultaneously interact in a complex interplay leading to a positive energy balance and overweight or obesity (Davison & Birch, 2001; Finegood, Merth, & Rutter, 2010; Frederick, Snellman, & Putnam, 2014; Lakshman, Elks, & Ong, 2012; Lobstein, Baur, Uauy, & Force, 2004; Sahoo et al., 2015).

Childhood overweight and obesity are perceived as two interchangeable concepts. Overweight can be defined as weighing over a weight standard, while obesity can be defined as having body fat over a body fat standard, why these concepts in some ways

are overlapping but also contrasting (Flegal & Ogden, 2011). This, as a child could be overweight but not obese if weighing over a weight standard and both overweight and obese at the same time as obesity is always associated with overweight (Flegal & Ogden, 2011). Defining and identifying COO require the use of an anthropometric measure, a reference population and a cut-off point (de Onis & Lobstein, 2010). A range of different anthropometric measures, references and cut-off points exist, which makes it possible to define COO using a large variety of different classifications (Rolland-Cachera, 2011). However, this differing use of classifications challenge comparison of results across studies.

Body mass index (BMI), a measure of body mass relative to height (de Onis & Lobstein, 2010), is one of the most commonly used measures of COO in research (Lobstein et al., 2004). This measure corresponds to how excessive body weight and body fat relate to the risk of disease and death (World Health Organization, 2018). A higher BMI therefore reflects a higher morbidity and mortality risk. The BMI cut-offs for bodyweight status are constant for adults over 18 years old (World Health Organization, 2018), while they are age- and sex-dependent for children due to biological growth (Lobstein et al., 2004; Rolland-Cachera, 2011).

Rolland-Cachera and the European Childhood Obesity Group (2011) have tried to reach consensus on a COO definition in research by recommending use of the World Health Organization (WHO) growth standards and associated cut-offs for children aged between 0 and 5 years (World Health Organization, 2006), the International Obesity Task Force reference and associated cut-offs for children aged between 2 and 18 years (Cole, Bellizzi, Flegal, & Dietz, 2000), and the WHO growth reference and associated cut-offs for children aged between 5 and 19 years (de Onis et al., 2007). The overlapping age intervals enable the use of more than one reference at most ages, and this practice is also recommended by Rolland-Cachera and the European Childhood Obesity Group (2011).

Overall, COO is a complex problem with physical, social and psychological consequences for the individual. Childhood overweight and obesity is often transferred into adulthood (Simmonds, Llewellyn, Owen, & Woolacott, 2016; Singh, Mulder, Twisk, Van Mechelen, & Chinapaw, 2008), as 70% of all adolescents with obesity are obese as adults (Reilly, 2006). Childhood overweight and obesity are detected already at early ages (Field, 2016), and the ongoing risk of experiencing physical, social and psychological consequences over the lifespan highlights that early prevention are of great importance.

1.2 Early origins to childhood overweight and obesity

Especially the first 1000 days of life, from conception until two years of age, has received much attention in research of COO, as it is considered a time where programming processes have the potential to affect the lifetime risk of disease (Koletzko, von Kries, et al., 2009; Stettler, 2007; Taylor & Poston, 2007). Programming is a concept used to explain that chronic conditions may originate in early-life (Stettler, 2007), where hormonal, placental and epigenetic changes in the utero caused by different factors related to maternal lifestyle, disease and stress alter the foetus' risk of later disease, including metabolic diseases and COO (Gluckman, Hanson, Cooper, & Thornburg, 2008; Padmanabhan, Cardoso, & Puttabyatappa, 2016). Physiological changes caused by these programming processes can be seen as a physiological mechanism that prepares the foetus to the subsequent environment, causing what is believed to be irreversible changes (Godfrey, Lillycrop, & Murray, 2016).

One programming mechanism hypothesised to increase the child's risk of COO is the transference of higher concentrations of glucose and amino acids across the placenta in obese pregnant women, which is hypothesised to increase foetal secretion of insulin leading to increased foetal growth, increased fat mass development and macrosomia which consequently increase the risk of developing obesity (Reynolds, 2012; Yu et al., 2013). Moreover, gestational diabetes is hypothesised to cause foetal hyperglycaemia and hyperinsulinemia, which can increase foetus' weight gain and growth of fat cells, thus increasing the risk of rapid postnatal weight gain and obesity (Lamb et al., 2010). This is by some named the *high* path to obesity, as these infants are adipose at birth and remain adipose during childhood (Godfrey et al., 2016).

Another programming mechanism assumed to increase the COO risk is related to maternal smoking during pregnancy. Smoking is thought to cause vasocontraction of nicotine and hypoxia in the foetus, which can induce in utero growth restrictions followed by an increased risk of accelerated postnatal weight gain and obesity (Ino, 2010; Oken, Levitan, & Gillman, 2008; Rayfield & Plugge, 2017). Similar growth patterns are observed in children born from mothers suffering from undernutrition during pregnancy (Godfrey et al., 2016). This mechanism is a part of the *thrifty phenotype hypothesis*, also called the *Barker hypothesis*, which suggests that these processes permanently changes infant insulin metabolism and body fat composition which subsequently increase the subsequent risk of COO (Hales & Barker, 2001). This path to obesity can also be named the *low* path, as children are born small due to in utero

growth restriction but gain adiposity at a rapid pace in early childhood years (Godfrey et al., 2016).

Furthermore, it has been suggested that processes induced by postnatal nutrition can alter children's risk of COO. Through the *early protein hypothesis,* Koletzko and colleagues (2013; 2005; 2011) propose that a high protein intake during infancy can increase the risks of both accelerated weight gain in infancy and COO, as a high protein intake accelerates the secretion of insulin and insulin-like growth factors that has both short- and long-term effects on child growth and weight gain.

Taken altogether, these early-life programming mechanisms propose that the early origins of COO risk represent a complex problem area, as several, potentially coinciding, hypotheses suggest different pathways through which early-life factors can cause obesity. One common element of these hypotheses is that they somehow involve accelerated postnatal weight gain, often referred to as *rapid infant weight gain* in the literature.

1.3 Rapid infant weight gain and childhood overweight and obesity

Accelerated postnatal weight gain, or *rapid infant weight gain* (RIWG), as frequently named in the literature, is most commonly defined as a change in weight-for-age z-scores (WAZ) of more than 0.67 between two time point during the first two years in life (Monteiro & Victora, 2005; Ong et al., 2000; Zheng et al., 2017). This change represents moving up at least one percentile band on a growth chart (Monteiro & Victora, 2005; Ong et al., 2000; Zheng et al., 2017), and can thus be considered a clinically meaningful definition. Different cut-offs, measures of weight gain and conditional weight gain scores have also been applied when studying RIWG (Griffiths, Smeeth, Hawkins, Cole, & Dezateux, 2009; Monteiro & Victora, 2005), but some consensus have been established around the use of this earlier presented definition (Monteiro & Victora, 2005; Ong et al., 2000; Zheng et al., 2017). The prevalence of RIWG varies across populations and ranged between 12.3% to 54.2% (median: 29.9%) in different populations in a recent systematic review on the topic (Zheng et al., 2018). This inconsistency in prevalence was observed despite the use of the same definition, why it can be suggested that variations in population characteristics or in timing of measurements are of importance for how many infants that are classified with RIWG in a population. As with COO, differences in definitions can challenge the cross-study comparison of RIWG research.

Accelerated postnatal weight gain or RIWG were primarily presented as a weight gain trajectory that precede childhood obesity in the previous presentation of programming mechanisms leading to COO. Instead of solely viewing RIWG as a marker for a weight gain trajectory leading to later obesity (Brands, Demmelmair, & Koletzko, 2014), the *accelerated weight gain hypothesis* proposes that RIWG itself can initiate physiological processes causing later metabolic abnormalities that facilitate obesity development (Brands et al., 2014; Singhal & Lucas, 2004; Young, Johnson, & Krebs, 2012). However, the mechanisms that explain how RIWG would cause COO still remains unclear (Stettler & Iotova, 2010), but it is suggested that RIWG could affect insulin-like growth factors in infants with a high postnatal protein intake (Brands et al., 2014). This links RIWG to COO through the *early protein hypothesis*. A similar explanation is proposed by Koletzko and colleagues (2012), where a high protein intake is thought to lead to metabolic and hormonal changes which would increase weight gain and fat accumulation. Although existing evidence does not enable firm presentation of exact mechanisms, observational evidence show that RIWG is associated with more central fat deposition and general fat accumulation (Durmuş et al., 2010; Ong et al., 2009; Stettler, 2007; Zheng et al., 2017).

A large quantity of observational evidence have tested the relationship between RIWG in the first two years in life and later risk of COO (Monteiro & Victora, 2005; Ong & Loos, 2006; Weng, Redsell, Swift, Yang, & Glazebrook, 2012; Woo Baidal et al., 2016; Zheng et al., 2017). This evidence has consistently detected a positive and strong association between RIWG and an increased risk of overweight and obesity in childhood, adolescence and adulthood, with the latest meta-analysis reporting a pooled odds ratio of 3.66 (95% confidence interval [2.59 to 5.17]) (Zheng et al., 2018). However, little experimental evidence exists on the relationship between RIWG and later obesity. The lack of experimental evidence might not be surprising, as it would be impossible to randomly allocate different weight gain rates to infants due to practical and ethical reasons (Stettler, 2007). However, the *early protein hypothesis* has been tested in a randomised controlled trial by randomly allocating infants to receive formula with high and low protein content (Koletzko, Kries, et al., 2009). Compared to the high protein formula group, the low protein formula group showed less weight gain during follow-up at two years of age without detecting any differences in length (Koletzko, Kries, et al., 2009). At long-term follow-up, higher BMI and increased risk of obesity at six years of age were observed in the high compared to the low protein formula group (Weber et al., 2014).

The evidence providing support for the *early protein hypothesis* highlight that infant feeding strategies are of great importance for the risk of RIWG. The shortage of experimental studies makes it difficult to determine whether a causal relationship between RIWG and COO actually exists and what mechanisms that would explain how RIWG cause COO. However, Stettler (2007) pinpoints that many of the criteria for causality in the relationship between RIWG and COO are fulfilled by current research, including the occurrence of dose-response relationships, temporality, biological plausibility and experimental reproducibility in animal models. Although experimental evidence to support a causal relationship is lacking, this suggest that prevention of RIWG could be a promising strategy for performing early-life obesity prevention.

Though little is known about the mechanisms linking RIWG to COO, considerable evidence exists on risk factors for RIWG. This knowledge is important for prevention of RIWG as a strategy for early-life obesity prevention.

1.4   Risk factors for rapid infant weight gain

A range of risk factors for RIWG has been identified. These risk factors are presented in three different categories in the following sections: 1) *Factors related to infant feeding*, 2) *Child and maternal factors*, and 3) *Social, environmental and background factors*.

1.4.1   Factors related to infant feeding

Most of the research on risk factors for RIWG have focused on aspects of infant feeding. Not surprisingly, *higher energy intake* at four months of age has been related to higher rates of rapid weight gain (Ong, 2006). However, this was only observed in formula- or mixed-fed infants, and not in fully breastfed infants. *Breastfeeding* have recurrently been identified as protective against RIWG (de Hoog, van Eijsden, Stronks, Gemke, & Vrijkotte, 2011; Griffiths et al., 2009), while *formula and bottle-feeding* has repeatedly been identified as a risk factor (Karaolis-Danckert et al., 2008; Mihrshahi, Battistutta, Magarey, & Daniels, 2011). As previously presented, experimental evidence provide support for the *early protein hypothesis* suggesting that formula feeding cause RIWG, as formula holds a higher protein content than breastmilk (Koletzko, Kries, et al., 2009). However, it has been suggested that *bottle-feeding itself* rather than formula feeding is the true risk factor for RIWG, as weight increase was observed regardless of the type of milk fed from the bottle (Li, Magadia, Fein, & Grummer-Strawn, 2012). The authors explain this by suggesting that bottle-fed children have poorer abilities to self-regulate their intake. A *large infant appetite* has also been identified as a risk factor (Patel et al., 2018; van Jaarsveld, Boniface, Llewellyn, & Wardle, 2014).

Moreover, certain practices related to formula feeding have also been associated with an increased risk of RIWG. A systematic review on the topic identifies *feeding of high protein formula, feeding of formula added with cereals, overfeeding formula* and *putting infants to bed with a bottle* as risk factors (Appleton et al., 2018). An increased risk of RIWG has also been observed in children *fed on a schedule* (Chrestani, Santos, Horta, Dumith, & De Oliveira Dode, 2013) and in children *fed using a large bottle size* (Wood et al., 2016). Finally, *early weaning* has too been highlighted as a potential risk factor (Baker, Michaelsen, Rasmussen, & Sørensen, 2004; Chrestani et al., 2013; Sloan, Gildea, Stewart, Sneddon, & Iwaniec, 2008). This was however, not confirmed by Griffiths and colleagues (2009).

1.4.2   Child and maternal factors

Being first born has been related to an increased risk of RIWG (Baker et al., 2004; Chrestani et al., 2013; Karaolis-Danckert et al., 2008; Ong et al., 2000). More nutritious breastmilk or an inadequate intrauterine environment in primiparous mothers has been suggested as potential mechanisms affecting postnatal weight gain in these children (Chrestani et al., 2013; Karaolis-Danckert et al., 2008). Having *low gestational age* (Karaolis-Danckert et al., 2008) or a *lower birthweight* has also been identified as a risk factor by several studies (Baker et al., 2004; Chrestani et al., 2013; Ong et al., 2000), as children born small are typically more prone to experience catch-up growth and accelerated postnatal weight gain in infancy (Hokken-Koelega et al., 1995).

Maternal smoking during pregnancy were previously related to RIWG through the low path to COO as presented in section 1.2, and several systematic reviews and observational studies have found support to this relationship (Baker et al., 2004; Chrestani et al., 2013; Mine et al., 2017; Ong et al., 2000). Apart from this, few studies have focussed specifically on how maternal and child lifestyle factors are related to RIWG. One Japanese study considered maternal lifestyle factors and observed that *drinking alcohol prior to pregnancy* or having *few meals a day during pregnancy* increased the risk of RIWG in their offspring (Oyama, Nakamura, Tsuchiya, & Yamamoto, 2009). Another study on infants activity level suggest that *more time spent in prone position* (tummy time) during the first four months of life reduce the risk of RIWG (Koren, Kahn-D'angelo, Reece, & Gore, 2019).

1.4.3   Social, environmental and background factors

Little research has been conducted on social and environmental risk factors for RIWG. Edmunds and colleagues (2014) studied the relationship between *timing of enrolment to The Special Supplemental Nutrition Program for Women, Infants, and Children* (WIC), a federal program that provide healthcare and nutrition support to low income families with children under five years (United States Department of Agriculture, 2013). Here, a lower risk of RIWG were observed in infants from mothers that enrolled early during pregnancy compared to infants from mothers who enrolled after giving birth (Edmunds et al., 2014). The timing of returning to work can also affect RIWG risk, as a higher risk were observed in infants from mothers that returned to work within the first 12 weeks after giving birth (Eagleton et al., 2019).

Considerably more research has been conducted on the role of ethnicity and socioeconomic position on the risk of RIWG. In the case of ethnicity, high risks of RIWG have been observed in *African American* (Bichteler & Gershoff, 2018; Taveras,

Gillman, Kleinman, Rich-Edwards, & Rifas-Shiman, 2010) and *Hispanic* infants (Taveras et al., 2010), and in infants with *migrant background* (Reeske et al., 2013) or infants of *minority races* in general (Boone-Heinonen, Messer, Andrade, & Takemoto, 2016; de Hoog et al., 2011). The evidence has however been less consistent when it comes to socioeconomic position (Boone-Heinonen et al., 2016). Wijlaars and colleagues (2011) found higher risk of RIWG in groups with less favourable occupational status and in mothers with poorer educational status. Reeske and colleagues (2013) also observed higher risk of RIWG in groups with lower SEP, but the risk-relationship were attenuated after adjusting for confounders. In contrast, Svensson and colleagues (Svensson et al., 2014) did not find any association between RIWG and family education level.

All things considered, the many risk factors and programming processes with significance for RIWG risk potentially occurring during pregnancy and in early life suggest that preventing RIWG from occurring can be a complex task. Some of these risk factors are modifiable, like maternal smoking during pregnancy or infant feeding practices, and is thus potentially amenable through interventions. Interventions for preventing childhood obesity have been developed and tested for decades, but mainly in populations aged older than five years (Brown et al., 2019; Summerbell et al., 2005; Waters et al., 2011). A much lower number of intervention studies have targeted children of younger ages, but this field of research, including prevention of RIWG, has been under rapid development over the last decade (Birch, Anzman-Frasca, & Paul, 2012; Hesketh & Campbell, 2010).

