Early Growth and Adult Health

Focus on Resting Metabolism, Non-alcoholic Fatty Liver Disease, Hypertension and Regional Differences in Birth Size

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ACADEMIC DISSERTATION

To be publicly discussed, with the permission of the Faculty of Medicine of the University of Helsinki, in Auditory XII, University Main Building, Unioninkatu 34, Helsinki on August 21st 2015 at 12 noon.

Helsinki 2015

Cover illustration: Bettina Sandboge

Dissertationes Scholae Doctoralis Ad Sanitatem Investigandam Universitatis Helsinkiensis

No 53/2015 http://ethesis.helsinki.fi

ISBN 978-951-51-1384-9 (paperback) ISSN 2342-3161 (print)
ISBN 978-951-51-1385-6 (PDF) ISSN 2342-317X (online)

Cover layout: Anita Tienhaara

Hansaprint
Vantaa, 2015

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To my family

The true delight is in the finding out, rather than in the knowing.

- Isaac Asimov

Abstract

Background. According to the Developmental Origins of Health and Disease (DOHaD) hypothesis, several non-communicable diseases (NCDs) have their origin *in utero* and during early childhood. The developing fetus responds to environmental cues including maternal nutritional and hormonal status, placental function and potential environmental toxins. This in turn affects organ development and growth, and the setting of hormonal axes, a process called *programming*. A suboptimal intrauterine environment often leads to a small body size at birth which is associated with the prevalence of several NCDs. These associations are in many cases further affected by childhood growth trajectories. NCD prevalence often varies according to region and potentially, this regional variation could partly have its origin in early development. Current lifestyle factors further influence NCD prevalence.

Aims. The main aim of this thesis was to explore the associations between early growth and outcomes directly or indirectly related to features of the metabolic syndrome, specifically hypertension, NAFLD, body composition, and resting metabolism. We also aimed to assess the association between fructose intake and NAFLD, and regional differences in birth size between Helsinki and the Åland Islands.

Subjects and methods. The Helsinki Birth Cohort Study consists of 13345 men and women born in Helsinki in 1934–44. A detailed set of records are available for the participants, including information on maternal and birth characteristics, childhood socioeconomic status, and serial measurements of childhood body size. In all, 2003 individuals participated in a clinical study in 2001–04 and 1083 of these additionally participated in a follow-up study in 2006–08. The clinical examinations included laboratory samples and measurement of body composition, resting metabolism and blood pressure. Information on dietary and lifestyle habits were collected using questionnaires. The Åland records included 1697 births for the years 1937–44.

Results. Birth weight was inversely associated with resting metabolic rate after adjustment for age, gestational age, and fat-free mass in women. In men, the association was quadratic (u-shaped), with and without additional adjustment for fat mass. A more rapid than expected conditional relative weight gain after age 11 years,

i.e. a higher attained adult weight than would have been expected based on adult height as well as weight and height measurements before age 11 years, was strongly associated with increase in adult fat mass and body fat percentage. These increased 8.6 kg (95% CI 8.4; 8.7) and 5.5% (95% CI 5.3; 5.7) per SD of the adult conditional relative weight variable, respectively.

The prevalence of NAFLD, defined by the NAFLD liver fat score algorithm test, was inversely associated with several measurements of childhood body size and growth. Conversely, individuals who belonged to the lowest tertile of BMI at age 2 years and subsequently were obese as adults, had an odds ratio (OR) of 18.5 (95% CI 10.1; 33.6) for NAFLD compared to those who were still lean or normal weight in adulthood.

The prevalence of NAFLD, defined by the fatty liver index (FLI) algorithm test, was inversely associated with fructose intake, independent of lifestyle and dietary factors, sex, and age. The OR for NAFLD in the quartile with the highest fructose intake was 0.68 (95% CI 0.47; 0.97) in the fully adjusted model compared to the quartile with the lowest intake.

Systolic blood pressure (SBP) and the presence of hypertension at mean age 66.4 years was inversely associated with linear (height) growth between ages 2 and 11 years. SBP was additionally inversely associated with relative weight gain in the same age range. Conversely, relative weight gain after age 11 years was positively associated with SBP at mean ages 61.5 years and 66.4 years.

Mean birth weight on the Åland Islands in the years 1937–44 was 3499 grams, 87 grams (95% CI 61; 111) more than in Helsinki during the same years. Ålandic babies were also 0.4 cm (95% CI 0.3; 0.5) longer than their Helsinki peers.

Conclusions. A more pronounced increase in body size than would be expected from previous body size after age 11 years was positively associated with increased body fat percentage and the presence of NAFLD at mean age 61.5 years and additionally with hypertension at mean age 66.4 years. While rapid growth during childhood in this cohort of Finnish men and women born 1934–44 most likely represents the influence of a beneficial postnatal environment, relative weight gain after age 11 years is

associated with increase in fat mass and the beginning of obesity and related conditions. Contrary to previous findings, we found that individuals with the highest intake of fructose were least likely to suffer from NAFLD. This inconsistency is most likely due to the fact that fructose intake in our cohort was relatively low and primarily from fruits rather than from soft drinks. We found a small but significant difference in body size at birth between the Åland Islands and Helsinki for the years 1937–44. Although insufficient to explain the differences in health and longevity between Åland and the rest of Finland, the findings indicate that regional health differences potentially were present during the period, meriting further studies of Ålandic health from a life-course perspective.

Keywords: basal metabolism, birth length, birth weight, blood pressure, body composition, fetal programming, fructose, hypertension, metabolic syndrome, non-alcoholic fatty liver disease, regional health differences.

Sammanfattning

Bakgrund. DOHaD-hypotesen (Developmental Origins of Health and Disease) föreslår att ett flertal folksjukdomar har sina ursprung under fosterlivet och tidig barndom. Det växande fostret exponeras för signaler från omgivningen, till exempel kopplade till moderkakans funktion, moderns hormonella status och näringsnivåer samt yttre miljöfaktorer. Dessa signaler påverkar fostrets utveckling och tillväxt samt de hormonella axlarnas funktion i en process som kallas *programmering*. En ogynnsam fostermiljö leder ofta till en liten födelsestorlek vilket i sin tur är kopplat till en ökad risk för ett flertal folksjukdomar. Dessa samband påverkas ofta ytterligare av tillväxtmönster under barndomen. Vidare finns i flertalet fall en regional variation i folksjukdomars prevalens. Denna variation skulle potentiellt delvis kunna ha sitt ursprung under tidig utveckling. Folksjukdomarnas förekomst påverkas också av livsstilsfaktorer.

Syften. Avhandlingens huvudsyfte var att studera sambanden mellan tidig tillväxt samt tillstånd direkt eller indirekt kopplade till det metabola syndromet, i första hand hypertoni, NAFLD (non-alcholic fatty liver disease), kroppsammansättning samt viloämnesomsättning. Vi avsåg vidare att studera sambanden mellan intag av fruktos och NAFLD samt regionala skillnader i födelsestorlek mellan Helsingfors och Åland.

Deltagare och metoder. Helsingfors födelsekohortstudie består av 13345 män och kvinnor födda i Helsingfors 1934–44. Omfattande uppgifter finns tillgängliga för alla deltagare avseende bland annat moderns och födelsens karaktäristika, barndomens socioekonomiska förhållanden samt upprepade mätningar av kroppsstorlek under barndomen. Sammanlagt 2003 individer deltog i en klinisk studie 2001–04 varav 1083 dessutom deltog i en uppföljningsstudie 2006–08. I de kliniska undersökningarna ingick blodprov samt mätning av kroppssammansättning, viloämnesomsättning och blodtryck. Frågeformulär användes för att samla in uppgifter om livsstilsvanor samt kost. Det åländska materialet innehöll 1697 födslar från åren 1937–44.

Resultat. Födelsevikt var negativt associerat till vilometabolism efter justering för ålder, gestationslängd samt fettfri kroppsmassa bland kvinnor. Bland män var association kvadratisk (u-formad), både före och efter ytterligare justering för mängd

kroppsfett. En snabbare relativ viktökning än förväntat efter 11 års ålder, det vill säga en högre uppnådd vuxen vikt än vad som skulle förväntats utifrån vuxen längd samt vikt- och längdmått innan 11 års ålder, var starkt positivt associerat till mängden kroppsfett samt fettprocent i vuxen ålder. Dessa ökade 8,6 kg (95% CI 8,4; 8,7) respektive 5,5% (95% konfidensintervall 5,3; 5,7) per standardavvikelse av tillväxt-variabeln.

Förekomsten av NAFLD, definierat medelst algoritmtest (NAFLD liver fat score), var negativt associerad med ett flertal kroppsstorleksmått i barndomen. Däremot hade personer som tillhörde kohortens lägsta tredjedel av BMI som 2 åringar men därefter var obesa som vuxna, en oddskvot på 18,5 (95% konfidensintervall 10,1; 33,6) för NAFLD jämfört med de individer som också var smala eller normalviktiga som vuxna.

Förekomsten av NAFLD, definierat medelst algoritmtest (Fatty Liver Index), var negativt associerat med fruktosintag, oberoende av kost- och livsstilsfaktorer, kön och ålder. Oddskvoten för NAFLD i kvartilen med högst fruktosintag var 0,68 (95% konfidensintervall 0,47; 0,97) i den fullt justerade modellen jämfört med kvartilen med lägst intag.

Systoliskt blodtryck (SBT) och förekomst av hypertoni vid genomsnittlig ålder 66,4 år var negativt associerat till linjär tillväxt (längdtillväxt) mellan 2 och 11 års ålder. SBT var dessutom negativt associerat till relativ viktökning under samma åldersintervall. Däremot var relativ viktökning efter 11 års ålder positivt associerat till SBT vid både 61,5 och 66,4 års genomsnittlig ålder.

Genomsnittlig födelsevikt på Åland under åren 1937–44 var 3499 gram, 87 gram (95% konfidensintervall 61; 111) mer än i Helsingfors under samma år. Åländska nyfödda var dessutom 0,4 cm (95% konfidensintervall 0,3; 0,5) längre än de som föddes i Helsingfors.

Slutsatser. En mer påtaglig ökning av kroppsstorlek, än vad som kunnat förutses från tidigare kroppsstorlek, efter 11 års ålder var positivt associerat till ökning av procent kroppsfett samt förekomst av NAFLD vid genomsnittsålder 61,5 år och dessutom med hypertoni vid genomsnittsålder 66,4 år. Emedan snabb tidig tillväxt i denna kohort

finländska män och kvinnor födda 1934–44 i första hand sannolikt är ett tecken på en fördelaktig uppväxtmiljö så verkar relativ viktökning efter 11 års ålder vara kopplat till ökad mängd kroppsfett samt vara början till fetma och fetmarelaterade tillstånd. I motsats till tidigare studiers fynd noterade vi att de individer som konsumerade mest fruktos hade lägst förekomst av NAFLD. Denna inkoherens härrör sig sannolikt från att fruktosintaget i vår studie var relativt lågt samt i första hand kom från frukt snarare än läskedrycker. Vi fann vidare en liten men signifikant skillnad i födelsestorlek mellan Åland och Helsingfors under åren 1937–44. Även om detta inte räcker för att förklara skillnaderna i hälsa och medellivslängd mellan Åland och resten av Finland antyder våra resultat att regionala hälsoskillnader förekom också under denna period vilket torde motivera ytterligare studier av åländsk hälsa ur ett livstidsperspektiv.

