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Rozenn Nedelec

METABOLIC HEALTH AND OBESITY: EARLY DETERMINANTS, TRAJECTORIES AND CAUSAL ANALYSIS

THE NORTHERN FINLAND BIRTH COHORT 1966 AND 1986 STUDIES

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE

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The Northern Finland Birth Cohort 1966 and 1986 studies

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Abstract

The obesity epidemic has grown over the last four decades in most European countries including Finland where 21.5% of women and 20% of men are now living with obesity. There is a large body of evidence establishing that the first years of life, including the foetal period, are critical for obesity and general health later in life. However, a better understanding of the link between early life determinants and the life-course trajectory of obesity is needed.

In this thesis, associations between early life determinants and cardio-metabolically healthy obesity, defined as obesity in the absence of any cardiometabolic disorders, were investigated. The relationships between early life determinants and developmental body mass index (BMI) trajectories were explored. Finally, the associations between temperament traits and cardiovascular health and whether eating behaviours and fitness mediated the associations were examined. The research was conducted on data from the prospective Northern Finland Birth Cohorts 1966 (NFBC1966) and 1986 (NFBC1986) using association analyses, latent trajectory modelling and causal mediation analysis.

The first study suggested that early life determinants such as age at adiposity rebound were associated with cardio-metabolically healthy obesity and that the association differed between males and females. In the second study, developmental BMI trajectories were modelled from NFBC1966 and NFBC1986. Adverse maternal factors were associated with unfavourable BMI trajectories. A different pattern of association between age at adiposity peak and BMI trajectories was found between the different cohorts, uncovering secular trends. The third study provided evidence that associations between temperament traits, established early in life, and cardiovascular health measures could be sex-specific. Furthermore, eating behaviours and mediators involved in the associations seemed to be associated with sex.

The research undertaken in this thesis provides evidence to support the effect of early life determinants on life-course metabolic health and highlights the role of sex in these pathways. In addition, this work further advances the importance of psychological factors in relation to metabolic health with a specific focus on sex-specific temperament and behavioural mediators.

Keywords: causal mediation, child adiposity, early life determinants, eating behaviours, growth trajectories, maternal BMI, obesity, temperament

Nedelec, Rozenn, Metabolinen terveys ja lihavuus: varhaiset tekijät, kehityskaaret ja kausaalisuhdeanalyysi Pohjois-Suomen syntymäkohorteissa 1966 ja 1986.
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Tiivistelmä

Lihavuus on yleistynyt viimeisen neljän vuosikymmenen aikana useimmissa Euroopan maissa, myös Suomessa. Suomessa naisista 21,5 % ja miehistä 20 % on ylipainoisia. Aiempien tutkimusten mukaan ensimmäiset elinvuodet, sikiökausi mukaan luettuna, ovat tärkeitä myöhemmän lihavuuden ja yleisen terveyden kannalta. Tieto elämän varhaisvaiheisiin liittyvien tekijöiden ja lihavuuden kehityksen välisestä yhteydestä on kuitenkin puutteellista.

Tämän väitöskirjan ensimmäisessä osatyössä tutkittiin elämän varhaisvaiheiden tekijöiden yhteyttä kardiometabolisesti terveeseen lihavuuteen, joka määritellään lihavuudeksi ilman verenkiertoelimistön sairauksia tai niiden tunnettuja riskitekijöitä. Toisessa osatyössä tutkittiin elämän varhaisvaiheiden tekijöiden ja painoindeksin kehityskaarten välisiä suhteita. Viimeisessä osatyössä tutkittiin temperamentin ja metabolisen terveyden, veren rasva-arvojen, välisiä yhteyksiä sekä näiden yhteyksien välittymistä syömiskäyttäytymisen ja fyysisen kunnon kautta. Tutkimus tehtiin Pohjois-Suomen syntymäkohorteissa 1966 (NFBC1966) ja 1986 (NFBC1986) käyttäen assosiaatioanalyysejä, latenttikasvukäyrämallinnusta sekä kausaalisuhdeanalyysejä.

Ensimmäisessä osatyössä havaittiin, että elämän varhaisvaiheiden tekijät vaikuttivat kardiometabolisesti terveeseen lihavuuteen. Tällainen tekijä oli esimerkiksi ikä, jossa leikki-ikäisen lapsen painoindeksi on pienin ennen kuin se alkaa jälleen kasvaa (engl. adiposity rebound). Vaikutus oli kuitenkin erilainen miehillä ja naisilla. Toisessa tutkimuksessa painoindeksin kehityskaaret mallinnettiin NFBC1966 ja NFBC1986 -kohorteissa. Äidin tupakointi ja raskautta edeltänyt korkeampi painoindeksi olivat yhteydessä lapsen epäsuotuisaan painoindeksin kehityskaareen. Yhteys imeväisiän painoindeksin kasvukäyrän huipun ajoittumisen ja mallinnetun painoindeksin kehityskaaren välillä oli kohorteissa erilainen, mikä viittaa aikakaudellisiin ympäristön vaikutuksiin. Kolmannessa työssä tutkittiin erilaisia temperamenttipiirteitä, jotka myös ilmenivät varhaisella iällä. Työ osoitti, että temperamentti on yhteydessä veren rasva-arvoihin, mutta osin eri tavoin eri sukupuolilla. Lisäksi havaittiin miesten ja naisten välisiä eroja siinä, miten elintavat välittivät temperamenttipiirteiden ja veren rasva-arvojen välisiä yhteyksiä.

Tämän väitöskirjan tulokset tarjoavat lisänäyttöä elämän varhaisvaiheen tekijöiden yhteyksistä metaboliseen terveyteen läpi elämän ja korostavat sukupuolten välisiä eroja. Tulokset vahvistavat käsitystä metaboliseen terveyteen vaikuttavien tekijöiden monimuotoisuudesta temperamentista terveyskäyttäytymiseen läpi elämän.

Asiasanat: elämän varhaisvaiheiden tekijät, kasvun kehityskaaret, kausaalisuus, lapsen lihavuus, lihavuus, syömiskäyttäytyminen, temperamentti, äidin painoindeksi

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Oulu, May 2023 Rozenn Nedelec

List of abbreviations and symbols

aRR	adjusted risk ratio
ATC	anatomical therapeutic chemical
AP	adiposity peak
AR	adiposity rebound
BIC	Bayesian information criterion
BMI	body mass index
CI	confidence intervals
DBP	diastolic blood pressure
GA	gestational age
GBTM	group-based trajectory modelling
GWAS	genome-wide association studies
HA	harm avoidance
HOMA-IR	homeostatic model assessment of insulin resistance
HDL-C	high-density lipoprotein cholesterol
hs-CRP	high-sensitivity C-reactive protein
IQR	interquartile range
LDL-C	low-density lipoprotein cholesterol
MET	metabolic equivalent of task
MHNW	cardio-metabolically healthy normal weight
MHO	cardio-metabolically healthy obesity
MHOW	cardio-metabolically healthy overweight
MHUNW	cardio-metabolically unhealthy normal weight
MUO	cardio-metabolically unhealthy obesity
MUOW	cardio-metabolically unhealthy overweight
NFBC1966	Northern Finland Birth Cohort 1966
NFBC1986	Northern Finland Birth Cohort 1986
NS	novelty seeking
P	persistence
PHV	peak height velocity
PWV	peak weight velocity
TCI	temperament and character inventory
RD	reward dependence
RR	risk ratio
SBP	systolic blood pressure
SD	standard deviation

SDS	standard deviation standardised
SES	socioeconomic status
TFEQ-R18	revised 18-Item three-factor eating questionnaire
WHO	World Health Organization

List of original publications

This thesis is based on the following publications, which are referred to throughout the text by Roman numerals:

I Nedelec, R., Jokelainen, J., Miettunen, J., Ruokonen, A., Herzig, K. H., Männikkö, M., Järvelin, M. R., & Sebert, S. (2018). Early determinants of metabolically healthy obesity in young adults: study of the Northern Finland Birth Cohort 1966. International Journal of Obesity, 42(10), 1704–1714. https://doi.org/10.1038/s41366-018-0115-0

II Nedelec, R., Miettunen, J., Männikkö, M., Järvelin, M. R., & Sebert, S. (2021). Maternal and infant prediction of the child BMI trajectories; studies across two generations of Northern Finland birth cohorts. *International Journal of Obesity*, *45*(2), 404–414. https://doi.org/10.1038/s41366-020-00695-0

III Nedelec R., Miettunen J., Männikkö M., Sebert S., Järvelin M.R. Temperament and lipid metabolism, a mediation analysis – A Northern Finland Birth Cohort 1966 study, manuscript.

Contents

1 Introduction

In the last four decades, obesity has escalated to a global epidemic that now represents a major threat to all socioeconomic groups at all ages. Obesity increases the risk of developing type 2 diabetes, high blood pressure, and glucose and cholesterol metabolism disorders in both adults and children (Norris et al., 2020). These are well-known risk factors for cardio-vascular diseases, stroke and cancers, whose health consequences are potentially severe, ranging from lifelong chronic conditions that decrease the quality of life to premature death (Global BMI Mortality Collaboration et al., 2016). Excess adiposity in childhood often persists into adulthood (Serdula et al., 1993); as a result, many pulmonary, cardiometabolic, and psychological disorders associated with obesity in children persevere in adulthood (Gurnani et al., 2015).

Time is paramount in the study of chronic diseases because cardiovascular disorders have a long latency period. Studies have shown that the duration of obesity is correlated with increased cardiometabolic risk factors (Norris et al., 2020). Timing must also be considered, as early life exposures have been shown to initialise the disease process years before any clinical symptoms. The period ranging from conception to early childhood has been identified as a critical period for later obesity and cardiometabolic health (Araujo de Franca et al., 2015; Rolland-Cachera et al., 2006). There is plasticity and malleability in the developmental processes that shape health trajectories in the long term (Kuh et al., 2003). The life-course perspective involves examining changes and can be defined as interlocking trajectories or pathways connecting changing environments with behavioural changes during the lifespan (Bernardi et al., 2019; Elder, 1998).

The causes of obesity are multiple and are intertwined in a network of interactions between biological, psychosocial, and societal factors. This multifactorial and complex aetiology results in an array of paths leading to obesity and invites the examination of obesity and associated cardiometabolic health from a life-course point of view, accounting for changes over time not exclusively in a cross-sectional manner. Methodology has progressed to meet the life-course framework expectations to study long-term biological, psychological, and behavioural processes. These are at play between physical or social exposures from gestation to adulthood, across generations, and in adult health and disease. New preconception cohorts have been initiated, and long-term and multi- and trans-generation cohorts are being developed and maintained to this end (Eaton, 2002; Konkel, 2019; Nordström et al., 2022).

The work presented in this thesis contributes to the study of obesity and associated disorders. The study employed longitudinal design and group-based trajectory modelling (GBTM) to investigate the impact of maternal and early adiposity markers on growth and later cardiometabolic health. In addition, a causal mediation approach involving lifestyle behaviours to assess the effects of psychobiological traits on dyslipidaemia, an obesity-associated disorder, was explored. The findings from this thesis support evidence of the role of early factors in life-course obesity and associated cardiometabolic health. In addition, they support the mediating role of lifestyle behaviours in the relationship between psychological traits and cardiometabolic health. Importantly, new insights into the sex specificity of the involved mechanisms may be relevant to clinical work.

2 Review of literature

2.1 Obesity

The most common and respected definition of obesity is provided by the World Health Organization (WHO), which defines obesity as 'abnormal or excessive fat accumulation that presents a risk to health' (WHO, 2022).

The primary cause of weight gain is an energy imbalance where energy intake exceeds energy expenditure, and the extra energy is stored in the adipose tissue. However, this is regarded as a simplistic view; the origins of obesity are more complex and multifaceted than energy imbalance alone.

2.1.1 Aetiology

The central organ in obesity is adipose tissue. It is an extraordinarily plastic endocrine structure of varying sizes, locations, and unlimited growth. Moreover, adipose tissue can respond to developmental programming during prenatal or early postnatal periods (Rodgers & Sferruzzi-Perri, 2021). In addition to developmental programming, an obesogenic environment is another major factor in the development of obesity and is perceived as a driving force behind the obesity epidemic. It refers to factors in our environment that stimulate weight gain and are not favourable to weight loss (Swinburn et al., 1999).

After decades of research and a large number of published scientific articles (a PubMed search for 'Obesity' for the last 10 years yielded 250,000 hits), obesity remains a challenge. It is now established that obesity is the consequence of complex interplay between a multitude of variables or determinants related to an individual's genetic, biological, social, and cultural components, environmental factors, urbanisation and pollution, and psychological, emotional, and behavioural elements. The underlying causes of obesity are manifold, and a multidimensional approach across disciplines is often necessary. However, some have appealed for this multidimensional aspect of obesity to be acknowledged and diverse obesity phenotypes to be called 'obesities'. Sylvia Karasu conceptualised obesity under five major paradigms, medical, evolutionary, sociocultural, environmental, and psychological/behavioural (Karasu, 2014), and proposed that each paradigm underlies a type of obesity.

2.1.2 Obesity epidemic

The prevalence of obesity has increased worldwide to epidemic proportions. Since 1975, worldwide obesity has nearly tripled, and in 2016, it was estimated that 1.9 billion adults (18 years and older), representing 39% of all adults, were overweight; of them, over 650 million (13% of adults) were obese. Moreover, over 340 million children between 5 and 19 years of age were overweight or obese in 2016 (WHO, 2021).

The WHO for the European region announced that in 2022, almost 60% of adults and nearly one in three school-aged children were overweight (WHO Regional Office for Europe, 2022). The prevalence of overweight and obesity has increased consistently in the European Region.

In Finland, it is estimated that 57.7% of adults are overweight, including 20.3% of individuals with obesity, which is above the European average of 51.3% and 16.0%, respectively (Eurostat, 2021). In 2019, 27% of Finnish boys and 17% of Finnish girls aged between 2 and 16 years were overweight, with 8% and 4% of boys and girls being obese, respectively (Jääskeläinen et al., 2020). It is concerning that being overweight starting in childhood often tracks into adulthood (Aarestrup et al., 2016; Simmonds et al., 2016).

2.1.3 Measures

There are several ways to measure adiposity (Appendix 1). Advanced methodologies such as dual-energy X-ray absorptiometry, underwater weighting, air displacement plethysmography, computed tomography, and magnetic resonance imaging, provide accurate measurements of body fat. However, they are difficult to interpret, time consuming, and expensive, and they are thus used almost exclusively in small-scale research settings (Kim, 2016). In clinical settings or large-scale data collections, easier, simpler, and less expensive methods are desirable. Field methods comprise body mass index (BMI), waist circumference, waist-hip ratio, skinfold thickness and bioelectrical impedance.

BMI is the most used proxy measure of body fat; it is easy and inexpensive to obtain from height and weight measures. It is defined as weight in kilograms divided by the square of height in meters. In correlation with body fat levels, international standardised cut-off points have been established. In adults, a BMI of 25 kg/m^2 or more indicates overweight, and a BMI of 30 kg/m^2 or more indicates obesity (WHO, 2021). In children and adolescents, the references are standardised

by sex and age (de Onis et al., 2007, 2012). However, BMI does not distinguish between body fat and lean body mass or between visceral and sub-cutaneous fat. Sex and ethnic differences exist; for the same BMI, women have more body fat than men, and Asian populations have more body fat than Caucasian populations. Furthermore, BMI is not accurate in the elderly (compared with young and middle-aged adults), body-builders, or pregnant women (Kim, 2016). However, at a population level, BMI is considered a good indicator to assess weight problems (Korpela et al., 2013).

2.1.4 Obesity and disease

Obesity as a cause of disease

Obesity is considered a major threat to public health. In the 19th century, a British surgeon, William Wadd, wrote '*Corpulency . . . is not only a disease itself, but the harbinger of others.*' (Wadd, 1816) (p.53). Studies have consistently shown that high BMI is a predictor of premature all-cause mortality (Global BMI Mortality Collaboration et al., 2016). Obesity increases the risk of developing cardiovascular disorders, diabetes, hypertension, and some cancers. Dyslipidaemia is another comorbidity commonly associated with obesity, and it increases as BMI increases (Bays et al., 2013). A recent study identified 109 causal outcomes of obesity, including 26 cardiovascular disease phenotypes, 22 anthropometric measurements, nine referring to the musculoskeletal system, and nine referring to lifestyle and behaviour, among others (García-Marín et al., 2021). In the coming decades, obesity is expected to surpass smoking as the primary risk factor for preventable cancer in some countries in the European region (WHO Regional Office for Europe, 2022).

Obesity has been studied in relation to mental health and quality of life. It has been suggested that between 20% and 60% of individuals with obesity suffer from mental or psychiatric disorders (Avila et al., 2015). Furthermore, the occurrence of obesity and metabolic disorders increases the impact of obesity on mental health and quality of life (Abiri et al., 2022). Depression and obesity often co-occur within individuals. The association between depression and obesity is bidirectional, meaning that one increases the risk of developing the other, especially in women (Pan et al., 2012; Vittengl, 2018).

Obesity as a disease

Obesity was first recognised as a disease in the International Classification of Diseases already in 1948, without significant impact; at the time, obesity was still considered a lifestyle choice. During a National Institutes of Health Consensus Development Conference in 1985, obesity was recognised as a chronic disease (NIH Consensus Development Panel on the Health Implications of Obesity, 1985), although it did not receive much attention from the medical community at the time. However, the last decade witnessed several changes. In 2013, the American Medical Association officially recognised obesity as a chronic disease. They stated that obesity is a disease state with multiple functional changes that require a range of treatment and prevention options (Martin, 2013). Recently, in March 2021, the European Commission recognised obesity as a non-communicable disease, leading to its subsequent recognition by other organisations (Burki, 2021). Following the classification of obesity as a disease, it is now important to revisit diagnostic criteria for obesity that rely heavily on BMI cut-offs. This could help differentiate obesity as a condition from obesity as a disease.

However, the concept of obesity as a disease is controversial, as not every individual with excess body fat shows evidence of metabolic disease, leading to the concept of metabolically healthy obesity.

The exception of cardio-metabolically healthy obesity

As previously presented in this chapter, obesity is a precursor of many cardiometabolic disorders. However, there is evidence that a subgroup of obese individuals does not suffer from obesity-related disorders, such as diabetes, hypertension, or dyslipidaemia. They are called metabolically or cardio-metabolically healthy obese (MHO).

The prevalence of MHO varies significatively between studies 10% to 30% of the obese population (Velho et al., 2010). Despite differences in design and population between studies, MHO is more prevalent in women and younger populations (Camhi et al., 2019; Velho et al., 2010). Importantly, the absence of a standard definition of MHO accentuates the discrepancies in studies. It was reported that more than 30 different definitions have been used (Rey-López et al., 2014); however, the most common definitions include the criteria used to define metabolic syndrome (Meigs et al., 2006; Wildman et al., 2008). Cardio-metabolically healthy individuals are characterised by insulin sensitivity, lower

inflammation, better cardiorespiratory fitness, lower visceral fat, but higher subcutaneous fat and better adipose tissue function than cardio-metabolically unhealthy obese (MUO) individuals (Bluher, 2020) (Figure 1).

Studies have investigated the stability of the MHO phenotype after years of follow-up. Some authors have reported that MHO individuals are susceptible to developing cardiometabolic abnormalities over time (Appleton et al., 2013; Soriguer et al., 2013). About 50% of MHO individuals transition to MUO after 20–30 years (Bell et al., 2015; Camhi et al., 2019). Those who transition to an unhealthy phenotype are more likely to be older, male and smokers, with a higher BMI (Schroder et al., 2014; Velho et al., 2010). Cardio-metabolically healthy obese individuals who remain stable over time seem to have an earlier onset and a shorter duration of obesity (Zamrazilova et al., 2016).