1.5   Prevention of rapid infant weight gain

The interest for RIWG prevention has grown parallel with the increasing focus on the first 1000 days of life in relation to obesity prevention. Despite the growing number of intervention studies on RIWG prevention, no attempts have been made to collate this experimental evidence. Several researchers like Cullum & Dumville (2015) and Gopalakrishnan & Ganeshkumar (2013) highlight that production of high-quality summaries of all relevant, existing research in a research field is important to support decision making in health-care by making evidence more accessible for practitioners, politicians and other decision-makers. In the field of COO prevention, Cauchi and colleagues (2016) report that there exist a lack in focus on feasibility and implementation strategies in intervention studies, which is information with great importance for the practice recommendations made for policymakers. Hence, summaries of existing intervention research should focus on understanding the perspectives of intervention recipients and providers in addition to evaluating intervention effectiveness, as summaries synthesising this type of evidence could lead to development of knowledge that are particularly valuable for practice (Sutcliffe, Thomas, Stokes, Hinds, & Bangpan, 2015). Taking this comprehensive approach when undertaking a systematic review could support the identification of potential effective intervention components, potential barriers and enablers for intervention implementation, as well as of a more rich understanding of the context where interventions are implemented (Rycroft-Malone & Burton, 2015). Collating all this existing and relevant evidence on RIWG prevention can thus be valuable for advancing the understanding on what, when and how prevention of this complex problem work or does not work in order to put forward qualified recommendations to policy and practice.

1.6   Prevention and socioeconomic position

Collating and analysing existing knowledge on RIWG prevention is a key task in facilitating development and implementation of effective prevention activities and strategies in the future. Another task essential for the development of effective intervention strategies is to determine whether any sub-groups in special need for prevention exist. Higher rates of both RIWG (Reeske et al., 2013; Wijlaars et al., 2011) and COO (Barriuso et al., 2015; Chung et al., 2016; Shrewsbury & Wardle, 2008) has been observed in populations with lower socioeconomic position. The relationship between RIWG and childhood obesity appears stronger in studies where low SEP is strongly represented in the study population (Andrea, Hooker, Messer, Tandy, & Boone-Heinonen, 2017). Hence, infants from low SEP families could potentially be in need of special preventive attention if infants from low compared to high SEP families are at higher risk of developing COO after RIWG.

Several arguments suggesting effect modification between infant weight gain velocity and SEP on the risk of COO can be stated. First, families of low SEP typically have less resources that can be used to avoid exposure to risk factors (Elstad, 1998; Link & Phelan, 1995). This is already observed, as Cameron and colleagues (2015) report of social patterning in the exposure to several pre- and postnatal obesity risk factors such as maternal pre-pregnancy obesity, gestational diabetes, maternal smoking during pregnancy and factors related to infant feeding. Several of these risk factors pre- and postnatal risk factors are associated with programming processes affecting RIWG as previously described in section 1.2. Thus, it can be suggested that low SEP groups are at higher risk of experiencing clustering of and interaction between these and other risk factors and processes, which can possibly further amplify their risk of developing COO (Diderichsen et al., 2012). Moreover, social differences in infant feeding and views on parenting (Baughcum, Chamberlin, Deeks, Powers, & Whitaker, 2000; Baughcum, Burklow, Deeks, Powers, & Whitaker, 1998; Cameron et al., 2015; Genovesi et al., 2005; Heinig et al., 2006), as well as in the macro-levelled determinants that shapes these behaviours like social support and parental behaviours practiced in their social network exists (Heinig et al., 2006; Mitra, Khoury, Hinton, & Carothers, 2004; Olson, Horodynski, Brophy-Herb, & Iwanski, 2010; Scott, Binns, Graham, & Oddy, 2009), which can lead to socioeconomic differences in how RIWG is perceived and acted upon. In the end, this may produce socioeconomic differences in children's succeeding weight trajectory.

Two previous studies have studied potential effect modification without finding signs of risk differences in the relationship between RIWG and COO between SEP groups

(Karaolis-Danckert et al., 2008; Stettler, Kumanyika, Katz, Zemel, & Stallings, 2003). However, these results may be subjected to type II error, as the sample sizes were small. A more comprehensive study is therefore needed to draw firm conclusions on whether infants from families of low compared to high SEP are at higher risk of developing COO after RIWG, and thus being in need for special prevention efforts.

1.7 Infant weight gain information and risk prediction

As stated earlier in the introduction, there exist a strong association between RIWG and COO (Monteiro & Victora, 2005; Ong & Loos, 2006; Weng et al., 2012; Woo Baidal et al., 2016; Zheng et al., 2017). Relative measures, most frequently odds ratios, are applied when measuring this association, and only a few of these many studies report how many children who actually develop obesity after experiencing RIWG. The few studies presenting these numbers report that only 8.8% (Akaboshi, Haraguchi, Mizumoto, Kitano, & Kan, 2008), 18.9% (Heppe et al., 2013), 30.5% (Karaolis-Danckert et al., 2006) and 15.9% (Ekelund et al., 2006) of infants who experience RIWG develop overweight or obesity at age 3, 4, 7 and 17 years of age, respectively. Methodological differences may make these numbers incomparable, but these numbers illustrate that a large proportion of infants with RIWG does not go on and develop overweight or obesity. These numbers highlight a need for developing methods that, already at an early stage in life, can be used to discriminate between children that do and do not develop overweight or obesity, as such methods could help to optimise early-life primary obesity prevention.

Statistical prediction models based on early-life risk factors can be utilized to identify individuals who have a particularly high risk of developing COO (Butler, Derraik, Taylor, & Cutfield, 2018b; Ziauddeen, Roderick, Macklon, & Alwan, 2018). A number of such prediction models currently exist (Ziauddeen et al., 2018), and these models have the potential to support early identification of infants at high risk of developing COO, which could help clinical decision-making, facilitate early initiation of appropriate actions for prevention, and enhance effectiveness of preventive interventions (Butler, Derraik, Taylor, & Cutfield, 2018a; Moons et al., 2012; Moons, Royston, Vergouwe, Grobbee, & Altman, 2009).

In a recent systematic review on early-life obesity prediction models by Ziauddeen and colleagues (2018), five of the eight reviewed prediction models included information on postnatal weight gain when predicting COO risk. When compared to prediction models that only include predictors obtainable at birth would models that include postnatally obtained predictors like postnatal weight gain have a later timing of risk prediction. The timing of initiating appropriate action would thus also be delayed from birth to later infancy. On the other hand, the additional information derived from postnatal weight gain data could be valuable for the prediction model performance, as previous studies identifies infancy weight gain as a particularly valuable predictor for later overweight and obesity risk (Druet et al., 2012; Robson, Verstraete, Shiboski, Heyman, & Wojcicki, 2016; Santorelli et al., 2013; Weng et al.,

2013). However, the extra value of adding information on infancy weight gain to a prediction model only consisting of predictors obtainable at birth are unknown and needs to be considered as this information could help to inform the development of future prediction models in respect of model content and appropriate timing of prediction.

1.8 Aim of the thesis

In the previous sections, it has been argued that childhood overweight and obesity is a public health problem that should be prevented at an early stage in life, as obesity tend to follow children into adulthood once manifested and as many risk factors and processes with implications for later obesity development occur during pregnancy and infancy. Rapid infant weight gain is one of these early-life risk factors that consistently has been strongly associated to COO, and prevention of this weight gain pattern may be a promising strategy to prevent obesity at an early life stage. However, RIWG appears to be a complex phenomenon affected by a range of factors, and this complexity complicate prevention. Although the interest has increased during the last decade, the research on RIWG prevention is novel. Overall, evidence on the role of RIWG prevention as a strategy for early-life prevention of COO is lacking, which is a gap in knowledge that this thesis sets out to address. The thesis aims to contribute with knowledge on *how* such prevention should be carried out, *who* such prevention should be targeted and *when* such prevention should be initiated, as production of this knowledge could help to advance research and practice in this field.

The general topic of this thesis was early-life prevention of childhood overweight and obesity, and a focus on the role of infancy weight gain in relation to this matter. Furthermore, the overall aim of this thesis was *to develop new knowledge on the who, when and how of early-life overweight and obesity prevention with a focus on infancy weight gain to strengthen the knowledge informing research and practice*. This overall aim was addressed through investigation of three specific aims:

1. To examine the impact of, and the enablers and barriers for, interventions that prevent rapid infant weight gain as a strategy for early-life overweight and obesity prevention (Study I)

2. To investigate whether infants from parents with low socioeconomic position are at increased risk of developing overweight or obesity after rapid weight gain and thus have a special need for prevention (Study II)

3. To evaluate the importance of infancy weight gain information for making early-life predictions on later childhood overweight and obesity risk (Study III)

The coherence between the overall aim of the thesis and the specific aims of each study is illustrated in Figure 1, where the solid lines denote the study's main contribution to the overall aim and the stippled lines denote supplementary contributions. The study results will later be discussed based on this figure.
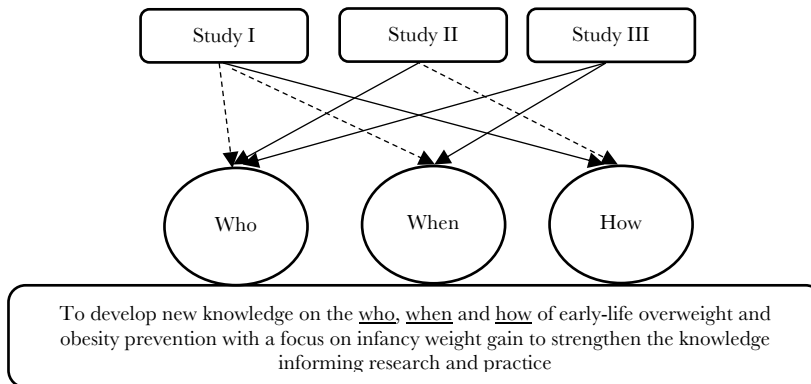
Figure 1. The figure illustrates how each study contributes to addressing the main aim of the thesis. Solid line denotes main contributions to the overall aim of the thesis, while stippled line denotes supplementary contributions.

2 Materials and methods

This chapter presents the materials and methods of the three studies that this thesis is based on. Some details have been left out of the thesis in order to reduce repetition from the information presented in the papers of each study. Thus, details on material and methods not presented here may be located in the specific paper. The three studies included in this thesis are based on two different types of study designs. Study I was designed as a *systematic review*, while Study II and Study III were formed as *historical cohort studies*, which is a type of *observational study design*. Table 1 gives a quick overview of essential details on the study aims and materials and methods of each study.

Table 1. The table presents an overview of the study aims and materials and methods of each study.			
Study	I	II	III
Specific aim in thesis	*To examine the impact of, and the enablers and barriers for, interventions that prevent rapid infant weight gain as a strategy for early-life overweight and obesity prevention*	*To investigate whether infants from parents with low socioeconomic position are at increased risk of developing overweight or obesity after rapid weight gain and thus have a special need for prevention*	*To evaluate the importance of infancy weight gain information for making early-life predictions on later childhood overweight and obesity risk*
Design	Systematic review	Historical cohort study	Historical cohort study
Data sources	PubMed, EMBASE, CINAHL, PsycINFO, The Cochrane Library, Web of Science, Scopus, grey literature databases	The Children's Database, The Medical Birth Register, The Population Education Register, The Income Statistics Register	The Children's Database, The Medical Birth Register, The Population Education Register, The Income Statistics Register
Population	Seven quantitative and seven qualitative studies	19 894 children	58 426 children
Exposure(s)		1) Infancy weight gain 2) Socioeconomic position	1) Infancy weight gain
Covariates/ predictors		Child sex, size for gestational age at birth, gestational age, mode of delivery, parity, maternal smoking status during pregnancy, gestational diabetes status, maternal pre-pregnancy BMI and breastfeeding duration	Child sex, size at birth, mode of delivery, parity, maternal smoking status during pregnancy, gestational diabetes status, maternal pre-pregnancy BMI, household income level, maternal education level
Outcomes	1) Intervention effects 2) Intervention enablers and barriers	1) Childhood overweight and obesity	1) Childhood obesity 2) Childhood overweight and obesity
Method of analysis	1) Narrative synthesis 2) Thematic synthesis 3) Intervention component analysis	1) Logistic regression models 2) Interaction analyses, including test for relative excess risk due to interaction	1) Logistic regression models 2) Area under the receiver operating characteristic curve 3) Reclassification table 4) Sensitivity and specificity

2.1 Study I: Systematic review

Study I was carried out as a systematic review, which involves answering predefined research questions through collation, critical evaluation and analysis of existing evidence (Higgins & Green, 2008). Study I was designed to answer the first specific aim of this thesis: *To examine the impact of, and the enablers and barriers for, interventions that prevent rapid infant weight gain as a strategy for early-life overweight and obesity prevention.* A systematic review was chosen among other less systematic and comprehensive review types, as it involves the development of a highly comprehensive search strategy that enhances the likelihood of identifying all relevant evidence on the subject under study, which is followed by a critical evaluation of the included evidence in order to evaluate its quality (Grant & Booth, 2009). Hence, a systematic review would enable identification and evaluation of the best available evidence and make this evidence more accessible for practitioners and policy makers (Centre for Reviews and Dissemination, 2009). This type of review was therefore considered suitable for informing practice on RIWG prevention, which was a part of the overall aim of the thesis.

A study protocol stating the planned rationale, objectives and methods were published in The International Prospective Register of Systematic Reviews (PROSPERO) prior to conducting the study, as recommended by *The Cochrane Collaboration* and *The Joanna Briggs Institute* (Higgins & Green, 2008; The Joanna Briggs Institute, 2014). The protocol is available at https://www.crd.york.ac.uk/prospero/ (ID: CRD42018076214).

2.1.1 Eligibility criteria and search strategy

It was necessary to obtain both quantitative and qualitative evidence in the review in order to address the study aim that involved acquiring information on intervention effectiveness in addition to information on intervention barriers and enables. Intervention effectiveness were studied through quantitative evidence on effectiveness, while intervention barriers and enables were studied through qualitative evidence on perspectives of intervention recipients and providers and from information related to intervention development and implementation processes. Overall, this information was thought to enhance the understanding of intervention effectiveness in the intervention context. Eligibility criteria were developed separately for quantitative and qualitative studies, but some criteria applied for both types of evidence. The eligibility criteria are presented in Table 2.

Table 2. The table shows the eligibility criteria for study inclusion in the systematic review. The information presented are obtained from the study protocol and paper of Study I.

Criteria for both quantitative and qualitative studies
o Studies reporting on any type of intervention that prevents rapid infant weight gain
o Studies reporting process information on intervention development, implementation or evaluation
o Published studies or grey literature
o Studies including healthy term infants between the age of 0 to 2 years
o Studies conducted in high income countries
o Studies written in English, Spanish or Nordic languages

Criteria for quantitative studies	Criteria for qualitative studies
o Studies reporting on intervention effects measured as differences in infant weight gain between two points in time	o Studies reporting on intervention deliverers' or recipients' experiences with involvement in relevant interventions
o Studies with randomised, non-randomised, or quasi-experimental designs, or as before-and-after or observational studies	o Studies of all qualitative study designs
o Studies including a control group if appropriate in terms of the study design	

As Table 2 shows, a broad range of quantitative and qualitative study designs were deemed eligible for inclusion in the review. This was chosen in order to identify all relevant evidence available. Both published studies and grey literature were eligible for inclusion in order to reduce the risk of publication bias (Higgins & Green, 2008). Grey literature are papers, reports or other documents not commercially published or indexed, which may complement the findings of published studies included in systematic searches (The Joanna Briggs Institute, 2014).

A block search strategy was applied to identify relevant citations, consisting of three blocks that represented the main concepts examined in the review (Higgins & Green, 2008): 1) The study population (*Infants*), 2) The phenomenon of interest (*Rapid infant weight gain*), and 3) The relevant study designs (*Quantitative or qualitative study design*). The search strategy was conducted as a three-phased process, as recommended by The Joanna Briggs Institute (The Joanna Briggs Institute, 2014). This involved initial identification of indexed terms and text words, which were subsequently used to develop database-specific search strategies. Finally, the reference lists of included studies were examined for additional relevant studies. Searches were carried out in a range of different databases that comprised health-related literature in order to identify all relevant evidence: PubMed, CINAHL, The Cochrane Library, PsycInfo, EMBASE, Web of Science, and Scopus. Relevant webpages were also searched using central keywords to identify relevant grey literature. The searches for quantitative and qualitative evidence were conducted on 31st October 2017 and 13th February 2018, respectively, and jointly rerun on 31st May 2018. Serving as an example, the search strategy carried out in PubMed can be located in Supplementary Table S1 in the paper of Study I.

2.1.2   Study selection, data extraction and quality appraisal

The processes of study selection, quality appraisal, and data extraction were conducted separately for quantitative and qualitative studies by at least two reviewers. This was done in order to reduce the risk of errors and bias, as recommended by *The Cochrane Collaboration* (Higgins & Green, 2008) and *The Joanna Briggs Institute* (The Joanna Briggs Institute, 2014). The review team consisted of the PhD candidate as primary reviewer and three co-reviewers. At least one co-reviewer supported the primary reviewer in all the tasks listed. The opinion of a third reviewer was considered when discrepancy between the two reviewers occurred. Microsoft Excel were utilised in the process of detecting duplicates, selecting studies and appraising study quality. Studies were initially selected based on the relevance of title and abstract. Relevant studies were then read in full text and further inclusion or exclusion were based on eligibility criteria.