Nyckelord: basal ämnesomsättning, blodtryck, fosterutveckling, fruktos, födelselängd, födelsevikt, icke alkoholbetingad fettlever, kroppssammansättning, metabola syndromet, regionala hälsoskillnader.

Tiivistelmä

Tausta. DOHaD-hypoteesin (Developmental Origins of Health and Disease) mukaan useat kansantaudit saavat alkunsa sikiöaikana tai varhaisessa lapsuudessa. Kehittyvä sikiö mukautuu ympäristönsä signaaleihin, joihin kuuluvat esimerkiksi äidin ravitsemus- ja hormonaalinen tila, istukan toiminta sekä mahdolliset ympäristömyrkyt. Nämä vuorostaan vaikuttavat elinten kehitykseen ja kasvuun sekä hormonaalisten akseleiden toimintaan eli ilmiöön, jota kutsutaan *ohjelmoinniksi*. Epäsuotuisa kohdunsisäinen ympäristö johtaa usein pieneen syntymäpainoon, mikä itsessään on yhteydessä monen kansantaudin esiintyvyyteen. Näihin yhteyksiin vaikuttaa monissa tapauksissa vielä lisäksi lapsuuden aikainen kasvu. Kansantautien esiintyvyydessä on usein paikallista vaihtelevuutta, ja on mahdollista, että näiden erojen alkuperä on sikiöaikaisessa kehityksessä. Elämäntavat ovat myös yhteydessä kansantautien esiintyvyyteen.

Tavoitteet. Tämän väitöskirjan tarkoituksena oli tutkia suoria ja epäsuoria yhteyksiä varhaisen kasvun ja metabolisen oireyhtymän välillä, ja keskittyä erityisesti verenpaineeseen, NAFLD:iin (non-alcoholic fatty liver disease), kehonkoostumukseen ja lepoaineenvaihduntaan. Tavoitteena oli myös arvioida yhteyttä nautitun fruktoosimäärän ja NAFLD:in välillä sekä lisäksi arvioida eroavaisuuksia syntymäkoossa Helsingin ja Ahvenanmaan välillä.

Aineisto ja menetelmät. Epidemiologisena kohorttina oli Helsingin Syntymäkohortti, joka koostuu 13345 Helsingissä vuosien 1934–44 välillä syntyneestä miehestä ja naisesta. Heistä on saatavilla yksityiskohtaiset tiedot, mukaan lukien äitiin ja lapsen syntymään liittyvät tiedot, perheen sosioekonominen asema ja jatkuva sarja lapsuuden kasvuun liittyviä mittauksia. Yhteensä 2003 henkilöä osallistui vuosien 2001–04 välillä kliiniseen tutkimukseen ja 1083 heistä osallistui vielä toisen kerran seurantatutkimukseen vuosien 2006–08 välillä. Kliinisiin tutkimuksiin sisältyivät verinäytteet sekä kehonkoostumuksen, lepoaineenvaihdunnan ja verenpaineen mittaukset. Ruokavalioon ja elintapaan liittyvät tiedot kerättiin kyselylomakkeilla. Ahvenanmaan aineistoon kuuluu 1697 syntymää vuosilta 1937–44.

Tulokset. Syntymäpaino oli naisilla käänteisesti yhteydessä lepoaineenvaihduntaan sen jälkeen kun se oli korjattu iän, gestaatioiän ja rasvattoman painon suhteen. Miehillä syntymäpainolla oli kvadraattinen (u-muotoinen) yhteys lepoaineenvaihduntaan, sekä vakioituna että ilman vakiointia rasvamassan suhteen. Odotettua nopeampi suhteellinen painonnousu 11. ikävuoden jälkeen, eli aikuisikään mennessä saavutettu paino on korkeampi kuin mitä voidaan odottaa huomioiden pituus aikuisiällä sekä paino- ja pituusmitat ennen 11 vuoden ikää, oli vahvasti yhteydessä lisääntyneeseen aikuisiän rasvamassaan ja kehon rasvaprosenttiin, eli 8,6 kg (95 % luottamusväli 8,4; 8,7) ja 5.5 % (95 % luottamusväli 5,3; 5,7) jokaista vastaavan muuttujan keskihajontaa (SD) kohden.

NAFLD:in esiintyvyys, NAFLD määritettynä maksan rasvoittumisasteen lasku-algoritmilla, oli käänteisesti yhteydessä useaan lapsuusiän kehonkoon ja kasvun mittariin. Henkilöillä, jotka kuuluivat BMI:n alimpaan kolmannekseen kahden vuoden iässä mutta olivat aikuisina ylipainoisia, oli 18,5-kertainen tautipaine (odds ratio (OR); 95 % luottamusväli 10,1; 33,6) saada NAFLD verrattuna henkilöihin, jotka olivat hoikkia tai normaalipainoisia aikuisiässä.

NAFLD:in esiintyvyys, määritettynä FLI (fatty liver index) laskualgoritmilla, oli käänteisesti yhteydessä nautittuun fruktoosimäärään riippumatta elintavoista, ruokavaliosta, sukupuolesta ja iästä. Vakioidussa mallissa korkeimman fruktoosin käytön neljänneksessä oli 0,68-kertainen tautipaine (OR; 95 % luottamusväli 0,47; 0,97) saada NAFLD verrattuna neljännekseen, jossa fruktoosin käyttö oli alhaisinta.

Systolinen verenpaine (SVP) ja verenpainetauti keskimäärin 66,4 vuoden iässä olivat käänteisesti yhteydessä lineaariseen pituuskasvuun 2. ja 11. ikävuosien välillä. SVP oli lisäksi käänteisesti yhteydessä suhteelliseen painonnousuun samassa iässä. Suhteellinen painonnousu 11. ikävuoden jälkeen oli sen sijaan suorassa yhteydessä SVP:hen 61,5 ja 66,4 vuoden iässä.

Keskimääräinen syntymäpaino oli Ahvenanmaalla vuosien 1937–44 välillä 3499 grammaa, eli 87 grammaa (95 % luottamusväli 61;111) suurempi kuin Helsingissä samoina vuosina. Ahvenanmaalaiset vauvat olivat 0,4 cm (95 % luottamusväli 0,3; 0,5) pidempiä kuin Helsingissä.

Päätelmät. Aikaisempaan kokoon nähden odotettua nopeampi kasvu 11. ikävuoden jälkeen oli suorassa yhteydessä lisääntyneeseen kehon rasvaprosenttiin ja sairastumiseen NAFLD:iin keskimäärin 61,5 vuoden iässä ja verenpainetautiin keskimäärin 66,4 vuoden iässä. Lapsuuden nopea kasvu vuosina 1934–44 syntyneillä suomalaisilla miehillä ja naisilla mitä todennäköisemmin johtuu suotuisasta syntymänjälkeisestä ympäristöstä. Suhteellinen painonnousu 11. ikävuoden jälkeen on yhteydessä lisääntyneeseen rasvamassaan ja ylipainon kehittymiseen sekä näihin liittyviin sairauksiin. Päinvastoin kuin aikaisemmista tutkimustuloksista on päätelty, tässä tutkimuksessa totesimme, että yksilöillä, jotka olivat käyttäneet eniten fruktoosia, oli pienin riski sairastua NAFLD:in. Tämä aiempiin tutkimustuloksiin nähden poikkeava tulos johtuu mitä todennäköisimmin siitä, että fruktoosin käyttömäärä tässä kohortissa oli suhteellisen vähäinen ja se oli ensisijaisesti saatu hedelmistä eikä virvoitusjuomista. Lisäksi vuosina 1937–44 syntyneiden ahvenanmaalaisten ja helsinkiläisten vauvojen välillä löytyi pieni mutta merkityksellinen ero syntymäpainossa ja -pituudessa. Vaikka näillä löydöksillä ei voida selittää eroja terveydessä ja eliniässä Ahvenanmaan ja muun Suomen välillä, löydökset viittaavat siihen, että paikallisia terveyseroja on ollut mahdollisesti olemassa jo ennen syntymää, mikä luo pohjaa ahvenanmaalaisten terveyteen liittyviin lisätutkimuksiin elämänkaarinäkökulmasta.

Avainsanat: aineenvaihdunta, syntymäpituus, syntymäpaino, verenpaine, kehonkoostumus, sikiökauden ohjelmointi, fruktoosi, verenpainetauti, metabolinen oireyhtymä, alkoholin käytöstä riippumaton rasvamaksa, paikalliset terveyserot.

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IV Sandboge, S, Osmond, C, Kajantie, E, Eriksson, JG. Early growth and changes in blood pressure during adult life – findings from the Helsinki Birth Cohort Study (HBCS). 2015: [submitted].

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Abbreviations

ALT	Alanine aminotransferase
AIC	Akaike's Information Criteria
AST	Aspartate aminotransferase
BIA	Bioelectrical impedance analysis
BMI	Body mass index
BP	Blood pressure
CHD	Coronary heart disease
CI	Confidence interval
CRH	Corticotropin-releasing hormone
CT	Computer tomography
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DEXA	Dual-energy x-ray absorptiometry
DNL	De novo lipogenesis
DOHaD	Developmental Origins of Health and Disease
FFM	Fat-free mass
FLI	Fatty liver index
FM	Fat mass
GGT	γ–glutamyl transferase
GWAS	Genome-wide association study
HBCS	Helsinki Birth Cohort Study
HCMC	Helsinki City Maternity Hospital
HDL	High density lipoprotein
HFD	High fat diet
HPAA	Hypothalamic-pituitary-adrenal axis
HUCH	Helsinki University Central Hospital
HW	Hydrostatic weighing
IUGR	Intrauterine growth retardation
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NCD	Non-communicable disease
OGTT	Oral glucose tolerance test
OR	Odds ratio
PI	Ponderal index
RMR	Resting metabolic rate
SAD	Sagittal abdominal diameter
SBP	Systolic blood pressure
SD	Standard deviation
SES	Socioeconomic status
SNP	Short nucleotide polymorphism
VLDL	Very low density lipoprotein
WHO	World Health Organization
WHR	Waist-hip ratio

1 INTRODUCTION

The Developmental Origins of Health and Disease (DOHaD) hypothesis posits that environmental exposures during sensitive periods of development can result in phenotypic alterations affecting later health and disease susceptibility (Gluckman and Hanson, 2006b). Fetal growth, cell and organ development and the setting of metabolism and endocrine function are influenced by the intrauterine environment via several mechanisms, among them placental function, the mother's hormonal, nutritional and metabolic status, and epigenetic signalling (Fowden et al., 2006). This phenomenon is called developmental programming. Traditionally, most studies within this field focused upon the long term consequences of being born small. A low birth weight, an indicator of a suboptimal intrauterine environment, is associated with an increased risk of several common non-communicable diseases (NCDs) in later life. This risk is however, in many cases, largely modified by childhood growth patterns.

Growth can be defined in several ways, e.g. through conditional growth modelling, which measures how a particular measurement of body size at one point in time relates to what would have been expected from previous measurements. Childhood growth predicts adult body composition which could be one mediating factor explaining the association between developmental programming and adult disease (Singhal et al., 2003). Lean body mass, mostly composed of muscle mass, is strongly associated with resting metabolism which could potentially also be programmed during early development.