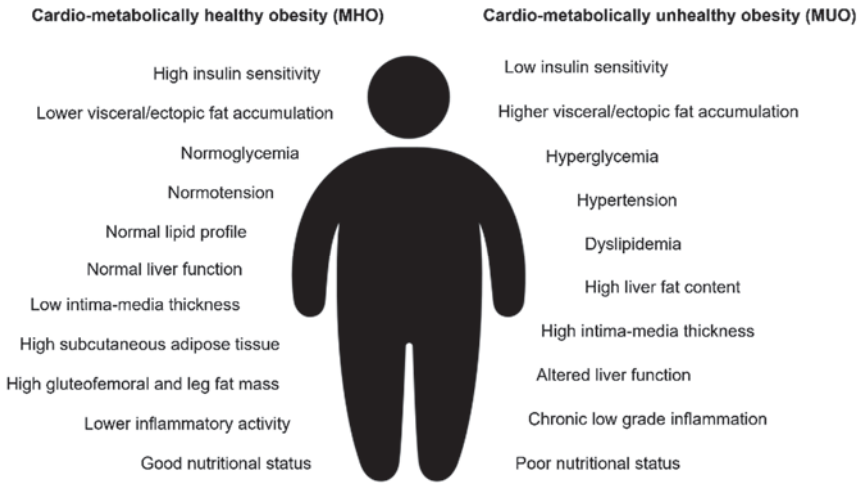

Fig. 1. Characteristics of cardio-metabolically healthy and unhealthy obese.

2.2 Early risk factors

2.2.1 Early adiposity

Although every individual follows the same physiological stages of development during their growth, BMI growth curves are personalised and are monitored closely by health professionals to assess the growth of the child. In epidemiological studies,

models based on repeated measurements of growth have allowed the identification of two characteristic points in a child's BMI curve (Rolland-Cachera et al., 1984). From birth to around 9 months of age, BMI increases to a maximum, called the adiposity peak (AP). From this maximum, BMI decreases, reaching a nadir in the curve called adiposity rebound (AR), between 5 and 7 years of age. From this point, BMI begins a sustained increase up to the end of growth (Figure 2). The timing and intensity of AP and AR may vary greatly according to prenatal, postnatal and childhood environments.

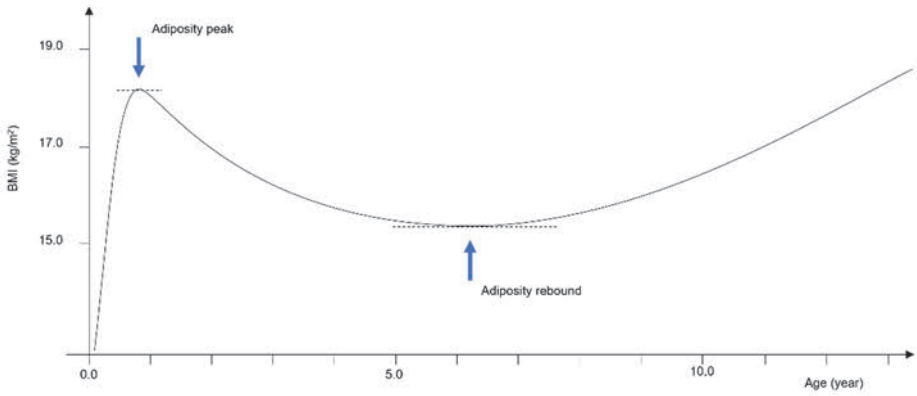

Fig. 2. BMI growth curve of a hypothetic child. BMI: body mass index

Studies mostly use two different approaches (i.e. visual estimation and polynomial models) to assess AP and AR (Eriksson et al., 2003; Freedman et al., 2001; Kroke et al., 2006; Rolland-Cachera et al., 1987).

Adiposity peak

Although AP represents an earlier marker of growth than AR, it has been less studied. One of the reasons might be the scarcity of repeated measurements around 9 months, which are needed to derive the AP. Studies have reported that a higher BMI at AP increases the risk of being overweight in childhood (Jensen et al., 2015; Kruithof et al., 2016; Silverwood et al., 2009). However, Silverwood and colleagues found a weak correlation between BMI at AP and adult BMI (Silverwood et al., 2009). High BMI at AP is also a predictor of adverse arterial health (Monasso et al., 2022). Moreover, a later AP is a predictor of overweight in first grade, aged 6–7 (Lin et al., 2022). Mixed results have been reported regarding

the effects of sex differences on age and BMI at AP (Jensen et al., 2015; Johnson et al., 2013). A change in AP has been observed over time; when compared with cohorts born before 1950, those born after 1970 have an earlier and higher AP (Johnson et al., 2013). Furthermore, there is evidence of an association between older age at AP and higher cardiovascular risk factors in childhood (Marinkovic et al., 2017).

Adiposity rebound

There is no evidence of an association between age at AP and age at AR (Sovio et al., 2014). However, Sovio et al. found a correlation between BMI at AP and BMI at AR. A vast body of evidence identified early AR as a predictor of child and adult obesity (Ohlsson et al., 2012; Rolland-Cachera et al., 1984; Zhou et al., 2022). Early AR is associated with a greater risk of developing metabolic syndrome (Koyama et al., 2014) and type 2 diabetes (Eriksson et al., 2003) in late childhood and adulthood.

Recently, a shift in the timing of AR has been observed; AR in contemporary cohorts occurs at increasingly earlier ages than in older cohorts (Johnson et al., 2012). Furthermore, it appears that the overall prevalence of early AR is increasing, especially in girls (Zhou et al., 2022). This time shift is supported by studies that reported links between early AR and early menarche and pubarche (German et al., 2015; Williams & Goulding, 2009). Moreover, AR has been associated with advanced skeletal maturity (Gonzalez et al., 2014), which is consistent with the rapid growth observed in all tissues in obese children. It was suggested that early AR is an indicator of physical maturity.

2.2.2 Maternal factors

Maternal health and lifestyle during pregnancy, even extended to pre-conception, can affect the health of the offspring from birth to later adulthood. Depression, mood disorders, gestational diabetes, hypertension, and obesity are all conditions that can be detrimental to both the mother and baby (Cattane et al., 2021; Shuffrey et al., 2022; Voerman et al., 2019). In addition, lifestyle factors such as smoking, alcohol use, and unhealthy eating, are harmful to the offspring's health. This section will consider two factors, high pre-pregnancy BMI and smoking during pregnancy, and their link to the child's health.

Maternal smoking

Exposure to maternal smoking during pregnancy increases the risk of small birth weight, neurological disabilities, and low education achievement (Rantakallio, 1988). Furthermore, associations between smoking during pregnancy and low levels of physical activity and cardiorespiratory fitness of the adolescent offspring have been uncovered (Tikanmäki et al., 2017). Studies have revealed links between maternal smoking and infant weight trajectories and BMI trajectories in European children (Börnhorst et al., 2016; Pizzi et al., 2014). Maternal smoking directly impacts growth via its negative effect on bone mineral density, growth, and bone mass in term babies (Jones et al., 1999). The authors suggested that the size and function of the placenta mediate this association. This is supported by research reporting a reduction of blood flow in smoking mothers, which is suggested to increase placental apoptosis and thereby induce growth restriction in the foetus (Isaksen et al., 2004).

Maternal BMI

Maternal obesity has increased concomitantly with the increase in obesity in the general population and is a significant factor for maternal and foetal complications. It is a risk factor for gestational diabetes, hypertension, pre-eclampsia, and caesarean delivery (Cedergren, 2004; Stüber et al., 2015). Moreover, high maternal BMI is associated with threatening complications for the offspring, including a three-fold increase in the risk of stillbirth (Cedergren, 2004) and, large for gestational age babies (Gaillard et al., 2013; Johnson et al., 2012). Past the perinatal period, high maternal BMI is a strong predictor of early AR (Cissé et al., 2021; Ip et al., 2017), which is a predictor of later obesity (Rolland-Cachera et al., 2006) and childhood obesity (Gaillard et al., 2013). Evidence from cohort studies shows that high maternal BMI is associated with a higher offspring BMI (Gademan et al., 2014; Jacota et al., 2017; Josey et al., 2019). Additionally, the interaction between maternal BMI and the sex of the child has been tested and showed mixed results. Associations observed between maternal BMI and child BMI were stronger in daughters than sons starting from 1.5 years and 6 years respectively, and up to 18 years (Swanton et al., 2017). Associations were found in infancy, childhood, and adolescence in females, and only in adolescence in males (Fujita et al., 2018). Conversely, some studies reported stronger interaction during infancy (Bridgman et al., 2018) and early childhood (Andres et al., 2015) for males. Furthermore,

maternal obesity is associated with the child's psychological development, which could influence learning, behavioural and cognitive abilities. There is evidence of an association between maternal obesity and sub-optimal neurodevelopment of the offspring, including poorer motor skills and communication, leading to developmental delay (Girchenko et al., 2018; Wylie et al., 2015). In addition, a non-linear association between pre-pregnancy BMI and preschool boys' emotional and behavioural development was reported (Lu et al., 2022).

2.3 Temperament

2.3.1 Definition of the Temperament and Character Inventory

Personality is a construct of thoughts, emotions, and behaviours that dictate an individual's unique adjustment to life and its environment. Although many models of personality coexist, the focus of this paragraph is on the Temperament and Character Inventory (TCI) developed by Robert Cloninger (Cloninger, 1993).

Cloninger hypothesised that temperament is organised according to independent systems of activation, inhibition, and maintenance of behaviours. Temperament traits are expressed early in life and are relatively stable (Cloninger, 1993).

Twin studies uncovered the genetic homogeneity and independence of each temperament and found that heritability could be between 20% and 60% (Gillespie et al., 2003; Saudino, 2005); another large study found that heritability could be between 50% and 65% (Heath et al., 1994). Single nucleotide polymorphism approaches and genome-wide association studies (GWAS) confirmed these findings (Cloninger et al., 2019; Zwir et al., 2020, 2021).

Initially, the model was called the Tridimensional Personality Questionnaire, and it comprised three independent dimensions of temperament: novelty seeking (NS), harm avoidance (HA), and reward dependence (RD) (Cloninger et al., 1991). Later, persistence (P), a subscale of RD, was included in the TCI as a fourth dimension (Cloninger, 1993). Cloninger defined temperament as follows (Cloninger et al., 1994).

Novelty seeking reflects behavioural activation; it is a tendency to respond with intense excitement to novel stimuli. It includes four facets: 1) exploratory excitability versus rigidity, 2) impulsiveness versus reflection, 3) extravagance versus reserve, and 4) disorderliness versus regimentation.

Harm avoidance reflects behavioural inhibition; it is a tendency to respond intensively to signals of aversive stimuli. Harm avoidance contains four subscales: 1) worry/pessimism versus optimism, 2) fear of uncertainty versus confidence, 3) shyness versus gregariousness, and 4) fatigability versus vigour.

Reward dependence indicates behavioural maintenance or continuation; it is a tendency to respond intensively to signals of previous reward. Reward dependence is a construct of three subscales: 1) sentimentality versus insensitivity, 2) attachment versus detachment, and 3) dependence versus independence.

In the ninth version of the TCI used in the present work, P is represented by a single scale. However, in the revised version, called TCI-R (Cloninger, 1999), P became a four-scale construct: 1) eagerness of effort, 2) work hardened, 3) ambitious, and 4) perfectionist. Persistence represents a tendency to persevere in behaviours to achieve goals despite frustration and fatigue.

According to Cloninger's theory, temperament finds its origin in brain structure. Personality is based on neurotransmitter systems with specific monoamine pathways corresponding to temperament traits: NS would be related to the dopaminergic system, HA to the serotonergic system and RD to the noradrenergic system (Cloninger, 1987)

The TCI is a seven-factor model, comprising four temperament traits (as seen earlier) and three character traits: self-directness, cooperativeness and self-transcendence. Temperament represents the biological aspects of personality, and character is built on both temperament and experiences. Temperament traits involve involuntary emotional and behavioural responses to stimuli, whereas character traits involve voluntary rational responses. Personality originates from the interactions between temperament and character (Cloninger, 1993). The data supporting this thesis contain temperament traits only; therefore, the character aspect of the TCI will not be discussed any further in this work. More details can be found in the TCI manual (Cloninger et al., 1994).

2.3.2 Temperament and mental health

Cloninger stated that temperament traits should be normally distributed in the population, and the presence of high or low levels of at least one of the traits may indicate a mental disorder (Cloninger, 1987). A large body of work investigating the relationship between temperament characteristics and mental and psychological disorders has been produced.

Evidence from a recent meta-analysis revealed that the four temperament traits are associated with mental disorders, notably HA, which is strongly and positively associated with psychopathology, and NS, which is positively associated with drug-related disorders (Komasi et al., 2022). Studies have reported associations between high HA and depression (Ahola et al., 2023; Gurpegui et al., 2019; Mochcovitch et al., 2012), high NS and overall suicide attempts, high HA, low RD, and low NS in prospective suicide attempts during follow-up (Jylhä et al., 2016), high HA and mood disorders (Harley et al., 2006; Zaninotto et al., 2016), high HA and low NS in autism spectrum disorders (Vuijk et al., 2018), and high HA and NS in attention deficit hyperactive disorder (Perroud et al., 2016; Pinzone et al., 2019). Temperament has also been studied in relation to addiction, as results indicate that high HA and NS are associated with smoking (Etter, 2010), high NS in younger individuals and low NS in older individuals are associated with alcohol use (Foulds et al., 2017; Vladimirov et al., 2018), high HA is associated with eating disorders, high NS with dual diagnosis (Fassino et al., 2004; Rosińska et al., 2020), and high NS and HA with pathological gambling (Nordin & Nylander, 2007). Harm avoidance refers to the avoidance of taking risks and remaining safe, and NS refers to the reward of positive experiences by trying new things; research shows that, in excess, they are both detrimental to mental health.

2.3.3 Temperament and physical health

Temperament has been widely used in connection to somatic disorders, including obesity and cardiometabolic health. Higher NS and RD and lower HA have been associated with higher intima media thickness, which is associated with atherosclerosis (Hintsanen et al., 2009). High levels of HA have been associated with decreased heart rate variability (Kao et al., 2016).

Previous findings from the Northern Finland Birth Cohort 1966 (NFBC1966) suggest that high levels of NS and HA increase the risk of developing cardiometabolic risk factors and metabolic syndrome, whereas high RD and P protect against them (Sovio et al., 2007). In addition, the authors found that high RD protected against metabolic syndrome, especially in women. Mixed results were reported in another Finnish cohort with a profile of high P, high RD, low HA, and average NS associated with coronary heart disease risk factors (Keltikangas-Järvinen et al., 1999). As explained previously, NS and impulsivity tend to be associated with adverse health behaviours, increasing a risk of developing metabolic syndrome (Benjamin & Wulfert, 2005; Courneya & Hellsten, 1998;

Terracciano et al., 2009; Terracciano & Costa, 2004). Sutin showed that impulsivity and poor health were mediated by such adverse health behaviours (Sutin et al., 2010). Temperament seems to be connected to BMI and changes in BMI due to NS (Hintsanen et al., 2012; Sullivan et al., 2007; Terracciano et al., 2009). Associations between temperament and individual parameters of the metabolic syndrome were revealed in children (Ravaja & Keltikangas-Järvinen, 1995). Furthermore, in boys, temperament characteristics were associated with all the components of metabolic syndrome at baseline and during the follow-up.

Temperament was also studied in association with blood lipids, and some results suggest an association between high NS scales and high levels of triglycerides (Puttonen et al., 2008) and low-density lipoprotein cholesterol (LDL-C) levels in women (Elovainio et al., 2005). Behavioural factors seem to be involved in these relationships (Sutin et al., 2010). Impulsivity was associated with triglyceride levels in individuals with bipolar disorders (Yaylacı et al., 2014).

2.4 Sex differences

Sex often refers to the biological characteristics of an individual at birth, and it is determined by sex chromosomes, and sex hormones.

In 2016, 11% of men and 15% of women of the adult world population were obese (WHO, 2017). Sex differences in body fat and its distribution are well reported (Mauvais-jarvis, 2015); women have a greater body fat mass, found in the gluteo-femoral area (sub-cutaneous fat), whereas men have more abdominal fat (visceral fat) (Fox et al., 2007; Palmer & Clegg, 2015). As developed previously, obesity is associated with a cluster of cardiometabolic risk factors, related to sex differences (Gerdts & Regitz-Zagrosek, 2019). Starting in adolescence and extending into most of adulthood, males have higher blood pressure than females (Dasgupta). From the sixth decade, the pattern changes and females develop higher blood pressure (Benjamin et al., 2018).

However, sex differences are already apparent in the very early stage of gestation; boys seem to grow faster than girls in utero (Pedersen, 1980). Furthermore, male foetuses grow faster already in the pre-implantation phase (Mittwoch, 1993). Boys seem more affected by adverse outcomes resulting in extreme premature births (Månsson et al., 2015). In the Dutch Famine Birth Cohort, maternal malnutrition during early gestation was associated with higher BMI and waist circumference in women but not in men later in life (Ravelli et al., 1999). Moreover, in the same cohort, prenatal undernutrition was associated with elevated

triglycerides and total cholesterol, independent of BMI, in women but not in men (Lumey et al., 2009). In the EarlyBird study, 5 years old girls were more insulin resistant than boys, and they had higher triglycerides and lower HDL-C (Murphy et al., 2004).

Sex differences were also reported in infant feeding practices; in a French birth cohort, breast-feeding was associated with a later age at AR for girls, whereas in boys, a later AR was associated with a delay in introducing complementary food (Camier et al., 2022). A positive association between age at AR and breastfeeding was also reported in a British birth cohort (Wu et al., 2020). Longitudinal measures of cardiovascular health in the same population between birth and 18 years of age showed changing patterns across childhood and adolescence (Keeffe et al., 2018).

Females are more sensitive to the effects of leptin on the regulation of food intake, this suggests a strong synergy between estrogens and leptin in the energy homeostasis (Clegg et al., 2006). Estrogens seem to facilitate adipose tissue function and deposition, either directly, or indirectly via estrogen receptors on adipocytes (Palmer & Clegg, 2015).

In addition, sex differences are observed in temperament; in a meta-analysis, women persistently score higher in harm avoidance than men (Miettunen et al., 2007). A study on children from 3 to 5 years old reported that early adversity influence child temperament and behaviour, with boys being more susceptible than girls (Coe et al., 2021).

2.5 Review of statistical methods

Based on the literature, statistical methods used in life-course epidemiology and relevant in this research work were carefully considered and are explained in the following section.

2.5.1 Developmental trajectories

A trajectory illustrates the developmental course of a measured variable or behaviour over time. Three methods for modelling individual-level developmental trajectories exist (Nagin & Odgers, 2010a). The first method is growth curve modelling and includes hierarchical modelling (Bryk & Raudenbush, 1987) and latent curve analysis (Willett & Sayer, 1994). Growth curve modelling is preferred when assessing monotonic trajectories and trajectories that vary regularly in the population. For non-monotonic trajectories, other methods are preferred, such as

GBTM, developed by Nagin (Nagin & Tremblay, 1999; Nagin, 2005) and growth mixture modelling, developed by Muthén (Muthén, 2001). The last two models are both finite mixture models, the main difference being that the growth mixture model includes random effects in each trajectory while the GBTM does not (Nagin & Odgers, 2010b). The rest of this paragraph focuses on GBTM, which is the model used in this thesis work.