Data from quantitative studies were extracted using Microsoft Excel. All relevant data on intervention effects, as well as intervention characteristics where extracted using a data extraction form. The form was developed and piloted together with a co-reviewer prior to extraction. Data from qualitative studies were extracted using QSR International's Nvivo 12 software. Whole result sections were extracted from qualitative studies in order to collect all relevant information and quotes, and *informal evidence*, authors explanations and interpretations on mechanisms for intervention failure or success often placed in the discussion section (Sutcliffe et al., 2015), were extracted from both quantitative and qualitative studies. These data were extracted directly into the Nvivo 12 software.

The quality of randomised controlled trials (RCTs) were appraised using The Cochrane risk of bias tool (Higgins et al., 2011), as recommended by The Cochrane Collaboration (Higgins & Green, 2008). Non-randomised studies were appraised using The Risk of Bias In Non-Randomised Studies – of Interventions (ROBINS-I) in order to secure a sufficient evaluation of the internal quality of the study (Sterne et al., 2016). Qualitative studies were appraised using the assessment criteria developed and presented by Rees and colleagues (Rees, Oliver, Woodman, & Thomas, 2011). These criteria were chosen as they have proven appropriate for evaluating the quality of qualitative studies that considers evaluation of intervention processes (Rees, Caird, Dickson, Vigurs, & Thomas, 2014; Rees et al., 2011). The results from quality appraisal using these criteria decided how much weight was placed on the qualitative study results in the synthesis.

2.1.3   Synthesis

Three forms of synthesis were conducted to make a comprehensive effort to address the broad study aim. First, a *narrative synthesis* was performed to evaluate intervention effectiveness. This synthesis was based on the extracted data from quantitative studies, where the extracted data on study characteristics and intervention effects were collated, compared and contrasted. Second, a *thematic analysis*, as described by Thomas and Harden (2008), was conducted in order to analyse the extracted data from qualitative studies on deliverers' and recipients' experiences of intervention involvement. The first step of this synthesis was to identify codes across studies. In the next step, these codes were merged into descriptive themes, which finally were analysed and developed into analytical themes consisting of knowledge going beyond the findings of the primary studies (Thomas & Harden, 2008; Tong, Flemming, McInnes, Oliver, & Craig, 2012). The process of developing these analytical themes are presented in Supplementary Figure S1 in the paper of Study I. Third, an *intervention component analysis*, as described by Sutcliffe and colleagues (2015), were carried out in order to identify and analyse key intervention components and processes. Here, data from all included studies were utilised in the process of describing and analysing features and processes central for intervention success or failure. Findings from the thematic synthesis guided the identification of these features and processes, but this information was also inductively identified when going through the studies. Information on identified features and processes for each intervention were listed in a table to allow cross-case comparison to be conducted (See Supplementary Table S4 in the paper of Study I). A central component of this analysis was the integration of *informal evidence*, as inclusion of this information could help to extend elaborations on the understanding of key intervention components and processes (Sutcliffe et al., 2015).

Findings from the thematic synthesis and the intervention component analysis guided the identification of barriers and enablers of intervention success. These enablers and barriers were sorted into a socio-ecological model. In brief, a socio-ecological model is a model consisting of several layers reflecting Bronfenbrenner's (1986) model of human development on micro, meso-, exo-, and macrosystem levels, which can be applied to describe how individual and environmental factors reciprocally affect human behaviour (Richard, Gauvin, & Raine, 2011). Behaviour is thus understood as a result of factors occurring on a range of different levels, more specifically *the interpersonal level*, *the intrapersonal level*, *the institutional level*, *the community level* and *the policy level* in accordance to McLeroy and colleagues (1988). Application of a socio-ecological model could help to provide a comprehensive overview of multiple and interacting factors and to disentangle their complex relationships (Richard et al., 2011; Sallis &

Owen, 2015). Identified intervention enablers and barriers were thus sorted into a model similar to the one presented by McLeroy and colleagues (1988) in order to obtain a comprehensive and joint overview of factors that could affect intervention implementation and effectiveness. Factors identified as barriers were reformulated into enablers before presented in the model in order to ease the overall presentation of these results. Some factors related to intervention development processes and intervention delivery were placed in separate boxes as it was difficult to integrate this information into a particular level in the socio-ecological model. This way of organising the study findings offer a particularly explicit presentation of information with importance for practitioners and decision-makers in their work on developing and implementing effective interventions in the future.

2.2   Study II & Study III: Cohort studies

The second specific aim of this thesis, *to investigate whether infants from parents with low socioeconomic position are at increased risk of developing overweight or obesity after rapid weight gain and thus have a special need for prevention*, was addressed in Study II, while Study III addressed the third specific aim of this thesis, which was *to evaluate the importance of infancy weight gain information for making early-life predictions on later childhood overweight and obesity risk*.

Study II and Study III are both cohort studies, which is a type of analytical observational study design (Szklo & Nieto, 2019). In a cohort study, a group of people who share a common exposure characteristic are followed over time in order to observe the occurrence of an outcome and to evaluate whether the incidence of the outcome is related to the specific exposure (Szklo & Nieto, 2019). Both Study II and Study III are *historical* cohort studies, as the cohorts are formed in the past and followed into present time (Szklo & Nieto, 2019). This differs from *concurrent/prospective* cohort studies, where the cohorts are formed in present time and followed into the future (Szklo & Nieto, 2019).

Study II and Study III are formed by the same study design, but they have different goals, which is *to explain* and *to predict*, respectively. In the background for Study II, it is suggested that the risk-relationship between RIWG and COO may be stronger for people of low SEP compared to those of high SEP. The objective of this study was to test this hypothesis statistically, where a theoretical model based on the hypothesis were tested in order to try *to explain* something in the real world. This illustrates that the role of theory is very strong in this approach to statistical modelling, termed *explanatory modelling* (Shmueli, 2010). Conversely, the aim of the analysis in Study III was to estimate and compare the predictive performance of prediction models based on predictors obtainable at birth, with and without information on infancy weight gain as a predictor. This involves utilisation of data to predict new or future observations, which by Shmueli (2010) is named *predictive modelling* that involves all methods that produce predictions. The different approaches of explanatory and predictive modelling have implications for the statistical modelling processes applied in these two different studies. More details on these differences will be further discussed in Chapter 5 (Section 5.3). The next sections will present the data sources and the study populations of Study II and Study III, as well as how data were operationalised in these studies.

2.2.1   Data sources

Both Study II and Study III are register-based cohort studies, as all sources of data applied in these studies are Danish nationwide databases. Register-based research in Denmark is unique. The whole Danish population can be viewed as a potential cohort (Frank, 2000), as every person who legally lives in Denmark for three months or more are assigned a ten-digit personal *Civil Personal Register* (CPR) number which is registered in the Danish *Civil Registration System* (Pedersen, 2011; Schmidt, Pedersen, & Sørensen, 2014). The Civil Registration System is continuously updated with individual's personal information like name, address, date of birth, civil, migration and vital status, as well as CPR numbers of parents and children (Pedersen, 2011; Schmidt et al., 2014). This registry can be considered virtually complete, only missing information on 0.3% of the entire population (Schmidt et al., 2014). The CPR number support linkage between nationwide registries at the individual level (Pedersen, 2011; Schmidt et al., 2014), which makes it possible to follow and analyse different cohorts over long periods of time as what was done in Study II and Study III. Other than the information from The Civil Registration System, both studies were based on data obtained from the Children's Database, the Medical Birth Registry, the Income Statistics Register, and the Population Education Register.

The Children's Database (CDB) holds information on the health status of children aged between 0 and 17 years (Høstgaard & Pape-Haugaard, 2012). The database include data on child height, weight, exposure to second-hand smoke and breastfeeding duration (Sundhedsdatastyrelsen, 2018). The CDB was established on 1th April 2009 with the aim of collating already existing municipal data on children's health status into a national database (Høstgaard & Pape-Haugaard, 2012; Sundhedsdatastyrelsen, 2018). Data existing in some municipalities before 2009 were also included, why the database holds data on children born a long time before the database's origin. The oldest data registered in CDB are on children born in the 1970's. The completeness of this data is however poor, but it improves over time. Data reported to the CDB are collected at preventive health checks offered to all children resident in Denmark by municipal health professionals for children aged 0 to 1 years and 5 to 17 years, and by general practitioners for children aged 1 to 5 years (Sundhedsdatastyrelsen, 2018). In December 2011, it became mandatory for municipalities to report data to the CDB, while this is still optional for general practitioners (Sundhedsdatastyrelsen, 2018). Thus, data completeness and quality improves from 2012 and onwards (Sundhedsdatastyrelsen, 2018).

The Medical Birth Register, established in 1973, holds information on all births in Denmark and contains data on maternal characteristics during pregnancy,

information concerning the delivery, and newborn health status (Bliddal, Broe, Pottegård, Olsen, & Langhoff-Roos, 2018). The data are collected when women are in contact with medical doctors and midwives during pregnancy and birth, and the validity of the basic information concerning mother and child are considered very high (Bliddal et al., 2018). The Medical Birth Register is primarily based on data from the National Patient Registry and is supplemented with data collected in relation to home deliveries and stillbirths and background data from the Civil Registration System (Bliddal et al., 2018). It is possible to identify child and parental CPR via the background data from the Civil Registration System, why the Medical Birth Register was utilised to identify the parents of children registered in CDB in the study populations in Study II and Study III. Figure 2 displays the different data sources and how they are associated in the final dataset applied in these studies.
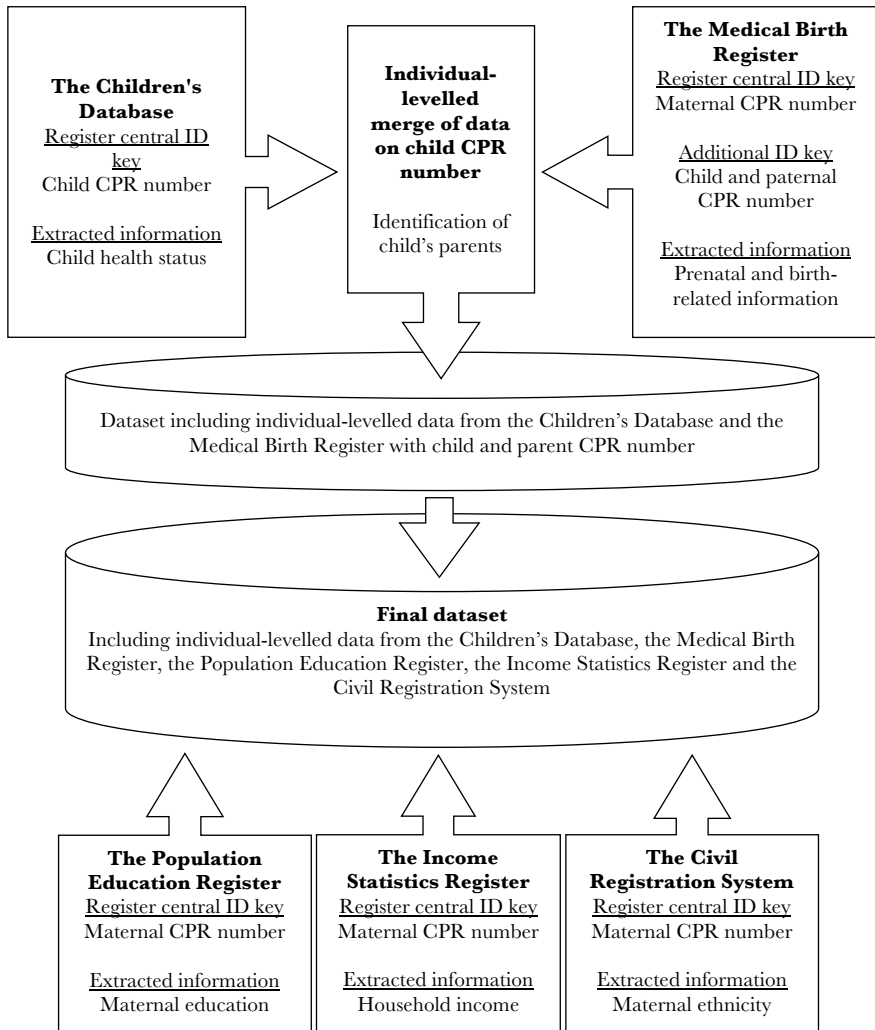
Figure 2. The figure shows the different data sources and how they are associated in the final dataset applied in the studies. CPR = Civil Personal Register.

The Population Education Register contains annual information on the highest completed level of education for all individuals who have attended or are attending an education in Denmark (Jensen & Rasmussen, 2011). The data origins from institutions' administrative records and surveys, has high validity and coverage as it holds data on 96% of all Danes age between 15 and 69 years and 85-90% of all immigrants (Jensen & Rasmussen, 2011).

The Income Statistics Register holds information related to individuals' economic situation, such as information on salaries, taxes and public transfer payments (Baadsgaard & Quitzau, 2011). The register holds high-quality data on all individuals that are economically active in Denmark from 1976 and onwards (Baadsgaard & Quitzau, 2011).

2.2.2 Study populations

As Figure 2 shows, children in the study populations in Study II and Study III were identified through the CDB, while their parents were identified through the Medical Birth Register. Eligible children had to be born at term with a birthweight of 2500g or more. These eligibility criteria were set in order to include predominantly healthy children that would have a similar basis for postnatal growth. Children with low birthweight were excluded, as infants with low birthweight due to in-utero growth restrictions can experience different postnatal growth trajectories compared to children with normal birthweight (Brands et al., 2014). Eligible children also had to be registered in the CDB with the anthropometric information necessary for analysis. Similar eligibility criteria were set in Study II and Study III, but the birth year intervals that defined the two study populations differed. The timeline for the two studies is illustrated in Figure 3.
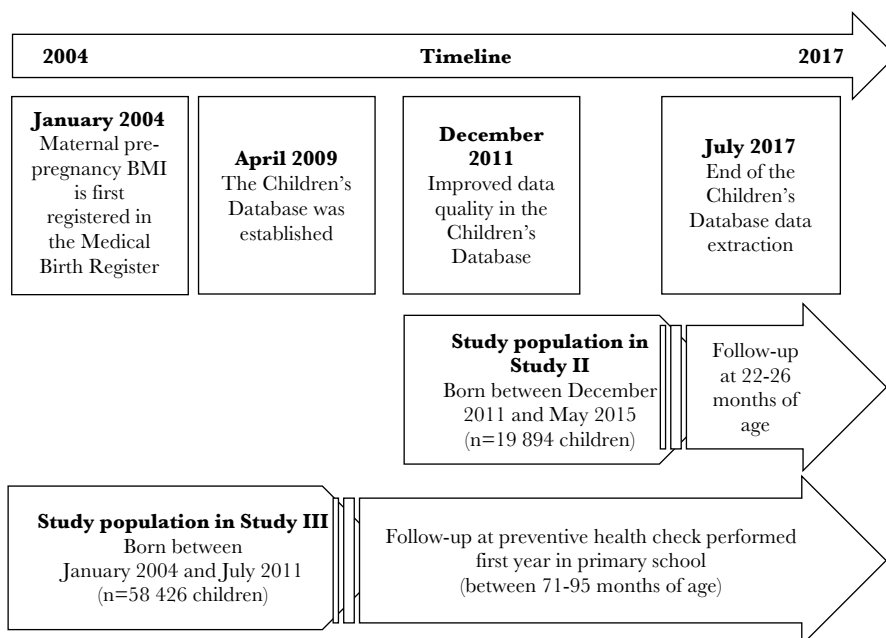
Figure 3. The figure presents the study populations and the timeline for the Study II and Study III.

The study population in Study II consisted of children born between December 2011 and May 2015. The lower limit of December 2011 was set as data quality and coverage in CDB improved after this time as it became mandatory for municipalities to report data to the database (Sundhedsdatastyrelsen, 2018). Especially information on *breastfeeding duration*, a possible confounder in Study II (Zheng et al., 2018), was poorly reported prior to December 2011, as more than 50% of data were missing from this time and back. The data extract of the CDB available for analysis consisted of data through July 2017, and the upper limit were thus set at May 2015 in order to allow a maximum follow-up at 26 months of age. This, as the 2-year health assessment could have been conducted with some delay.

Study III included children born between January 2004 and July 2011. Information on breastfeeding duration was not included in this study, which allowed inclusion of children born in earlier years than in Study II. Thus, data older than 2011 were applied in order to be able to make longer-termed predictions, although these data presumably were of poorer quality. The upper limit for inclusion (July 2011) was set in order to allow longer-termed follow-up and prediction of obesity risk in school-aged children using data obtained at the preventive health check performed during the first year of primary school. Information on *maternal pre-pregnancy BMI*, an important predictor of childhood overweight and obesity (Ziauddeen et al., 2018), was not registered before 2004 (Bliddal et al., 2018). Thus, the earliest time of birth that allowed inclusion was set to January 2004.