The metabolic syndrome is a cluster of conditions related to an increased risk of developing cardiovascular disease and type 2 diabetes (Alberti et al., 2006). According to the Joint International Statement diagnosis criteria from 2009, the syndrome is present if three of the following conditions are present: central obesity, raised triglycerides, reduced HDL-cholesterol, raised blood pressure and raised fasting glucose (Alberti et al., 2009). Non-alcoholic fatty liver disease (NAFLD), characterized by a liver fat content above 5–10% in absence of excessive alcohol intake or other liver pathology, has been suggested as the hepatic manifestation of the metabolic syndrome (Marchesini et al., 2001). The developmental origins of

hypertension have been studied extensively and there is strong experimental and epidemiological evidence for the inverse association between body size at birth and adult blood pressure. Fewer studies have explored the early origins of NAFLD but due to its close association with the metabolic syndrome and type 2 diabetes, a common developmental background is likely. Besides traditional risk factors, fructose intake has been suggested as a potential risk factor for NAFLD but findings have been conflicting.

There are regional variations in the prevalence of several NCDs, in part explained by geographic, socioeconomic, and genetic factors. In Finland, people living on the Åland Islands are healthier and live longer than their mainland peers. Mean life expectancy on the islands has been greater than on the mainland from the second quarter of the nineteenth century and at least until the beginning of the twentieth. Few studies have explored the background of Ålandic health and longevity.

The works included in this thesis explore a number of aspects of the DOHaD hypothesis and are part of the Helsinki Birth Cohort Study (HBCS) which includes 13345 individuals born in Helsinki 1934–44. A detailed data set, including birth and childhood growth measurements, is available for all individuals, based on birth, childhood welfare, and school records. Data from Åland Islands birth records for the years 1937–44 were also analysed in the study of regional differences in birth size. In addition to the studies based on the DOHaD hypothesis, the cross-sectional associations between NAFLD, assessed by algorithm scores, and fructose intake, were also focused upon.

2 REVIEW OF THE LITERATURE

2.1 Developmental origins of health and disease

Some of the first human studies suggesting an association between the intrauterine environment, early life, and later health outcomes were published almost forty years ago. Ravelli and colleagues reported higher rates of obesity in nineteen-year-old men who were exposed to the Dutch famine of 1944–45 *in utero* during the first half of the pregnancy, whereas those who were exposed during the last trimester or during the first months of life had lower obesity rates (Ravelli et al., 1976). In 1977, Forsdahl demonstrated a positive association between infant mortality and death from cardiovascular disease in a study of mortality data from Norway's 20 counties, suggesting that poverty in early life, followed by prosperity, increases the risk of cardiovascular disease (Forsdahl, 1977). In fact, Forsdahl suggested an association between poor childhood living conditions and high adult mortality rates in an even earlier publication in the Journal of the Norwegian Medical Association (Forsdahl, 1973).

A decade after the publications by Ravelli and Forsdahl, the research of David Barker and colleagues expanded upon the theory that early life events could influence later health and disease risk. In a 1986 study on variations in mortality data in England and Wales, a strong positive geographical association was found between infant mortality during the years 1921–25 and ischaemic heart disease mortality 1968–78, suggesting an increased disease susceptibility related to adult affluent diet, following poor early life nutrition (Barker and Osmond, 1986). To explore this hypothesis, Barker and colleagues traced a cohort of 5654 men born in Hertfordshire, England, during the years 1911–30. The study demonstrated that those who weighed the least at birth and at age one year had the highest ischaemic heart disease mortality (Barker et al., 1989b). These and subsequent findings gave rise to the Fetal Origins Hypothesis, also known as the Barker hypothesis, proposing that cardiovascular disease and related conditions are programmed *in utero* following lasting changes to e.g. developing organs, metabolic activity, and hormonal secretion due to fetal malnutrition (Barker, 1995). The Fetal Origins hypothesis has since been expanded into the DOHaD

hypothesis, placing emphasis not only on the prenatal period but on the entire plastic phase of development including infancy and early childhood. One of the central concepts in the DOHaD hypothesis is that of mismatch. Mismatch occurs when phenotypic changes caused by environmental cues in early development do not reflect the later environment, for example if fetal undernutrition is followed by childhood overnutrition (Gluckman et al., 2008). The mismatch phenomenon is especially relevant in societies undergoing rapid socioeconomic transitions.

The original findings of Barker and colleagues on the early life origins of coronary heart disease (CHD) have since been reproduced and expanded upon in a large number of studies in several different populations (Stein et al., 1996, Leon et al., 1998, Rich-Edwards et al., 1997, Frankel et al., 1996, Lawlor et al., 2005, Huxley et al., 2007, Eriksson et al., 1999). Additionally, several related conditions have been shown to be inversely associated with birth size, including type 2 diabetes (Lithell et al., 1996, Forsén et al., 2000, Whincup et al., 2008, Kajantie et al., 2010), stroke (Rich-Edwards et al., 1997, Lawlor et al., 2005, Eriksson et al., 2000), the metabolic syndrome (Nobili et al., 2008, Fagerberg et al., 2004), and hypertension (Barker et al., 1989a, Lenfant, 2008, Curhan et al., 1996). There have also been studies linking a small size at birth with renal disease (Vikse et al., 2008) hypothyroidism (Kajantie et al., 2006), osteoporosis (Baird et al., 2011), and depression (Gale and Martyn, 2004, Paile-Hyvärinen et al., 2007). A large birth size, on the other hand, has been linked to obesity (Curhan et al., 1996), rheumatoid arthritis (Mandl et al., 2009), and various cancers (McCormack et al., 2005). All-cause mortality was demonstrated to be inversely associated with birth weight in a large review and meta-analysis (Risnes et al., 2011).

Table 1. Conditions associated with low and high birth weight.

Low birth weight	**High birth weight**
Coronary heart disease	Obesity
Type 2 diabetes	Rheumatoid arthritis
Hypertension	Certain cancers
Stroke	
Insulin resistance	
Metabolic syndrome	
Renal disease	
Hypothyroidism	
Osteoporosis	
Depression	
Sarcopenia	
Premature mortality	

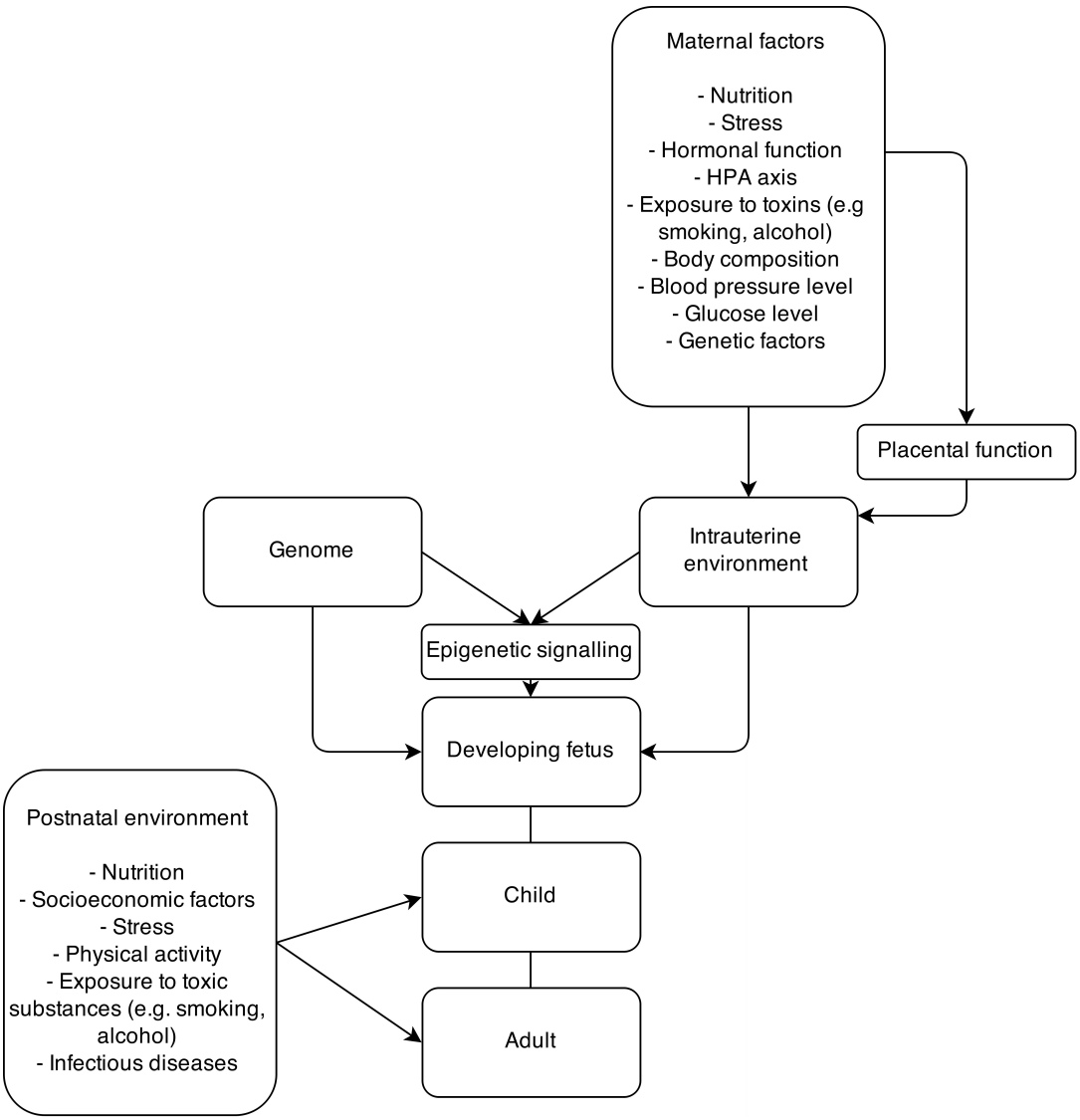
There are several studies focusing upon the associations between postnatal growth and later health and disease risk. A slow growth in infancy, followed by a faster growth in later childhood, has been linked to an increased risk of CHD (Eriksson et al., 2001, Barker et al., 2005, Eriksson et al., 1999), and type 2 diabetes (Forsén et al., 2000). Conversely, a rapid postnatal growth has also been linked to an increased risk of obesity (Tzoulaki et al., 2010, Ong et al., 2000). One study, focusing on obese individuals, reported that those who developed the metabolic syndrome as adults were smaller than their peers from age 2 to 11 years (Salonen et al., 2009a) whereas another study showed that low birth weight, in combination with accelerated catch-up growth between birth and age 18 years, was positively associated with the metabolic syndrome (Fagerberg et al., 2004). A slow weight gain between birth and age 2 years and small attained body size at age 2 years has been shown to be associated with an increased risk of stroke (Osmond et al., 2007). Unfortunately, studies on childhood growth are difficult to compare, due to differences in methodology in regards to how and which aspect of growth is measured, as well as which age ranges have been studied. A large study, analysing data from four prospective cohorts, demonstrated an increased cardiovascular risk in individuals who were obese in both childhood and adulthood (Juonala et al., 2011). Obese children who were subsequently non-obese as adults,

however, had a similar adult risk to that of individuals who were never obese. Although this study did not account for prenatal growth, it still demonstrates the importance of a life-course approach when evaluating cardiovascular risk.