Group-based trajectory modelling assumes that the population is composed of a mixture of distinct groups or clusters of individuals, each characterised by an underlying trajectory and following similar behaviour over time (Nagin et al., 2016). This semi-parametric group-based approach was first applied in the fields of psychology and criminology (Nagin & Tremblay, 2001; Nagin & Tremblay, 1999) before gaining popularity in other fields, including epidemiology. Group-based trajectory modelling parameters are generated via maximum likelihood estimation. Modern longitudinal studies come with numbers of repeated measures, and this translates into the complexity of the models. therefore, it is not surprising that researchers saw in GBTM a way to effectively map the development of the studied behaviour and a way to untangle the heterogeneity of the population during their life span and move away from the 'one size fits all' approach. According to the assumptions of GBTM, time-independent covariates influence variation between groups, whereas time-dependent covariates influence variation within each group (Frankfurt et al., 2016; Jones et al., 2001).

Using this person-orientated method, various types of trajectories have been modelled, including cigarette use (Xie et al., 2013), markers of cerebrospinal fluid (Niyonkuru et al., 2013), symptom burden (Shi et al., 2013), and adherence to medications (Lo-Ciganic et al., 2016). Moreover, numerous studies have modelled trajectories of BMI during childhood or across the life-course and have analysed the group trajectories in relation to adolescent insulin resistance (Huang et al., 2011), maternal BMI (Haga et al., 2012), maternal smoking during pregnancy (Ziyab et al., 2014), and rural environment (Carter et al., 2012).

2.5.2 Causal mediation analysis

Causation

Causation is a paramount concept in the study of epidemiology. To assess the causality of an association, Bradford-Hill's recommendations have been widely

used as a framework to aid researchers in investigating causal inference. He proposed a reflective method based on eight viewpoints to inform on causation: strength of the association, consistency of the findings, specificity of the association, temporal sequence of the association, biological gradient, biological plausibility, coherence, and experiment (Bradford-Hill, 1965). These are not proofs that an observed association is causal; however, they allow the researcher to reflect on the possible causal pathways linking an exposure to its possible cause in the absence of a causality-testing experiment (e.g. randomised controlled trial).

Mediation

Mediation is a statistical concept that assesses the effects of an intermediary variable on the association between independent and dependent variables. This concept and the associated methods allow investigation of the mechanisms underlying the association.

Initially, mediation implied that a variable, the mediator, was in the middle of the causal chain, between predictor and outcome, and the mediation was based on traditional regression analysis (Judd & Kenny, 1981; Jung, 2021). This method, also called the difference method, lacked causal interpretation and was replaced by the product method, where exposure and mediator predict the outcome in a multivariate regression (Baron & Kenny, 1986). Results for both methods coincide when the outcome is continuous and linear regression models are used; however, they differ when logistic regression is used for binary outcomes (VanderWeele, 2016).

Causal mediation analysis

In past decades, mediation analysis evolved from regression analysis to causal mediation analysis (Pearl, 2001; Robins & Greenland, 1992). Causal mediation analysis is a modern statistical method that evaluates the potential causal roles of mediators by dissecting the total effect of an exposure on an outcome into natural direct and indirect (mediated) effects. Causal mediation requires four strong assumptions: control for exposure-outcome confounders, control for mediator-outcome confounders, control for exposure-mediator confounders, and no mediator-outcome confounders affected by the exposure (VanderWeele, 2016) (Figure 3).

Causal mediation analysis is built on the counterfactual framework; it is a key conceptual framework that is considered the basis of causal thinking in epidemiology and associated fields (Höfler, 2005). The concept is intuitive; an individual is hypothetically compared in the presence and absence of an exposure in identical situations. Because an individual cannot be in the presence and absence of an exposure at the same time, causal inferences contrast actual values with counterfactual values. However, in a mediation model, counterfactual outcomes are not only dependent on the values of the exposure, they also depend on the values of the mediator (Berzuini et al., 2012; Pearl, 2001). These new methods fulfil the causal basis of mediation, which was criticised in mediation analysis (Bullock et al., 2010; Sobel, 2008).

The improvement of causal mediation analysis led to the development of new programmes and macros in most statistical software: R, Mplus, SAS, SPSS, and Stata (Valente et al., 2021). This causal inference approach is highly flexible and adaptable to any model (VanderWeele, 2016).

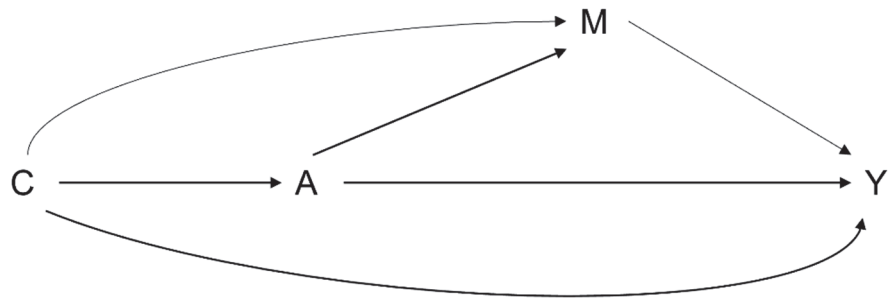

Fig. 3. Generic causal diagram in mediation analysis. A: exposure, M: mediator, Y: outcome and C: set of confounding factors.

3 Aims of the study

3.1 Overall aim

The overarching aim of this thesis work was to further understand the early aetiology of obesity and to provide new insights into the psychobiological determinants of associated disorders.

3.2 Specific aims

Study I

- To assess the prevalence of the MHO sub-population in NFBC1966 in early adulthood.
- To investigate the early origins of MHO in NFBC1966.
- To explore sex specificity in MHO.

Study II

- To model BMI child trajectories in NFBC studies.
- To examine whether maternal and early life factors are determinants of child BMI trajectories.
- To explore a possible generation effect occurring within 20 years.

Study III

- To explore the relationships between temperament and blood lipids.
- To assess the sex specificity of the associations.
- To investigate the causal mediations involved in the associations between temperament and blood lipids.

4 Material and Methods

4.1 Study population

This work used two different population studies, the NFBC1966 for Studies I, II and III and the NFBC1986 for Study II.

4.1.1 Northern Finland Birth Cohort 1966

The NFBC1966 originated in the two northernmost provinces of Finland: Oulu and Lapland. Pregnant women whose expected date of delivery was between the 1st of January and the 31st of December 1966 were invited to participate in the study during their first antenatal clinic appointment. In total, 12,055 recruited mothers gave birth to 12,058 liveborn children, covering 96.3% of the births in the target area in 1966 (Rantakallio, 1969, 1988) (Figure 4).

Between the 24th to 28th weeks of gestation, mothers were given questionnaires by midwifes at the antenatal clinic. The questionnaires related to health, background, socio-economic factors, and lifestyle and health habits. Medical records provided data from the time of birth. The participants have been followed-up ever since at 1 (N=10,821), 14 (N=11,010), 31 (N=8,690) and 46 years of age (N= 7,146) via questionnaires (Nordström et al., 2022; *University of Oulu: Northern Finland Birth Cohort 1966*). In addition, a complementary clinical examination including blood collection, was offered to 6,007 and 5,832 participants at 31 and 46 years of age, (Järvelin et al., 2004; Nordström et al., 2022).

Health and Welfare Clinic records and school health records, encompassing height and weight measurements and development during infancy, childhood, and adolescence were retrieved retrospectively.

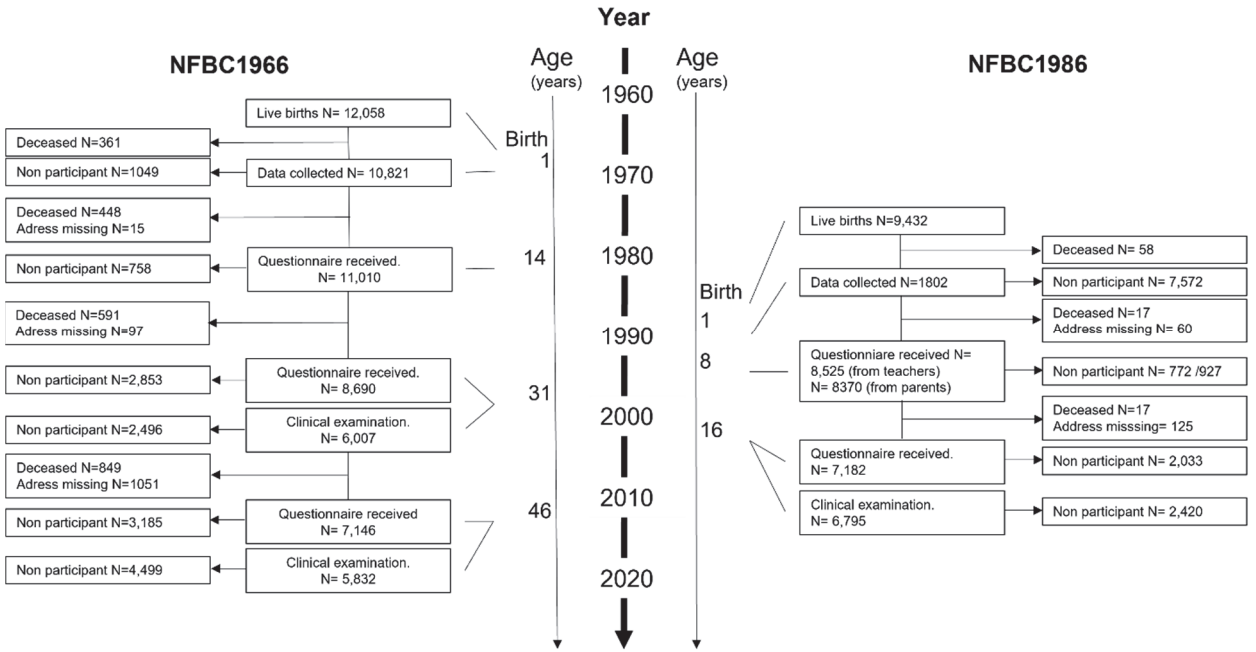

Fig. 4. Flowchart describing the Northern Finland Birth Cohort 1966 and 1986. NFBC1966: Northern Finland Birth Cohort 1966, MFBC1986: Northern Finland Birth Cohort 1986.

4.1.2 Northern Finland Birth Cohort 1986

The NFBC1986 bears similarities to the 20-year older NFBC1966 study. The target area is the same, the northernmost provinces of Finland, namely Oulu and Lapland, and pregnant women were invited to participate in the study at the beginning of their pregnancy. They were expected to give birth between 1st of July 1985 and 30th of June 1986. In total, 9,362 mothers were recruited, and they delivered 9,432 liveborn children, representing 99% of all the births in the target period and area (Järvelin et al., 1993, 1997) (Figure 4).

The mothers were given initial questionnaires about their background, lifestyle, and socioeconomic factors at their first antenatal appointment. Another questionnaire was completed by the midwifes at the end of the pregnancy or shortly after birth and supplied with data from the Health and Welfare Clinic about the delivery. The first follow-ups occurred at 7 and 8 years of age, with questionnaires sent to parents and the teachers at 8 years of age. When they were 16 years old, a new wave of data collection included questionnaires to the parents and the participants in addition to a clinical examination and a blood draw. The most recent data collection took place when the participants were 33–35 years old and consisted of questionnaires and clinical examination. Like in NFBC1966, the data were retrospectively completed with Health and Welfare and school health reports, containing information about child and adolescent growth (*University of Oulu. Northern Finland Birth Cohort 1986*).

4.2 Variables used in the original publications

All three studies used data spanning over the life-course of the participants and issued from questionnaires and analyses of biological samples. Table 1 shows the variables used from NFBC1966 and NFBC1986. They are briefly described in the following sections according to the periods of life in which they were collected.

Table 1. Variables used in Studies I – III.

Variables		Unit/Categories	Cohort	Study	Notes
Mother					**Period during pregnancy**
	Age	years	NFBC1966 NFBC1986	I, II	
	Height	cm	NFBC1966 NFBC1986	II	
	Pre-pregnancy weight	kg	NFBC1966 NFBC1986	II	
	Pre-pregnancy BMI	kg/m^2	NFBC1966 NFBC1986	I, II	Calculated from self-reported weight and measured weight
	Education	a) elementary; b) vocational or secondary; c) matriculation level; d) matriculation and more	NFBC1966 NFBC1986	I, II, III	In Study III, maternal education of NFBC1966 mothers was categorised as a) elementary, b) secondar, or c) matriculation.
	Smoking at 8 weeks of pregnancy	a) smoker; b) non-smoker	NFBC1966 NFBC1986	I, II	In Study I, smoking at 2 months of pregnancy in NFBC1966 mothers was categorised as a) smoker, b) former smoker, or c) non-smoker.
	Marital status	a) married/cohabitating; b) single; c) widowed/divorced	NFBC1966 NFBC1986	I, III	
	Wantedness of pregnancy	a) suitable time; b) better later; c) unwanted	NFBC1966	I, III	
	Parity	Children	NFBC1966 NFBC1986	I, II	
Father					**Period during pregnancy**
	Occupation	a) no occupation; b) professionals and white-collar upper level;	NFBC1966	I	

Variables	Unit/Categories	Cohort	Study	Notes
	c) white-collar lower level; d) blue collars; e) farmers			
Offspring - Birth				
Sex	a) male; b) female	NFBC1966 NFBC1986	I, II	
Gestational age (GA)	weeks	NFBC1966 NFBC1986	I, II	In NFBC1966, GA was calculated from the last period and in NFBC1986, GA is additionally confirmed by ultrasound.
Operative delivery	a) non-instrumental vaginal delivery; b) caesarean section; c) Others (vacuum extraction, forceps)	NFBC1966 NFBC1986	II	
Birth weight	g	NFBC1966 NFBC1986	I, II	
Birth weight z-score	SDS	NFBC1966 NFBC1986	II	Birth weight adjusted for sex, gestational age, and cohort.
Birth length	cm	NFBC1966 NFBC1986	I, II	
Ponderal index	g/cm^3	NFBC1966	I	Weight in grams divided by cubic length in cm.
Offspring – Infancy				**Period covering 0 to 2 years old**
Peak weight velocity	kg/year	NFBC1966 NFBC1986	I, II	Peak height and peak weight velocities were derived from the Reed1 model (Berkey & Reed, 1987), fitted by sex on all weight and height measurements taken at 0–3 years of age, including birth weight and length (Sovio et al., 2009).
Peak height velocity	cm/year	NFBC1966 NFBC1986	I, II	
Age at adiposity peak	years	NFBC1966 NFBC1986	I, II	Adiposity peak derived from growth fitted curves for the period between 2 weeks and 18 months (Sovio et al., 2014).

Variables	Unit/Categories	Cohort	Study	Notes
BMI at adiposity peak	kg/m^2	NFBC1966 NFBC1986	I, II	
Offspring – Childhood				**Period covering 2–11 years old**
BMI 2–11y	kg/m^2	NFBC1966 NFBC1986	II	Repeated measurements of BMI calculated from height and weight measured by Health and Welfare Clinics and school nurses.
BMI z-scores	SDS	NFBC1966 NFBC1986	II	Repeated measurements of BMI were adjusted for age, sex, and cohort.
Age at adiposity rebound	years	NFBC1966 NFBC1986	I, II	Adiposity rebound was derived from growth-fitted curves for the period between 18 months and 13 years of age (Sovio et al., 2014).
BMI at adiposity rebound	kg/m^2	NFBC1966 NFBC1986	I, II	
Offspring – Adolescence				**Period covering 11–20 years old**
BMI 11–20y	kg/m^2	NFBC1966 NFBC1986	II	Repeated measurements of BMI calculated from weight and height measured by school nurses.
BMI z-scores 11–20y	SDS	NFBC1966 NFBC1986	II	Repeated measurements of BMI were adjusted for age, sex and cohort.
Group trajectories 2–20 years	a) stable low; b) normal; c) stable high; d) early increase	NFBC1966 NFBC1986	II	Group trajectories were identified using group-based trajectory modelling for repeated measurements of BMI between 2 and 20 years (Nagin, 2005).
Offspring – early adulthood				**Data collection at 31 years old**
Weight	kg	NFBC1966	I	
BMI	kg/m^2	NFBC1966	I	BMI calculated from height and weight measured during clinical examination.
BMI	a) normal weight; b) overweight; c) obese		I	Categorisation of BMI according to the WHO definition (WHO, 2017).

Variables	Unit/Categories	Cohort	Study	Notes
Waist circumference	cm	NFBC1966	I	
Waist/Hip ratio		NFBC1966	I	Calculated from measurements of waist (cm) and hip (cm).
HDL-C	mmol/l	NFBC1966	I	
HDL-C	a) healthy; b) unhealthy	NFBC1966	I	HDL-C criteria: Unhealthy <1.04 mmol/l for men; <1.30 mmol/l for women or lipid-lowering medication (Wildman et al., 2008).
Triglycerides	mmol/l	NFBC1966	I	
Triglycerides	a) healthy; b) unhealthy	NFBC1966	I	Triglyceride criteria: unhealthy ≥1.70 mmol/l (Wildman et al., 2008).
SBP, SDP	mmHg	NFBC1966	I	
SBP, DBP	a) healthy; b) unhealthy	NFBC1966	I	Blood pressure criteria: unhealthy SBP ≥130 mmHg or DBP ≥85 mmHg or antihypertensive medication (Wildman et al., 2008).
Fasting glucose	mmol/l	NFBC1966	I	
Fasting glucose	a) healthy; b) unhealthy	NFBC1966	I	Glucose criteria: unhealthy ≥5.55mmol/l or diabetes medication (Wildman et al., 2008).
Insulin	ulU/ml	NFBC1966	I	
hs-CRP	mg/l	NFBC1966	I	
hs-CRP	a) healthy; b) unhealthy	NFBC1966	I	CRP criteria: unhealthy >90th percentile (3.50 mg/l for men; 5.40mg/l for women) (Wildman et al., 2008).
HOMA-IR		NFBC1966	I	Derived from: fasting insulin (μU/L) × fasting glucose (nmol/L)/22.5
HOMA-IR	a) healthy; b) unhealthy	NFBC1966	I	HOMA-IR criteria: unhealthy >90th percentile (1.66 for men; 1.52 for women) (Wildman et al., 2008).

Variables	Unit/Categories	Cohort	Study	Notes
Medication		NFBC1966	I	Self-reported medication classified according to ATC codes (WHO Collaborating Centre for Drug Statistics Methodology, 2011).
Metabolic health status	a) healthy; b) unhealthy	NFBC1966	I	Sum of 6 cardiometabolic criteria (0 / 1). A score of 0 indicated healthy and a score of 1 or more indicated unhealthy (Wildman et al., 2008).
SES	a) professional; b) skilled worker; c) unskilled worker; d) farmer; e) other	NFBC1966	I	
Smoking	a) no smoker; b) smoker	NFBC1966	I	Derived from self-reported questionnaires
Alcohol consumption	g/day	NFBC1966	I	Calculated from self-reported consumption of beer, wine and spirits during the last 12 months (Laitinen et al., 2004).
Light physical activity	MET min/week	NFBC1966	I	Derived from duration, frequency and intensity of light physical activity (intensity=3) (Suija et al., 2013).
Brisk physical activity	MET min/week	NFBC1966	I	Derived from duration, frequency and intensity of brisk physical activity (intensity=5) (Suija et al., 2013).
Diet score	0 to 5	NFBC1966	I	Score derived from consumption frequency of rye or crisp bread, sausages, berries or fruits, fresh vegetables and salads (Laitinen et al., 2004). Each food category was assigned one point.
Diet score	a) healthy; b) unhealthy	NFBC1966	I	A score of 3 or less indicates a healthy diet whereas a score of 4 or 5 indicates an unhealthy diet.
Step test	heart beats/min	NFBC1966	I, III	Heart rate was measured immediately after stepping up and down a bench (33 cm high for women and 40 cm for men) for 4 minutes, paced by a metronome, (Tammelin et al., 2002).