2.2.3   Operationalisation of exposures, outcomes and covariates
This section describes the exposures, outcomes and covariates applied in Study II and Study III and how these were operationalised.

2.2.3.1   *Main exposure: Infancy weight gain*
Infancy weight gain, including rapid infant weight gain, was set as the main *exposure* in Study II and the core predictor in Study III. As previously described in Section 1.3, RIWG is most commonly defined as a change in WAZ of >0.67 between two time points during the first two years in life, which equals moving up at least one centile band on a growth chart (Monteiro & Victora, 2005; Ong & Loos, 2006; Zheng et al., 2018). This definition guided the operationalisation of infancy weight gain in this project.

The relationship between RIWG and childhood obesity appears stronger when weight change is measured during the first compared to the second year of life (Zheng et al., 2018). Thus, both cohort studies measured infancy weight gain during the first

year of life: between birth and 8 to 10 months of age in Study II and between birth and 6 to 12 months of age in Study III. These specific timings were chosen as they cover the time period of one or more preventive health checks (Sundhedsdatastyrelsen, 2018; Sundhedsstyrelsen, 2015). The wider age span of 6 to 12 months applied in Study III enabled inclusion of a large sample size, which, in according to Shmueli (2010), is particularly important for making accurate predictions in a prediction study (see Section 5.3 for further discussion).

Data on birthweight were obtained from the Medical Birth Register and data on infant weight status were obtained from the CDB. These data were transformed into z-scores using WHO Anthro Software (Blössner et al., 2010). Thus, infancy weight gain was defined as the difference in z-scores between birth and in later infancy. Although most research have applied a dichotomous categorical variable using the cut-off >0.67 when defining infant weight gain (Monteiro & Victora, 2005; Ong & Loos, 2006; Zheng et al., 2018), infants experiencing a z-score change of more than 0.67 were further divided into two categories (*rapid* and *very rapid weight gain*) in order to study internal differences in these infants. This was possible due to the large study populations. Furthermore, it was considered inappropriate to categorise infants experiencing slow weight gain together with infants experiencing mean weight gain, due to potential between-group differences explaining the slow weight gain. The final categorisation of infancy weight gain was therefore: *slow* (≤-0.67), *mean* (>-0.67 to 0.67), *rapid* (>0.67 to 1.34), and *very rapid* (>1.34).

2.2.3.2 Additional exposure: Socioeconomic position

In Study II, socioeconomic position was set as additional exposure, as the aim of the study was to analyse the relationship between infancy weight gain and SEP on the risk of COO. Maternal education level and household income were used as proxies for SEP in the study. While maternal education may better reflect the resources held on an individual level, household income may better reflect the resources shared at the household and family level (Solar & Irwin, 2010). Nevertheless, parental SEP has shown to be of great importance for the health status of their children, including child overweight status (Diderichsen et al., 2012), and SEP measured at both the household and the parental level can serve as a measure for childhood SEP (Galobardes, Shaw, Lawlor, Lynch, & Davey Smith, 2006).

Socioeconomic position is related to health through a number of different pathways, such affecting one's access to resources like money, knowledge, power and social support that can affect housing and work opportunities, access to health care and social support, and exposure to certain risk factors for disease and psychosocial

stressors (Link & Phelan, 1995; Solar & Irwin, 2010). In further detail, education status is thought to affect health through the ability to benefit from the health care system, as the general level of knowledge and skills are though as important for accessing the health care system and in communicating with health professionals (Galobardes et al., 2006; Solar & Irwin, 2010). Furthermore, income is the proxy of socioeconomic position most closely related to material resources and is generally though to affect health status through one's ability to exchange financial resources into health enhancing commodities and services (Galobardes et al., 2006; Solar & Irwin, 2010). Both of maternal education and household income were applied as proxies for SEP in Study II, as it was assumed that they measured different theoretical aspects of the relationship between SEP and health status.

Data from the Population Education Register were applied to identify maternal education level. This was defined as the mother's highest achieved education registered in the year before or the year after giving birth. This information was categorised in accordance with the International Standard Classification of Education (ISCED) 2011, which are international standards developed by the United Nations Educational, Science and Cultural Organization (UNESCO) (UNESCO Institute for Statistics, 2012). The categorization was adjusted to fit a Danish education context, as done by Ullits and colleagues (2015): 1) *Level 0 to 2*, which comprise education up to and including lower secondary education, 2) *Level 4*, which comprise post-secondary non-tertiary education, 3) *Level 5 to 6*, which comprise short-cycle tertiary education, a Bachelor's degree, or equivalent, and 4) *Level 7 to 8*, which comprise a Master's and Doctoral degree, or equivalent. This classification system was applied in order to secure international comparability (Schneider, 2013; UNESCO Institute for Statistics, 2012).

Information on annual income in the household registered on the maternal CPR number was obtained from the Income Statistics Register. Annual household income in the two years prior to birth were obtained in order to calculate a mean household income. This was done in order to reduce potential bias related to changes in maternal occupational status and income during pregnancy. This mean household income was further divided into quartiles.

2.2.3.3 *Outcome: Childhood overweight and obesity*
Childhood overweight and obesity were set as the *outcome* in both Study II and Study III. Information on child weight and height obtained from the CDB were, together with child age, utilised to calculate BMI-for-age, which was applied to define COO. The study populations differed in ages at the time of outcome assessment in Study II

and Study III, and different references and cut-offs were thus applied in the two studies.

In Study II, overweight and obesity at 22 to 26 months of age were set as the outcome. The timing for this outcome was chosen as the data available did not allow longer follow-up. However, overweight or obesity around or before the age of 2 years have been associated with an increased risk of later overweight and obesity (Freedman et al., 2005; Johannsson, Arngrimsson, Thorsdottir, & Sveinsson, 2006; Smego et al., 2017). Thus, overweight and obesity status around this early age can give an indication of later weight status. Overweight and obesity at age 22 to 26 months of age were defined using the WHO growth standards (World Health Organization, 2006), and BMI-for-age z-scores were calculated using WHO Anthro Software (Blössner et al., 2010). A BMI-for-age z-score of more than 2 denoted overweight including obesity (World Health Organization, 2008). The prevalence of obesity, defined as having a BMI-for-age z-score of more than 3 (World Health Organization, 2008), was low in the study population (0.9%). Overweight including obesity rather than obesity alone was thus set as outcome, as a higher number of outcome events could help to strengthen the statistical power when testing the study hypothesis (Biau, Kernéis, & Porcher, 2008).

In Study III, childhood obesity in the first year of primary school was set as primary outcome. Childhood overweight including obesity was set as secondary outcome in order to examine whether the results differed across outcomes. The IOTF reference was applied to define childhood overweight and obesity, as children were aged over two years at follow-up (Cole et al., 2000). Childhood obesity was defined as having a BMI-for-age of more than 30, and childhood overweight including obesity were defined as having a BMI-for-age of more than 25 (Cole et al., 2000).

2.2.3.4   Covariates

Many of the covariates included in Study II and Study III were similar and based on the same information. Table 3 presents an overview of these covariates, including information on the variable data source, how variables were managed and which study they were applied in. The covariates for Study II were identified through a recent systematic review on the risk-relationship between RIWG and COO (Zheng et al., 2018), while they in Study III were identified through a comprehensive systematic review on pre- and postnatal risk factors for childhood overweight and obesity (Woo Baidal et al., 2016).

Table 3. The table presents an overview of the covariates included in Study II and Study III, as well as information on their data source and how they were managed.

Variables	Variable description and management	Applied in
	The Children's Database	
Child sex	1) Male 2) Female	Study II, Study III
Breastfeeding duration	Continuous information in days categorised into: 1) 0 to <2 months 2) 2 to <4 months 3) 4 to <6 months 4) >6 months	Study II
Child birthyear	Each year (2011, 2012, 2013, 2014 and 2015) was given a number (1 to 5)	Study II (control variable[a])
Number of registrations in the database	Variable denoting how many times the child had length/weight measured during the study period	Study II (control variable)
Region of habitation	Each region (Capital City Region, Region Zealand, Region of Southern Denmark, Mid Jutland Region and North Jutland Region) was given a number (1 to 5)	Study II (control variable)
	The Medical Birth Register	
Size for gestational age at birth	Birthweight in grams and gestational age were applied to calculate size-for-gestational age at birth, using cut-offs presented by Kramer et al. (2001): 1) Small-for-gestational age 2) Appropriate-for-gestational age 3) Large-for-gestational age	Study II
Size at birth	Continuous information in grams transformed into weight-for-age z-scores and categorised into: 1) Smaller than mean (≤-1) 2) Mean (>-1 to 1) 3) Larger than mean (>1)	Study III
Birth length	Continuous information in centimetres categorised into: 1) ≤50 cm 2) 51 to 52 cm 3) 53 cm 4) ≥53 cm	Study II (auxiliary variable[b])
Mode of delivery	1) Vaginal delivery 2) Caesarean section	Study II, Study III
Maternal pre-pregnancy BMI	Continuous information categorised into: 1) <18.5 (underweight) 2) 18.5 to <25 (normal weight) 3) 25 to <30 (overweight) 4) 30 to <35 (obesity class I) 5) >35 (obesity class II+III)	Study II, Study III
Maternal smoking status during pregnancy	All categories denoting numbers of cigarettes smoked were categorised as *smoking during pregnancy*. The other original categories were retained: 1) Yes 2) Stopped during pregnancy 3) No	Study II, Study III
Maternal age	Continuous information in years, categorised into: 1) <22 years 2) 22 to 29 years 3) 30 to 37 years 4) ≥38 years	Study II (auxiliary variable)
Gestational age	Continuous information in days, categorised into: 1) 37+0 to 37+6 weeks of gestation 2) 38+0 to 38+6 weeks of gestation	Study II

	3) 39+0 to 39+6 weeks of gestation	
	4) 40+0 to 40+6 weeks of gestation	
	5) 41+0 to 41+6 weeks of gestation	
Parity	Continuous information in number of times giving birth, categorised into:	Study II, Study III
	1) 1	
	2) 2	
	3) >2	
Gestational diabetes status	1) Yes	Study II, Study III
	2) No	
	The Population Education Register	
Maternal education attainment	Categorical information describing highest maternal education attainment the year before or after birth, classified in accordance to the International Standard Classification of Education (ISCED) 2011, adjusted to a Danish setting:	Study II, Study III
	1) ISCED level 0 to 2	
	2) ISCED level 4,	
	3) ISCED level 5 to 6	
	4) ISCED level 7 to 8	
	The Income Statistics Register	
Annual household income	Continuous information on annual household income in the two years prior to giving birth. The mean value was categorised into quartiles:	Study II, Study III
	1) Low	
	2) Low-middle	
	3) High-middle	
	4) High	
	The Danish Civil Registration System	
Maternal ethnicity	Categorical information on maternal ethnicity, categorised into:	Study II (auxiliary variable)
	1) Danish	
	2) Immigrant/descendant	

[a]Control variable = Applied to control for individual differences not captured by covariates
[b]Auxiliary variable = Variables included in the multiple imputation that is not a part of the theoretical model (Newman, 2014)

2.3   Methods of analysis

This section presents the methods of analysis applied in Study II and Study III: interaction analysis and estimation of prediction model performance, respectively. The section is however introduced by an explanation of how missing data were handled in these studies.

2.3.1   Handling of missing data

The problem of missing data leading to information loss is common in medical research, and failing to address this issue could potentially lead to calculation of biased estimates (Bartlett, Seaman, White, & Carpenter, 2015). Missing data were likewise a problem in both Study II and Study III, but there exist different methods in which to handle this problem, and the choice of method would depend on the type of mechanism explaining the missingness (Buhi, Goodson, & Neilands, 2008; Newman, 2014). Missing data are generally categorised into three different missing data mechanisms: missing completely at random, where the missingness is completely random and does not depend on observed or missing data values, missing at random, where the missingness partly depends on other observed data but not on the missing data itself, or missing not at random, where the missingness depends on the missing data values (Buhi et al., 2008; Newman, 2014).

Study II was based on a dataset with variables having a generally low percentage of missingness (<1%), but the variable denoting breastfeeding duration was an exception, where data was missing in 32.7% of the cases. It was assumed that these data were missing at random, as the missingness were hypothesised to be related to geographic and annual differences in the reporting of data to the CDB. Multiple imputation techniques were used to handle the missing data in Study II, as this method has been considered suitable for dealing with missing data assumed to be missing at random (Bartlett & Morris, 2015; Buhi et al., 2008). This procedure involves replacing missing values by values derived from an appropriate distribution based on the available data (Bartlett & Morris, 2015). This procedure was repeated *n* times resulting in the construction of *n* datasets, where the number of datasets constructed equalled the highest proportion of missingness (Von Hippel, 2009; White, Royston, & Wood, 2011). Thus, this number were in this case set to 33. Each dataset was imputed in *m* cycles with imputed values being updated at each cycle (van Buuren, Brand, Groothuis-Oudshoorn, & Rubin, 2006), and the procedure was finalised by fitting the original statistical models onto each of these imputed datasets before the results from each dataset were combined into one joint estimate (Bartlett & Morris, 2015). Inclusion of *auxiliary variables*, variables included in the multiple imputation that is not

a part of the theoretical model (Newman, 2014), can improve the imputation quality (Azur, Stuart, Frangakis, & Leaf, 2011), and three auxiliary variables (*infant birth length, maternal age* and *maternal ethnicity*) were therefor included in the imputation. However, immigrants with missing data on education attainment and income were excluded from the analysis prior to imputation, as we suspected these data to be not missing at random and thus not suitable for multiple imputation (Buhi et al., 2008). The applied databases tended to lack these data on immigrant populations, and one of the reasons could be a lack in registration of education achieved before entering Denmark. Complete case analyses were conducted as sensitivity analyses.

In Study III, the proportion of missing data were low in most variables, where included variables had proportions of missingness ranging between 1.5% to 2.2%. However, the proportion of missing data for maternal pre-pregnancy BMI was 8.2%. It has been suggested that missingness of less than 5% is insignificant (Schafer, 1999) and that a proportion of missingness greater than 10% is likely to cause bias (Bennett, 2001). Thus, it was decided to apply *listwise deletion*, where all cases with any missing data are excluded from the analysis before proceeding with the analysis (Newman, 2014). Sensitivity analyses were carried out to test the robustness of the results based on the complete case data. Here, best- and worst-case scenarios of the missing data on maternal pre-pregnancy BMI were tested, where the main analyses were repeated with missing data all categorised as *normal weight* or as *obesity, class II + III*, respectively.

2.3.2   Interaction analyses
The aim of the analysis in Study II was to evaluate whether the relationship between infancy weight gain and COO risk were modified by level of SEP, why a test for interaction was performed. *Interaction* involves a situation where two or more risk factors modify the effect of each other on the outcome of interest (Szklo & Nieto, 2019). This term is often used interchangeably with *effect modification*, which is a related concept which in general are assumed to coincide (Szklo & Nieto, 2019; VanderWeele, 2009). This assumption is also what applies in this thesis, and only the term interaction is therefore used forward on. Further discussion on the difference between these concepts can be found in the method discussion (Section 5.2).

Interaction can appear both on an additive and a multiplicative scale (Szklo & Nieto, 2019; VanderWeele & Knol, 2014). The testing of these different types involves the evaluation of differences between two absolute risk estimates (e.g. attributable risks), or two relative risk estimates (e.g. odds ratios) (Szklo & Nieto, 2019). The default in epidemiology has been to test for interaction only on the multiplicative scale (Rothman, Greenland, & Lash, 2008), as this is convenient if multiplicative models

and relative risk measures are already applied. However, it is also of great importance to study additive interaction in public health, as results from additive interaction analyses can help to identify groups that are likely to benefit most from treatment/intervention, which is information with great relevance for the allocation of public health resources (VanderWeele & Knol, 2014). Furthermore, VanderWeele and Knol (2014) have demonstrated that the direction of interaction can differ depending on the scale tested and that interaction can be present on one scale and absent on the other at the same time. For these reasons, interactions were tested both on the additive and multiplicative scale in Study II.

Details on the strategy for the statistical analyses are presented in detail in the paper of Study II. In summary, multiplicative interaction was tested using logistic regression models through stratification of levels of *household income* and *maternal education attainment*, as well as through a Wald test that compared model fit of models with and without an interaction term (*infancy weight gain category* x *level of household income/maternal education attainment*) (Harrell, 2015). Additive interaction was tested by calculating the Relative Excess Risk due to Interaction (RERI), which is a measure of additive interaction based on relative risks (VanderWeele & Knol, 2014). The full model, including the specific interaction term, were utilised to calculate RERI for categorical outcomes, as described by VanderWeele and Knol (2014). To reduce complexity, the variables denoting SEP were dichotomised (*high* vs. *low* level) in these analyses. All analyses in Study II were based on multiply imputed data, but the calculation of RERI was based on complete case data, as no method were available for imputed data.