Programming

The associations between birth size and later health have been demonstrated for both men and women, people of different ethnicity and in different age groups, independently of current exercise level and body composition. Animal studies have been essential in elucidating the underlying mechanisms of the association between early development and later health outcomes. Birth size reflects intrauterine growth and development – a small birth size often reflects a suboptimal intrauterine environment. In addition to nutritional factors, highlighted in the early studies in the DOHaD field, fetal development is affected by a number of other circumstances, including maternal hormonal and metabolic factors, placental function, and external environmental exposures (e.g. high altitude, maternal smoking) (Fowden et al., 2006). It is important to note that intrauterine challenges are not always associated with reduced fetal growth and low birth weight (Gluckman and Hanson, 2006a). Epigenetic modification of non-imprinted genes, affecting gene expression and bringing about phenotypic changes, is thought to be a key mechanism underlying the intrauterine environment's influence on the developing fetus. Fetal responses to the intrauterine environment are called fetal adaptive responses and take place during plastic periods of development. Based on environmental cues, fetal development adapts to correspond to the predicted postnatal environment. These adaptations can have immediate beneficial effects and promote survival in the short term but can also lead to increased disease susceptibility in the long term (Gluckman and Hanson, 2004, Gluckman et al., 2005).

Figure 1. Pathways of programming.



HPA axis: Hypothalamic-pituitary-adrenal axis.

2.2 Body composition and resting metabolic rate

2.2.1 Assessment of body composition

Measurement of body mass index (BMI, kg/m^2) is, albeit crude, a useful method of assessing overweight and obesity – both in the clinical setting, and at the population-level (World Health Organization, 2000). BMI, however, does not distinguish between fat mass (FM) and fat-free mass (FFM), and neither does it assess the distribution of fat mass. It is, however, strongly associated with cardiovascular risk and in many aspects comparable to measurements specifically addressing central obesity, e.g. waist circumference and waist-hip ratio (WHR) (Huxley et al., 2010). The review by Huxley and colleagues concluded that there was some evidence of a stronger association with risk for the measurements of central obesity compared to BMI in the case of type 2 diabetes, but that no such difference was seen for dyslipidaemia and hypertension. Other methods of assessing central obesity include android/gynoid ratio and measurement of sagittal abdominal diameter (SAD). A higher android/gynoid value indicates greater fat distribution intra-abdominally than at the hips. SAD measures the distance between the small of the back and the upper abdomen. A greater value indicates an increased risk of coronary disease, independent of BMI.

Several methods, including, but not limited to, hydrostatic (underwater) weighing (HW), dual-energy x-ray absorptiometry (DEXA), magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), dilution techniques, and bioelectrical impedance analysis (BIA), are available for more detailed assessment of body composition (Lee, 2008). HW is considered the gold standard method and, based on Archimedes' principle, estimates whole-body density by measuring the difference between a subject's underwater weight and weight in air (Biaggi et al., 1999). Apart from BIA and, to a lesser degree, DEXA, the methods described above are impractical in larger epidemiological settings, as they are expensive, and time consuming. BIA estimates the total body water pool by sending a small electrical current through the body and measuring its impedance. FFM is then calculated based on the assumption that 73% of the body's FFM consists of water (Lee, 2008). There are several different types of BIA devices available, e.g. single frequency devices with four electrodes and multi-frequency devices with eight electrodes. In a validation study against DEXA and

HW, the most precise estimates were found for the multi-frequency device (Demura et al., 2004). Total body fat can also be estimated by measurement of skinfold thickness, a simple method requiring only the use of calipers. The method is primarily used in children. Compared to other measurements of body composition, there are more pronounced validity issues. Nevertheless, the method can be used for estimating the degree of fatness in groups, as well as in individuals, to obtain indices, rather than measures, of body fat (Reilly et al., 1995).

2.2.2 Resting metabolism – background and assessment

Resting metabolic rate (RMR) accounts for about 80% of energy expenditure in sedentary individuals (Landsberg et al., 2009). It has been suggested that a low RMR is a contributing factor in the development of obesity but results have been contradictory. Whereas some longitudinal studies have reported an association between low energy expenditure in infancy, childhood and adulthood, and later weight gain and obesity development (Roberts et al., 1988, DeLany et al., 2006, Ravussin et al., 1988, Tataranni et al., 2003), others have not (Stunkard et al., 1999, Goran et al., 1998, Weinsier et al., 1995). A meta-analysis of studies focusing on the RMR of formerly obese individuals showed that these had a RMR that is 3–5% lower than controls, after adjustment for differences in FM and FFM. This could potentially contribute to the tendency of weight regain among formerly obese individuals (Astrup et al., 1999).

Several methods of various complexity are available for the assessment of energy expenditure. BIA, described above, can be used for estimation of RMR by predictive equations based on the measurement of FFM. Other methods include direct and indirect calorimetry and various predictive equations. The first predictive equations, based on age, sex, weight, and height were published in the beginning of the 20th century and several alternative ones have since been developed. Direct calorimetry measures the heat exchange between body and environment. It requires a hermetically sealed isolation chamber and confines the examined individual for 24 hours or more making it both costly and difficult to use in a wider setting. Indirect calorimetry, while still expensive, allows for short-term measurement of energy expenditure. It measures

heat expended by nutrient oxidation indirectly, by monitoring oxygen consumption and carbon dioxide production (Pinheiro Volp et al., 2011).

2.2.3 Size at birth, childhood growth and adult body composition

It is well established that birth weight is positively associated with adult FFM (Sachdev et al., 2005, Gale et al., 2001, Sayer et al., 2004, Ylihärsila et al., 2007, Singhal et al., 2003). Birth weight has been demonstrated to be inversely associated with adult FM after adjustment for adult BMI (Ylihärsila et al., 2007) in men and women aged 56 to 70 years, as well as inversely associated with android/gynoid ratio in men and women aged 60 to 64 years (Bann et al., 2014). Bann and colleagues additionally reported a positive association between weight gain in infancy and adult lean body mass whereas later weight gain additionally predicted higher FM and higher android/gynoid and fat/lean ratios. Height gain throughout childhood was positively associated with adult lean body mass and inversely with android/gynoid and fat/lean ratios. Similar findings in regards to childhood growth patterns have been reported from the New Delhi Birth Cohort where higher levels of BMI and greater BMI increase during late childhood and adolescence were associated with higher degrees of adiposity at ages 26–32 years (Adair et al., 2013).

2.2.4 Size at birth and adult resting metabolic rate

A relatively small number of studies have examined the associations between birth size and adult resting metabolic rate. A study from the 1924–33 Helsinki Birth Cohort Study (n = 318) demonstrated an inverse association between birth weight and RMR expressed per unit of FFM (Eriksson et al., 2002). Similar results have also been reported in a study of young non-diabetic Pima Indians (n = 272), a population known for high prevalence for type 2 diabetes and obesity (Weyer et al., 2000). In a study from the Helsinki Study of Very Low Birth Weight Adults, the resting energy expenditure/lean body mass ratio was 6.1% higher in the study population (n = 116) compared to controls (n = 118) (Sipola-Leppänen et al., 2011). Mean age in this study was 22.5 years. A small study (n = 29) on healthy men aged 64–72 years by Kensara and colleagues demonstrated lower resting energy expenditure in individuals with birth weights below the 25th percentile compared to those with birth weights above the 75th

percentile, after adjustment for adult height and weight (Kensara et al., 2006). Results from a relatively small case-control study (n = 59) demonstrated that infants born to mothers with well-controlled diabetes had reduced resting energy expenditure and fat oxidation compared to controls 30–40 days post partum (Short et al., 2015).

2.3 Non-alcoholic fatty liver disease (NAFLD)

2.3.1 Definition, prevalence, and pathogenesis

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in developed countries with a prevalence of 20–30 % (Bellentani et al., 2010, Loomba and Sanyal, 2013). It is frequently referred to as the hepatic manifestation of the metabolic syndrome (Marchesini et al., 2001) and is closely associated with type 2 diabetes, obesity and morbid obesity (Musso et al., 2011, Nakao and Yoneda, 2009), with a prevalence of 70%, 57%, and 90% with these conditions, respectively (Gaggini et al., 2013). Furthermore, ectopic fat accumulation, i.e. lipid accumulation in the liver, skeletal muscle and other insulin-sensitive tissues, would seem to be associated with insulin resistance independent of obesity (Yki-Järvinen, 2002). NAFLD is defined as a liver fat content exceeding 5–10% of liver mass, in absence of other liver disease or excessive alcohol intake (Puri and Sanyal, 2012). It is a continuum of conditions including simple steatosis, non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis (Than and Newsome, 2015).

Figure 2. Factors associated with NAFLD

Metabolic syndrome
Obesity
Type 2 diabetes
Total parenteral nutrition
Jejunoileal bypass operation
Use of specific medication
Dietary factors, potentially including high intake of fructose

The pathogenesis of NAFLD is described by a “multi-hit” hypothesis and involves the complex interplay of several factors with special emphasis on insulin resistance (Lewis and Mohanty, 2010). In the insulin resistant state, lipolysis in peripheral adipose tissue

leads to an increased influx of free fatty acids to the liver, resulting in hepatic lipid accumulation and a stimulation of de novo lipogenesis, representing the first hit. Several second hits, e.g. inflammatory cytokines, dysregulated apoptosis, and reactive oxygen species, are involved in the progression of the disease. (Than and Newsome, 2015, Lewis and Mohanty, 2010).

2.3.2 Diagnosis of NAFLD

The gold standard diagnostic method, liver biopsy, is currently the only method able to tell simple steatosis and NASH apart (Palekar et al., 2006). Imaging techniques, including ultrasonography, MRI, MRS, and computer tomography (CT) can also be used to diagnose NAFLD, but only in the assessment of hepatic fat content (Roldan-Valadez et al., 2008). The above methods are all relatively costly, time consuming and in the case of liver biopsy associated with a small degree of procedure-related morbidity and rarely even mortality (Weigand and Weigand, 2009). In comparison, recently developed algorithm scores, based on readily available clinical and biochemical markers, offer an attractive alternative in the setting of large epidemiological studies.

2.3.3 Developmental origins of NAFLD

During recent years, a number of studies have explored the developmental origins of NAFLD. Evidence from animal studies show that both maternal undernutrition and overnutrition are associated with the development of NAFLD. A recent study on rats showed that female rats exposed to nicotine in utero, in order to induce intrauterine growth retardation (IUGR), were at a higher risk of developing diet-induced NAFLD in adulthood (Xu et al., 2015). Similar findings have been reported for rats prenatally exposed to caffeine and ethanol, respectively (Wang et al., 2014a, Shen et al., 2014). In mice, maternal high fat diet (HFD), as well as maternal obesity, have been linked to NAFLD in the offspring (Bruce et al., 2009, Pruis et al., 2014, Oben et al., 2010, Mouralidarane et al., 2013).

In human studies, IUGR has been demonstrated to be associated with pediatric NAFLD (Nobili et al., 2007). MRI studies of newborn infants have demonstrated that

maternal BMI is positively associated with intrahepatocellular lipid content in the offspring (Brumbaugh et al., 2013, Modi et al., 2011). The risk of developing NAFLD is also influenced by childhood growth patterns. In one study, assessing the prevalence of NAFLD using the fatty liver index (FLI) algorithm test, an accelerated gain in weight-for-height from birth to age 3 months was associated with higher NAFLD risk at mean ages 18–24 years. No associations with birth weight were found, however (Breij et al., 2014). Greater rates of weight-for-height gain between ages 1 and 10 years have also been linked to liver fat content and liver stiffness as assessed by ultrasonography, as well as higher levels of blood-based markers of liver disease at mean age 17.8 years (Anderson et al., 2014). After adjusting for fat mass, these associations attenuated towards the null. Another study demonstrated that adiposity attained from age 3 years and onwards was associated with diagnosis and severity of NAFLD, as assessed by ultrasonography at mean age 17 years (Ayonrinde et al., 2015).