Variables	Unit/Categories	Cohort	Study	Notes
Handgrip test	kg	NFBC1966	I	Holding a hand dynamometer, with wrist and elbow extended, the highest value of three trials of 2 to 4 seconds comprised the test result (Tammelin et al., 2002).
Back endurance test	seconds	NFBC1966	I, III	Consists in holding the body in an horizontal position, with the lower body on a bench and the upper body unsupported, for a maximum of 4 minutes. (Tammelin et al., 2002).
FEV1/FVC ratio		NFBC1966	I	Calculated from forced expiratory volumes (FEV1, litres) and forced vital capacity (FVC, litres) during spirometry measurement (Canoy et al., 2007).
Oral contraceptive	a) Yes; b) No	NFBC1966	I	
Education	a) no degree; b) vocational degree; c) university degree	NFBC1966	III	
Temperament novelty seeking (NS)	score of 40 items	NFBC1966	III	Sum of facet scales, exploratory excitability, impulsiveness, extravagance and disorderliness (Cloninger, 1987).
NS z-scores	SDS	NFBC1966	III	
Temperament harm avoidance (HA)	score of 35 items	NFBC1966	III	Sum of facet scales, anticipatory worry, fear of uncertainty, shyness and fatigability (Cloninger, 1987).
HA z-scores	SDS	NFBC1966	III	
Temperament reward dependence (RD)	score of 24 items	NFBC1966	III	Sum of facet scales, sentimentality, attachment, dependence (Cloninger, 1987).
RD z-scores	SDS	NFBC1966	III	
Temperament persistence (P)	score of 8 items	NFBC1966	III	Domain constituted of only one facet scale (Cloninger, 1993).
P z-scores	SDS	NFBC1966	III	

Variables	Unit/Categories	Cohort	Study	Notes
Offspring – Mid-adulthood				**Data collection at 46 years old**
HDL-C	mmol/l	NFBC1966	III	
LDL-C	mmol/l	NFBC1966	III	
Triglycerides	mmol/l	NFBC1966	III	
Medication		NFBC1966	III	Self-reported medication translated into ATC codes (WHO Collaborating Centre for Drug Statistics Methodology, 2011).
Cognitive restraint score		NFBC1966	III	Cognitive restraint, uncontrolled eating and emotional eating are derived from the revised Three-Factor Eating questionnaire (TFEQ) R-18 (De Lauzon et al., 2004).
Uncontrolled eating score		NFBC1966	III	
Emotional eating score		NFBC1966	III	

ATC: anatomical therapeutic chemical, BMI: body mass index, DBP: diastolic blood pressure, FEV1: forced expiratory volume, FVC: forced vital capacity, GA: gestational age, HA: harm avoidance, HDL-C: high-density lipoprotein cholesterol, HOMA-IR: homeostatic model assessment for insulin resistance, hs-CRP: high sensitivity C-reactive protein, LDL-C: low-density lipoprotein cholesterol, MET: metabolic equivalent of task, NFBC: Northern Finland Birth Cohort, NS: novelty seeking, P: persistence, RD: reward dependence, SBP: systolic blood pressure, SDS: standardised standard deviation, SES: socioeconomic status, WHO: World Health Organization.

4.2.1 Perinatal period

During pregnancy, questionnaires about lifestyle, socioeconomic status (SES), and maternal health were administered by the community midwives. The maternal variables from questionnaires included age, education, smoking habits, marital status, and parity. Maternal education is an effective proxy measure for SES. Pre-pregnancy BMI was derived from measured height during the first antenatal appointment and the questionnaire's self-reported weight before pregnancy.

Information about delivery was incorporated into the antenatal cards and included the sex of the child, birthweight, birth length, gestational age at birth and mode of delivery. Gestational age at birth was calculated from the mother's last menstrual period in NFBC1966 and in priority from ultrasound complemented with the last menstrual period, where necessary, in NFBC1986. Birth weight z-scores (i.e. birth weight standard deviation scores) are measurements of birth weight adjusted for sex and gestational age.

In Study II, pre-pregnancy BMI, maternal smoking, and birth weight z-scores were considered as exposure variables.

4.2.2 Infancy, childhood, and adolescence

From birth to 7 years of age, the children's height and weight were obtained from Health and Welfare Clinics, and from 7 years onwards, growth measurements were obtained from the school medical records. These data were supplemented by self-reported height and weight at the age of 14 years in NFBC1966 and measured at 15–16 years as part of the clinical examination in NFBC1986. BMI was derived from the height and weight measurements. In Study II, 16 age windows were defined, with one per year from age 2–16.9 years, and due to the dearth of regular measurements in late adolescence, the last window encompassed 17–20 years. BMI corresponding to these age windows were sex and cohort standardised using z-scores. Due to the high representativity of each cohort in the general population, the z-scores were calculated internally (Bradfield et al., 2019; Felix et al., 2016).

Using the repeated BMI measurements, latent classes of BMI growth trajectories were modelled. The trajectory groups represented the outcomes in Study II.

Peak height velocity (PHV) and peak weight velocity (PWV) were derived from Reed1 models (Sovio et al., 2009). The model was fitted by sex to all weight

and height measurements between birth and 3 years of age. In Study II, PHV and PWV were exposure variables of interest.

A nonlinear BMI pattern is part of a normal child growth and development. To obtain child adiposity variables from fitted growth curves, two periods were considered: infancy from 2 weeks to 18 months, and childhood, from 18 months to 13 years. From these two growth periods, AP, around 9 months of age, and AR, usually between 5 and 7 years, were identified from infancy and childhood respectively (Sovio et al., 2014; Tzoulaki et al., 2010). Age and BMI at AP and age and BMI at AR were used as exposure variables in Study I and age at AP was an exposure variable in Study II.

4.2.3 Early adulthood

At 31 years of age, NFBC1966 members were sent postal questionnaires and were invited to participate in a clinical examination.

Lifestyle variables

Variables on smoking status and SES based on occupation and employment status were obtained from the questionnaires on lifestyle. Alcohol consumption was calculated for beer, wine, and spirits and the amount of alcohol per day was calculated based on estimates of alcohol content for each beverage: beer 4.8 vol%, light wine 5.0 vol%, wine 14.5 vol%, and spirits 37.0 vol% (Laitinen et al., 2004). A diet score was calculated based on a food frequency questionnaire over the previous 6 months. The food variables considered for this diet score included food rich in saturated fats, such as sausages, and food rich in fibre, such as rye bread, or crisp bread, salad, or fresh vegetables, fruits or berries. A score of 3 or less determined a healthy diet whereas an unhealthy diet was attributed to a score of 4 or 5 (Laitinen et al., 2004).

Using the self-reported duration and frequency of physical activity, the metabolic equivalent of task (MET) score was calculated for light physical activity, defined as no sweating or shortness of breath, and brisk physical activity, defined as sweating or shortness of breath (Tammelin et al., 2002).

The medications used by the participants were self-reported in the questionnaire and were classified according to the anatomical therapeutic chemical (ATC) classification system at the time (WHO Collaborating Centre for Drug Statistics Methodology, 1996).

Clinical variables

Trained nurses measured weight, height, and systolic (SBP) and diastolic blood pressure (DBP) during the clinical examinations. The participants performed a back endurance test and a maximal isometric hand grip test of the dominant hand to assess their muscular fitness. Cardiorespiratory fitness was evaluated using spirometry and the step test.

Triglycerides, high-density lipoprotein cholesterol (HDL-C), fasting glucose, insulin, and high-sensitivity C-reactive protein (hs-CRP) were analysed from the collected blood. Insulin sensitivity was based on the homeostatic model assessment for insulin resistance (HOMA-IR), calculated from the formula (glucose mmol/l * insulin mmol/l)/22.5.

Cardiometabolic risk factors

A cardiometabolic risk score derived from Wildman's definition was calculated (Wildman et al., 2008). In the original definition, a score of none or one criterion indicated that the respondent was cardio-metabolically healthy, and two or more criteria indicated that the respondent was cardio-metabolically unhealthy. However, as NFBC1966 participants were only 31 years of age at the time of data collection, a stricter definition was applied, with cardio-metabolically healthy status characterised by the absence of all six criteria.

Table 2 shows the selection of the cardiometabolic criteria and their cut-offs. Each criterion was dichotomised into healthy (0) or unhealthy (1) according to the cut-off values set in the cardiometabolic health definition. The six scores were summed up; a zero total score indicated healthiness (category 0), and a score of one or more indicated unhealthiness (category 1). The medications used by the participants were self-reported and were converted into ATC codes.

Table 2. Cardiometabolic risk score.

Variables	Cardiometabolic abnormalities
Blood pressure	SBP ≥ 130 mmHg
	DBP ≥ 85 mmHg
	Or anti-hypertensive treatment (ATC codes C02, C03, C07, C08, C09)
Triglycerides	≥ 1.70 mmol/l (150 mg/dl)
HDL-cholesterol	< 1.04 mmol/l (40 mg/dl) for men
	< 1.30mmol/l (50 mg/dl) for women

Variables	Cardiometabolic abnormalities
	Or lipid-lowering treatment (ATC codes B04, C10)
Fasting glucose	≥ 5.55 mmol/l (100 mg/dl)
	Or anti-diabetic treatment (ATC code A10)
HOMA-IR	≥ 90th percentile value
	(≥ 1.66 for men and ≥ 1.52 for women)
hs-CRP	≥ 90th percentile value
	(≥ 3.50mg/l for men, and ≥ 5.40 mg/l for women)
Criteria for cardiometabolic health	none of the above

ATC: anatomical therapeutic chemical, DBP: diastolic blood pressure, HDL-C: high-density lipoprotein cholesterol, HOMA-IR: homeostatic model assessment for insulin resistance, hsCRP: high-sensitivity C-reactive protein, SBP: systolic blood pressure.

The participants' BMIs were stratified according to the WHO definition (WHO, 2000) into normal weight (18.5–24.9kg/m^2), overweight (25–29.9kg/m^2) and obese (≥30 kg/m^2). The resulting six groups are presented in Table 3.

Table 3. Cardiometabolic risk groups according to BMI.

Group abbreviation	Group full name
MHNW	Cardio-metabolically healthy normal weight
MUNW	Cardio-metabolically unhealthy normal weight
MHOW	Cardio-metabolically healthy overweight
MUOW	Cardio-metabolically unhealthy overweight
MHO	Cardio-metabolically healthy obese
MUO	Cardio-metabolically unhealthy obese

In Study I, the metabolic groups represented the outcomes. Due to differences in their physiology, the analyses were conducted separately for men and women.

Temperament variables

During the clinical examination, participants were given Cloninger's TCI questionnaire (Cloninger, 1987) to complete at home and return by mail. The questionnaire is divided in four domain scales, with the first three reflecting the sum of facet scales. Novelty seeking is composed of exploratory excitability (11 items), impulsiveness (10 items), extravagance (9 items) and disorderliness (10 items). Harm avoidance is constituted by anticipatory worry (11 items), fear of uncertainty (7 items), shyness (8 items) and fatigability (9 items). Reward dependence is the sum of sentimentality (10 items), attachment (8 items) and

dependence (6 items) scores. Persistence, as previously mentioned, consists of a single scale. In Study III, the temperament domains and facet scales were standardised by sex using Z-scores, and they were considered exposure variables.

4.2.4 Mid-adulthood

At 46 years of age, the NFBC1966 participants were sent postal questionnaires and an invitation for a clinical examination.

Eating behaviour

The Three-Factor Eating Questionnaire revised 18 items (TFEQ-R18) was included in the postal questionnaire (Karlsson et al., 2000). It is a reduced version of the original 51-item questionnaire developed by Stunkard and Messick (Stunkard & Messick, 1985).

The TFEQ-R18 consists of 18 questions measuring the three dimensions of human eating behaviour via the assessment of cognitive restraint, emotional eating, and uncontrolled eating. The responses are coded on a four-point Likert scale, with a higher score indicating increased behaviour. Cognitive restraint score is the sum of six items and evaluates conscious restriction of food intake to control body weight or to promote weight loss. Uncontrolled eating score is the sum of nine items and indicates a tendency to eat more than usual due to a loss of control over food intake together with subjective feelings of hunger. Emotional eating score is the sum of three items and assesses the ability to resist emotional cues. In Study III, uncontrolled eating and emotional eating were mediator variables of interest.

Medication variables

NFBC1966 participants self-reported their medications in the questionnaire. The medications were later coded according to ATC classification system in use at the time of data collection (WHO Collaborating Centre for Drug Statistics Methodology, 2011).

Lipoproteins and clinical variables

Blood samples were collected during clinical examination. Triglycerides were measured according to standardized protocol in the laboratory of the University

hospital of Oulu. Fasting serum circulating lipoprotein HDL-C and LDL-C, were analysed via a high-throughput quantitative serum nuclear magnetic resonance (NMR) metabolomics platform described in details by Soininen and colleagues (Soininen et al., 2009). Basically, NMR spectroscopy is based on the physical property of nuclei of many isotopes to absorb radiation and resonate at a specific frequency when placed in a magnetic field. Depending on the targeted atom nuclei, a large number of metabolites can be quantified. However, compared to other methods, NMR is less sensitive, limiting its use in the detection of medium to high concentrations of circulating metabolites. In Study III, HDL-C, LDL-C, and triglycerides were outcome variables of interest.

During the clinical examination, the participants performed fitness exercises measured by the research nurse. The back endurance test consisted of the participant holding a prone position, the lower body lying on a stand with the upper body unsupported for a maximum of 4 minutes or as long as possible (Tammelin et al., 2002). The step test is a cardio-fitness exercise that consists of stepping up and down on a bench 33 cm high for women and 40 cm high for men for a maximum of 4 minutes (Canoy et al., 2007).

In Study III, the back endurance test and step test were mediating variables of interest.

Correction factors

In Study III, correction constants were applied to the lipoproteins measurements for participants who were prescribed lipid-lowering medications (Wu et al., 2007), and they are presented in Table 4.

Table 4. Correction constants for lipid-lowering medication.

Medication	ATC code	Lipoprotein	Correction (mmol/l)
HMG-CoA reductase inhibitors (statins)	C10AA	Triglycerides	+0.208
		HDL-cholesterol	-0.060
		LDL-cholesterol	+1.290
Fibrates	C10AB	Triglycerides	+0.645
		HDL-cholesterol	-0.153
		LDL-cholesterol	+1.037
Bile acid sequestrants	C10AC	Triglycerides	+0
		HDL-cholesterol	-0.049
		LDL-cholesterol	+1.047

ATC: anatomical therapeutical chemical, HDL: high-density lipoprotein, LDL: low-density lipoprotein

4.3 Statistical analysis

This section describes the different statistical approaches and models performed in the original publications using SAS software version 9.4 (SAS Institute Inc, Cary, NC).

4.3.1 Descriptive analysis

Continuous variables are presented as means and standard deviation (SD), and skewed variables are presented as medians and interquartile range. Categorical variables are expressed as percentages. Chi-squares and t-tests were performed to evaluate differences between groups.

4.3.2 Linear and logistic regression analysis

In Study I, the LSMeans statement in the Proc Genmod SAS procedure was computed to compare least squares means of fixed effects or marginal means. Dunnett's test was applied to correct multiple comparison for p-values and confidence intervals in the differences in marginal means. The effect size statistics were reported as partial omega squared, and the results were reported as percentages of difference between cardiometabolic groups. The reference used in the pairwise comparisons was the cardio-metabolically healthy group. The models were adjusted for birth weight, gestational age, maternal age, maternal smoking at 2 months of pregnancy, maternal BMI, maternal marital status, parity, and child wantedness during pregnancy.

In Study II, the Proc Genmod SAS procedure was used in multivariate models to understand associations between maternal and early life factors and BMI z-scores trajectories. The results were reported as risk ratios (RR) and their 95% confidence intervals (CI). Trajectory 2, labelled 'normal', was the reference trajectory. For maternal factors, three models were tested: unadjusted, adjusted for maternal education, and fully adjusted for maternal education, parity, maternal age, and maternal smoking or pre-pregnancy BMI, depending on the exposure. For early life factors, four models were tested: unadjusted, adjusted for birthweight z-scores, adjusted for pre-pregnancy BMI, and fully adjusted for birthweight z-scores, pre-pregnancy BMI, parity, maternal age, maternal education, and maternal smoking. For birthweight z-scores, three models were tested: unadjusted, adjusted for pre-pregnancy BMI, and adjusted for pre-pregnancy BMI, parity, maternal age, maternal education, and maternal smoking.

In Study III, linear regression analysis was applied and the evidence of association between temperament domains and facets and lipoproteins was interpreted according to the effects sizes, their confidence intervals and the consistency of the results. To further explore the associations and robustness of the results, Bonferroni correction for multiple testing was applied with a threshold of 0.0033. The models were adjusted for maternal education and wantedness of pregnancy.

4.3.3 Discrete mixture model for clustering of longitudinal data

In Study II, GBTM was conducted to identify latent class BMI z-score trajectories between 2 and 20 years of age in pooled NFBC cohorts. The Proc Traj procedure, an application of finite mixture modelling, was used (Nagin, 2005; Nagin & Odgers, 2010b). Proc Traj is not part of the original SAS package; it is a user-written SAS procedure, that can be freely downloaded (http://www.andrew.cmu.edu/user/–bjones/index.htm).

GBTM is a person-centered statistical approach. It assumes that a population comprises distinct groups or latent classes of individuals, each one sharing similar patterns or behaviour over time. A minimum of three measurements are required for the modelling. GBTM is fitted to the longitudinal data, starting from a one-group trajectory model, and increasing one group at a time up to a maximum number of groups decided a priori. Bayesian information criterion (BIC) values are compared from one model to the next, and the model with the smallest absolute value is selected as the optimal model. Model adequacy rests on the evaluation and

interpretation of fit indices. These statistical criteria are: 1) the average of the posterior probabilities of belonging to a group is at least 0.7 and preferably closest to 1, 2) the odds of correct classification exceeding a minimum threshold of 5, 3) a close correspondence between observed and predicted group membership probabilities, 4) narrow CI around estimated group trajectories, and 5) a recommended group size of minimum 5%. However, the trajectory group size could be less than 5% if it represents the group of interest and the population is large. Finally, parsimony and a-priori knowledge of the subject should be considered when choosing the optimal model.

In Study II, the trajectories were first modelled separately for each cohort. Both cohorts (NFBC1966 and NFBC1986) produced consistent models. Therefore, to allow comparisons between the two cohorts, they had to be modelled together, controlling for sex and cohort in the process. However, it was not possible to identify the optimal number of trajectories based on the BIC value because it never stopped decreasing through the seven models tested, and the choice of the optimal model of four trajectories (polynomials 4, 3, 4, 3) was made using the other goodness-of-fit criteria and the visual analysis of the trajectory graphs. The study population consisted of 12,040 individuals from NFBC1966 (n=6,864) and NFBC1986 (n=5,176).

4.3.4 Causal mediation analysis

Causal mediation analysis allows for the dissection of total effect into direct and indirect effects under the assumptions of the counterfactual framework (Pearl, 2001; Robins & Greenland, 1992). Counterfactual framework concedes modern causal inference. Causal mediation analysis explores models where a third variable influences the direction or strength of the association between independent and dependent variables. It models two concurrent pathways, direct and indirect, and determines which one accounts for most of the effect. The latter ascertains the in-between process involving mediators that can explain the underlying causal pathway. In causal mediation analysis, temporal precedence is an assumption that stipulates that exposure occurs before the outcome and that the mediating variables should be assessed prior to the outcome.