2.3.3   Estimating prediction model performance

The aim of the analysis in Study III was to assess the predictive performance of prediction models consisting of predictors obtainable at birth, with and without information of infancy weight gain. Predictive performance can be evaluated through measures of discrimination and calibration (Moons et al., 2012). *Calibration*, the agreement between the predicted probabilities of developing the outcome and the actually observed outcome frequencies (Moons et al., 2012), were not utilised in this study, as predicted risk and observed incidence will be equal when working at the model development stage that not includes testing the model in new data (Steyerberg & Vergouwe, 2014). Rather, the analysis focused on assessing models' discriminative abilities. *Discrimination* is a model's ability to differentiate between individuals who do and do not experience the outcome (Moons et al., 2012; Steyerberg, 2009). In Study III, discrimination was measured by calculating the area under the receiver operating characteristic curve (AUC). This measure of discrimination is appropriate when working with binary outcomes and logistics regression models (Moons et al., 2012;

Steyerberg & Vergouwe, 2014), as the AUC represent the probability that one individual with the outcome is assigned a higher outcome risk than another individual without the outcome (Hendriksen, Geersing, Moons, & de Groot, 2013). An AUC of 0.5 represent a poor model with predictive abilities equal to a coin-toss, while a perfect model that discriminate perfectly between those with and without the outcome holds an AUC of 1 (Steyerberg, 2009).

The discriminative ability of Model 1, a prediction model consisting of nine predictors obtainable at birth, was compared to Model 2 which consisted of Model 1 plus infancy weight gain as additional predictor, by comparing the AUC derived from the two models (Fawcett, 2006). Moreover, a reclassification table for Model 1 and 2 was developed to further test whether adding infancy weight gain information to the model led to better classification of individuals into certain risk categories (Cook, 2007; Cook & Ridker, 2009). Here, a risk threshold at the 90th percentile (10% of the population with the highest risk) was applied to construct two risk categories (high vs. low risk). Finally, the sensitivity and specificity of both models were compared in order to evaluate model usefulness when using the same risk threshold (Steyerberg & Vergouwe, 2014).

2.4   Additional analyses

Additional analyses was performed in order to further study the relationship between infancy weight gain and birth size on the risk of COO. This relationship was further analysed, as the risk estimates of overweight and obesity for both the rapid and very rapid weight gain category and for the large-for-gestational age (LGA) category increased considerably after introducing the covariate denoting size for gestational age at birth into the logistic regression model in Study II. Based on this observation, it was hypothesised that children born LGA were at specific risk COO if these children also experienced rapid and very rapid weight gain postnatally, and this hypothesis were tested in the additional analyses.

The additional analyses were conducted using the same methods applied when testing for additive and multiplicative interaction in Study II, where the interaction between size for gestational age at birth and infancy weight gain on the risk of COO were considered. As such, multiplicative interaction was tested by comparing models with and without an interaction term using a Wald test (Harrell, 2015). If the Wald test showed any signs of a significant interaction, further analysis on potential risk differences across groups were conducted by stratifying the logistic regression models by size for gestational age at birth. As in Study II, additive interaction was tested using RERI. Only the combination comparing mean weight gain and rapid or very rapid weight gain, and appropriate-for-gestational age (AGA) and LGA were tested, as the risk of COO were greatest in these groups. These additional analyses were performed both on data from Study II and Study III in order to test whether the proposed hypothesis appeared differently on the short- (22-26 months of age) and long-term (71-95 months of age). This, as an interaction could potentially be stronger on the short- than long-termed risk of COO, as children's weight development, in theory, would have had more time to stabilise after being born large and having experienced rapid/very rapid weight gain in infancy in the long term.

The most considerably adjusted regression model from each study was applied when testing for interactions. However, the models applied in the additional studies did not include gestational diabetes status, as this information was unavailable at the time of analysis (see Section 2.5). Furthermore, household income was included as the only proxy for socioeconomic position in these analyses, as this variable were most consistently related to COO risk in Study II. The model applied on data from Study II therefore included child sex, size for gestational age at birth, mode of delivery, parity, gestational age, maternal pre-pregnancy BMI, maternal smoking status during pregnancy, breastfeeding duration and household income as covariates, while the

model applied on data from Study III included the same covariates except from gestational age and breastfeeding duration. Moreover, the same variable denoting size for gestational age at birth were included in the analyses carried out both on data from Study II and Study III in order to enhance comparability between analyses. For the same reason were the control variables included in Study II not included in the additional analyses. Variables applied in the additional analyses corresponds to the variables presented in Table 3. Furthermore, all additional analyses were conducted as complete case analyses as RERI only could be calculated using complete case data.

2.5 Update in register data extract

The available extract of the Medical Birth Register was updated shortly before this thesis was to be submitted. Unfortunately, this had some consequences as it was no longer possible to obtain information on gestational diabetes status. This had implications for the analyses in Study III, as these analyses were not updated as planned. First, it was planned to revise the inclusion criteria for term births to 37+0 to 41+6 weeks of gestation in accordance with the definition of term births presented by The International Classification of Diseases, 10th revision (World Health Organization, 2004), as it was discovered that this inclusion criteria included seven days too much (37+0 to 42+6 weeks of gestation). Second, it was planned to apply the same definition on size for gestational age at birth as used in Study II in order to take gestational age into account in the birth size variable. It is the unrevised results from Study III that are presented in both the paper and the thesis, as it was impossible to make these revisions at the time when this thesis was submitted. However, these corrections are planned to be conducted when the necessary data again becomes available, so that the manuscript is revised prior to journal submission.

Furthermore, the additional analyses were not conducted before after the data update. Consequently, gestational diabetes status was not included as a covariate in these analyses, but the previously presented corrections were made in the Study III data. Table 4 gives an overview of the discrepancies between the data and analyses applied in the papers of Study II and Study III and in the additional analyses.

Table 4. The table presents an overview of the discrepancies between the data and analyses applied in the papers of Study II and Study III and in the additional analyses.

	Study II	Study III	Additional analyses, Study II data	Additional analyses, Study III data
Complete case population	13 157	58 426	13 433	55 046
Gestational diabetes status as covariate	Yes	Yes	No	No
Criteria for term birth (weeks of gestation)	37+0 to 41+6	37+0 to 42+6	37+0 to 41+6	37+0 to 41+6
Variable denoting birth size[a]	Size for gestational age at birth	Size at birth based on weight-for-age z-scores	Size for gestational age at birth	Size for gestational age at birth

[a]See Table 3 for details on operationalisations of these variables

2.6 Ethics and regulations

In Denmark, it is possible to work with individual-levelled data as long as confidentiality and full anonymity is preserved for all subjects (Thygesen, Daasnes, Thaulow, & Brønnum-Hansen, 2011). The Data Protection Act presents these rules and regulations which applies for working with individual-levelled data (Danish Data Protection Agency, 2018), such as in register-based research.

Statistics Denmark is a central authority that provides register data and produces official statistics concerning the Danish society, and access to pseudonymised individual-levelled data to researchers (Thygesen et al., 2011). The data applied in Study II and Study III were kept in a pseudonymised form at an external server maintained by Statistics Denmark, and this data were accessed online after the Danish Data Protection Agency granted an approval (reference: 2008-58-0028, internal reference: 2017-67). All results in any part of this thesis are presented at an aggregated level in order to comply to the Data Protection Act.

According to Danish law it is unnecessary to obtain informed consent when conducting research projects based on data obtained from registries if no health risks or strain are put on the participants (The National Committee on Health Research Ethics, 2018). Furthermore, it is not necessary to report register-based research projects to the research ethics committee system if they do not involve any forms of human biological material (The National Committee on Health Research Ethics, 2018). On this basis, this research project was not reported to any research ethics committee.

3 Results

This chapter gives an overview of the main results derived from Study I, Study II, Study III and the additional analyses, which were conducted to address the aim of the thesis: *to develop new knowledge on the who, when and how of early-life overweight and obesity prevention with a focus on infancy weight gain to strengthen the knowledge informing research and practice*. Further details on the study result can be located in the paper of each study.

3.1   Study I

A total of seven quantitative (Daniels et al., 2012; Edmunds et al., 2014; Karanja et al., 2010; Koletzko, Kries, et al., 2009; Lakshman et al., 2018; Paul et al., 2011; Savage, Birch, Marini, Anzman-Frasca, & Paul, 2016) and seven qualitative papers (Guell, Whittle, Ong, & Lakshman, 2018; Lakshman et al., 2014, 2012; Redsell et al., 2017; Redsell et al., 2010; Thebaud, 2015; Valencia, Thomson, Duncan, & Arthur, 2016) were deemed eligible for inclusion in the systematic review. The overall quality of these included studies varied greatly and ranged between low to high (See Supplementary Table S3 in Study I). Figure 4 presents an overview of which papers that were included in each type of synthesis.
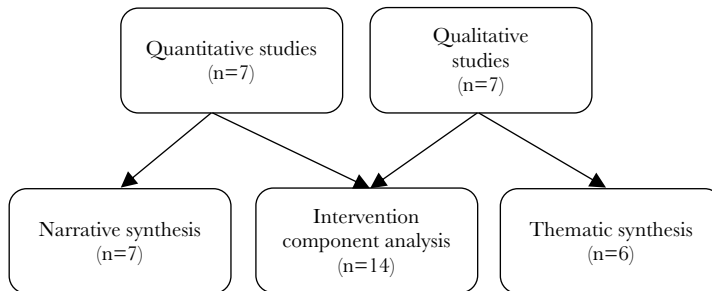
Figure 4. The figure shows which studies that were included in the different syntheses in Study I.

3.1.1   Impact of rapid infant weight gain prevention

The narrative synthesis considered intervention effectiveness and were based on data extracted from all seven quantitative papers which represented seven individual interventions: *the NOURISH RCT* (Daniels et al., 2012)*, timing of enrolment to the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC)* (Edmunds et al.,

2014), *the TOTS Trial* (Karanja et al., 2010), *the CHOP Study* (Koletzko, Kries, et al., 2009), *the Baby Milk Trial* (Lakshman et al., 2018), *the SLIMTIME Pilot Study* (Paul et al., 2011), and *the INSIGHT Trial* (Savage et al., 2016).

Three different outcome definitions denoting change in infancy weight gain were applied in these included studies: Risk of experiencing a change in WAZ of >0.67, mean change in WAZ between two points in time and conditional weight gain scores, the latter as explained by Griffiths et al. (2009). Changes in weight gain were measured between different time periods, and these periods were grouped into the following categories: *birth to 6 months of age*, *birth to 12 months of age*, and *birth to 24 months of age*. Some studies reported intervention effects using several measures and several timings of outcome measurement. Figure 5 provides an overview of outcome measures, timings of outcome measurement and effectiveness for each intervention.
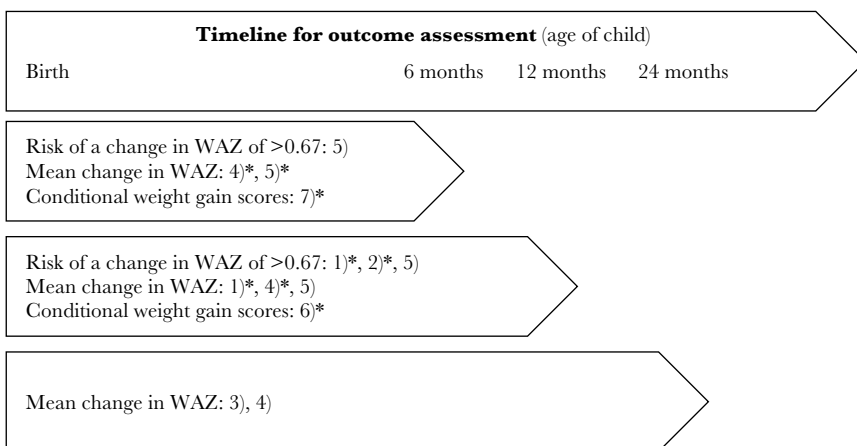
Figure 5. The figure presents an overview of outcome measurements, when these were obtained and intervention effectiveness for interventions included in Study I. * = Denote significant intervention effects at follow-up. The numbers correspond to the following trials: 1) The NOURISH RCT, 2) WIC, 3) The TOTS Trial, 4) The CHOP Study, 5) The Baby Milk Trial, 6) The SLIMTIME Pilot Study, 7) The INSIGHT Trial. Abbreviations: WAZ = Weight-for-age z-score

As Figure 5 shows, all intervention studies except from *the TOTS Trial* reported significant intervention effects on at least one outcome. Overall, the figure shows a tendency towards more significant intervention effects being measured in the first rather than in the second year in life. The effect sizes were generally small, and the exact exacted results can be viewed in Table 2 in the paper of Study I.

The intervention content varied greatly across interventions, with promotion of responsive feeding, healthy introduction to solid foods, breastfeeding promotion, prevention of sugar-sweetened beverage drinking and reduced protein intake as some examples. All interventions had more than one intervention focus (see more details in Supplementary Table S4 in Study I). No adverse intervention effects were reported by the three studies reporting such information (Supplementary Table S2 in Study I). Long-term results on the risk of COO were only reported for two interventions: *the NOURISH RCT* (Daniels, Mallan, Nicholson, Battistutta, & Magarey, 2013; Daniels et al., 2015) and *the CHOP Study* (Weber et al., 2014). No such intervention effects were reported for *the NOURISH RCT*, but children in the intervention group in *the CHOP Study* who received low protein content formula had significantly lower mean BMI and risk of obesity at six years of age compared to children in the control group who received high protein content formula (Weber et al., 2014). As Figure 5 shows, intervention children in this study also had a significantly lower mean change in WAZ at 6 and 12 months compared to control infants, which suggest that preventing a lower mean change in WAZ during the first year of age through reducing infant's intake of protein could be an effective strategy for preventing childhood obesity.

3.1.2   Enablers and barriers for rapid infant weight gain prevention

This section is based on the results from the thematic synthesis and the intervention component analysis. As Figure 4 demonstrate, six qualitative papers were included in the thematic synthesis, of which two studies were related to *the Baby Milk Trial* (Guell et al., 2018; Lakshman et al., 2012), one study were related to *the NOURISH RCT* (Thebaud, 2015), one study were indirectly related to WIC as being based on a WIC population (Valencia et al., 2016), and two studies were unrelated to any included trial (Redsell et al., 2017; Redsell et al., 2010). All of these studies, including one additional qualitative study describing the process of developing the *Baby Milk Trial* (Lakshman et al., 2014), were included in the intervention component analysis.

The results from these two syntheses enabled identification of several factors of significance for participation, compliance and effectiveness of RIWG prevention activities. These factors were sorted into a socio-ecological model (Figure 6), as explained in Section 2.1.3.

Policy level
(national, state, local laws)
o Allocate sufficient resources to prevention
o Develop national and local guidelines for prevention

Community level
(relationships between organizations)
o Focus on enhancing the collaboration between relevant sectors and organizations

Institutional level
(organizations and social institutions)
o Prioritize relevant prevention in the organization
o Provide support to health professionals in how to address the sensitive topic of rapid weight gain and early childhood obesity prevention
o Align interventions to health professional identify and tasks
o Address potential misconceptions on infant weight gain and feeding in health professionals
o Provide health professionals with the support and training necessary for intervention delivery

Interpersonal level
(families, friends, social networks)
o Involve the social environment and social relations as a part of the intervention to enhance social support for intervention activities
o Address potential misconceptions on infant weight gain and feeding existing in the social environment

Intrapersonal level
(knowledge, attitudes, behaviors of parents)
o Provide non-judgmental and flexible support to parents
o Emphasize consistency in intervention messages delivered to parents
o Address potential misconceptions on infant weight gain and feeding existing in parents

Intervention development
o Address problem complexity and explain change through explicit use of appropriate theory
o Involve relevant stakeholders from different population groups
o Develop and maintain constructive collaborations between researchers and stakeholders

Intervention delivery
o Immediate initiation of interventions after recruitment
o Deliver intervention through frequent and continuous contacts
o Deliver consistent and tailored support at home through familiar health professionals
o Deliver intervention in a non-judgmental manner
o Deliver intervention through a focus on healthy growth rather than though a focus of obesity prevention

Figure 6. The figure illustrates a socio-ecological model including factors of significance for the success of rapid infant weight gain prevention identified in Study I.

Figure 6 shows that parents, their social networks and health professionals could be potential points of target by RIWG prevention, as such prevention could be facilitated by enhancing the topic knowledge, the social support given to prevention activities and the training of intervention delivery in these groups. Furthermore, intervention success may depend on how the intervention is aligned with health professionals' everyday practice and to what extent decision-makers at the organisational and policy level prioritise and allocate a sufficient amount of resources to relevant prevention activities. Involvement of a range of different stakeholders and recognition of the complexity of the intervention context may also be important for developing effective interventions. Finally, interventions should focus on healthy infant weight gain and should be delivered to families shortly after recruitment in a flexible and non-judgmental way with a high frequency.