2.3.4 Fructose and NAFLD

Fructose intake has been implicated as a potential risk factor in the development of NAFLD. Fructose is primarily metabolized in the liver and provides substrates for gluconeogenesis, glycolysis, and de novo lipogenesis (DNL). The fatty acids created through DNL are incorporated into triglycerides that can be secreted as very low density lipoproteins (VLDL). If this process is impaired, triglycerides can accumulate intracellularly leading to steatosis (Neuschwander-Tetri, 2013, Vos and Lavine, 2013). Rodent studies have demonstrated that a high fructose diet induces NAFLD and also leads to increased serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), triglycerides, and total cholesterol (de Castro et al., 2013, Ackerman et al., 2005). However, animal models studying the associations between fructose and NAFLD have been criticized for featuring supraphysiological levels of fructose intake (Chiu et al., 2014). In a recent review and meta-analysis of six observational and 21 intervention studies in humans, the authors conclude that the associations between intake of fructose and sucrose and various indices of liver health (e.g. liver fat content, hepatic DNL, and serological markers) is possibly confounded by excessive energy intake (Chung et al., 2014). Another recent review, focusing on controlled feeding diets, reached similar conclusions. Here, no evidence was found that

fructose induced NAFLD in studies where it isocalorically replaced other carbohydrate sources. In hypercaloric studies, where fructose was administered in high doses, intrahepatocellular lipids and ALT did increase, an effect that might be attributable to excessive energy intake rather than to fructose (Chiu et al., 2014).

2.4 Hypertension

2.4.1 Definition, prevalence, and pathogenesis

Hypertension is present in adults when the average of multiple measurements of systolic blood pressure on at least two different occasions is ≥ 140 mmHg or the average of at least two measurements of diastolic blood pressure on at least two different occasions is ≥ 90 mmHg (Carretero and Oparil, 2000). The prevalence of hypertension in Western countries is estimated to be 30–45% (Mancia et al., 2013, Centers for Disease Control Prevention, 2011). The pathogenesis of essential hypertension is complex, multifactorial and only partly known. Several factors with various degrees of interplay have been suggested in the development of the condition, including, but not limited to, various genetic factors, high sodium intake, overactivity of the renin-angiotensin-aldosterone system, increased sympathetic tone, obesity, diabetes mellitus, low nephron number, and insulin resistance (Suzanne and Amin, 2003, Johnson et al., 2008).

Figure 3. Some conditions involved in the development of hypertension

Low birth weight	Overactivity of renin-angiotensin system
Smoking	Stress
Obesity	Excessive salt intake
Lack of exercise	Excessive intake of food stuffs containing glycyrrhizin
Genetic factors	Excessive intake of alcohol
Insulin resistance	Excessive intake of sugar
Low nephron number	Excessive intake of caffeine
Increased sympathetic tone	Use of specific medication
Diabetes mellitus	

2.4.2 Developmental origins of hypertension

Birth size

A large number of studies have explored the association between body size at birth and later blood pressure. In a systematic review by Huxley and colleagues, including eighty studies and more than 444000 men and women aged 0–84 years, a one kg higher birth weight was estimated to be associated with 2 mmHg lower systolic blood pressure (Huxley et al., 2000). However, in a subsequent review, also written by Huxley and colleagues, this conclusion was called into question. Here, the authors suggested that the inverse association between birth weight and later blood pressure might primarily reflect publication bias, random error and inappropriate adjustment for current weight and potential confounding factors (Huxley et al., 2002). A review of 55 studies including more than 382000 men and women aged 0–75 years, supported the suggestion of publication bias but found that the inverse association between birth weight and later systolic blood pressure remained significant despite adjustment for this bias (Schluchter, 2003). A more recent meta-analysis, including both published and unpublished data on almost 200000 individuals from 20 Nordic cohorts, once again showed an inverse association between birth weight and later systolic blood pressure (Gamborg et al., 2007). Importantly, this association remained significant despite adjustment for current BMI and was stronger in older age groups. The latter could potentially either be caused by a birth cohort effect, or be due to amplification, described below. Lastly, the review demonstrated a sex-difference in the association between birth weight and blood pressure. Whereas the association was linear and inverse for the entire range among men, it became positive in birth weights above 4 kg in women. Additionally, the association was stronger in women than in men. For example, the effect of birth weight on systolic blood pressure at age 50 years was estimated to be -2.80 mmHg/kg in women and -1.52 mmHg/kg in men. A meta-analysis of 20 studies published between 1998 and 2011 applied a dichotomized approach to assess the association between birth weight and systolic blood pressure. In this study, a birth weight below 2500 grams was associated with 2.28 mmHg higher systolic blood pressure, compared to individuals with birth weights above 2500 grams. A birth weight above 4000 grams was associated with 2.08 mmHg lower systolic

blood pressure, compared to individuals with birth weights below 4000 grams (Mu et al., 2012).

Amplification

The association between birth weight and blood pressure has been suggested to amplify with age, meaning that the most pronounced age-related blood pressure increase should be seen in those with the lowest birth weights. In a pooled analysis of one longitudinal study of children and three follow-up studies of adults, Law et al demonstrated that the magnitude of the association between birth weight and systolic blood pressure increases with age from childhood to adulthood (Law et al., 1993). A longitudinal study of 584 men and women from Adelaide, Australia, found a stronger influence of birth weight on systolic blood pressure at age 20 years, compared to age 8 years, supporting the amplification hypothesis (Moore et al., 1999). In a study from the 1946 British Birth Cohort, 3634 men and women were examined at ages 36, 43, and 53 years. Systolic blood pressure increased 1 mmHg for every 10 year increase in age but this was largely accounted for by current BMI (Hardy et al., 2003). Conversely, a more recent study, from the Bogalusa Heart Study, including 6251 individuals (64.5% white, 35.6% black, 50% male) with up to 15 examinations of blood pressure from childhood to adulthood, demonstrated increased magnitude in the association between birth weight and systolic blood pressure, regardless of adjustment for current BMI (Chen et al., 2010). Further support for the amplification hypothesis has been found in cross-sectional (Davies et al., 2006) and meta-regression analysis studies (Gamborg et al., 2007).

Growth in infancy and childhood

Several studies, including individuals of various ethnicity and age groups, have explored the influence of growth patterns in infancy and childhood on later blood pressure. In a study of 102 three-year-old boys and girls, systolic blood pressure was positively associated with current weight as well as weight gain based on birth weight. Systolic blood pressure was 0.2 mmHg higher per 100 grams of current weight and 1.5 mmHg higher per 100-unit increase in conditional weight gain, defined as difference in growth between birth and age 3 years divided by growth at birth. No association was

demonstrated with birth weight, however (Min et al., 2007). Findings from the Avon Longitudinal Study of Parents and Children (ALSPAC) indicate that later childhood growth has a greater influence on blood pressure, compared to prenatal growth and growth in infancy. Inverse associations with systolic blood pressure at age 10 years were found for birth weight and weight-for-height, but not for birth length. Conversely, gains in height, weight, and weight-for-height in infancy and later childhood, as measured using conditional modelling, were all positively associated with systolic blood pressure at age 10 years. For later childhood conditional height, weight, and weight-for-height conditional variables, systolic blood pressure increased 1.91, 1.56, and 1.20 mmHg per SD of the conditional variables, respectively. Similar, but weaker associations were demonstrated for diastolic blood pressure (Jones et al., 2012). These findings were expanded upon by Chiolero et al, who in a letter to the editor demonstrated a stronger influence of conditional weight gain between ages 12.5 – 15.5 years, compared to weight gain between 1 and 12.5 years, on systolic blood pressure at age 15.5 years, supporting the hypothesis that blood pressure is more responsive to current, rather than earlier, weight change (Chiolero et al., 2012). A study of 1284 Danish men born between 1936 and 1970 from Gamborg et al compared four models of assessing the association between growth and later blood pressure: simple linear regression, multiple linear regression, conditional linear regression, and path analysis. Path analysis is an extension of regression analysis. In the context of the above study, it was used to analyse the associations between body sizes at various ages as well as the associations between systolic blood pressure and all body sizes. The main findings were that path analysis produced better statistical power than the other methods and, in agreement with previous findings, that the effect of change in relative body size on adult systolic blood pressure, was more pronounced after age 11 years, compared to changes in earlier childhood (Gamborg et al., 2009). In a study from the 1934–44 Helsinki Birth Cohort Study, including 2003 individuals at mean age of 62 years, two paths of growth were identified among hypertensive individuals. The first group, who were already diagnosed with hypertension at the commencement of the clinical study, were born thin and short, grew slowly up until age 2 years and thereafter grew more rapidly, ending up with an average body size at age 11 years. The second group, who were not previously diagnosed with hypertension but had blood pressures within the hypertensive range when visiting the clinic, were short at birth and grew

slowly throughout childhood, ending up short and thin at age 11 years (Eriksson et al., 2007).

Potential mechanisms for the association between early growth and hypertension

The underlying mechanisms of the association between birth weight and blood pressure are only partly understood. Low birth weight and prematurity have been demonstrated to be associated with a reduced number of nephrons at birth, which in turn is associated with an increased risk of adult hypertension and susceptibility to renal disease (Luyckx et al., 2013). In a study examining autopsied kidneys from 56 individuals, a linear association was found between birth weight and nephron number with a regression coefficient predicting an increase of more than 250000 nephrons per kg of birth weight (Hughson et al., 2003). Furthermore, rapid childhood weight and BMI gain, especially following a low birth weight, has been suggested to contribute to a faster progression of renal disease (Luyckx et al., 2013). Early programming of the hypothalamic-pituitary-adrenal axis (HPAA) has also been implicated as a potential contributor in the association between birth weight and adult blood pressure. In a composite study, including 165 men and women born in Adelaide, South Australia, between 1975 and 1976, 199 men and women born in Preston, UK, between 1935 and 1943, and 306 women born in East Hertfordshire, UK, between 1923 and 1930, a low birth weight was associated with raised fasting plasma cortisol concentrations in all three cohorts. Furthermore, fasting plasma cortisol was associated with increased blood pressure, most markedly so among obese individuals (Phillips et al., 2000). In a study comparing normal birth weight children (n = 37) with children born small for gestational age (SGA) (n = 29), and preterm children (n = 39) at mean age 9.6 years, dopamine, adrenaline, and noradrenaline concentrations in urine were significantly higher in SGA and preterm children compared to controls. Furthermore, heart rate was higher both at rest and after mental stress (mathematical test) among SGA and preterm children compared to the controls (Johansson et al., 2007).

2.5 Regional differences in health and disease

The prevalence of NCDs show both within- and between-country variation. The background of this variation is multifactorial with contributions from e.g. genetic,

socioeconomic, environmental, and dietary factors, as well as general education level, historical context, and several other factors. As previously noted, Barker and colleagues demonstrated a strong geographical association between infant mortality during the years 1921–25 and ischaemic heart disease mortality 43–57 years later (Barker and Osmond, 1986). In a 2007 study including almost 18000 mostly white, apparently healthy men aged 40–80 years from the US Physicians Health Study, no regional differences were found for risk of major CVD. However, the risk of total stroke and ischemic stroke was associated with living in the Southeast, compared to the rest of the US, after adjustment for traditional CVD risk factors (Rich et al., 2007).