Proc Causalmed is based on the maximum likelihood method and estimates total, controlled direct, natural direct, and natural indirect effects (Yung et al., 2018). The procedure can include covariates and interactions between exposure and

mediator variables. In addition to the estimates, Proc Causalmed displays two-way to four-way decomposition orders and CI from bootstrap replication.

In Study III, the potential mediators of eating and fitness behaviours on the association between temperament and lipoproteins were evaluated using Proc Causalmed. Data on eating behaviour mediators were collected at the same time as the outcome, potentially violating the temporal precedence assumption. However, because eating behaviours was found to be quite stable in children (Ashcroft et al., 2008; Farrow & Blissett, 2012) and in adult women (Rizvi et al., 1999), temporal precedence of the mediator was circumvented in this model.

4.3.5 Missing data

Due to the longitudinal design of the NFBC studies, with recurring waves of data collection, missing data are unavoidable. Missing data can lead to a loss of statistical power and introduce biased estimates; therefore, it must be addressed in the study design.

In Study I, the investigations were performed via complete case analysis, and sensitivity analyses were completed. In Study II, missing longitudinal BMI data in the GBTM (Proc Traj) were generated using maximum likelihood estimation approach. In Study III, the causal mediation analysis programme (Proc Causalmed) relied on the maximum likelihood method to estimate causal mediation effects. the maximum likelihood method computes maximum likelihood estimates, calculated separately for cases with complete data on a set of variables and complete data on all the variables, and they are then maximised together. The maximum likelihood provides unbiased parameter estimates and standard errors; it represents the value of a variable that would most likely have resulted in the observed data.

4.4 Ethical considerations

The Ethics Committee of the Northern Ostrobothnia Hospital District reviewed and approved the NFBC1966 (Northern Ostrobothnia Hospital District Ethical Committee 94/2011 [12.12.2011]) and NFBC1986 (Northern Ostrobothnia Hospital District Ethical Committee 108/2017 [15.1.2018]) studies. The NFBC studies are in accordance with the 1964 Helsinki declaration.

During their pregnancy, mothers of NFBC children were informed of the purpose of the study and enrolled voluntarily. Upon reaching adulthood, participants voluntary signed informed written consent forms to take part in the

subsequent waves of data collection. After the European Union Data Protection Act came into force in May 2018, all cohort participants were informed of their rights and about the use of their data.

This thesis complies with data protection regulations and only uses data from participants who signed informed consent forms.

5 Study-specific results and discussions

In this chapter, the main results from the three individual studies are presented, each followed by a discussion of the results. An overall discussion of the three studies is provided in chapter 6. Table 5 presents general characteristics of the studies used in each article.

Table 5. Summary of general characteristics of the studies.

Characteristics	Study I	Study II	Study III
Design	Prospective	Longitudinal	Longitudinal
Cohort	NFBC1966	NFBC1966 NFBC1986	NFBC1966
N	3,205	6,864 (NFBC1966) 5,176 (NFBC1986)	4,904
Sex (% males)	52	53.7 (NFBC1966) 49.4 (NFBC1986)	44.7
Age	Birth to 31 years	2 to 20 years	31 to 46 years

5.1 Childhood determinants of metabolically healthy obesity (Study I)

5.1.1 Characteristics of the population

The study population in Study I comprised 3,205 cohort members at the age of 31 years, with 52.0% men. Table 6 shows the differences between the initial population and the study population. The mean (SD) BMI was 25.3 (3.5) kg/m^2 for males and 24.5 (4.7) kg/m^2 for females. Alcohol consumption was 13.9 (20.1) g/day for males and 5.2 (8.1) g/day for females, and 62.6% of males smoked compared with 52.8% of women.

Table 6. Characteristics of the study population and the total population at birth.

Characteristics	Study population	Total population	p-value
Maternal BMI (kg/m^2)	23.3 (3.3)	23.0 (3.2)	<0.0001
Parity	2.9 (2.2)	2.9 (2.2)	0.11
Gestational age (week)	40.1 (1.3)	39.8 (2.5)	<0.0001
Birthweight (g)	3541.0 (482.9)	3408.4 (624.9)	<0.0001
Maternal age at birth (y)	28.3 (6.7)	27.6 (6.7)	<0.0001
Gender (males)	52.04	48.0	0.27

Characteristics	Study population	Total population	p-value
Maternal smoking			<0.0001
1: smoker	13.4	16.3	
2: former smoker	6.0	6.8	
4: non-smoker	80.6	76.9	
Maternal marital status			<0.0001
1: married	97.2	95.0	
2: unmarried	2.3	4.2	
3: widowed	0.2	0.3	
4: divorced	0.3	0.5	

5.1.2 Cardiometabolic health

Table 7 describes the six criteria constituting the cardiometabolic health status and the final score. The females had better scores in all criteria except HDL-C. Consequently, the sum of scores for females indicated better cardiometabolic health than males; altogether, 50% of females and 25.4% of males were classified as cardio-metabolically healthy. For both sexes, blood pressure was the main driver of cardiometabolic unhealthiness, with 57.8% of the males and 29.7% of the females having a blood pressure over the limit of 130/85 mmHg. Of note, few participants used anti-hypertensive medications (24 males and 26 females) and lipid-lowering medications (four males and one female).

Table 7. Characteristics of cardiometabolic criteria and overall cardiometabolic health in males and females.

Cardiometabolic criteria	Males N=1668 Mean (SD) / %	Females N=1537 Mean (SD) / %	p-value
Blood pressure			
Systolic BP (mmHg)	130.4 (12.4)	120.5 (12.4)	
Diastolic BP (mmHg)	80.5 (11.3)	75.5 (10.6)	
Anti-hypertensive medication use	1.44	1.69	
0: ‘healthy’ (<130/85 mmHg)	42.2	70.3	<0.0001
1: ‘unhealthy’ (≥130/85 mmHg)	57.8	29.7	
Triglycerides (mmol/l)	1.35 (0.84)	1.03 (0.53)	
0: ‘healthy’ (<1.70 mmol/l)	77.5	90.6	<0.0001
1: ‘unhealthy’ (≥1.70 mmol/l)	22.5	9.4	
HDL-C (mmol/l)	1.41 (0.32)	1.67 (0.37)	
Lipid-lowering medication use	0.24	0.06	
0: ‘healthy’ (men: ≥1.04 mmol/l, women: ≥1.30 mmol/l)	90.9	84.6	<0.0001

Cardiometabolic criteria	Males N=1668 Mean (SD) / %	Females N=1537 Mean (SD) / %	p-value
1: 'unhealthy' (men: <1.04 mmol/l, women:1.30 mmol/l)	9.1	15.4	
Glucose (mmol/l)	5.16 (0.52)	4.92 (0.44)	
Anti-diabetic medication use	0	0	
0: 'healthy' (<5.55 mmol/l)	82.4	93.9	<0.0001
1: 'unhealthy' (≥5.55 mmol/l)	17.6	6.1	
HOMA-IR	1.14 (0.55)	1.06 (0.46)	
0: 'healthy' (men: <1.66, women: <1.52)	90.0	90.0	0.99
1: 'unhealth'y (men: ≥1.66, women: ≥1.52)	10.0	10.0	
hsCRP (mg/l)	1.63 (3.19)	2.25 (4.08)	
0: 'healthy' (men: <3.50 mg/l, women: <5.40 mg/l)	90.0	90.0	0.99
1: 'unhealthy' (men: ≥3.50 mg/l, women: ≥5.40 mg/l)	10.0	10.0	
Cardiometabolic health			
MH: sum of scores=0	25.4	50.0	<0.0001
MUH: sum of scores ≥1	74.6	50.0	

BP: blood pressure, HDL-C: high-density lipoprotein cholesterol, HOMA-IR: homeostatic model assessment of insulin resistance, hsCRP: high-sensitivity C-reactive protein, MH: cardiometabolic health, MUH: cardiometabolic unhealthiness.

5.1.3 Early life factors and cardiometabolic health

Table 8 presents the characteristics of early life factors by BMI category and cardiometabolic health for both males and females.

A gradual increasing pattern was observed for BMI at AR across BMI categories in both cardiometabolic groups, reaching 16.5 (1.0) kg/m^2 for MHO and 16.3 (1.1) kg/m^2 for MUO participants. The same pattern was observed in females, with 16.1 (1.1) kg/m2 and 16.4 (1.4) kg/m^2, respectively. A gradually increasing pattern across BMI categories for age at AR was observed in both males and females. Of note, there was a trend for BMI at AR to be higher in the cardio-metabolically healthy group compared with the unhealthy group, but not in the female obese groups, with 16.4 (1.4) in MUO vs 16.1 (1.1) in MHO. A similar trend was observed for age at AR, from 5.94 (0.67) years for cardio-metabolically healthy normal weight (MHNW) to 4.62 (1.05) years for MHO and from 6.06 (0.67) years for cardio-metabolically unhealthy normal weight (MUNW) to 4.97 (0.89) for MUO. Like to males, females had a gradual decrease in age at AR according to increased BMI categories in the cardio-metabolically healthy groups. However, there was a

discrepancy in the pattern between obese groups; MUO males rebounded later than MHO males, with 4.97 (0.89) years and 4.62 (1.05) years respectively, whereas MUO females rebounded earlier than MHO females, with 4.37 (0.94) years and 4.66 (1.05) years, respectively.

Table 8. Characteristics of early life factors and cardiometabolic health groups by sex.

Variables	Cardio-metabolically healthy						Cardio-metabolically unhealthy						
	Normal weight (MHNW)		Overweight (MHOW)		Obese (MHO)		Normal weight (MUNW)		Overweight (MUOW)		Obese (MUO)		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	p-value
Males													
Birth weight (g)	302	3,650 (531)	113	3,682 (490)	9	3,672 (336)	527	3,552 (483)	577	3,589 (483)	140	3,624 (531)	0.0352
Gestational age at birth (weeks)	302	40.2 (1.3)	113	40.2 (1.2)	9	40.7 (1.0)	527	40.0 (1.4)	577	40.1 (1.3)	140	40.4 (1.1)	0.0219
PHV (cm/month)	270	4.36 (0.25)	99	4.38 (0.22)	9	4.28 (0.23)	475	4.39 (0.23)	519	4.39 (0.24)	126	4.39 (0.25)	0.42
PWV (kg/month)	271	1.11 (0.12)	99	1.14 (0.14)	9	1.15 (0.15)	476	1.10 (0.13)	520	1.13 (0.14)	126	1.16 (0.14)	<0.0001
Adiposity peak													
BMI (kg/m^2)	233	18.2 (0.8)	89	18.3 (0.8)	9	18.6 (0.8)	431	18.1 (0.7)	459	18.2 (0.8)	110	18.4 (0.8)	0.0003
Age (years)	233	0.75 (0.03)	89	0.76 (0.03)	9	0.77 (0.03)	431	0.76 (0.03)	459	0.76 (0.03)	110	0.76 (0.04)	0.14
Adiposity rebound													
BMI (kg/m^2)	296	15.2 (0.8)	113	15.8 (0.9)	9	16.5 (1.0)	525	15.1 (0.8)	572	15.6 (0.9)	140	16.3 (1.1)	<0.0001
Age (years)	296	5.94 (0.67)	113	5.42 (0.69)	9	4.62 (1.05)	525	6.06 (0.67)	572	5.52 (0.74)	140	4.97 (0.89)	<0.0001
Females													
Birth weight (g)	625	3,471 (465)	121	3,564 (451)	22	3,581 (390)	390	3,446 (435)	238	3,479 (492)	141	3,514 (451)	0.15
Gestational age at birth (weeks)	625	40.2 (1.2)	121	40.4 (1.3)	22	39.8 (1.7)	390	40.2 (1.2)	238	40.1 (1.3)	141	40.1 (1.3)	0.12
PHV (cm/month)	568	4.03 (0.28)	109	3.99 (0.27)	20	4.09 (0.27)	350	4.02 (0.27)	211	4.03 (0.25)	126	4.05 (0.31)	0.53
PWV (kg/month)	570	1.00 (0.13)	109	1.01 (0.14)	20	1.05 (0.14)	353	1.00 (0.12)	211	1.02 (0.12)	126	1.02 (0.14)	0.12

Variables	Cardio-metabolically healthy						Cardio-metabolically unhealthy						
	Normal weight (MHNW)		Overweight (MHOW)		Obese (MHO)		Normal weight (MUNW)		Overweight (MUOW)		Obese (MUO)		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	p-value
Adiposity peak													
BMI (kg/m^2)	514	17.7 (0.8)	96	17.9 (1.0)	15	17.9 (0.6)	312	17.7 (0.7)	192	17.9 (0.8)	111	17.9 (0.9)	0.0268
Age (years)	514	0.76 (0.04)	96	0.76 (0.03)	15	0.76 (0.04)	312	0.76 (0.03)	192	0.76 (0.03)	111	0.76 (0.03)	0.69
Adiposity rebound													
BMI (kg/m^2)	621	15.1 (0.9)	121	15.9 (1.2)	21	16.1 (1.1)	389	15.0 (0.9)	234	15.6 (0.9)	141	16.4 (1.4)	<0.0001
Age (years)	621	5.77 (0.72)	121	5.01 (0.84)	21	4.66 (1.05)	389	5.83 (0.74)	234	5.31 (0.76)	141	4.37 (0.94)	<0.0001

BMI: body mass index, MHNW: cardio-metabolically healthy normal weight, MHO: cardio-metabolically healthy obesity, MNOW: cardio-metabolically healthy overweight, MUNW: cardio-metabolically unhealthy normal weight, MUO: cardio-metabolically unhealthy obesity, MUOW: cardio-metabolically unhealthy overweight, PHV: peak height velocity in infancy, PWV: peak weight velocity in infancy, SD: standard deviation.

5.1.4 Association between growth factors and cardiometabolic health

Males showed significant differences in age at AR between the MHO reference group and the other cardiometabolic groups (Figure 5). The differences in age at AR between cardiometabolic groups and MHO were clustered according to BMI: 1.53 (0.96; 2.10) and 1.64 (1.08; 2.21) for MHNW and MHNW respectively and 1.01 (0.43; 1.59) and 1.09 (0.52; 1.65) for cardio-metabolically healthy overweight (MHOW) and cardio-metabolically unhealthy overweight (MUOW), respectively. The difference between MUO and MHO was 0.61 (0.03; 1.18). The effect sizes were weak; age at AR explained a maximum of 3% of the variance in the groups. In females, the effects were similar to males although effect sizes were even weaker, and differences in the groups were smaller. However, of note, the difference between MUO and MHO was negative: -0.45 (-0.88; -0.02).

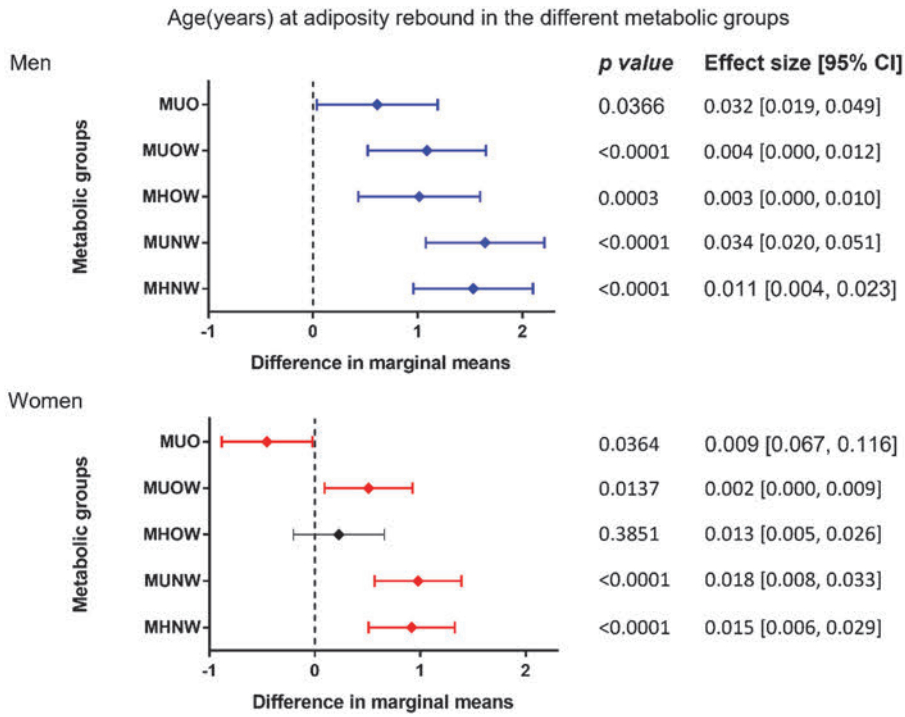

Fig. 5. Differences in marginal means for age at adiposity rebound between cardiometabolic groups. Figure modified from (Nedelec et al., 2018). Cardio-metabolically healthy obesity (MHO) is the reference group. MHNW: cardio-metabolically healthy normal weight, MUNW: cardio-metabolically unhealthy normal weight, MHOW: cardio-metabolically healthy overweight, MUOW: cardio-metabolically unhealthy overweight, MUO: cardio-metabolically unhealthy obese. The effect size is represented by partial omega squared which estimates how much variance in the response variable is accounted for by the explanatory variable. The model is adjusted for birth weight, gestational age, maternal age, maternal BMI, maternal marital status, maternal smoking, maternal education, paternal occupation, parity, and wantedness of pregnancy.

5.1.5 Summary and discussion

Cardiometabolic health score was calculated using criteria proposed by Wildman and colleagues (Wildman et al., 2008) applying a stricter threshold for cardiometabolic health than proposed originally (zero criteria vs. zero or one initially). Early life predictors were investigated in relation to metabolic health. The

findings suggested that early timing and BMI at AR are associated with MHO in men.

This study is the first to characterise MHO in NFBC1966. The choice to modify the initial cardiometabolic health definition by Wildman and colleagues was driven by the young age of the population, which was 31 years at the time, and their high blood pressure. Historically, blood pressure is high in Finland (Vartiainen et al., 2010) and the current blood pressure threshold guidelines are 140/90 (Update on Current Care Guideline: Hypertension, 2014).

The study results are in line with earlier studies reporting links between early life factors and adverse cardiometabolic health (Araujo de Franca et al., 2016; Bouhours-Nouet et al., 2008). An earlier AR is a well-known marker of child and adult obesity (Johnson et al., 2012; Rolland-Cachera et al., 2006; Taylor et al., 2005). These results confirm previous findings that early AR is associated with unfavourable adult BMI (Boonpleng et al., 2012; Williams, 2005). In a previous NFBC1966 study, early AR was associated with metabolic syndrome (Sovio et al., 2014).

So far, the general hypothesis suggest that early AR predicts unhealthy metabolite phenotypes. The study results are consistent with this hypothesis in females only, with MUO females rebounding earlier than their healthy counterparts. In contrast, males in the cardio-metabolically healthy group rebounded earlier than the unhealthy group. In a study from New Zealand, variations in BMI between early and late rebounders were attributed to weight and not height (Taylor et al., 2011); early rebounder males were heavier, with higher fat-free mass than fat mass compared with late rebounders. In comparison, early rebounder girls were not taller but were considerably heavier, with greater fat mass over fat-free mass than their late counterparts. Visceral fat is associated with cardiometabolic unhealthiness, and subcutaneous fat with cardiometabolic health (Goossens, 2017). Early AR is associated with greater subcutaneous fat in adulthood than late rebounders in the Good study (Ohlsson et al., 2012). These findings support the study results suggesting that cardiometabolic health originates early in life via a sex-specific pathway. It is important to emphasise that AR is an a-posteriori variable, reflecting phenomena that occurred earlier in life.