3.2   Study II

The final study population in Study II consisted of 19 894 children. See Figure 1 in the paper of Study II for more details on the study selection process. In total, 3 800 (19.1%) and 2 998 (15.1%) of these children experienced rapid and very rapid weight gain, respectively. A social gradient was observed in prevalence of rapid and very rapid weight gain, where higher prevalence of these weight gain patterns was observed in groups in lower socioeconomic positions (Table 1, Study II). 1 497 (7.5%) were categorised with COO at follow-up when children were two years (22 to 26 months) of age. The unadjusted risk of COO were significantly higher in children experiencing rapid (odds ratio (OR) 2.18 [95% confidence interval (CI) 1.90 to 2.51]) and very rapid weight gain (OR 4.10 [95%CI 3.59 to 4.68]), when compared to children who experienced mean weight gain in infancy (Table 2, Study II). These estimates almost doubled in size in the fully adjusted models.

Overall, the analyses carried out in the study did not detect any statistically significant interactions between infancy weight gain category and SEP on neither a multiplicative nor an additive scale. The results from the Wald test assessing multiplicative interactions were statistically insignificant (maternal education: p=0.89, household income: p=0.24). Furthermore, the RERI calculated when comparing groups with mean vs. rapid weight gain, and high vs. low level of maternal education (RERI 0.11 [95%CI -0.82 to 1.05]) and household income (RERI -0.19 [95%CI -1.19 to 0.81]) were too statistical insignificant as both these estimates included 0 in their 95% confidence intervals (Table 4, Study II). Similar results were observed when comparing groups with mean vs. very rapid weight gain, and high vs. low level of maternal education (RERI 0.62 [95%CI -1.32 to 2.56]) and household income (RERI 1.07 [95%CI -0.97 to 3.11]), although these estimates were somewhat larger (Table 4, Study II). Thus, the signs of additive interaction were stronger when comparing mean and very rapid weight gain than when comparing mean and rapid weight gain, even though no significant additive interactions were detected. In sum, the null-hypothesis stating that there were no differences in the risk-relationship between infancy weight gain category and overweight and obesity at 2 years of age across SEP could thus not be rejected. Translated into practice, this indicate that no specific socioeconomic group would benefit more from RIWG prevention than other when preventing COO, and that such preventive activities therefore would be equally relevant for all groups across the socioeconomic strata.

3.3 Study III

The final study population in Study III consisted of 58 426 children. At follow-up (first year of primary school, children aged between 71 to 95 months of age), 1 382 (2.4%) of these children were categorised with obesity and 6 759 (11.5%) with overweight including obesity. Model discriminative abilities were measured by the area under the receiver operating characteristic curve as described in Section 2.3.3. Table 5 present these results for each model for the primary (childhood obesity) and secondary (childhood overweight and obesity) outcome.

Table 5. The table presents the results derived from analyses of the area under the receiver operating characteristic curve for each predicytion model and outcome, as well as model specificity and sensitivity[*].

	Childhood obesity		Childhood overweight and obesity	
	Model 1	Model 2	Model 1	Model 2
AUC [95% CI]	0.787 [0.776 to 0.800]	0.820 [0.809 to 0.831]	0.698 [0.691 to 0.705]	0.728 [0.721 to 0.734]
Between-model difference in AUC [95% CI]	0.033 [0.026 to 0.040]		0.030 [0.026 to 0.033]	
Specificity	0.91	0.91	0.92	0.91
Sensitivity	0.43	0.50	0.26	0.32

[*]The results extracted from the manuscript of Study III.
Abbreviations: AUC = the area under the receiver operating characteristic curve.

These results show that the model without postnatally obtained infancy weight gain information (Model 1) yielded an AUC that were 0.033 [0.026 to 0.040] lower than the model including infancy weight gain information (Model 2), and show that Model 2 performed statistically significantly better than Model 1 in correctly discriminating between children with and without obesity at follow-up. Similar results were observed when models were set to predict both childhood overweight and obesity (a between-model differene in AUC of 0.030 (95%CI [0.026 to 0.033])). However, the AUC's derived when predicting both childhood overweight and obesity were generally lower than the AUC's derived when predicting childhood obesity only (Table 5). Thus, the prediction models applied in Study III appear to have better discriminative abilities when predicting childhood obesity than when predicting childhood overweight.

The results from the reclassification table (Table 2, Study III) showed that 33% of the non-obese children that were originally assigned a risk score above or equal to the 90th percentile by Model 1 were correctly reclassified into the lower risk category (<90th percentile) after adding infancy weight gain information to the prediction model when predicting obesity only. Only 4% of the non-obese children were incorrectly

reclassified the other way. 24% of children with obesity at follow-up were correctly reclassified from the low (<90th percentile) to the high-risk category (≥90th percentile) by Model 2, while 15% of these children made the opposite and incorrect shift. Similar results were observed when predicting both overweight and obesity, although a lower proportion of children with overweight and obesity than with obesity were correctly reclassified into a high risk category after adding infancy weight gain information to the prediction model (13% vs. 24%, Table 2, Study III). Specificity, a model's ability to detect the true negatives, were high both for models without (Model 1) and with (Model 2) information on infancy weight gain and ranged between 91% to 92%. The sensitivity, a model's ability to detect the true positives, were generally much lower and ranged between 26% to 50%. The highest sensitivity were observed for the model including infancy weight gain information (Model 2) when predicting obesity only (50%), where the inclusion of infancy weight gain information improved the model sensitivity by seven percentage points.

Overall, inclusion of infancy weight gain information to a prediction model consisting of nine predictors obtainable at birth improved model's discriminative abilities as well as reclassification and sensitivity. Thus, the results of Study III indicate that infancy weight gain information are of importance for making early-life predictions on later childhood obesity risk, as this improves prediction model abilities to discriminative between children with and without obesity first year in primary school and to correctly classify children that later develop obesity as being in high risk (≥90th percentile).

3.4   Additional analyses

The purpose of the additional analyses was to test whether any signs of interaction between infancy weight gain category and size for gestational age at birth on the risk of COO existed. No multiplicative interaction was detected on COO risk in Study II data (p=0.09) or on childhood obesity risk in Study III data (p=0.11). However, a statistically significant Wald test indicated that an interaction between infancy weight gain category and size for gestational age at birth on COO risk existed in Study III data (p<0.001). This risk relationship was thus further considered by stratifying the results derived from the logistic regression model by size for gestational age at birth. The stratified analysis showed that the risk of COO in the first year of primary school were larger for children born LGA that subsequently experienced rapid or very rapid weight gain compared to children born AGA that also experienced rapid or very rapid weight gain during infancy (Table 6). These results provide support for the suggested hypothesis stating that children born LGA who subsequently experience rapid or very rapid weight gain during infancy are at higher risk of developing COO.

Table 6. The table shows the odds ratios [95% confidence intervals] of the childhood overweight and obesity risk for each category of infancy weight gain when stratified by the size for gestational age at birth.

	SGA	AGA	LGA
Slow weight gain	0.66 [0.10 to 2.26]	0.58 [0.51 to 0.65]	0.48 [0.42 to 0.56]
Mean weight gain	-	-	-
Rapid weight gain	1.59 [1.01 to 2.56]	1.71 [1.57 to 1.85]	2.67 [2.12 to 3.35]
Very rapid weight gain	3.47 [2.35 to 5.27]	3.08 [2.84 to 3.33]	5.13 [3.61 to 7.33]

Abbreviations: SGA = small for gestational age, AGA = appropriate for gestational age, LGA = large for gestational age

Furthermore, the tests for additive interaction also provided support for the stated hypothesis, as the analyses showed several signs of statistically significant interactions (Table 7).

Table 7. The table presents the results from the analyses of additive interaction between infancy weight gain category and size for gestational age at birth on overweight and obesity risk in childhood, performed on data from Study II and Study III.

Groups compared		n^a	Childhood obesity RERI [95%CI]	Childhood overweight and obesity RERI [95%CI]
			Data from Study II	
Mean vs. rapid weight gain	AGA vs. LGA	8323	-	7.76 [1.75 to 13.78]
Mean vs. very rapid weight gain	AGA vs. LGA	7706	-	18.55 [0.58 to 36.53]
			Data from Study III	
Mean vs. rapid weight gain	AGA vs. LGA	33 981	2.69 [0.78 to 4.61]	3.45 [2.04 to 4.86]
Mean vs. very rapid weight gain	AGA vs. LGA	31 491	4.50 [0.07 to 8.93]	8.07 [3.79 to 12.35]

[a]Number of children considered in each analysis
Abbreviations: RERI = Relative excessive risk due to interaction, SGA = small for gestational age, AGA = appropriate for gestational age, LGA = large for gestational age

All estimated RERIs were statistically significant and sub-additive, which indicate that prevention of rapid and very rapid infant weight gain would potentially benefit children born LGA more than children born AGA. The statistically significant RERIs identified both when applying Study II and Study III data suggest that additive interaction between infancy weight gain category and size for gestational age at birth exist both on short and long-termed risk of childhood overweight and obesity. However, this was not supported by the results from the multiplicative interaction analyses, as a statistically significant interaction were only detected in Study III data where the longer-termed risk of childhood overweight and obesity were considered. Anyhow, the results from the additive interaction analyses suggest that children born LGA could be a particular important risk-group who would have additional benefits from receiving RIWG prevention activities in terms of preventing later overweight and obesity.

4 Discussion of results

This chapter contains a discussion of the results included in this thesis, which aimed to address the overall aim: *to develop new knowledge on the who, when and how of early-life overweight and obesity prevention with a focus on infancy weight gain to strengthen the knowledge informing research and practice*. This discussion also includes existing literature that can help to shine light on the aspects of to whom, when and how RIWG prevention should be carried out as a strategy of early-life COO prevention. The structure of this discussion is based on Figure 1 in Section 1.8. The *who*, *when* and *how* are not explicitly applied as subtitles, as these matters appear intertwined and interconnected, why the discussion is presented through sections which inductively emerged while writing. This chapter is however introduced with a brief outline of the key results derived from each study and the additional analyses.

4.1 Key results

The specific aim of Study I was *to examine the impact of, and the enablers and barriers for, interventions that prevent rapid infant weight gain as a strategy for early-life overweight and obesity prevention*. The studies included in the systematic review largely reported of positive and significant intervention effects of RIWG prevention on at least one outcome measure, but the effects were generally small. Significant intervention effects were more frequently reported for interventions that measured results over the first rather than the first two years of life. Few studies reported long-term results on the risk for COO. Several barriers and enhancers for prevention were identified. When placing these factors in a socio-ecological model, it became evident that parents, their social context and health professionals are all relevant to involve in RIWG prevention, but that implementation of prevention activities should be supported by appropriate prioritisation and allocation of resources at the organisational and policy level. Overall, the research field of RIWG prevention is at an early stage of development and few studies consider how these interventions affect COO risk in the long term.

The specific aim of Study II was *to investigate whether infants from parents with low socioeconomic position are at increased risk of developing overweight or obesity after rapid weight gain and thus have a special need for prevention*. In summary, the study results did not detect any statistically significant interactions on a multiplicative nor an additive scale. There was therefore no support for our hypothesis that socioeconomic position modified the risk-relationship between infancy weight gain and childhood overweight and obesity at two years of age. This indicate that RIWG prevention activities would be equally relevant for all socioeconomic groups when aiming to prevent COO. However, a specific risk group with extra need for preventive attention were identified from the results of the additive analyses, as these results suggest that the COO risk are higher in children with rapid or very rapid weight gain during infancy if they were born LGA rather than AGA.

The specific aim of Study III was *to evaluate the importance of infancy weight gain information for making early-life predictions on later childhood overweight and obesity risk*. The results of this study indicate that infancy weight gain information are of importance for the quality of early-life predictions on later childhood obesity risk, as inclusion of infancy weight gain information to a prediction model consisting of nine predictors obtainable at birth improved the model's ability to correctly discriminate between children with and without obesity first year in primary school and to correctly classify children that later develop obesity as being in a high risk group ($\geq$90th percentile).

4.2   Socioeconomic position and populations-based prevention

As the background for Study II, a hypothesis was stated suggesting that children from low SEP families would have higher risk of COO after experiencing RIWG, which were tested to consider whether low SEP families would be in particular need of preventive attention. No support were found for this hypothesis, and the results from this comprehensive study confirms the results reported in the previous, smaller studies (Karaolis-Danckert et al., 2008; Stettler et al., 2003). Overall, these results suggest that socioeconomic differences in parental beliefs, views and practices does not exaggerates the weight gain trajectory after experiencing RIWG, which were believed to increase the risk of COO. These social differences might however increase the risk of RIWG itself, as observed through the social gradient in RIWG prevalence.

It is possible that social differences in exposure to prenatal risk factors like maternal obesity, gestational diabetes or smoking during pregnancy cause these socioeconomic differences in RIWG prevalence through *in utero* programming processes, as explained in Section 1.2. Furthermore, socioeconomic differences in infant feeding practices may also be of importance for the social gradient in RIWG prevalence. For instance, low SEP women tend to have shorter breastfeeding durations (Van Rossem et al., 2009) and to practice formula feeding more frequently (Gibbs & Forste, 2014), which through the *early protein hypothesis* could cause higher prevalence of RIWG and COO in these groups, as formula have a higher protein content than breastmilk (Martin, Ling, & Blackburn, 2016). Reeske and colleagues (2013) observed an attenuation in the risk-relationship between SEP and RIWG after adjusting for covariates like breastfeeding and smoking during pregnancy, which indicate that these factors are important drivers of this risk relationship. Hence, preventing short breastfeeding duration and smoking during pregnancy could be important targets of prevention for low SEP groups when it comes to RIWG prevention. Regardless of mechanisms at play, the results from Study II suggest that activities aiming to prevent RIWG would have an equally large value for the prevention of COO in all socioeconomic groups. Such preventive activities should thus target all population groups irrespective of their socioeconomic position, which suggest that *a population strategy*, a strategy targeting the population as a whole (Rose, 2001), rather than a strategy only targeting certain high-risk groups should be taken.

Like previous research (Reeske et al., 2013; Wijlaars et al., 2011), a proportion of rapid and very rapid weight gain were observed in groups with lower SEP in Study II. This highlights that a higher number of infants from low SEP groups experience RIWG, and this pattern of weight gain could be an important driver to later socioeconomic

inequalities in COO. The fact that no interaction between SEP and infant weight gain category on COO risk were detected indicate that similar mechanisms are at play across the socioeconomic strata, but the social gradient in RIWG prevalence propose that population strategies should build upon approaches that have proven effective in low SEP groups. Thus, these strategies should be based upon community-based strategies and policies aiming for structural changes in the environment (Beauchamp, Backholer, Magliano, & Peeters, 2014). These strategies does not demand high levels of individual agency to result in behaviour change, as changes are made at the structural environment level (McLaren, McIntyre, & Kirkpatrick, 2010). Conversely, strategies building on information campaigns would demand much more individual agency in order to result in behaviour change (McLaren et al., 2010). The potentially poorer access to resources like knowledge, social support, money and power in low SEP groups (Link & Phelan, 1995) could reduce the possibilities of such agency, which is why strategies like information campaigns could be less effective in these groups. Thus, interventions need to target the fundamental causes of disease, which is the lack in access to key resources like social support and connections, knowledge, power and money itself (Link & Phelan, 1995), in order to be effective across the socioeconomic strata.

Drawing parallels to the socio-ecological model presented in Study I, this implies that interventions should not only focus on making changes merely at the intrapersonal level and at least secure that these changes are supported by higher-levelled changes make at the organisational, community and/or policy level. This statement is supported by Di Cesare and colleagues (2013), who, based on their literature review, concludes that structural changes like removal of barriers to secure employment in disadvantaged groups, universal and accessible delivery of primary health care, universal insurance and other mechanisms to reduce financial barriers to health care are effective strategies to reduce inequalities in non-communicable diseases, like obesity. However, the results from Study I show that few existing RIWG prevention interventions comprise these types of structural prevention strategies. Only two of the seven included intervention studies covered interventions where changes were made at the community or policy level (Edmunds et al., 2014; Karanja et al., 2010). The remaining studies focused on the parents at the intrapersonal level. Based on these findings, it can be stressed that future RIWG prevention should have a stronger focus on structural strategies to prevent further development of social inequalities in RIWG and COO. However, Savage et al. (2018) have recently published a trial protocol presenting a promising intervention *WEE Baby Care*, which aims to improve the coordination of care to subsequently promote the practice of parenting strategies that prevent RIWG.