In Finland, the Swedish speaking minority accounts for 5.5% of the population. In a large register study from 2003, the age-standardized relative mortality was lower among Swedish-speaking women, compared to Finnish-speaking (0.93). After adjustment for socio-economic and geographical factors, these differences disappeared. In men, the relative age-standardized mortality was 0.73 among Swedish-speakers. After adjustments, this attenuated to 0.83 with the remaining difference primarily explained by non-natural deaths and cardiovascular mortality among Finnish-speaking men (Koskinen and Martelin, 2003). In another study, poor self-rated health was found to be less common among Swedish-speaking than Finnish-speaking Finns (Hyyppä and Mäki, 2001). Within Finland, there have been marked differences in health between the western and eastern part of the country. In the 1980s, eastern Finland had the highest CHD mortality rates in the world with significantly lower incidence in western Finland (Tunstall-Pedoe et al., 1994). Although the situation has since improved, more recent studies have shown persistent differences between east and west Finland in regards to cardiovascular risk factors (Juonala et al., 2004). Differences in early life living conditions and parental socioeconomic status may partly explain this geographical difference. In a longitudinal study comparing 823 men born in 1900–1919 in eastern Finland with 888 men born in the western part of the country, those born landless, i.e. to parents not owning land, in eastern Finland had systematically increased relative risk of cardiovascular mortality and morbidity (Notkola et al., 1985). A more recent study based on the same cohort demonstrated that men born in western Finland were significantly taller than those born in eastern Finland (Forsen et al., 2000). Cardiovascular morbidity and mortality was inversely associated with height. Interestingly, no geographical differences in the cardiovascular

outcomes were seen in men above 172 cm in height. These findings indicate that the geographical differences in Finnish health might have developmental origins, as a higher attained adult stature is a sign of a beneficial intrauterine and postnatal environment.

The Åland Islands, an autonomous province of Finland consisting of around 6000 islands, were recently ranked as Finland's healthiest region according to a composite index of disease prevalence developed by the Finnish National Institute of Health and Welfare. The islands received a composite score of 68.9 (the national mean is set at 100) with significantly lower scores than the national mean for five of the seven included disease categories: CHD, psychiatric disease, dementia, accidents, and musculoskeletal disorders. The scores for the remaining two categories, cerebrovascular disease and cancer, were not significantly different from the national mean (Terveyden ja hyvinvoinnin laitos (Finnish National Insititute for Health and Welfare), 2012). In 2005–09, the mean life expectancy at birth for Ålandic men was 79.7 years, 3.2 years longer than for men living on the mainland. For women, the corresponding figure was 83.9 years, the same as for mainland peers. Furthermore, Ålandic women have the longest prospected remaining years alive at age 80 years in the Nordic countries, with a mean of an additional 10 years (NOMESCO (Nordisk Medicinalstatistisk Komité), 2011). Historically, mean life expectancy at birth has been higher on the Åland Islands than in the rest of Finland from the second quarter of the 19th century and at least until the beginning of the 20th century (Mielke et al., 1987).

3 AIMS OF THE STUDY

The primary aim of this study was to explore aspects of the developmental origins of health and disease hypothesis from a public health perspective by studying associations between early growth and a number of health outcomes directly or indirectly related to common non-communicable diseases, specifically features of the metabolic syndrome, including non-alcoholic fatty liver disease and hypertension. Secondary aims included exploring the association between fructose intake and the presence of non-alcoholic fatty liver disease, as well as comparing birth records from the Helsinki Birth Cohort Study with contemporaneous births on the Åland Islands.

The specific objectives were:

1. To assess the association between birth weight and adult resting metabolic rate, also taking current body composition into account (Study I).

2. To explore the associations between childhood growth and adult non-alcoholic fatty liver disease (Study II).

3. To explore the influence of fructose intake on non-alcoholic fatty liver disease (Study III).

4. To explore the associations between childhood growth and adult blood pressure and to assess whether this association amplifies with age (Study IV).

5. To compare birth weights from the Helsinki Birth Cohort Study with contemporaneous births on the Åland Islands as a first step in a future potential analysis of Ålandic health and longevity from a life-course perspective (Study V).

4 SUBJECTS AND METHODS

4.1 The Helsinki Birth Cohort Study

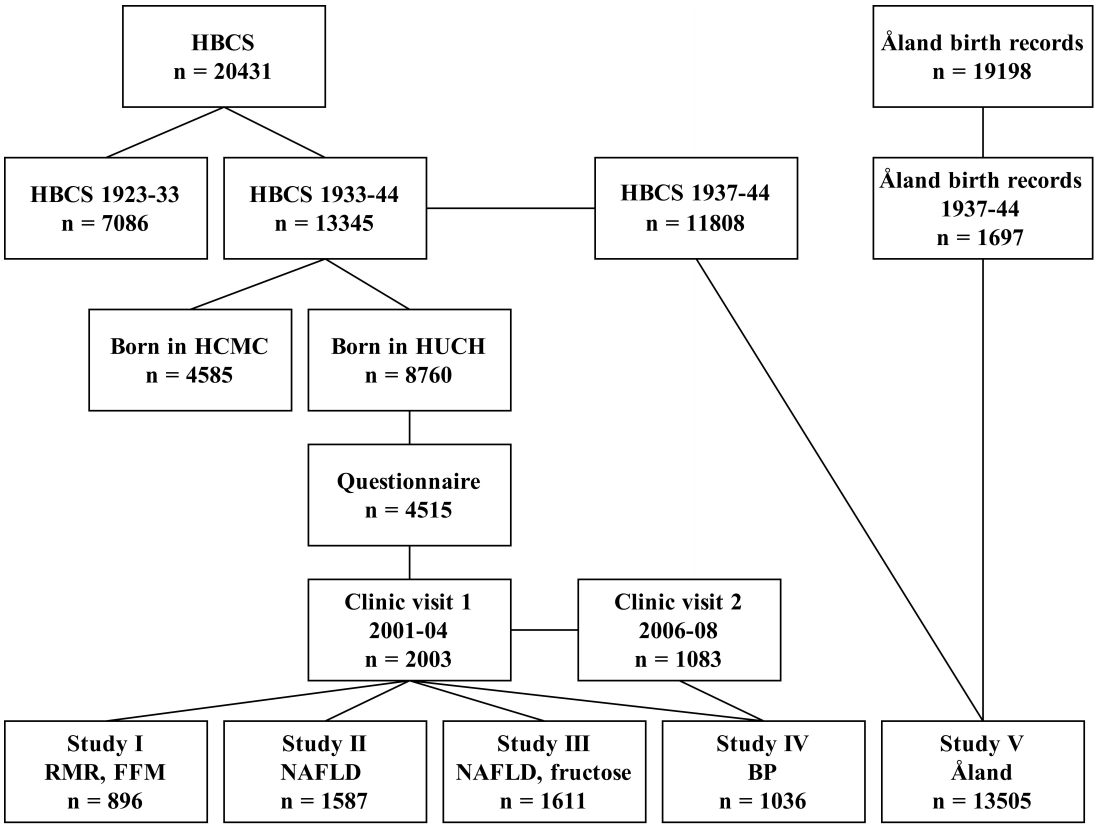
The Helsinki Birth Cohort Study (HBCS) consists of two birth cohorts, one comprising 7086 individuals born 1923–33 and the other one comprising 13345 individuals born 1934–44. All participants of the older cohort, and 8760 participants (66%) of the younger were born in the Helsinki University Central Hospital (HUCH). The remaining 34% of the younger cohort were born in the Helsinki City Maternity Hospital (HCMC). The studies included in this thesis are based on the younger cohort only. The study participants attended child welfare clinics in the city of Helsinki and the majority also went to school there. All were alive in 1971 when residents in Finland received a unique identification number, allowing for tracing and inclusion into the cohort study.

The birth records include information on birth weight, length, head circumference, and placental measurements. Ponderal index at birth was calculated for all participants by dividing birth weight in kg by birth length in metres cubed (kg/m^3). The birth records additionally include information on maternal age, parity, last menstrual period, and weight and length prior to delivery. Child welfare clinic records include serial weight and length/height measurements through infancy and early childhood. School records include weight and height measurements from ages 7 to 12 years. An average of 18 measurements of weight and length/height are available from birth to age 12 years. In addition, the records include information on living conditions and paternal (and in some cases maternal) occupation. Childhood socioeconomic status was determined based on paternal occupation using three categories (labourer, lower middle and upper middle class) based upon an original classification by Statistics Finland.

7079 study participants born in HUCS 1934–44 were still alive in 2000 and were sent a questionnaire based on questions used in the Health 2000 and FINRISK studies. The questionnaire included questions relating to the respondents' health status, medication, height and weight, lifestyle, socioeconomic circumstances, and parental background. 4515 of those who received the questionnaire replied and out of these, 2902 were

selected by use of random number tables for invitation to a clinical study. 2003 of these (928 men and 1075 women) accepted the invitation and were included in the clinical study which took place in 2001–04. A follow-up study, including 1083 individuals (486 men and 597 women) without diagnosis of type 2 diabetes at the time of the first clinic visit, took place in 2006–08.

Figure 4. Flow chart describing distribution of subjects in studies I–V.



HBCS: Helsinki Birth Cohort Study; HCMC: Helsinki City Maternity Hospital; HUCH: Helsinki University Central Hospital; RMR: Resting metabolic rate; FFM: Fat-free mass; NAFLD: non-alcoholic fatty liver disease; BP: blood pressure.

4.2 Åland birth records

The Åland birth records are based on official birth certificates collected between 1885 and 1998. In the context of study V, records from the years 1937–44 were included. For these years, the data set includes 1803 births. Records for the years 1934–36 only consisted of birth records from three out of Åland's thirteen parishes, and consequently were not included. After further exclusions due to missing data on child sex, missing data on both birth weight and length, stillbirth, twin birth, and one individual with an

impossible live birth weight (200 grams), the remaining number of individuals included in the study were 1697 (877 men and 820 women). Information on birth weight was available for all but one subject, and information on birth length was available for 1551 individuals. In addition, information on maternal age and maternal marital status was available for the majority of the subjects.

4.3 Adult characteristics

The subjects attended the clinic after an overnight fast. Participants provided written informed consent before the examination took place. All measurements were performed by trained study nurses.

Anthropometry

Weight was measured in light clothing without shoes to the nearest 0.1 kg, height was measured to the nearest 0.1 cm. BMI was calculated by dividing weight in kilograms by the square of height in metres (kg/m^2). Waist circumference was measured halfway between the lowest rib and the iliac crest.

Blood pressure

Blood pressure was measured from the right arm with the participant in a sitting position using a standard sphygmomanometer. The mean of two measurements was recorded.

Body Composition

The Inbody 3.0 eight-polar tactile electrode system (Biospace Co Ltd, Seoul, Korea) was used in study I for bioelectrical impedance (BIA) measurement of body composition. This method estimates fat mass and fat-free mass through segmental impedance measurement for the trunk as well as each limb at four electrical frequencies (5, 50, 250, and 500 kHz). It has been found to give accurate estimates of body composition when validated against dual-energy x-ray absorptiometry and

measurements of total body water by use of bromine and deuterium dilution (Sartorio et al., 2005, Kushner et al., 1990, Malavolti et al., 2003).