5.2 Early determinants of BMI trajectories (Study II)

In Study II, the two NFBC studies, which were set 20 years apart, were modelled together to identify BMI z-score trajectories. The roles of maternal and early life predictors were assessed in relation to the BMI developmental trajectories.

5.2.1 Characteristics of the population

Table 9 describes the characteristics of both cohorts. Mothers in NFBC1986 had a 0.9 kg/m^2 lower average BMI before pregnancy than mothers in NFBC1966, and they had on average 1.4 fewer children. In addition, they smoked more, with 19.4% smokers in NFBC1986 compared with 13.9% in NFBC1966. The NFBC1986 offspring had a 3.7% increase in PHV and a 2.3% decrease in PWV. The NFBC1986 offspring reached their AP 3.6 weeks earlier, with a lower BMI (NFBC1986: 17.6 kg/m^2; NFBC1966: 18.0 kg/m^2), and their AR occurred 7.7 months earlier and at a higher BMI (NFBC1986: 15.6 kg/m^2; NFBC1966: 15.4 kg/m^2).

Table 9. Characteristics of the study population.

Variables	NFBC1966 N=6864		NFBC1986 N=5176		p-value
	N	mean (SD)/%	N	mean (SD)/%	
Maternal height (cm)	6539	160.2 (5.4)	5133	163.2 (5.5)	<0.0001
Maternal weight (kg)	6542	59.7 (9.1)	5084	59.5 (9.6)	0.006
Maternal BMI (kg/m^2)	6291	23.2 (3.3)	5062	22.3 (3.4)	<0.0001
Maternal age (years)	6828	28.2 (6.6)	5176	28.0 (5.5)	0.2
Parity	6858	2.9 (2.2)	5160	1.5 (1.9)	<0.0001
Birth length (cm)	6809	50.5 (2.0)	5157	50.8 (1.9)	<0.0001
Birthweight (g)	6864	3544 (489)	5176	3630 (468)	<0.0001
Birthweight adjusted for GA	6894	0.04 (0.97)	5173	0.04 (0.98)	0.7
PHV in infancy (cm/year)	6085	50.6 (3.8)	5027	52.5 (6.7)	<0.0001
PWV in infancy (kg/year)	6260	12.9 (1.7)	5063	12.6 (2.9)	<0.0001
Age at adiposity peak (years)	5391	0.76 (0.03)	4944	0.69 (0.02)	<0.0001
BMI at adiposity peak (kg/m^2)	5391	18.0 (0.8)	4944	17.6 (0.7)	<0.0001
Age at adiposity rebound (years)	6755	5.63 (0.87)	5130	4.99 (1.04)	<0.0001
BMI at adiposity rebound (kg/m^2)	6755	15.4 (1.0)	5130	15.6 (1.1)	<0.0001
Sex					
male	3685	53.7	2558	49.4	<0.0001
female	3179	46.3	2618	50.6	
Maternal smoking (pregnancy)					

Variables	NFBC1966 N=6864		NFBC1986 N=5176		p-value
smoker	932	13.9	1000	19.4	<0.0001
non-smoker	5794	86.1	4152	80.6	
Maternal marital status					
married/cohabiting	6647	97.0	4949	95.8	0.0013
single	170	2.5	169	3.3	
widowed/divorced	38	0.5	49	0.9	
Maternal education					<0.0001
elementary	4535	67.1	1129	24.7	
vocational or secondary	1935	28.6	2068	45.3	
matriculation	49	0.7	266	5.8	
beyond matriculation	243	3.6	1105	24.2	
Operative delivery					<0.0001
non-instrumental vaginal delivery	1846	74.9	4245	82.0	
caesarean section					
others (vacuum extraction,	301	12.2	619	12.0	
forceps)	317	12.9	312	6.0	

BMI: body mass index, GA: gestational age, NFBC: Northern Finland Birth Cohort, PHV: peak height velocity, PWV: peak weight velocity, SD: standard deviation,

5.2.2 BMI trajectories

Developmental trajectories were modelled using the BMI z-scores of both NFBC1966 and NFBC1986 from 2 to 20 years. Several model adequacy criteria have been used to assess the best model; Figure 6 illustrates the best fit model, which consists of four BMI trajectories. The first category, ‘stable low’, represents 34.8% of the total population (N=4,195), the second category, ‘normal’, represents 44% of the total population (N=5,299), the third category, ‘stable high’, represents 17.5% (N=2,106), and the fourth category, ‘early increase’, represents 3.7% of the population (N=440).

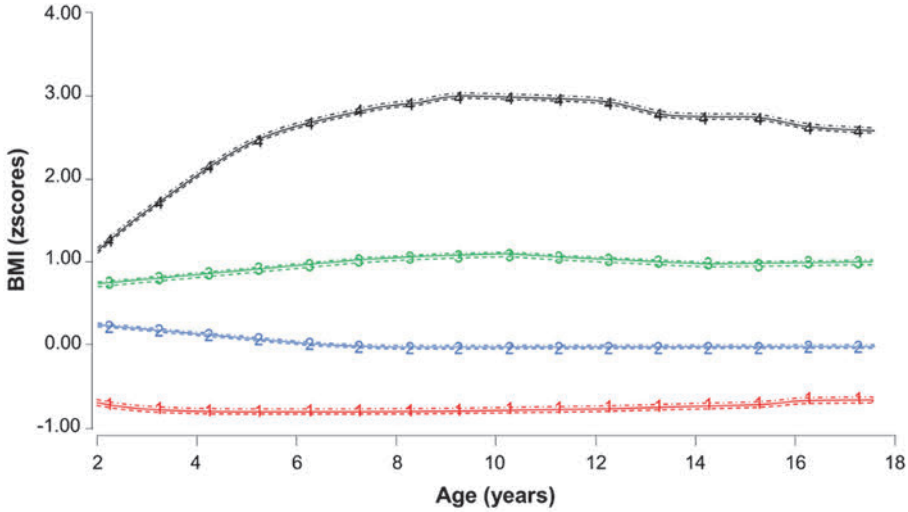

Fig. 6. BMI z-score trajectories from 2 to 20 years in NFBC1966 and NFBC1986 (Nedelec et al., 2021). Trajectory 1: stable low (34.8%), trajectory 2: normal (44%), trajectory 3: stable high (17.5%) and trajectory 4: early increase (3.7%). Dashed lines represent the 95% confidence intervals.

5.2.3 Characteristics of the trajectories

Table 10 presents the characteristics of maternal factors for each group's trajectories. Pre-pregnancy BMI was higher in NFBC1966 mothers compared with NFBC1986 mothers in each trajectory and in each cohort; it increased from the first BMI trajectory, 'stable low', to the fourth, 'early increase'. The proportion of maternal smokers was higher in the younger cohort and followed the same increase throughout the trajectory groups. In both cohorts, mothers of children in the early increase trajectory group were less likely to be married or in a relationship compared with mothers in the other trajectories.

Table 11 presents the characteristics of the children for each group trajectories. In NFBC1966 and NFBC1986, respectively, birthweight was 245 g and 270 g higher and PWV in infancy increased by 2.13 kg/year and 1.99 kg/year from trajectory one to four, respectively. BMI at AP followed the same pattern and increased by 1.2 kg/m^2 and 0.8 kg/m^2 from trajectory one to four for NFBC1966 and NFBC1986 respectively.

Table 10. Characteristics of maternal variables according to BMI group trajectories.

Variables	Trajectories								
	1: Stable-low		2: Normal		3: Stable-high		4: Early increase		
	N	mean (SD)/%	N	mean (SD)/%	N	mean (SD)/%	N	mean (SD)/%	***p*-value [a]**
Maternal pre-pregnancy BMI									
NFBC1966	2171	22.5 (3.0)	2814	23.3 (3.2)	1091	24.2 (3.5)	215	25.1 (3.8)	**<0.0001**
NFBC1986	1795	21.5 (3.0)	2175	22.3 (3.2)	891	23.3 (3.6)	201	25.1 (5.1)	**<0.0001**
***p*-value [b]**		**<0.0001**		**<0.0001**		**<0.0001**		0.295	
Parity									
NFBC1966	2358	3.0 (2.2)	3078	3.0 (2.2)	1188	2.8 (2.1)	234	2.6 (2.1)	**0.0006**
NFBC1986	1828	1.6 (2.0)	2212	1.5 (1.9)	914	1.3 (1.7)	206	1.4 (1.7)	0.1
***p*-value [b]**		**<0.0001**		**<0.0001**		**<0.0001**		**<0.0001**	
Maternal smoking									
NFBC1966	2321		3008		1167		230		**0.0038**
Smoker	309	13.3	388	12.9	194	16.6	41	17.8	
Non-smoker	2012	86.7	2620	87.1	973	83.4	189	82.2	
NFBC1986	1827		2208		912		205		**<0.0001**
Smoker	302	16.5	400	18.1	236	25.9	62	30.2	
Non smoker	1525	83.5	1808	81.9	676	74.1	143	69.8	
***p*-value [b]**		**0.0037**		**<0.0001**		**<0.0001**		**0.0024**	
Maternal marital status									
NFBC1966	2358		3078		1185		234		**0.0419**
Married/cohabiting	2291	97.1	2995	97.3	1139	96.1	222	94.9	
Single	56	2.4	71	2.3	35	3.0	8	3.4	
Widowed/divorced	11	0.5	12	0.4	11	0.9	4	1.7	
NFBC1986	1831		2213		917		206		0.13
Married/cohabiting	1750	95.6	2124	96.0	881	96.1	194	94.2	
Single	56	3.0	73	3.3	32	3.5	8	3.9	
Widowed/divorced	25	1.4	16	0.7	4	0.4	4	1.9	

Variables	Trajectories								
	1: Stable-low		2: Normal		3: Stable-high		4: Early increase		
	N	mean (SD)/%	N	mean (SD)/%	N	mean (SD)/%	N	mean (SD)/%	***p*-value [a]**
***p*-value [b]**		**0.0028**		**0.0225**		0.33		0.95	
Operative delivery									
NFBC1966	839		1087		441		97		**0.0009**
Non-instrumental	642	76.5	822	75.6	323	73.2	59	60.8	
Caesarean Section	90	10.7	131	12.1	54	12.3	26	26.8	
Other	107	12.8	134	12.3	64	14.5	12	12.4	
NFBC1986	1834		2218		918		206		**<0.0001**
Non-instrumental vaginal	1545	84.2	1828	82.4	714	77.8	158	76.7	
Caesarean Section	177	9.7	278	12.5	133	14.5	31	15.1	
Other	112	6.1	112	5.1	71	7.7	17	8.3	
***p*-value [b]**		**<0.0001**		**<0.0001**		**0.0004**		**0.0155**	

Statistical tests performed between trajectories by cohorts (*p*-value [a]) and between cohorts by trajectories (*p*-value [b]). P-value <0.05 are denoted by bold numbers. BMI: body mass index, NFBC: Northern Finland Birth Cohort, SD: standard deviation.

Table 11. Characteristics of offspring variables according to group trajectories.

Variables	Trajectories								
	1: Stable-low		2: Normal		3: Stable-high		4: Early increase		
	N	mean (SD)/%	N	mean (SD)/%	N	mean (SD)/%	N	mean (SD)/%	***p*-value [a]**
Sex (% male)									
NFBC1966	2361	51.8	3081	56.2	1188	50.6	234	54.7	**0.0010**
NFBC1986	1834	48.7	2218	51.4	918	45.7	206	50.5	**0.0286**
***p*-value [b]**		**0.0458**		**0.0005**		**0.0276**		0.38	
Birthweight (g)									
NFBC1966	2361	3450 (467)	3081	3568 (481)	1188	3642 (520)	234	3695 (465)	**<0.0001**
NFBC1986	1834	3519 (440)	2218	3662 (460)	918	3739 (479)	206	3789 (517)	**<0.0001**

Variables	Trajectories								
	1: Stable-low		2: Normal		3: Stable-high		4: Early increase		
	N	mean (SD)/%	N	mean (SD)/%	N	mean (SD)/%	N	mean (SD)/%	***p*-value** [a]
***p*-value** [b]		**0.0001**		**<0.0001**		**<0.0001**		**0.0369**	
Birthweight z-score									
NFBC1966	2361	-0.14 (0.94)	3081	0.08 (0.95)	1188	0.25 (1.03)	234	0.35 (0.94)	**<0.0001**
NFBC1986	1834	-0.19 (0.93)	2218	0.10 (0.96)	918	0.27 (1.00)	206	0.36 (1.11)	**<0.0001**
***p*-value** [b]		0.063		0.49		0.46		0.93	
PHV in infancy (cm/year)									
NFBC1966	2081	50.31 (3.72)	2726	50.67 (3.71)	1069	50.92 (3.90)	209	51.41 (4.06)	**<0.0001**
NFBC1986	1785	52.42 (6.72)	2150	52.49 (6.74)	893	52.61 (6.83)	199	52.28 (6.54)	0.95
***p*-value** [b]		**<0.0001**		**<0.0001**		**<0.0001**		0.2705	
PWV in infancy (kg/year)									
NFBC1966	2145	12.03 (1.43)	2806	13.07 (1.56)	1096	13.65 (1.89)	213	14.16 (2.07)	**<0.0001**
NFBC1986	1798	11.65 (2.39)	2167	13.01 (2.85)	898	13.42 (3.05)	200	13.64 (3.40)	**<0.0001**
***p*-value** [b]		**<0.0001**		**<0.0001**		**<0.0001**		**0.0029**	
Age at AP (years)									
NFBC1966	1817	0.75 (0.03)	2427	0.76 (0.03)	959	0.77 (0.04)	188	0.77 (0.04)	**<0.0001**
NFBC1986	1753	0.70 (0.02)	2114	0.69 (0.02)	882	0.69 (0.02)	195	0.69 (0.02)	**<0.0001**
***p*-value** [b]		**<0.0001**		**<0.0001**		**<0.0001**		**<0.0001**	
BMI at AP (kg/m^2)									
NFBC1966	1817	17.5 (0.7)	2427	18.1 (0.7)	959	18.4 (0.8)	188	18.7 (0.9)	**<0.0001**
NFBC1986	1753	17.2 (0.6)	2114	17.7 (0.6)	882	17.9 (0.7)	195	18.0 (0.8)	**<0.0001**
***p*-value** [b]		**<0.0001**		**<0.0001**		**<0.0001**		**<0.0001**	
Age at AR (years)									
NFBC1966	2323	6.20 (0.59)	3033	5.67 (0.60)	1168	4.79 (0.71)	231	3.59 (0.71)	**<0.0001**
NFBC1986	1822	5.72 (0.72)	2197	5.02 (0.73)	911	3.92 (0.71)	200	2.83 (0.42)	**<0.0001**
p-value [b]		**<0.0001**		**<0.0001**		**<0.0001**		**<0.0001**	

Variables	Trajectories								
	1: Stable-low		2: Normal		3: Stable-high		4: Early increase		
	N	mean (SD)/%	N	mean (SD)/%	N	mean (SD)/%	N	mean (SD)/%	***p*-value [a]**
BMI at AR (kg/m^2)									
NFBC1966	2323	14.4 (0.5)	3033	15.5 (0.4)	1168	16.6 (0.6)	231	18.1 (1.1)	**<0.0001**
NFBC1986	1822	14.6 (0.5)	2197	15.8 (0.4)	911	16.95 (0.6)	200	18.3 (1.1)	**<0.0001**
***p*-value [b]**		**<0.0001**		**<0.0001**		**<0.0001**		**0.0503**	

Statistical tests performed between trajectories by cohorts (*p*-value [a]) and between cohorts by trajectories (*p*-value [b]). P-value <0.05 are featured in bold numbers. AP: adiposity peak, AR: adiposity rebound, BMI: body mass index, NFBC: Northern Finland Birth Cohort, PHV: peak height velocity, PWV: peak weight velocity, SD: standard deviation.

5.2.4 Maternal factors and offspring BMI trajectories

Figure 7 shows the associations between two maternal parameters, maternal pre-pregnancy BMI and maternal smoking, and the BMI trajectory classes, using the 'normal' trajectory group 2 as a reference. According to Figure 7a, pre-pregnancy BMI was associated with group trajectories, with similar results in both cohorts. Pre-pregnancy BMI was associated with a 4% decreased risk of belonging to the stable low group (NFBC1966, adjusted risk ratio [aRR]=0.96; 95% CI [0.96; 0.97]; NFBC1986, aRR=0.96; 95% CI [0.95; 0.97]). The risk increased in a stepwise manner to an aRR of 1.08; 95% CI (1.06; 1.10) and 1.12; 95% CI (0.9; 1.15) in the early increase group for NFBC1966 and NFBC1986, respectively. In Figure 7b, maternal smoking was associated with a 34% (aRR=1.34; 95% CI [1.14; 1.59]) and a 42% (aRR=1.42; 95% CI [1.22; 1.64]) increased risk of belonging to the stable high trajectory group for NFBC1966 and NFBC1986, respectively. The risk increased further to 44% for NFBC1966 and 48% for NFBC1986 in the early increase trajectory group.

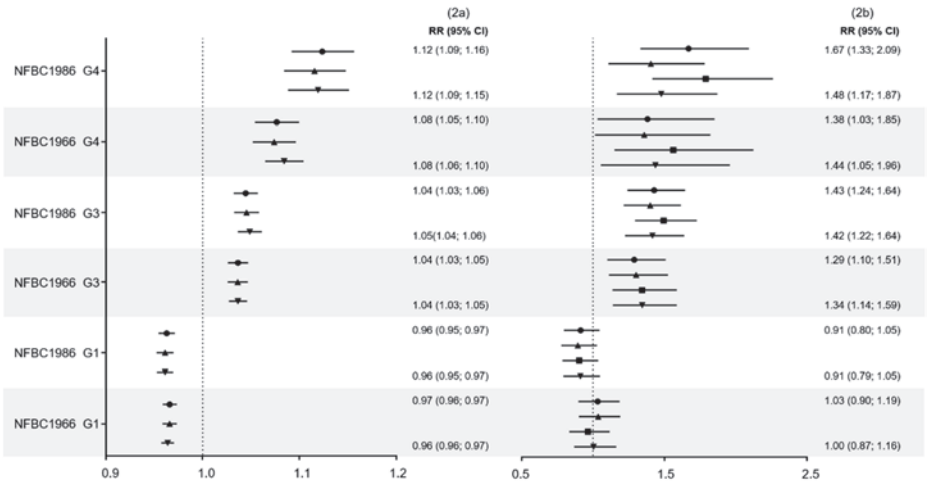

Fig. 7. Associations between maternal factors and BMI z-score trajectory classes (Nedelec et al., 2021). a) pre-pregnancy BMI in unit of BMI; b) maternal smoking during pregnancy.