4.3   Size for gestational age at birth and targeted prevention

The results from the additional analysis, revealed significant interactions between size of gestational age at birth and infancy weight gain on the risk of childhood overweight and obesity, suggesting that infants born LGA that subsequently experience rapid or very rapid weight gain are at higher risk of developing COO than children born AGA that experience the same weight gain patterns. Similar results have been reported by Taal and colleagues (2013), who identified a considerable increase in childhood overweight risk in the children born LGA who did not experience postnatal catch-down growth. These results suggest that the combination of being born LGA and experiencing accelerated postnatal weight gain is a combination which can be particularly unfavourable for the risk of COO.

As explained by the *high path* to COO presented in Section 1.2, a large size at birth followed by an accelerated postnatal weight gain trajectory could be caused by *in utero* programming processes occurring due to maternal obesity or gestational diabetes. However, the results from the additional analysis were adjusted for maternal pre-pregnancy BMI, which could have attenuated this association. The analyses were although not adjusted for gestational diabetes status, as this data were unavailable due to the updated data extract of the *Medical Birth Registry*. Thus, this mechanism might still be at play in the results. If considering the *accelerated weight gain hypothesis* (see Section 1.3) together with the *high path* to COO (see Section 1.2), it is possible that RIWG itself could have accelerated the subsequent weight gain trajectory even further in children who after *in utero* programming already were on this *high path* to COO. More knowledge is needed on the mechanisms at play in this situation, and future studies should therefore further study potential differences between the children born LGA that postnatally catch-down and those continuing on an accelerated weight gain trajectory. For instance, it would be relevant to further consider whether all children born LGA who subsequently experience rapid/very rapid infancy weight gain have an increased risk of COO, or whether this mechanism is related to programming processes related to the *high path* to obesity and would thus only apply for children born from mothers with obesity or gestational diabetes.

Although results from the additional analyses suggest that LGA children might be a high-risk group when it comes to prevention of RIWG and COO, contrasting findings have been reported by other researchers. Bichteler and Gershoff (2018) found RIWG disadvantageous both for infants with low and high birthweight in relation to middle childhood BMI, and the researchers therefore suggest that infancy weight gain should be monitored in all infants despite their birthweight. Similarly, Singhal (2017) argue

that RIWG is equally disadvantageous for long-term cardiovascular and metabolic health in all children born at term in developed countries regardless of size for gestational age, and RIWG should thus generally be prevented. On the contrary, Taal and colleagues (2013) support the suggestion of targeting RIWG prevention to LGA children after finding a higher risk of overweight in children born LGA that did not experienced catch-down growth. Overall, this discrepancy in evidence should be further studied in order to improve the recommendations for prevention put forward based on birth size.

One relevant high-risk strategy could be to monitor LGA children's postnatal weight gain particularly close in order to enable timely intervention if accelerated weight gain is continued postnatally. However, some precautions should be taken when applying targeted strategies in obesity prevention, as obesity is highly stigmatized in Western cultures (Have, van der Heide, Mackenbach, & de Beaufort, 2013; Puhl & Heuer, 2009). The focus put on RIWG prevention should thus be thoroughly considered. As explained by findings in Study I, it can be more acceptable for parents to focus on promoting healthy infant weight gain than on preventing overweight and obesity when it comes to early-life COO prevention. Such a focus could also be more acceptable for health professionals, as it would potentially better align with their professional values and identity.

4.4   Applying prediction models to detect high-risk individuals

Prediction models can also be valuable in identifying high-risk children who may benefit extra from prevention by estimating their individual risk of developing COO. In Study III, the specificity of models both with and without infancy weight gain information showed high specificity that ranged between 91% to 92% when a risk threshold at the 90th percentile was applied. These high specificity rates express that the large majority of children without overweight or obesity would be correctly categorised as being in the low-risk group (<90th percentile) if these prediction models were applied in practice. Similarly high specificity rates ranging between 90.9% to 99% has been derived by other COO prediction models when using this same threshold (Druet et al., 2012; Robson et al., 2016; Santorelli et al., 2013). In contrast, these prediction models showed much lower sensitivity rates of these models when using this threshold, which ranged between 24% and 65% (Druet et al., 2012; Robson et al., 2016; Santorelli et al., 2013), and similarly low sensitivity were estimated for the prediction models applied in Study III (ranging between 26% and 50%). This indicate that a large proportion of children with COO would not be detected as being in a high-risk group at the time of prediction, why the practice value of these prediction models would be poor. Results from Study I highlight that childhood obesity can be a sensitive topic which could make it difficult for health professionals to bring it up with parents. As the topic can be this sensitive to address, it would be particularly important for health professionals to know that they base their COO risk communication on accurate prediction models. Altogether, it would thus be important that the sensitivity of these models is improved before they are deemed appropriate to implement into practice.

A way to increase model sensitivity would be to lower the applied risk threshold (Steyerberg, 2009). It does not currently exist any clinical guidelines on risk thresholds for childhood obesity prediction models (Butler et al., 2018b). The risk threshold at the 90th percentile was thus set in Study III to secure cross-study comparability, as well as it previously has been assumed manageable for clinical practice to focus on the 10% of children with the highest predicted risk (Graversen et al., 2015). Identification of the appropriate risk threshold can be further studied through statistical tests (Butler et al., 2018b), but identification of appropriate risk thresholds would also depend on the invasiveness of subsequent interventions, the capacity of the health care system, as well as how sensitivity, specificity, feasibility, costs and timing of risk detection are valued in clinical practice.

4.5   Timing of intervention

Another central question for RIWG prevention is when relevant activities should be initiated in order to be most effective. Few experimental studies have analysed the timing of weight gain change and subsequent risk of COO, but a recent systematic review on observational studies suggests that RIWG during the first compared to the second year of life are more critical in terms of later obesity risk (Zheng et al., 2018). In Study I, more significant intervention effects on infancy weight gain were measured over the first 12 months of life than over the first 24 months of age, but the lack of long-term follow-up on COO risk makes it unclear whether a change in infancy weight gain during the first rather than the second year of life are more important for prevention of COO. In one of the few studies on RIWG prevention that actually reported long-term results on COO risk (Weber et al., 2014), the *Baby Milk Trial* which tested formula with different protein content, the authors measured intervention effects on weight gain between 0 and 6 months and 0 and 12 months of age, but not between 0 and 24 months of age. Interestingly, intervention children receiving formula with a lower content protein had lower mean BMI and risk of obesity at six years of age (Weber et al., 2014), which support that a weight gain change during the first rather than the second year of life is important for reducing later COO risk. These findings support that prevention of RIWG occurring in the first rather than the second year of life would be more beneficial as an early-life COO prevention strategy.

It would be an advantage to identify high-risk individuals before initiating RIWG prevention, why these children need to be detected during pregnancy or shortly after birth if appropriate interventions were to be initiated at this early stage in life. Results from Study III show that prediction model performance improved after adding infancy weight gain information to the model but adding this postnatally obtained predictor to the prediction model would delay the timing of COO risk prediction than if applying a model only consisting of predictors obtainable at birth. This delayed timing of risk prediction could reduce the opportunity to intervene before RIWG occurred. On the contrary, the improved prediction model performance leading to more correct identification of high-risk children argues for including this postnatally obtained information. Moreover, qualitative evidence indicate that parents might consider obesity risk information irrelevant if delivered already around the time of birth, as some parents first consider this information to be relevant after their child have started being physically active (Redsell et al., 2010). However, prediction model sensitivity must be improved before further decisions on practice application can be considered for these models.

4.6   Infant feeding practices as prevention target

Results from Study I showed that few RIWG prevention studies also reported long-term results on COO risk. The *Baby Milk Trial* were however an exception, as previously mentioned. The significant intervention effects on long-term COO risk reported for this trial suggest that infant feeding practices could be an important focus for effective RIWG prevention. Long-term results on COO risk were also reported for two other trials included in Study I: the *NOURISH RCT* (Daniels et al., 2013, 2015), and the *INSIGHT Trial* (Paul et al., 2018). The results from the *INSIGHT Trial* were however not included in Study I, as these results were published after the search for literature was ended. In the *INSIGHT Trial*, a lower mean BMI z-score was observed in the intervention group at three years of age after being exposed to a responsive parenting intervention, but no statistically significant differences were observed between intervention and control children in mean BMI percentiles or in COO prevalence (Paul et al., 2018). However, the causal relationship between RIWG and COO were not truly tested in this trial, as the intervention did not lead to fewer cases of rapid weight gain in the intervention group (Paul et al., 2018). In the *NOURISH RCT*, promotion of infant feeding practices assumed protective against RIWG led to lower risks of RIWG in the intervention group (Daniels et al., 2012), but no long-term intervention effects were observed on COO prevalence at two (Daniels et al., 2013) or at five years of age (Daniels et al., 2015). It is possible that the intervention in the *NOURISH RCT*, which focussed on infant feeding strategies, was relevant for weight gain trajectories in the short, but not in the long term. Thus, it can be suggested that prevention of both RIWG and COO must involve several different age-appropriate and relevant activities affecting weight gain trajectories at different ages.

The *Baby Milk Trial* differs from the *INSIGHT Trial* and the *NOURISH RCT* by explicitly targeting the protein content consumed by intervention and control infants, and the significant intervention effects provide support to the *early protein hypothesis*. Similarly, Oropeza-Ceja and colleagues (2018) compared weight gain patterns in infants receiving high vs. low protein content formula and observed that infants consuming the low protein content formula showed slower weight gain compared to infants consuming the high protein content formula at the same time as promoting growth patterns that were in accordance with the WHO growth standards. The protein content in the reduced formula in this study were actually lower than what international committees on nutrition recommend (European Commission, 2016; Koletzko, Baker, et al., 2005), why the results from Oropeza-Ceja and colleagues (2018) support that reducing the protein intake is a safe strategy to promote healthy

weight gain in formula-fed infants. Overall, the findings from the *Baby Milk Trial* and Oropeza-Ceja and colleagues (2018) suggest that the *early protein hypothesis* is a promising field of research in terms of RIWG prevention, as a reduction in protein intake in infancy could reduce the risk of both RIWG and COO.

4.7   Prenatal processes and opportunities for prevention

As argued in the introduction in Section 1.2 and 1.3, the mechanisms linking RIWG to later obesity are not clearly known, but it is suggested that prenatally occurring factors and processes play a role. However, Study I revealed that little preventive focus has been placed on the prenatal period when it comes to RIWG prevention, as no included intervention study explicitly targeted prenatally occurring factors and processes. Only two intervention studies included in Study I involved prenatally initiated activities (Edmunds et al., 2014; Karanja et al., 2010). One intervention included enrolment to WIC during pregnancy (Edmunds et al., 2014), and the other intervention involved home visits performed by community health workers delivering breastfeeding support and nutrition advices (Karanja et al., 2010). However, none of these interventions explicitly targeted any of the programming mechanisms proposed to cause RIWG and COO, such as foetal hyperglycaemia and hyperinsulinemia after gestational diabetes (Lamb et al., 2010) or hypoxia and in utero growth restriction due to maternal smoking during pregnancy (Ino, 2010; Oken et al., 2008; Rayfield & Plugge, 2017). Karaolis-Danckert and colleagues (2008) have shown that infants that were exposed to tobacco in utero and experienced RIWG postnatally gained statistically significantly more body fat between 2 to 6 years of age compared to infants with RIWG who were not exposed to tobacco during pregnancy. Similar results were also observed for RIWG infants born from overweight mothers when compared to normal-weight mothers (Karaolis-Danckert et al., 2008). These results suggest that preventing pre-pregnancy maternal overweight and smoking during pregnancy could be potential targets for preventing both RIWG and subsequent obesity. However, the preventive potential of targeting programming mechanisms occurring during pregnancy is currently largely unexplored and future intervention research should further consider this potential.

5   Discussion of materials and methods

This chapter contains a discussion of aspects related to the materials and methods applied in the three studies and in the additional analyses forming this thesis.

5.1   Study designs

Study I was formed as a systematic review in order to collate and evaluate all evidence available on RIWG prevention. Systematic reviews were originally restricted to comprise of RCTs (Grant & Booth, 2009), due to its superior placement in the pyramid of evidence owing to the relatively low risk of bias (Burns, Rohrich, & Chung, 2011). Even though features in the RCT can lead a high level of internal validity (Higgins & Green, 2008), it might not always be possible to randomise people into an intervention and a control group due to ethical or practical reasons (Bonell et al., 2011). Thus, a broad range of study designs, including non-randomised and observational designs, were thus deemed eligible for inclusion in Study I. Although this decision might have increased the risk of including studies attached with a higher risk of bias, this was evaluated to improve the review quality as more potentially relevant evidence in the field of RIWG prevention could be considered. For the same reason, no studies were excluded from the review due to poor study quality, and transparency in study quality was secured by reporting the different quality judgments. However, excluding lower-quality studies in order to enhance review quality could be relevant for similar reviews in the future when the evidence base on RIWG prevention has evolved.

Study II and Study III in this thesis were *historical* cohort studies, which is a type of an observational study design. As they were historical and based on register-data, data were not collected for the purpose of the current studies (Szklo & Nieto, 2019). In contrast, data collection for *prospective* cohort studies are planned and adjusted to the specific study leading to collection of data with potentially higher quality (Cheng & Phillips, 2014; Szklo & Nieto, 2019). Study II and Study III could have been conducted as prospective cohort studies by collecting survey data, although this would have demanded considerably more resources like time and costs (Szklo & Nieto, 2019). Conversely, it would almost be impossible to obtain as much individual-levelled data through collecting survey data as what was possible to obtain through using already existing data from nationwide registries. The risk of *information bias*, bias originating from systematic measurement error (Rothman et al., 2008), may have been larger when applying register data than survey data obtained for the study purpose only, but

this risk might have been reduced in Study II and Study III by the application of validated and widely used exposure and outcome definitions. On the other hand, the risk of *selection bias*, the risk of systematic error in recruitment or retention of study participants (Szklo & Nieto, 2019), could potentially be lower when applying register data than survey data, as the risk of non-responder bias and differential loss to follow-up could be lower due to the high completeness of data in the registries applied. The completeness of data in the Danish nationwide registries made it possible to obtain detailed information on potential confounders, and adjustment for these in multivariate analyses have presumably reduced the risk of bias in the results.

Overall, the results from the thesis can only be generalised to healthy term infants, as this eligibility criteria were set in all studies. Low birthweight infants were furthermore excluded from Study II and Study III. Altogether, these decisions were made in order to study the weight gain patterns and COO risk of fairly similar populations, where disease and restricted growth did not affect the study results. This decision restricts the generalisability of the results. It is possible that the results would have differed if wider criteria of inclusion were applied, as the postnatal growth of infants born with low birthweight after experiencing in utero growth may differ from other infants (Brands et al., 2014).

5.2   Methods of analysis

Analyses of interactions were central in Study II and in the additional analyses. As stated in the method chapter (Section 2.3.2), the term *interaction* is often used interchangeably with *effect modification*, even though these terms are basically two distinct concepts (Szklo & Nieto, 2019; VanderWeele, 2009). The term *interaction* covered both of these terms in this thesis, as these concepts normally are assumed to coincide (Szklo & Nieto, 2019). However, an explicit distinction between these concepts would have had implications for the statistical modelling strategy and the interpretation of the results in Study II and the additional analyses. First, different strategies for analysis would have been applied to detect whether *effect modification* were present through assessing differences in the effect of a risk factor on the outcome across the strata created by a third variable (Szklo & Nieto, 2019; VanderWeele, 2009), or whether *interaction* were present by assessing whether the joint effect of the risk factor and the third variable on the outcome differed from the independent effect of these variables on the outcome (Szklo & Nieto, 2019; VanderWeele, 2009). Second, only the risk factor is considered for intervention in effect modification, while both the risk factor and the third variable are considered as possible intervention targets in interaction (VanderWeele, 2009). Third, test for effect modification only requires adjustment for confounding in the relationship between the risk factor and the outcome, while test for interaction require additional adjustment for confounding in the relationship between the third variable and the outcome (VanderWeele, 2015; VanderWeele & Knol, 2014). Based on these information, it can be said that *effect modification* rather than *interaction* was measured in Study II and the additional analyses, as the overall interest of analysis was to identify subpopulations that rapid infancy weight gain prevention would be best targeted to, as only intervention on infancy weight gain and not socioeconomic status/size for gestational age at birth were considered, and as only confounders in the relationship between infancy weight gain and risk of COO were included. Hence, it could have been more appropriate to apply the term *effect modification* rather than *interaction* when referring to these analyses.

The field of early obesity prevention is complex as many different factors affect early-life growth. Thus, it could have been an advantage to have based the statistical models in Study II on causal inference thinking through using a directed acyclic graph (DAG) framework. In this framework, a model comprising of relevant variables is constructed to show how the reality under study is theorised, and this model can then be used to detect which confounders that need to be taken into account in order to make causal inference (Greenland, Pearl, & Robins, 1999; Shrier & Platt, 2008). Application of the DAG framework could have supported development of more interpretable models

including fewer covariates, as many of the covariates included in Study II are closely linked and correlated. Although the DAG framework not was explicitly applied in Study II, a conceptual model was built in order to detect important confounders. In this complex field of research, it was also decided to lean on existing research in relation to which confounders they considered significant. Furthermore, the DAG framework was not applied as causal inference was not the primary aim of study.