Resting metabolism

The Datex Deltatrac™ device (Helsinki, Finland) was used in study I for measurement of resting metabolic rate (RMR), expressed as total kilocalories expended/24 hours. The device measures oxygen consumption and carbon dioxide production through a transparent plastic canopy. These measurements are used in the calculation of respiratory quotient and energy expenditure. The test was recorded after an overnight fast for 40 minutes, 10 minutes of which were discarded as acclimatization artefact. The device has been described elsewhere in detail (Meriläinen, 1987). Only individuals who underwent both measurement of body composition and resting metabolism were included in study I (n = 896, 408 men and 488 women).

Laboratory methods

Fasting plasma (fP)-glucose was measured using a hexokinase method (Kunst et al., 1984). A 2-site immunometric assay was used to measure fasting serum (fS)-insulin (Sobey et al., 1989). fS-AST, fS-ALT, and fS-γ–glutamyl transferase (GGT) were measured through a photometric International Federation of Clinical Chemistry (IFCC) method using an Architect ci 82000 analyser (Abbott Laboratories). High density lipoprotein (HDL) and triglyceride concentrations were measured using standard enzymatic methods (Lie et al., 1976, Fossati and Prencipe, 1982). Laboratory tests also included a standard 75 g oral glucose tolerance test (OGTT).

Questionnaires

Information on leisure-time physical activity, smoking status, marital status, medication, and medical history was obtained from a self-administered questionnaire. Individuals with a moderate physical activity, defined as brisk walking or comparable activity, at least three times per week, were defined as physically active. Those who smoked at least one cigarette per day were defined as smokers.

The participants additionally completed a validated food-frequency questionnaire (FFQ) (Männistö et al., 1996, Paalanen et al., 2006) measuring habitual diet over a one-year period. The FFQ included 128 items with pre-defined sex-specific sizes. Participants entered frequency of consumption of each item according to nine categories: from never or seldom to ≥ 6 times per day. Average intake of nutrients, foods, and energy intake were calculated using the Finnish National Food Composition Database (Fineli) and in-house software (Reinivuo et al., 2010). Based on the FFQ results, daily energy intake (kJ/d) and alcohol intake (g/d) were estimated. Study III additionally included estimation of daily intake of fat (g/d), fiber (g/d), vitamin E (alphatocopherol equivalents in mg/d), and fructose (g/d). In study IV, daily sodium intake (g/d) was estimated from FFQ data.

Socioeconomic status

In study II, adult socioeconomic status was based on occupation and derived from 1980 census data. In study IV, adult socioeconomic status was derived from census data collected every fifth year from 1970 to 2000.

Definition of hypertension

Hypertension diagnosis was based on the use of antihypertensive medication, according to either questionnaire information or register data of reimbursement, and/or systolic blood pressure values ≥ 140 mmHg and/or diastolic blood pressure values ≥ 90 mmHg.

Definition of type 2 diabetes

Type 2 diabetes diagnosis was based on current use of diabetes medication and/or on the 1999 WHO criteria, i.e. fP-glucose ≥ 7.0 mmol/l at two different occasions (one measurement sufficient if concurrent symptoms) and/or plasma glucose ≥ 11.1 mmol/l two hours after a 75 gram OGTT (World Health Organization, 1999).

Definition of the metabolic syndrome

Diagnosis of the metabolic syndrome was defined according to the 2009 harmonized criteria, i.e. presence of at least three of the following conditions: central obesity (waist circumference ≥ 94 cm in men, ≥ 80 cm in women); elevated serum triglycerides (≥ 1.7 mmol/l), alternatively specific drug treatment for elevated triglycerides; reduced HDL cholesterol (HDL-C) (≤ 1.0 mmol/l in men, ≤ 1.3 mmol/l in women), alternatively specific drug treatment for reduced HDL-C; elevated blood pressure (systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg), alternatively antihypertensive medication; elevated fasting glucose (≥ 5.6 mmol/l), alternatively diabetes medication (Alberti et al., 2009).

Definition of NAFLD

The NAFLD liver fat score, the NAFLD liver fat equation, (Kotronen et al., 2009) and the fatty liver index (FLI) (Bedogni et al., 2006) were used to define the presence of NAFLD in studies II and III.

Kotronen's score and equation (figures 5 and 6) are calculated using the following variables: presence of type 2 diabetes, presence of the metabolic syndrome, fS-insulin, fS-AST, and the ratio between fS-AST and fS-ALT. A score above the optimal cut-off point of -0.640 predicted NAFLD with a specificity of 71% and a sensitivity of 86% against proton-MRS in the original study. The correlation coefficient between liver fat percent as estimated by the NAFLD liver fat equation and liver fat percent according to proton-MRS was 0.70 (<0.001) (Kotronen et al., 2009).

The FLI (figure 7) is calculated from the following variables: BMI, waist circumference, fS-triglycerides, and fS-GGT. An FLI > 60 predicted NAFLD with a specificity of 86% and a positive likelihood ratio of 4.3 compared to diagnosis with ultrasound in the original study (Bedogni et al., 2006).

Figure 5. The NAFLD liver fat score.

NAFLD liver fat score = -2.89 + 1.18 * metabolic syndrome (yes = 1, no = 0) + 0.45 * type 2 diabetes (yes = 2, no = 0) + 0.15 * fS-insulin (mU/l) + 0.04 * fS-AST (U/l) – 0.94 * AST/ALT

Figure 6. The NAFLD liver fat equation.

Liver fat (%) = 10^(-0.805 + 0.282 * metabolic syndrome (yes = 1, no = 0) + 0.708 * type 2 diabetes (yes = 2, no = 0) + 0.525 * log (fS-insulin (mU/l)) + 0.521 * log (fS-AST (U/l)) – 0.454 * log (AST/ALT))

Figure 7. The Fatty Liver Index (FLI)

FLI = (e^0.953 * loge (triglycerides) + 0.139 *BMI + 0.718 * loge (ggt) + 0.053 * waist circumference - 15.745) / (1 +e^0.953 * loge (triglycerides) + 0.139 * BMI + 0.718 * loge (ggt)+ 0.053 * waist circumference - 15.745) * 100

Individuals with an alcohol intake greater than 20 grams per day, according to FFQ data, were excluded from the analysis. Those with current or previous liver disease were also excluded. To identify these individuals, a search for relevant ICD codes was performed in hospital discharge records, the national cancer register and the national mortality register. The following codes were basis for exclusion: ICD 8–9; 070, 155, 291, 303, 570, 571, 572, and 573; ICD 10: B15–19, C22, F10, G62, K70–77, and K86. Furthermore, individuals with medication potentially associated with secondary hepatic steatosis were also excluded (Chalasani et al., 2012). In Study II, morbid obesity (BMI $\geq$ 40 kg/m^2) was basis for exclusion. Only individuals with all data necessary for calculating the NAFLD liver fat score were included in study II. A small number of individuals were excluded from study III due to implausible energy intake and missing information for the calculation of the FLI. The final number of subjects in study II and III were 1587 and 1611, respectively.

Follow-up study

1083 individuals without diagnosis of type 2 diabetes at the time of the first clinic visit were included in a follow-up study which took place in 2006–08. During this visit, measurements were made of current weight, height, and blood pressure according to the protocols described above. Information on current medication was obtained from a questionnaire. An estimate of daily sodium intake (g/d) was once again obtained from FFQ data collected at the time of the clinic visit. Only individuals with available weight and height measurements for birth and ages 6 months, 2 years, and 11 years were included in study IV (n = 1036).

4.4 Statistical methods

Study I

Clinical characteristics at birth and in adulthood were calculated as means with standard deviations and ranges, separately for men and women. Preliminary analysis of the data suggested a quadratic association between birth weight and RMR in men and a linear association in women. Accordingly, the analysis was stratified by sex. The associations were analysed using multiple linear regression, adjusting for sex, and either FFM, FM or both. The goodness-of-fit of models, with and without quadratic terms for birth weight, were analysed for both sexes using Akaike's information criteria (AIC) (Akaike, 1998). AIC takes the number of fitted parameters into account making it suitable for comparing models with an unequal number of covariates. The smallest AIC (indicating the best model fit) were produced by quadratic models in men and linear models in women. All statistical analyses were performed using the R environment for statistical computing (R Team, 2007).

Study II

The study participants' characteristics at birth, ages 2, 7, and 11 years, and adulthood, were calculated as means with SDs (or medians with interquartile ranges for skewed variables) and percentages. Measurements of weight, height, and BMI for each individual at all ages from birth to 11 years were converted to z scores (SD scores).

Z scores were obtained through interpolation as most measurements were not collected exactly on birthdays. Height and weight observations were available for 1435 individuals for ages 0–2 years and 7–11 years. For ages 3, 4, 5, and 6 years, 1060, 728, 822 and 1387 observations, respectively, were available for weight and 1023, 682, 795 and 1386, respectively, were available for height. Residuals from linear regression analysis were used to measure how much the body size at a certain age differed from what would be predicted from size at an earlier age. This method is referred to as conditional growth. In other words, an individual with e.g. a negative value for conditional height growth but a positive value for conditional weight growth between ages 2 and 7 years would have gained less height but more weight during this interval than would have been expected from his or her previous body size and that of his or her peers of the same age. The intervals 0–2, 2–7, and 7–11 years were used in the conditional analysis of changes in weight, height and BMI. In addition, an interval between 2 and 11 years was calculated for BMI.

The NAFLD liver fat score was a converted to a dichotomous variable, with values greater than -0.640 defined as a positive NAFLD score. This variable was entered as the dependant variable into a series of logistic regression models. Each model included one childhood body size measurement or conditional growth variable as predictor variable, along with age, sex, and gestational age as covariates. When additionally adjusting for adult BMI, an interaction was found between sex and BMI. In an omnibus test of model coefficients, a model including birth weight, age, sex, gestational age, BMI, as well as an interaction term between sex and BMI, showed a significance level of 0.04 compared to a model without the interaction term (p for the interaction term 0.04). Accordingly, models adjusting for BMI were stratified by sex. Further adjustments for current and previous smoking status, daily energy intake, physical activity, and socioeconomic status in childhood and adulthood were explored but yielded no additional information compared to the sex-stratified BMI models. An additional model, including both BMI at age 2 years, and adult BMI, along with sex and age, was constructed to explore the combined effects of body size in infancy and BMI gain after age 11 years. Adjustment for gestational age was also explored but gave no additional information. BMI at 2 years was divided into tertiles while adult BMI was divided into groups reflecting the cut-off points for overweight and obesity (<25, 25–30, >30).

The NAFLD liver fat equation was used to estimate liver fat percent for all participants. After log-transformation due to skewedness, the variable was entered as the dependant variable in a series of multiple linear regression models. The covariates included were the same as for the logistic models. A model adjusting for sex, age, gestational age, birth weight, and BMI was compared with a model also including an interaction term between sex and BMI. The significant F change between models was 0.001 ($p = 0.001$ for the interaction term). Accordingly, the models controlling for adult BMI were stratified by sex. Additional adjustments for current and previous smoking status, daily energy intake, physical activity, and socioeconomic status in childhood and adulthood did not affect the results significantly. Based on the results from the regression models, change in the unlogged variable (regression coefficient) per unit predictor variable was calculated by (exp (regression coefficient) – 1) x 100.

FLI was calculated for all participants but only applied for estimating the prevalence of NAFLD in the cohort, not in regression models. FLI was dichotomized at the cut-off point from the original study, i.e. at 60 and above. All statistical analyses were performed using SPSS version 21 (SPSS, Inc., Chicago, IL).