5.2.5 Early life factors and BMI trajectories

Figure 8 illustrates the associations between factors in infancy and BMI group trajectories. In Figure 8a, associations between birthweight z-scores and group trajectories followed the same pattern observed with pre-pregnancy BMI. The risk gradually increased to 18% (aRR=1.18; 95% CI [1.05; 1.33]) and 28% (aRR=1.28; 95% CI [1.12; 1.46]) in NFBC1966 and NFBC1986, respectively, when associated with the early increase trajectory. The same pattern of gradual risk increase, paralleled in both cohorts, was observed with PWV. PWV was associated with a higher risk of belonging to the early increase group (NFBC1966: aRR=1.08; 95% CI [1.05; 1.10]; NFBC1986: aRR=1.07; 95% CI [1.03; 1.12]). There was a weak negative association between PHV and the stable low trajectory (NFBC1966: aRR=0.992 95% CI [0.988; 0.997]; NFBC1986: aRR=0.990; 95% CI [0.981; 0.998]) (Figure 8c). There was no association between PHV and the stable high trajectory, in either cohort, and PHW increased the risk of belonging to the early increase group only in NFBC1966 (aRR=1.014; 95% CI [1.002; 1.026]). In the younger cohort, age at AP was not associated with stable high or early increase groups, and the association with stable low group was close to 1 (aRR=1.002; 95% CI [1.000; 1.003]). In NFBC1966, a gradual increase in risk was observed and reached an aRR of 1.015; 95% CI (1.008; 1.022) in the association between age at AP and early increase group trajectory.

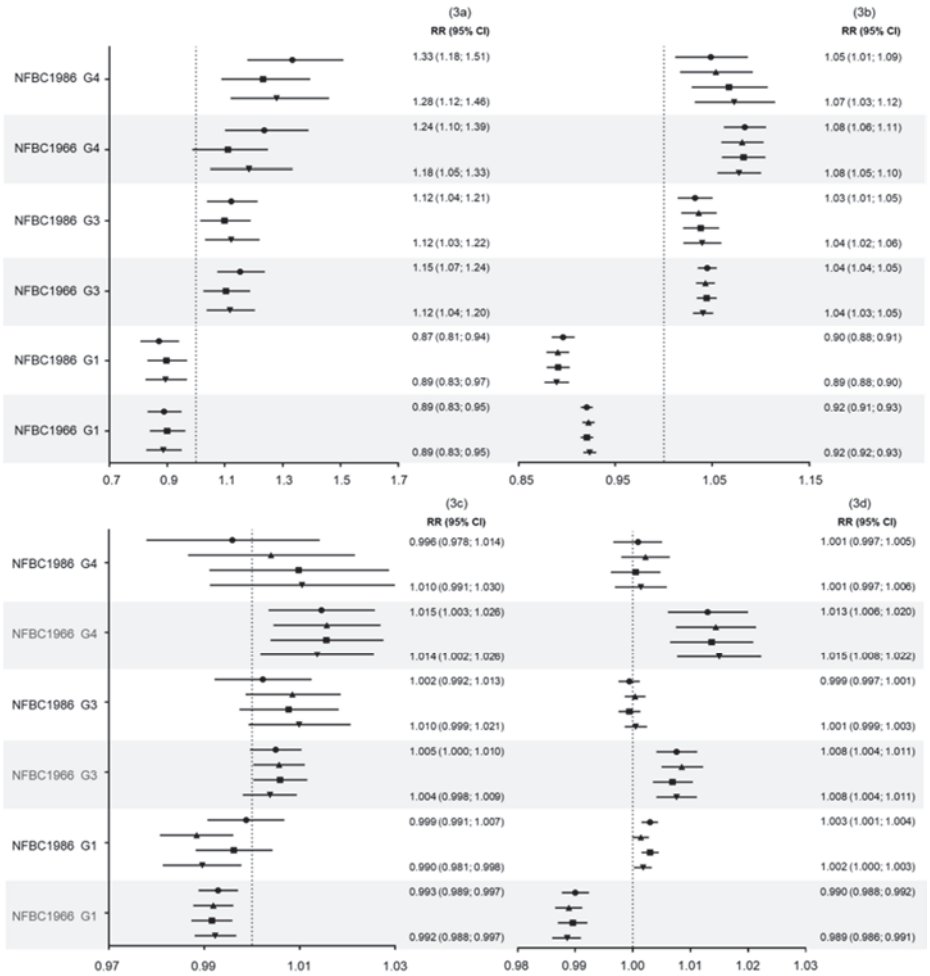

Fig. 8. Associations between early growth factors and BMI z-score trajectory classes (Nedelec et al., 2021). a) birthweight z-scores; b) peak weight velocity in infancy (kg/year); c) peak height velocity in infancy (cm/year); d) age at adiposity peak (years).

5.2.6 Summary and discussion

BMI trajectories were modelled on two birth cohorts from the same geographical area of Northern Finland but born 20 years apart. The older cohort was initiated in 1966 before the obesity epidemic, and the younger was initiated at the start of the

epidemic, in 1986. Four BMI trajectories from 2 to 20 years of age were identified in the combined cohorts. The effects of maternal and early determinants covering critical periods of infancy and childhood were evaluated in relation to these trajectories. The results suggest that in both cohorts, high pre-pregnancy BMI and maternal smoking increased chances of following the more adverse BMI trajectory, while lower pre-pregnancy BMI and maternal non-smoking increased the chances of following more favourable group trajectories. Furthermore, higher peak weight and height velocities in infancy were associated with the fourth adverse BMI trajectory. Interestingly, age at AP was associated in a gradual manner with all BMI trajectories in NFBC1966, but no association was found in NFBC1986.

These results reinforce previous evidence of the detrimental effect of maternal factors, such as BMI and smoking, on the offspring's BMI growth (Montazeri et al., 2018; Tu et al., 2015). The presence of the same association pattern in both cohorts suggests that the maternal smoking and pre-pregnancy BMI effects were consistent over a 20-year period. However, a difference in amplitude was noted. Pre-pregnancy BMI was lower in NFBC1986, but its effect on the early increase group was greater than in NFBC1966.

The effect of birthweight on BMI trajectories was unchanged during the 20-year period. Birthweight is a common marker of foetal growth. Its association with overweight children has been stable during the development of the obesity epidemic (Graversen et al., 2014) and for 50 years in the Danish population (Rugholm et al., 2005). In contrast, PWV and PHV, occurring within weeks of birth, can be considered markers of very early growth. The association pattern between PHV and BMI group trajectories in NFBC1966 was not replicated in the younger cohort. Early nutrition, especially protein intake, might be an important source of this variation and moderation in these relationships (Michaelsen et al., 2012; Ren et al., 2022; Tang, 2018). Inter-individual and inter-generational differences might explain the lack of replication observed for PWV and the large CI observed in NFBC1986.

One of the main findings of this study was the gradual pattern of associations between age at AP and BMI trajectories in NFBC1966, which was not replicated in NFBC1986 20 years later. Early childhood growth has been identified as a risk factor for later obesity, and there is evidence that BMI at AP is associated with the development of obesity later in life (Kruithof et al., 2016; Silverwood et al., 2009). However, recent GWAS uncovered overlapping genetics for child and adult BMI and a distinct genetic makeup for BMI in infancy (Couto Alves et al., 2019; Helgeland et al., 2019). In the 1970's, a new trend appeared in contemporary

Western populations, differing from older cohorts by a lower BMI at 2 years of age, a higher BMI growth velocity, and earlier AR followed by rapid weight gain (Johnson et al., 2012). The inconsistent effect of age at AP on BMI trajectories modelled from the same founder population underscores the role of an indirect factor factor — residual confounding — that we were unable to account for. During the 20-year gap between the birth cohorts, many changes accompanying the transition from an agricultural to a high-tech society occurred in Finland. Better pre- and postnatal care, changes in the prevalence of breastfeeding, and more convenient access to dense foods by both mothers and babies could have influenced these changes.

5.3 Effect of temperament on blood lipoproteins mediated by behaviour mediators (Study III)

5.3.1 Characteristics of the population

The study population consisted of 4,904 individuals from NFBC1966 (44.7% males). A few participants, 123 males and 60 females, were using lipid-lowering medication; statins was the most prescribed with 90.2 and 95.0% for males and females respectively (Table 12). Lipoproteins values were corrected, taking into account the lipid-lowering medication (Table 13). The value of HDL-C and triglycerides did not change after adjustment, they were 1.47 (0.37) and 1.20; 95% CI (0.89; 1.74)/ (0.89; 1.75) in males respectively and 1.66 (0.39) and 0.92; 95% CI (0.71; 1.25)/ (0.71;1.26) in females. However, the values of LDL-C changed from 2.38 (0.65) to 2.47 (0.66) after correction in males and from 2.11 (0.56) to 2.15 (0.58) after correction in females. In addition, females showed higher scores in every domain and facets of temperament, except for disorderliness and P. However, there was no difference in maternal education or wantedness of pregnancy between males and females.

Table 12. Lipid-lowering medication in the study population.

ATC code	Definition	Males		Females	
		N	%	N	%
C10AA	Statins	111	90.2	57	95.0
C10AB	Fibrates	3	2.5	0	10
C10AC	Bile acid sequestrants	1	0.8	1	1
C10AX	Other lipid modifying agents	8	6.5	2	2

Table 13. Characteristics of lipoproteins, before and after adjustment for lipid-lowering medication.

Lipoproteins	Males	Females
	mean (SD) / median (IQR)	mean (SD) /median (IQR)
HDL-C measured (mmol/l)	1.47 (0.37)	1.66 (0.39)
HDL-C corrected (mmol/l)	1.47 (0.37)	1.66 (0.39)
LDL-C measured (mmol/l)	2.38 (0.65)	2.11 (0.56)
LDL-C corrected (mmol/l)	2.47 (0.66)	2.15 (0.58)
Triglycerides measured (mmol/l)	1.20 (0.89; 1.74)	0.92 (0.71; 1.25)
Triglycerides corrected (mmol/l)	1.22 (0.90; 1.75)	0.92 (0.71; 1.26)

HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, SD: standard deviation, IQR: interquartile range.

5.3.2 Temperament and blood lipoproteins

Figure 9 shows the associations between temperament domains and their facets and the outcomes of HDL-C, triglycerides, and LDL-C, adjusted for maternal education and wantedness of pregnancy. A negative association between extravagance and HDL-C was found in men (β=-0.029, 95% CI [-0.049; -0.009]). Anticipatory worry (β=0.020, 95% CI [0.003; 0.038]), dependence (β=0.027, 95% CI [0.009; 0.044]) and persistence (β=0.019, 95% CI [0.002; 0.037]) were positively associated with HDL-C in females. Furthermore, there was a positive association between dependence and LDL-C in men (β=0.048, 95% CI [0.013; 0.083]). Novelty seeking and its facets of impulsiveness, extravagance and disorderliness were positively associated with triglyceride levels in both sexes, while dependence was negatively associated with triglyceride levels in females (β=-0.043, 95% CI [-0.071; -0.016]).

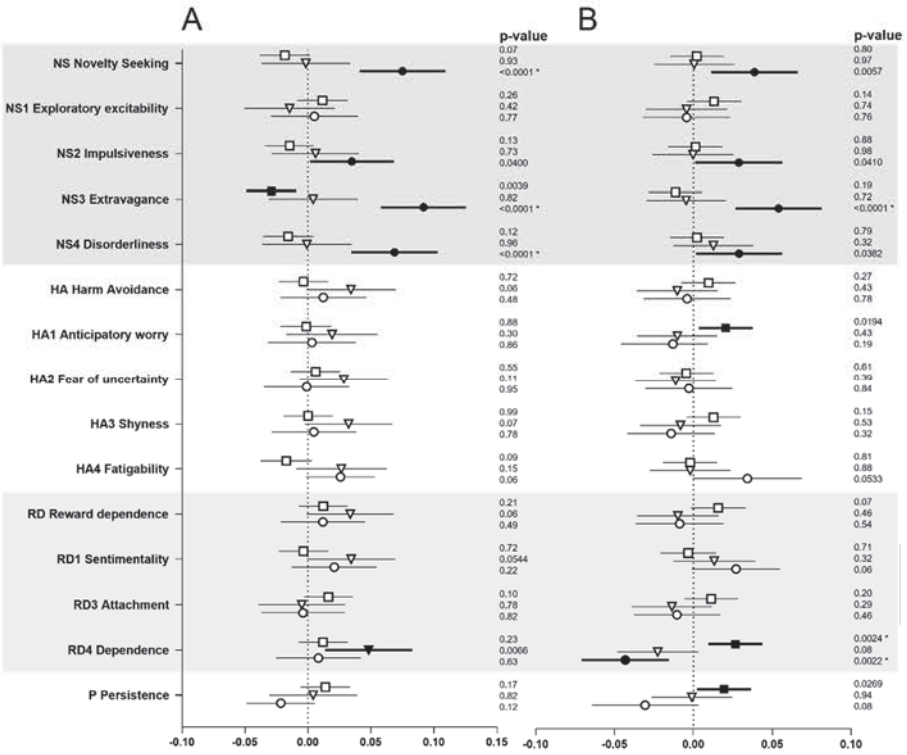

Fig. 9. Sex-specific associations between temperament domains and facets and lipoproteins (HDL-C, LDL-C, and triglycerides). Results are presented adjusted for maternal education and wantedness of pregnancy. Panel A represents males and panel B represents females. □: high-density lipid cholesterol (HDL-C), ▽: low-density lipid cholesterol (LDL-C). ○: Triglycerides. Bolded errors bars refer to p-value<0.05 and * refer to p-value<0.0033 (Bonferroni correction for multiple testing threshold).

5.3.3 Mediation analyses

A causal mediation analysis approach was applied to evaluate the effects of fitness and eating behaviours on the relationships between temperament and lipoprotein levels.

Identifying mediators

The lipoprotein outcomes were regressed by the potential mediators in linear regression analysis adjusted for the model confounders. The potential mediators were then regressed by the temperament variables in linear regression models adjusted for the model confounders. The results from both series of regression analyses were combined to select the mediators. Table 14 summarises the causal mediation analyses to be modelled. None of the tested variables were potential mediators of the association between temperament and LDL-C.

Table 14. Causal mediation models.

Sex	Exposure	Outcome	Mediator
Males	NS3	HDL-C	Muscular fitness
	NS3	HDL-C	Cardio-fitness
	NS	Triglycerides	Muscular fitness
	NS2	Triglycerides	Uncontrolled eating
	NS2	Triglycerides	Emotional eating
	NS2	Triglycerides	Muscular fitness
	NS3	Triglycerides	Cognitive restraint
	NS3	Triglycerides	Muscular fitness
Females	HA1	HDL-C	Uncontrolled eating
	HA1	HDL-C	Emotional eating
	HA1	HDL-C	Muscular fitness
	RD4	HDL-C	Muscular fitness
	P	HDL-C	Uncontrolled eating
	P	HDL-C	Muscular fitness
	P	HDL-C	Cardio-fitness
	NS2	Triglycerides	Uncontrolled eating
	NS3	Triglycerides	Uncontrolled eating
	NS4	Triglycerides	Uncontrolled eating
	RD4	Triglycerides	Muscular fitness

HA1: anticipatory worry, HDL-C: high-density lipoprotein cholesterol, NS: novelty seeking, NS2: impulsiveness, NS3: extravagance, NS4: disorderliness, P: persistence, RD4: dependence.

Mediation in the associations between temperament and HDL-C

Table 15 shows the mediating effects of eating and fitness behaviours in the associations between temperament characteristics and HDL-C. In males, muscular and cardio fitness mediated 34% and 19%, respectively of the association between extravagance and HDL-C. In females, uncontrolled and emotional eating were antagonistic mediators (opposite signs from the natural direct effect) of the association between anticipatory worry and HDL-C. Uncontrolled eating was a mediator in the association between P and HDL-C, together with muscular and cardio-fitness, although there were no total effect associations. Furthermore, muscular fitness mediated the association between dependence and HDL-C; however, the total effect was lost.

Mediation in the associations between temperament and triglycerides

Table 16 shows the mediating effects of eating and fitness behaviours in the associations between temperament characteristics and triglycerides. In males, muscular fitness mediated 14% of the association between NS and triglycerides. Uncontrolled and emotional eating were mediators of the association between impulsiveness and triglycerides, but the total effect associations were lost. Uncontrolled eating was also a mediator of the same association in females. In males, muscular and cardio-fitness mediated 18% and 13%, respectively, of the association between extravagance and triglycerides, while in females, uncontrolled eating mediated 16% of this association. Cognitive restraint was an antagonistic mediator of the association between disorderliness and triglycerides in males, and uncontrolled eating mediated 26% of this association in females. As observed between dependence and HDL-C, muscular fitness was a mediator of the association between dependence and triglycerides in females.

Table 15. Mediation analysis of the associations between temperament and HDL-C.

Temperament		Cognitive restraint β (95% CI)	Uncontrolled eating β (95% CI)	Emotional eating β (95% CI)	Muscular fitness β (95% CI)	Cardio-fitness β (95% CI)
Males						
NS3: Extravagance	TE	–	–	–	**-0.035 (-0.056; -0.057)**	**-0.032 (-0.054; -0.010)**
	NDE	–	–	–	**-0.023 (-0.044; -0.002)**	**-0.026 (-0.048; -0.005)**
	NIE	–	–	–	**-0.012 (-0.019; -0.006)**	**-0.006 (-0.012; -0.001)**
Females						
HA1: Anticipatory	TE	–	**0.027 (0.007; 0.047)**	**0.026 (0.007; 0.046)**	**0.029 (0.008; 0.049)**	–
worry	NDE	–	**0.037 (0.016; 0.058)**	**0.039 (0.020; 0.060)**	**0.031 (0.011; 0.051)**	–
	NIE	–	**-0.010 (-0.015; -0.005)**	**-0.013 (-0.019; -0.008)**	-0.003 (-0.007; 0.001)	–
RD4: Dependence	TE	–	–	–	0.019 (-0.001; 0.039)	–
	NDE	–	–	–	0.013 (-0.006; 0.033)	–
	NIE	–	–	–	**0.005 (0.001; 0.011)**	–
P: Persistence	TE	–	0.015 (-0.005; 0.035)	–	0.015 (-0.004; 0.035)	0.015 (-0.006; 0.036)
	NDE	–	0.012 (-0.008; 0.032)	–	0.010 (-0.009; 0.030)	0.010 (-0.011; 0.031)
	NIE	–	**0.0032 (0.0007; 0.0065)**	–	**0.005 (0.001; 0.009)**	**0.005 (0.001; 0.009)**

The numbers in bold reflect estimates with 95%CI not capturing the zero. CI: confidence interval, HA1: anticipatory worry, HDL-C: high-density lipoprotein cholesterol, NDE: natural direct effect, NIE: natural indirect effect, NS3: extravagance, P: persistence, RD4: dependence, TE: total effect.

Table 16. Mediation analysis of the associations between temperament and triglycerides.