The method to handle missing data differed in Study II and Study III. In Study II, missing data were handled through multiple imputation, while listwise deletion were carried out in Study III. None of the existing methods for handling missing data such as listwise deletion, pairwise deletion, single imputation, maximum likelihood or multiple imputation appears flawless and the method applied should be chosen in relation to the characteristics of the missing data (Newman, 2014). However, Newman (2014) strongly argues against ever using listwise deletion due to the risk of generating biased estimates and the potentially large reduction in sample size and statistical power. Other researchers have less strict views on the use of listwise deletion. As written in Section 2.3.1, Schafer (1999) argues that missingness under 5% is of little significance, while Bennett (2001) indicate that missingness under 10% is little likely to cause bias. Although listwise deletion did not lead to a notable reduction in statistical power in Study III, deleting all individuals with missing data could have biased the risk estimates to some extent. The proportion of covariate missingness in Study III were generally low and ranged between 1.5% to 2.2%, but maternal pre-pregnancy BMI was missing for 8.2% of the population. However, based on Schafer (1999) and Bennett (2001), the use of listwise deletion in Study III would not appear problematic.

In Study II, data also contained generally small proportions of missing data, but 33% of cases lacked data on breastfeeding duration. We assumed that data on breastfeeding were missing at random, as the missingness were assumed related to geographic and annual differences in the reporting of data to the Children's Database. As considered a valid tool under the missing at random assumption (Dong & Peng, 2013; Newman, 2014; Pedersen et al., 2017; White & Carlin, 2010), multiple imputation was used to handle the large missingness in the covariate on breastfeeding duration. No clear guidelines exist on when the proportion of missing data is too high to be handled through multiple imputation (Harel et al., 2018), but simulation studies have shown that multiple imputation can appropriately handle high proportions of missing data (up to 60% missingness) (Dong & Peng, 2013). The use of multiple imputation in Study II may thus be justified.

5.3   The differences between explaining and predicting

The differences in concepts between studies aiming to explain (Study II) and predict (Study III) have differing implications for how the statistical modelling processes are performed in these studies. First, the quality of data and its ability to measure the underlying constructs are of particular importance for explanatory studies, while predictive studies are more dependent on a large sample size in order to make accurate predictions (Shmueli, 2010). Thus, it was prioritized to apply more up-to-date data of higher quality in Study II, while it was prioritized to obtain a large sample size in Study III by applying data tracing much further back in time.

Second, application of high-quality experimental data or primary data collected solely for the purpose of the particular study would be most appropriate for explanatory studies in order to secure the quality of how the theory under study is operationalized (Shmueli, 2010). Converseley, it is preferred to use observational or secondary data that contain noise and complexity from the real world in studies with a predictive aim (Shmueli, 2010). On this basis, the application of register data, a type of secondary data, would be most suitable for Study III. It is possible that collection and application of survey data would have led to higher quality operationalization of the constructs under study in Study II, but the high quality and coverage of the applied nationwide registers may also have increased the quality of the operationalization of these constructs.

Third, variable selection in an explanatory study is guided by causal interpretation due to the need to rule out confounders and moderators, while the causal role of variables has little importance in a predictive study, and that predictors are rather selected depending on how they are associated to the response variable, the data quality, and the availability of data at the time of prediction (Shmueli, 2010). Operationalization of exposures, covariates and the outcome were thus thoroughly described in Study II in order to make the process of operationalization and modelling transparent for the reader. In some contrast to the more pragmatic variable selection criteria for predictive studies put forward by Shmueli (2010), variable selection in Study III were based on prior knowledge as recommended by Moons and colleagues (2012) and Hendriksen and colleagues (2013). Here, predictors were selected based on prior knowledge and followed by a full model approach to model development (Hendriksen et al., 2013), which were done to reduce the risk of developing an unreliable model due to inclusion of spurious or exclusion of relevant predictors (Hendriksen et al., 2013; Moons et al., 2012).

Finally, some differences between explanatory and predictive studies lie in their use and reporting. As Shmueli (2010) pinpoints, the overall ambition with explanatory models is to develop statistical conclusion that can be translated into scientific conclusions as well as to compare causal theories. This is what was done in Study II, where no statistical support was found for the proposed hypothesis why it was suggested that relevant prevention focusing on infant weight gain was equally relevant for all population groups regardless of their socioeconomic position. The general objective of predictive modelling is to generate predictions for new data that can be useful for practice (Shmueli, 2010). In Study III, this involved comparing prediction models to study their ability to predict COO risk, and the study findings have implications for practice as it highlights the predictive value of infancy weight gain information which can inform development of similar prediction models in the future.

5.4 Operationalisation of exposures and outcomes

5.4.1 Rapid infant weight gain

As previously stated in Section 1.3, rapid infant weight gain have generally been defined as a change in WAZ of more than 0.67 between two time-points sometime during the first two years of life (Monteiro & Victora, 2005; Ong & Loos, 2006; Zheng et al., 2017). However, a range of other definitions on accelerated, excessive and rapid infant weight gain have been applied in describing the same phenomenon in the literature, and this inconsistency have challenged cross-study comparison. The inconsistency was particularly an issue in Study I, as a range of differing measurement timings, growth references, cut-off points and ways of handling differences in z-scores were applied in the studies considered for inclusion in the systematic review. The pre-published protocol guided the identification of eligible papers (https://www.crd.york.ac.uk/prospero/, ID: CRD42018076214), but the low number of studies deemed eligible after the search made it necessary to make some small adjustment to the outcome definition criteria. A stronger focus was thus placed on the use of WAZ to define infancy weight gain changes in the final review than what was stated in the protocol, which allowed inclusion of additional papers that measured intervention effects through mean changes in WAZ between two time-point. However, including this definition could have caused some limitations, as this definition does not describe whether RIWG, defined by a WAZ change of more than 0.67, actually happened or were prevented. Conversely, this way of measuring changes in infant weight gain can be more sensitive in measuring short-term changes, as this measure capture any changes in WAZ including those not exceeding 0.67. Overall, it was deemed more beneficial than disadvantageous to include these differing definitions, as it enabled development of a wider overview of the literature on a research field where relatively little evidence existed. Future intervention studies should report their outcomes on infancy weight gain change through several measures so cross-study comparison is better supported, as this could support the development of recommendations for practice.

Rapid infant weight gain was in Study II and Study III primarily defined in accordance with previous research, but the large sample size in these studies made it possible to construct a more detailed definition that separated rapid from very rapid weight gain. Although this new definition deviates slightly from the dichotomous definition most frequently applied (≤0.67 vs >0.67 change in WAZ) (Monteiro & Victora, 2005; Ong & Loos, 2006; Zheng et al., 2018), results from Study II show that the COO risk for children with rapid vs. very rapid weight gain were considerably

different, when these groups were compared to children with mean infancy weight gain. This considerable difference in COO risk suggests that future research should consider these between-groups differences by adapting the more refined definition on infancy weight gain as it could advance the knowledge on differences in group characteristics and aetiology, and thus possibilities for prevention.

5.4.2   Childhood overweight and obesity

As with RIWG, the different definitions of COO operating in the literature have challenged cross-study comparison. The application of BMI when defining COO demands a reference population and a cut-off point (de Onis & Lobstein, 2010), and the lack of consensus in research have led to application of a range of different definitions (Flegal & Ogden, 2011). As stated in the introduction (Section 1.1) , effort has been made by Rolland-Cachera and the European Childhood Obesity Group (2011) to come to a consensus that involves applying different cut-off scores and growth references depending on the age of the child. Hence, the WHO growth standards (World Health Organization, 2006) were applied in Study II and the International Obesity Task Force reference (Cole et al., 2000) were applied in Study III. However, Rolland-Cachera and the European Childhood Obesity Group (2011) additionally recommend that COO prevalence are reported using several references in the same study if possible. This could ease cross-study comparison, as great differences in obesity prevalence have been detected when using the WHO reference and the International Obesity Task Force reference on the same populations (Flegal, Ogden, Wei, Kuczmarski, & Johnson, 2001; Gonzalez-Casanova et al., 2013; Kêkê et al., 2015). In Study II, only the WHO growth standards (World Health Organization, 2006) was applicable in the young study population, while both the International Obesity Task Force reference (Cole et al., 2000) and the WHO growth reference (de Onis et al., 2007) were applicable in Study III. Despite this, only the International Obesity Task Force reference was applied in Study III, which could have reduced the international generalisability of the study results. It is however planned to additionally report COO prevalence using the WHO reference in the paper of Study III before journal submission.

The terms childhood overweight and childhood obesity are often used interchangeably in research, although these concepts are considered as two different terms (Flegal & Ogden, 2011). All three papers in this thesis included overweight together with obesity in the outcome definition to some extent. In Study I, outcomes of both overweight and obesity were reported as secondary intervention outcomes, which was chosen in order to obtain as much information as possible on the long-term intervention effectiveness on weight status. In Study II, both overweight and obesity

were set as primary outcome as the number of children with obesity was low at the age of follow-up. No firm conclusions could be drawn in relation to childhood obesity alone due to this decision, but inclusion of overweight in the outcome increased the number of cases, which strengthened the statistical power of the analysis (Biau et al., 2008). Another problem by using this wider term is the potential risk of misclassifying children who after experiencing longitudinal growth grow out of an excessive weight category. On the contrary, including children with overweight in the outcome could be important as these children are in higher risk of being overweight or obese later in life (Simmonds et al., 2016; Singh et al., 2008). Childhood obesity was set as primary outcome in Study III, but childhood overweight including obesity were additionally included as secondary outcome in order to study potential differences in prediction models performance across these outcomes. Also, obesity may be more detrimental for later health status than overweight, but prediction of overweight would still of large public health value as childhood overweight can develop into later obesity (Simmonds et al., 2016; Singh et al., 2008).

5.5 The use of data from the Children's Database

The Children's Database is relatively new, as it was first established in 2009 (Sundhedsdatastyrelsen, 2018). Although it is assumed that data completeness and quality improved from December 2011 when it became mandatory for municipalities to report data to the CDB (see Section 2.2.1), the level of validity remains unknown as no studies have evaluated the validity of data in this register. An ethnographic study that considered potential causes of error in data registration to the CDB discovered that some health visitors registered the data with some delay, as they felt it inappropriate to shift the attention away from the child and parent onto the computer (Pape-Haugaard, Haugaard, Carøe, & Høstgaard, 2013). As an alternative, they would write the data down on a piece of paper and reported it to the database after the health assessment or later when returning to the office, which would increase the risk of erroneous data entries (Pape-Haugaard et al., 2013). It is not known to what extent this practice was carried out or whether this practice have changed since the time of study, but changes in practice is unlikely if the problem still is apparent.

Furthermore, these authors identified that the CDB contained several records with different data on the same child registered on the same date (Høstgaard & Pape-Haugaard, 2012; Pape-Haugaard et al., 2013). Although duplicate entries containing similar data were merged in Study II and Study III, it is possible that these problems have reduced the validity of the data to some extent. It is possible that this might be a greater concern for Study III than for Study II, as Study III applied data from before December 2011 which is data considered to be of poorer quality. Despite the challenges in relation to data quality, the COO prevalence in Study II and Study III appears similar to the prevalence observed in other similar, large, Danish populations (Larsen et al., 2012; Pearson, Hansen, Sørensen, & Baker, 2010; Sjöberg Brixval, Johansen, Rasmussen, & Due, 2017), which indicate that the populations and data obtained from CDB are representable for these populations.

A large proportion of children were excluded from both Study II and Study III as they lacked the anthropometric data necessary for analysis. In Study II, a particularly large proportion lacked data on height and weight at follow-up (Figure 1, Study II), which were information used to define COO. However, children with missing anthropometric data did not statistically significantly differ from children with complete anthropometric data on the exposure or the outcome (Additional table 5, Study II). A slightly larger proportion of children from parent of low SEP did however lack anthropometric data (Additional table 5, Study II). This skewness across SEP could have introduced selection bias, but this potential bias might be of little

importance due to the small difference in proportions of missing data across SEP and the similarities on exposure and outcome between these groups.

As stated in Section 2.2.2, Study III was based on data from children born between January 2004 and July 2011. The outcome of this study was based on anthropometric data collected at preventive health checks performed at some point during the first year in primary school. In Denmark, children commence primary school in August in the year the child turns six years, but this can be delayed one year if deemed necessary (Børne- og Undervisningsministeriet, 2018). With the preventive health check occurring at some point during the first year in primary school, and with children having varying ages when entering school, the age of children at follow-up ranged between 71 to 95 months. The available data extract of the CDB contained data throughout July 2017, which means that children born at the end of the inclusion period would be in risk of not having had their preventive health check performed yet. These children would be excluded from the study population if they lacked the data necessary for analysis, which could have introduced selection bias. However, as the preventive health checks is performed class-wise and not in accordance to a child's weight status, it is not likely that this would lead to selection bias.

It is optional to receive the preventive health check where data for the CDB are obtained. Anyhow, it is assumed that the large majority receive these services, as they are generally well accepted by parents (Ammitzbøll, Holstein, Wilms, Andersen, & Skovgaard, 2016). Recently it was shown that more than 90% of children in municipalities around the city of Copenhagen received an early home visit by a health visitor after birth (Pedersen, Pant, Holstein, Ammitzbøll, & Due, 2016). Altogether, these results indicate that most children born in recent years will be registered in the CDB, at least in relation to preventive health checks performed by municipal health professionals. However, studies considering the validity of data in the CDB are needed before conclusions can be drawn on the representability of the study population and on the generalisability of results based on data from the CDB. It was not possible to identify which children who not were registered in the CDB, as the population in this database was used to define the study populations obtained from the other nationwide registries. Conversely, if the study populations were defined based on the Medical Birth Register, it would have been possible to examine which children who did not appear in the CDB. This approach can be applied in future studies aiming to validate the CDB, as data from the Medical Birth Register have high quality and coverage as well as it holds information on all births in Denmark (Bliddal et al., 2018).

6 Conclusion

The field of early-life obesity prevention is complex, as a large number of risk factors and processes with implication for later overweight and obesity risk may operate during this period and as many of these factors are strongly associated and interconnected. Rapid infant weigh gain is strongly associated to the risk of COO, but the causal relationship between RIWG and COO are not yet disentangled, which makes it unclear what mechanisms prevention of RIWG as an early-life strategy for COO prevention should focus on.

Prevention of RIWG itself is also a complex field of research, as a range of barriers and enhancers operating at several contextual levels are of importance for intervention effectiveness and success. Hence, it is important to identify potential barriers and enhancers in the intervention context and to consider these in the planning and implementation of relevant RIWG prevention activities. Existing evidence on RIWG prevention shows promising effects in on reducing infancy weight gain velocity in the short term, but evidence describing the long-term effects on COO risk are currently lacking. These gaps in knowledge make it impossible to put forward recommendations for RIWG prevention when used as a strategy to prevent COO at an early stage in life at the present time. Although some evidence suggest that a reduction of the protein intake in infancy can be a promising strategy to prevent RIWG and COO in formula-fed infants, the great variability in RIWG definitions and the modest experimental evidence existing on RIWG prevention makes it difficult to recommend certain RIWG prevention strategies over others. More experimental research addressing these gaps in knowledge are needed to strengthen the recommendations for practice.

In general, it appears that RIWG prevention as a strategy to prevent COO would be equally relevant for all SEP groups even though the relationship between RIWG and COO appears stronger in populations with higher proportions of lower SEP. However, it could be relevant to target such prevention to children born LGA, as these children might have a particularly high risk of COO if they experience rapid or very rapid infant weight gain. More knowledge is however needed on potential mechanisms that lies behind the risk increase observed in LGA children, which is information that could guide the development of appropriate RIWG prevention strategies. Prediction models including infancy weight gain information can be an important tool to further identify individuals at particularly high-risk for later COO development, but current prediction models show very poor sensitivity at the

commonly applied 90th percentile risk threshold. Thus, the sensitivity of these models must be considerably improved before being ready for use in practice. Further research should also focus on identifying appropriate and clinically significant risk thresholds that can be used in detecting high-risk children.

Although RIWG is an important predictor in predicting COO risk at school-age, it can be too late to predict COO risk after obtaining information on postnatal weight gain at one year of age, as a weight gain trajectory leading to COO could already have been commenced. However, it could also be too late to predict this risk at birth if programming effects occurring during pregnancy already have initiated processes leading to accelerated postnatal weight gain and COO. Relevant prevention should in this case already have been carried out during or before pregnancy, but more experimental research is needed to consider the role of programming processes in relation to prevention of RIWG as a strategy for early-life COO prevention. Some evidence indicate that prevention activities should focus on preventing excessive weight gain occurring during the first rather than the second year of life in order to be most effective as COO prevention, but there is generally a long way to go in this complex research field before clear recommendations on the who, when and how of RIWG prevention as a strategy for COO prevention can be put forward.

7 References

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