Temperament		Cognitive restraint β (95% CI)	Uncontrolled eating β (95% CI)	Emotional eating β (95% CI)	Muscular fitness β (95% CI)	Cardio-fitness β (95% CI)
Males						
NS: Novelty seeking	TE	–	–	–	**0.077 (0.040; 0.112)**	–
	NDE	–	–	–	**0.066 (0.031; 0.010)**	–
	NIE	–	–	–	**0.011 (0.002; 0.020)**	–
NS2: Impulsiveness	TE	–	0.036 (-0.001; 0.074)	0.036 (-0.001; 0.074)	0.035 (-0.004; 0.071)	–
	NDE	–	0.029 (-0.007; 0.067)	0.027 (-0.010; 0.065)	0.028 (-0.009; 0.063)	–
	NIE	–	**0.006 (0.002; 0.012)**	**0.008 (0.003; 0.015)**	0.006 (-0.001; 0.015)	–
NS3: Extravagance	TE	–	–	–	**0.101 (0.064; 0.139)**	**0.101 (0.065; 0.139)**
	NDE	–	–	–	**0.083 (0.047; 0.121)**	**0.088 (0.052; 0.124)**
	NIE	–	–	–	**0.018 (0.009; 0.029)**	**0.0132 (0.003; 0.025)**
NS4: Disorderliness	TE	**0.037 (0.030; 0.105)**	–	–	**0.036 (0.008; 0.075)**	–
	NDE	**0.071 (0.035; 0.109)**	–	–	**0.029 (0.002; 0.057)**	–
	NIE	**-0.004 (-0.010; -0.0003)**	–	–	0.007 (-0.001; 0.016)	–
Females						
NS2: Impulsiveness	TE	–	0.025 (-0.007; 0.056)	–	–	–
	NDE	–	0.014 (-0.018; 0.046)	–	–	–
	NIE	–	**0.010 (0.004; 0.018)**	–	–	–
NS3: Extravagance	TE	–	**0.048 (0.018; 0.080)**	–	–	–
	NDE	–	**0.040 (0.010; 0.071)**	–	–	–
	NIE	–	**0.008 (0.001; 0.015)**	–	–	–
NS4: Disorderliness	TE	–	**0.035 (0.004; 0.065)**	–	–	–
	NDE	–	0.025 (-0.005; 0.055)	–	–	–
	NIE	–	**0.009 (0.003; 0.016)**	–	–	–

Temperament		Cognitive restraint β (95% CI)	Uncontrolled eating β (95% CI)	Emotional eating β (95% CI)	Muscular fitness β (95% CI)	Cardio-fitness β (95% CI)
RD4: Dependence	TE	–	–	–	**-0.036 (-0.068; -0.004)**	–
	NDE	–	–	–	-0.026 (-0.056; 0.005)	–

The numbers in bold reflect estimates with 95%CI not capturing the zero.CI: confidence interval, NDE: natural direct effect, NIE: natural indirect effect, NS: novelty seeking, NS2: impulsiveness, NS3: extravagance, NS4: disorderliness, RD4: dependence, TE: total effect.

5.3.4 Summary and discussion

In this study, associations between temperament characteristics and blood lipids were explored, and the mediating effects of eating and fitness behaviours were considered.

The findings suggest that associations between temperament subdomains and HDL-C are sex dependent. In males, only extravagance, an NS subdomain, was associated with HDL-C. In females, associations were found between anticipatory worry, dependence, and P and HDL-C. Anticipatory worry represents a pessimistic view of the future, and the present findings would indicate a protective effect of HDL-C. This is in line with previous studies on the NFBC1966 study (Puttonen et al., 2008; Sovio et al., 2007). Causal mediation analysis was used to investigate these relationships. Both fitness behaviours that were evaluated (i.e. muscular and cardio-fitness), were identified as mediators of the association between extravagance and HDL-C in males. In females, uncontrolled and emotional eating inconsistently mediated the association between anticipatory worry and HDL-C, and the negative direct effect attenuated the impact of the direct effect. Uncontrolled eating and muscular and cardio-fitness mediated the association between P and HDL-C, whereas the relationship between dependence and HDL-C was mediated by muscular fitness. Dependence is an RD subscale that implies reliance on others' approval and eagerness to please (Cloninger & Przybeck, 1994). The findings suggest a beneficial role of dependence on HDL-C and triglycerides in females, which is mediated by muscular fitness. It could be hypothesised that females respond to others' support of healthy choices and reward good health.

Interestingly, NS subdomains of impulsiveness, extravagance, and disorderliness were associated with triglyceride levels in both sexes. This is consistent with previous studies linking NS to metabolic syndrome (Sutin, Costa et al., 2010) and detrimental health behaviours (Puttonen et al., 2008). However, differences in these mediators were observed according to sex. In females, uncontrolled eating mediated all associations; in males, uncontrolled and emotional eating were both mediators of the association between impulsiveness and triglycerides, and cognitive restraint inconsistently mediated the association between disorderliness and triglycerides. Other studies found correlations between impulsiveness and disinhibited eating (Goldstein et al., 2014; Legenbauer et al., 2018) and between impulsivity and binge eating, over-eating, and obesity (Emery

& Levine, 2017; Lelakowska et al., 2019). Like HDL-C, the relationship between extravagance and triglycerides was mediated by muscular and cardio-fitness.

Of note, although an association was observed between dependence and LDL-C in males, no indirect effects from the potential mediators were observed. This is in line with other studies where no associations were found between temperament and LDL-C in women (Roh et al., 2014) or in the total population (Armon, 2014). It has been hypothesised that personality is linked to lipid levels via lifestyle factors; therefore, because LDL-C is less dependent on healthy behaviours, there is lower likekihood that it would be associated with personality (Bogg & Roberts, 2013). This supports the lack of indirect associations between eating and fitness behaviours.

Emotions, behaviour, and temperament vary between males and females. The present work supports previous studies reporting differences in temperament scores (Mendlowicz et al., 2000; Miettunen et al., 2007) and eating behaviours according to sex (De Lauzon et al., 2004; Poínhos et al., 2015; Weinstein et al., 1997). There is evidence of an association between brain structure and personality initiated by the interplay between sex and hormones (Stam et al., 2019).

6 General discussion

Using longitudinal data from the NFBC studies, this thesis aimed to improve understanding of the longitudinal aspect of obesity and related disorders, focusing on the effects of adverse maternal factors, the offspring's early adiposity and psychological characteristics. Adverse prenatal factors and early growth determinants have long-term impacts on a child's growth trajectory. Furthermore, inter-generational effects between the cohorts were revealed that need to be further assessed. Interestingly, sex dimorphism was observed between temperament and blood lipid levels, and it was further highlighted in mediating behaviours. In line with this new evidence, sex specificities were uncovered between early adiposity and cardiometabolic health in obesity later in adulthood.

The results are discussed in more detail in the previous chapter. In this chapter, the focus is on a critical assessment of the results based on the strengths and limitations disclosed from the data, methods used in this thesis, and possible mechanisms involved.

6.1 Strengths of the study

The present work has many strengths. The main strength of the study is the use of NFBC data in all three studies. Studies I and III were based on NFBC1966, and Study II was based on both NFBC1966 and NFBC1986. NFBC studies are ongoing homogeneous prospective studies that offer a high-quality and unique set of data over the lifespan of the participants. In this work, numerous sources of NFBC data, such as questionnaires, clinical examinations, and Health and Welfare Clinic data, were included. The wealth of repeated growth measurements during childhood supported the earlier modelling of adiposity peak and rebound, which were used in Studies I and II, and the modelling of BMI trajectories in study II.

In Study II, one additional strength was the concomitant use of the two NFBC studies to highlight a generational effect between identical population cohorts that pre- and post-dated the obesity epidemic. Another strength resided in the use of developmental trajectories, a longitudinal method to model repeated measurements of height and weight.

The strength of Study III was its design, which involved building causal mediation models based on data from NFBC1966. This design permitted the study of sex differences in a population of the same age. Moreover, the relationship between temperament, established early in life, and blood lipids was better

understood through the use of temperament subdomains alongside temperament domains.

6.2 Limitations of the study

The main limitation is attrition due to the loss of follow-up, which is common in life-course epidemiology studies due to the nature of longitudinal designs, which leads to missing data (Haapea et al., 2008; Nordström et al., 2022). In Study I, analysis was performed on complete cases, while in Studies II and III, both Proc Traj and Causalmed procedures, which are maximum likelihood methods, were capable of handling missing values.

More specifically, one of the limitations in Study I was the relatively young age of the participants. They were 31 years old, and few were obese or had cardiometabolic disorders at that age. Another limitation of the study was the absence of a consensus on the definition of MHO and the difficulty comparing these results with those of other studies.

Although NFBC1966 represents a rich source of data, some early factors were not collected. For example, paternal determinants, maternal weight gain during pregnancy, and infant feeding are important factors that are missing from this dataset. In Study II, the potential role of these factors in the development of BMI trajectories could not be evaluated between both cohorts. Furthermore, due to the methodological constraints of the BMI growth model, individuals with missing growth data were excluded. Another methodological limitation in Study II was the use of BMI measurements, which represent a ratio of weight and height. Taken separately, each of these measurements is susceptible to its own trajectory during childhood. When using BMI trajectory models, individuals show homogeneous patterns within their trajectories but distinct patterns from other trajectories; this allows the identification of longitudinal patterns but makes the model highly specific to the studied population.

The use of any questionnaire can lead to information bias. In Study III, the use of self-reported eating behaviour might have resulted in overestimation of healthy or desirable behaviour and underestimation of undesirable behaviour by the participants. This is also relevant for self-reported smoking, alcohol consumption, and physical activity in Studies I and II. Due to the causal mediation analysis assumptions, it is important to acknowledge that unobserved confounding may still exist. Moreover, the temporal precedence assumption might not be completely true;

there was no intermediary collection point for mediators between exposures at 31 years and outcomes at 46 years. It must be acknowledged that although BMI is associated with blood lipids, it is part of the causal pathway and thus could not be included with the confounders. Finally, the population, which was representative of a specific age group and geographic area, might not have been representative of other age groups or countries because of cultural and behavioural differences.

6.3 Mechanisms

Several mechanisms could explain the links between early life factors and cardiometabolic health, and temperament.

Early life factors such as prenatal stress, maternal smoking, maternal obesity, or malnutrition can lead to epigenetic modifications that affect gene expression and alter the development of different organs and systems, including the cardiovascular and metabolic systems (Murray et al., 2021; Parmar et al., 2018). These epigenetic changes can also influence the development of temperamental traits.

The developmental origins of health and disease theory proposes that environmental exposures and experiences during early life can influence the development of chronic diseases later in life (Barker, 2007). Specifically, this theory suggests that adverse early-life experiences such as poor nutrition, stress, or exposure to toxins can alter the development and function of different physiological systems. This could lead to long-term changes in metabolism, immune function, and other pathways that increase the risk of chronic diseases such as obesity, diabetes, or cardiovascular disease. Environment, including parental SES, parental education, and early nutrition, can have long-lasting effects on health and behaviour, and they can contribute to the development of cardiometabolic disorders and influence temperamental traits (Blair & Raver, 2016).

However, temperament, refers to individual differences in personality and behaviour that are relatively stable across time and situations, but there is some evidence to suggest that temperament may play a role in this pathway. Studies have shown that children who are exposed to adverse early-life experiences such as poverty, malnutrition, or maternal stress may be more likely to develop certain temperamental traits such as anxiety or aggression, which in turn can influence their health outcomes later in life (Carver et al., 2014).

Another potential mechanism could involve the hypothalamic-pituitary-adrenal axis; it is a key stress-response system that regulates the release of cortisol and other hormones in response to stressors. Early life stress and adversity can lead

to hypothalamic-pituitary-adrenal axis dysregulation, which can affect the stress response, inflammation, and metabolism, and contribute to the development of cardiometabolic disorders and influence temperamental traits (Danese & Mcewen, 2012), which are linked to neurotransmitters systems.

The findings on sex differences suggest a link to the estrogen pathway. Estrogens have been shown to have a protective effect on cardiovascular health by reducing the risk of coronary artery disease, stroke, and heart failure (Mendelsohn & Karas, 2005). They improve blood vessel function, reducing inflammation, and regulate lipid metabolism (Miller et al., 2009). In addition, estrogens are linked to mood disorders, depression and anxiety and they play a role in the development and function of the brain (McEwen & Alves, 1999).

7 Conclusion and implications

The present research included three studies aimed at improving our understanding of obesity and cardiometabolic health across the life course, stressing the role of early factors and psychological determinants. Together, the studies offer new findings and corroborate results from earlier studies.

7.1 Summary of the findings and conclusion

In Study I, in agreement with the study hypothesis, a subpopulation of MHO individuals was identified in NFBC1966. Consistent with other studies, the prevalence of females was higher in the cardio-metabolically healthy group. Furthermore, evidence of a link between early age at AR and MHO was found in males. This suggests that MHO originates in early childhood and that sex-specific pathways, which require further investigation, influence cardiometabolic health later in life.

In Study II, the main hypothesis was that maternal and early life factors are determinants of the BMI trajectory a child embarks. Four BMI latent growth trajectories were modelled in two generations of NFBC studies, set 20 years apart, one pre-dating the obesity epidemic and the other at the beginning of the epidemic. In both cohorts, unfavourable maternal factors during pregnancy were associated with adverse BMI trajectories in the offspring. In accordance with the hypothesis, rapid growth velocity was associated with adverse BMI trajectories in both cohorts. The second hypothesis of the study stated that a generational effect could modify the intensity of the associations. A larger amplitude of effects was observed in the younger cohort, and this could indicate moderation by a more obesogenic environment in the 1980s. Furthermore, associations between age at AP and BMI trajectories were uncovered in NFBC1966 but were non-existent in NFBC1986. These findings support existing evidence of mechanisms operating during the prenatal and infancy periods that influence BMI over the course of one generation.

In Study III, in line with the study hypothesis, associations between temperament traits and blood lipids were observed, and fitness and eating behaviours mediated these associations. Sex differences appeared in the associations between temperament traits and blood lipids and in the mediations between fitness and eating behaviours. Ultimately, the present findings acknowledge the contribution of psychological traits in dyslipidaemia and highlight

the importance of sex-specific studies to improve our understanding of the mechanisms involved.

7.2 Implications for future research

Results from this research confirm the link between early factors and the development of obesity later in life and the influence of psychological determinants on certain cardiometabolic consequences of obesity.

Although there is a large body of evidence pointing to the role of early life factors in health in adulthood, many important questions remain, and one discipline is not broad enough to answer them. Twenty five years ago, researchers called for a holistic approach to epidemiology when they defined life-course epidemiology as 'the study of long-term biological, behavioural and psychosocial processes that link adult health and disease to physical or social exposures acting during gestation, childhood, adolescence, earlier in adult life or across generations' (Kuh & Ben-Shlomo, 1997). The study of life-course trajectories echoes this framework of investigating changes in individuals from birth to death, whether these changes are developmental, biological, psychological, social, or economic.

To improve understanding of the mechanisms at play, it is important to consider sex and gender in the studies. Already from foetal stage, there is evidence of growth differences between males and females. Furthermore, alongside sex, gender is a social construct little used in medical research although there is growing evidence about its role in health.

There is evidence of associations between psychological determinants and metabolic health, and recently, there has been a growing interest in the study of gene-environment interactions associated with temperament variations. The foetal period is considered one of these environments. There is some overlap across various theories involving early determinants of health, either biological, behavioural, or psychological, which all point to the formation of a multilevel theory spanning multiple disciplines.

For a comprehensive understanding of the underlying biological mechanisms, transgenerational associations need to be followed. As evidenced by this work, changes can occur from one generation to the next. To better understand the stability and loss of associations, new cohorts with a focus on parental (maternal and paternal) data are required. An important development would be the replication of findings in a larger cohort with enough power to facilitate the study of sex effects

and epigenetic inheritance in addition to critical periods and environmental exposures.

An abundance of mediators affects life-course trajectories, and although the analysis of mediator-specific effects is desired, mediators often influence each other, and the study of their interactions is essential. There is great interest in developing methodology that can investigate such complex systems.

From a public health perspective, the findings of this thesis encourage and support follow-ups and interventions from pre-conception, pregnancy, and childhood to help mothers make informed decisions about their health and the health of their babies. By targeting critical stages, such interventions would improve the likelihood of healthy development and prevent or mitigate adverse health effects. Furthermore, it is important to consider temperament in clinical practice; it can be a risk factor, and it can affect how individuals respond to different medications and therapies. Healthcare providers would better tailor their diagnosis and treatment plans to the specific needs and preferences of each patient. This would lead to more personalised and effective therapies.

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Appendix

Appendix 1: Methods to measure adiposity.

Method	Definition	Advantages	Disadvantages
BMI	Ratio of weight to height. weight (kg) / height squared (m^2)	* Simple and commonly used * Easy and inexpensive * Correlations with body fat levels * International standardised cut-offs for adults and children	* No distinction between body fat and lean body mass *No distinction between visceral and sub-cutaneous fat * Sex differences * Ethnic differences * Not accurate in elderly, athletes with high muscle mass, or pregnant women
Waist circumference	Circumference of the abdomen, measured at the natural waist (between the lowest rib and the top of the hip bone), the umbilicus (belly button), or at the narrowest point of the midsection.	* Simple and commonly used * Easy and inexpensive * Correlations with body fat levels	* Measurement procedure not standardised * Lack of reference data in children * Difficulty measuring individuals with BMI over 35 kg/m^2
Waist-hip ratio (WHR)	Ratio between the waist (cf. above) and hip circumferences Hip circumference measured at the widest diameter of the buttocks.	* Good correlation with body fat levels * Inexpensive	* More measurement errors because of the two measures needed * Ratio leads to a loss of information (same BMI, different WHR) * More difficulty in measuring hip than waist * Complex to interpret * Difficulty measuring individuals with BMI over 35 kg/m^2
Skinfold thickness	Use of a special calliper to measure the thickness of a 'pinch' of skin and the fat beneath it in specific areas of the body (trunk, thighs, front and back of the upper arm, and under the shoulder blade). Equations based on these measurements can predict body fat percentage.	* Convenient, safe and simple * Inexpensive	* Not as accurate and reproductible as other methods * Difficulty measuring individuals with BMI over 35 kg/m^2
Bioelectrical impedance	Measures the resistance of a small, imperceptible, safe electric current through the body. The current faces more resistance passing through body fat than it does passing through lean body mass or water. Equations are used to estimate body fat	* Convenient, safe and simple * Relatively inexpensive	* Difficult to calibrate * Ratio of body water to fat my change (illness, dehydration, exercise, weight loss) * Not as accurate or reproductible as other methods

Method	Definition	Advantages	Disadvantages
	percentage and fat-free mass		* Difficulty measuring individuals with BMI over 35 kg/m^2
Dual-energy X-Ray absorptiometry (DEXA)	X-ray beams pass through different body tissues at different rates. Therefore, DEXA uses two low-level X-ray beams to produce estimates of fat-free mass, fat mass, and bone mineral density	* Accurate	* Expensive * Equipment cannot be moved * Cannot distinguish type of fat * Cannot be used on pregnant women * Difficulty measuring individuals with BMI over 35 kg/m^2
Underwater weighing	Individuals are weighed in air and while submerged in a tank. Researchers use formulas to estimate body volume, body density, and body fat percentage	* Very accurate	* Time consuming * Not easy (submersion in water) * Not generally used on children and elderly * All air must be expelled from the lungs during the test * Difficult for BMI over 40 kg/m^2
Air displacement plethysmography	Similar principle to underwater weighing but in the air instead of water. Individuals sit in a small chamber wearing a bathing suit. The machine estimates the body volume based on air pressure differences between the empty chamber and the occupied chamber.	* Relatively quick and comfortable * Accurate * Good option for children, elderly, pregnant women and BMI over 40 kg/m^2	* Expensive
Computed tomography (CT)	Measures tissue mass, organ mass, and whole-body fat mass, lean muscle mass and bone mass	* Very accurate * Measurement of specific body fat compartments, such as abdominal fat and subcutaneous fat	* Extremely expensive * Equipment cannot be moved * Cannot be used on pregnant women or children * Difficult for BMI over 35 kg/m^2
Dilution method (hydrometry)	Individuals drink isotope-labelled water and give body fluid samples. Researchers analyze these samples for isotope levels, which are used to calculate total body water, fat-free body mass, and body fat mass.	* Relatively inexpensive * Accurate and safe * Good option for children, pregnant women and BMI over 40 kg/m^2	* Ratio of body water to fat free mass may change due to illness, dehydration, or weight loss
Magnetic resonance imaging (MRI)	Measures tissue mass, organ mass, and whole-body fat mass, lean muscle mass and bone mass		* Extremely expensive * Equipment cannot be moved

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III Nedelec R., Miettunen J., Männikkö M., Sebert S., Järvelin M.R. Temperament and lipid metabolism, a mediation analysis – A Northern Finland Birth Cohort 1966 study. *Manuscript*.

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