Study III

FLI and the NAFLD liver fat score were calculated for all participants. The scores were dichotomized as in study II and entered into logistic regression models with energy-adjusted quartiles of fructose intake as the predictor variables of interest. The residual method was applied for energy adjustment of all nutrient variables (Willett and Stampfer, 1986). Covariates were selected based on current literature. Four models were analysed for each dichotomous algorithm score outcome: "Model 0", with no adjustments; model 1 with adjustments for sex, age and energy intake; model 2 with additional adjustments for smoking status and physical activity; and model 3, with further adjustments for alcohol, fiber, vitamin E, and total fat intake. The likelihood ratio test (LRT) was used to test each variable's significance. An interaction test was performed between sex and the outcome variables. This revealed a non-significant interaction term ($p > 0.05$) and accordingly, analysis was combined for men and women. All analyses were performed using the R environment for statistical computing (R Team, 2013).

Study IV

Z scores (SD scores) for weight and length/height measurements were obtained by applying the same methodology as in study II. Current size measures (represented by z scores) were regressed on previous size to obtain conditional size measures. Conditional relative birth weight was calculated by regressing birth weight on birth length. This measure represents how much an individual's birth weight differs from what would have been expected based on his or her birth length and in relation to the other cohort members. Conditional relative weight represents current weight accounting for current height as well as previous weight and height. Conditional height represents current height taking previous weight and height into account. A negative conditional relative weight or negative conditional height represents a slower gain in relative weight or linear growth, respectively, than would have been expected based on the individual's previous size and the growth of the other cohort participants. These conditional variables can be entered simultaneously into the same regression model, as they are statistically independent from each other. The following growth intervals were studied: birth to 6 months, 6 months to 2 years, 2 years to 11 years, and 11 years to adulthood.

Multiple linear regression was used to study the associations between growth and adult systolic blood pressure at the first and second clinic visit, respectively. The predictive variables of primary interest were birth length (expressed as a z score), birth weight conditioned on birth length, and the conditional growth variables for relative weight gain and linear growth. These were entered into the regression model together with sex, age, childhood SES (ordinal, three levels), daily sodium intake in grams (log-transformed due to skewedness), and antihypertensive medication (dichotomous, no/yes). The dependant variable was systolic blood pressure at either the first or the second clinic visit. In the latter cases, the analysis was also performed with systolic blood pressure at the first clinic visit as a covariate. This was done to see whether the birth size and conditional growth variables predicted current blood pressure independent of previous blood pressure. Additional adjustments for adult socioeconomic status, daily energy intake (available for both visits), current and previous smoking status (available only for the 2001–04 visit), and leisure-time

physical activity (available only for the 2001–04 visit), were explored but did not significantly affect the results.

Dichotomous hypertension variables were created for each clinic visit based on the following three criteria: current use of antihypertensive medication, systolic blood pressure ≥ 140 mmHg, and diastolic blood pressure ≥ 90 mmHg. Individuals with at least one of these criteria present at the time of the clinical examinations were defined as hypertensive. The dichotomous variable was entered into a logistic regression model with the birth size and conditional growth variables as predictors of primary interest along with the same covariates as for the linear regression models, excluding current antihypertensive medication as this was part of the outcome variable. Systolic and diastolic blood pressure at the first clinic visit were added as covariates to the second visit model, after an omnibus test of model coefficients revealed a significance level of 0.03 in a model including these variables compared to a model without them. Only individuals without hypertension, defined as above, at the first clinic visit were included in the second visit model (n = 311). All statistical analyses were performed using SPSS version 21 (SPSS, Inc., Chicago, IL).

Study V

Means and SDs were calculated for the participants' characteristics in each cohort. A t-test was used for calculating 95% confidence intervals for the differences in means between cohorts. To explore the influence of birth year, dummy variables were created for each year of birth with 1943, the year with most births, as reference. Marital status was divided into three categories: married, unmarried, and unknown/other. The latter category represented widows and divorcees in the HBCS, whereas it represented those of unknown marital status in the Åland cohort. Dummy variables were created for the unmarried, and unknown/other categories with the married category as the reference. Birth weight was entered as the dependent variable into a multiple linear regression model with maternal age (centred at 28 years), the dummy variables for birth year and marital status, sex, and cohort of birth as model coefficients. Potential cohort specific associations were explored through interaction testing. Interaction terms were created between cohort of birth and each of the other covariates. For each covariate, a model including all covariates was compared to one additionally including the covariate of

interest's interaction term. Only one interaction term was tested per model, with exception for the maternal marital status and birth year variables, respectively, which were analysed simultaneously. Significant F changes ≤ 0.05 were demonstrated for the marital status variables and maternal age and hence, the regression analysis was stratified by cohort. Furthermore, we created two sub-cohorts from the Åland material, representing those born in the regional capital of Mariehamn, and those born in rural areas. No sub-cohort specific effects were found in interaction testing, however. All statistical analyses were performed using SPSS version 21 (SPSS, Inc., Chicago, IL).

Additional analyses performed after publication of the original articles

The analyses included in study I were expanded upon to explore the associations between conditional growth and adult body composition applying the multiple linear regression methodology used in study IV. These analyses were performed using SPSS version 21 (SPSS, Inc., Chicago, IL).

4.5 Ethical considerations

The Helsinki Birth Cohort Study has been approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa. All participants in the clinical studies provided written informed consent. The study adheres to the declaration of Helsinki.

5 RESULTS

5.1 Birth weight, body composition and resting metabolic rate

The study population consisted of 408 men, and 488 women of mean ages 61.5 (SD 2.7) and 61.6 (SD 3.1) years, respectively. Characteristics of the 896 study participants are found in **table 2**.

Table 2. Characteristics of participants in Study I.

	Men (n = 408)		Women (n = 488)	
	Mean	**SD**	**Mean**	**SD**
Birth characteristics				
Birth weight (g)	3472	509	3347	478
Gestational age (days)	279.7	11.2	280.7	10.8
Adult characteristics				
Age (years)	61.5	2.7	61.6	3.1
Height (cm)	176.4	6.1	163.2	5.6
Weight (kg)	85.0	13.4	73.7	14.4
Body mass index (kg/m^2)	27.3	4.0	27.7	5.2
Fat percentage (%)	23.4	5.9	33.9	7.1
Fat-free mass (kg)	64.5	7.8	47.9	6.0
Fat mass (kg)	20.4	8.0	25.8	10.0
Resting metabolic rate (kcal/24h)	1708	203	1380	143

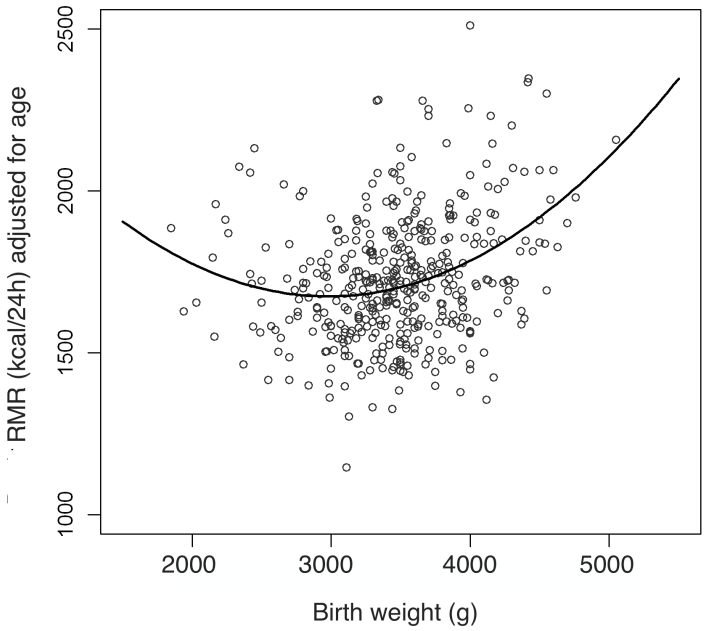
SD: Standard deviation.

Birth weight was positively correlated with FFM ($r = 0.27$, $p < 0.001$ for both sexes combined as well as separately for men and women). Birth weight was weakly correlated with FM in the combined analysis ($r = 0.06$, $p < 0.01$) but in the stratified analysis only significant for men ($r = 0.15$, $p < 0.001$) and not in women ($r = 0.06$, $p = 0.20$). FFM was more strongly correlated to FM in men than in women ($r = 0.61$, $p < 0.001$ and $r = 0.45$, $p < 0.001$, respectively). The correlation for both sexes combined, adjusted for sex, was $r = 0.52$ ($p < 0.001$). The correlation between FFM

and RMR was strong and significant ($r = 0.88$ for both sexes combined, $r = 0.89$ for men, and $r = 0.86$ for women, all p-values < 0.001). FM was also strongly and positively associated with RMR ($r = 0.81$ for both sexes combined, $r = 0.78$ for men, and $r = 0.91$ for women, all p-values < 0.001).

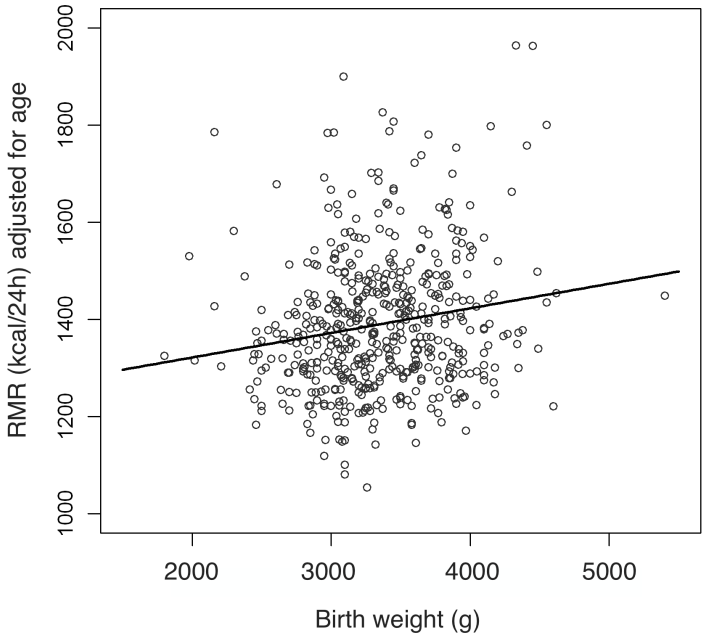
A quadratic (u-shaped) association was found between age-adjusted RMR and birth weight among men ($p < 0.001$) whereas the association was linear and positive among women ($p < 0.001$). Additional adjustment for gestational age did not affect these trends. The association for men remained quadratic after further adjustment for FFM or FM, ($p < 0.01$, and $p < 0.001$, respectively). In women, adjustment for FM did not change the direction of the association ($r = 0.25$, $p < 0.001$). However, when adjusting for FFM the association was inverted ($r = -0.12$, $p < 0.01$). Further adjustment for gestational age did not significantly affect the associations. Simultaneous adjustment for age, FFM, and FM led to loss of significance at the 0.05 level for women ($p = 0.16$) but not among men ($p = 0.05$). According to Akaike's information criteria of goodness-of-fit, all quadratic models were superior to the linear ones for men while the opposite was true for women. **Figures 8–11** shows the associations between birth weight and RMR separately for men and women with adjustments for only age, as well as for age and FFM.

Figure 8. The association between birth weight and age-adjusted RMR in men.



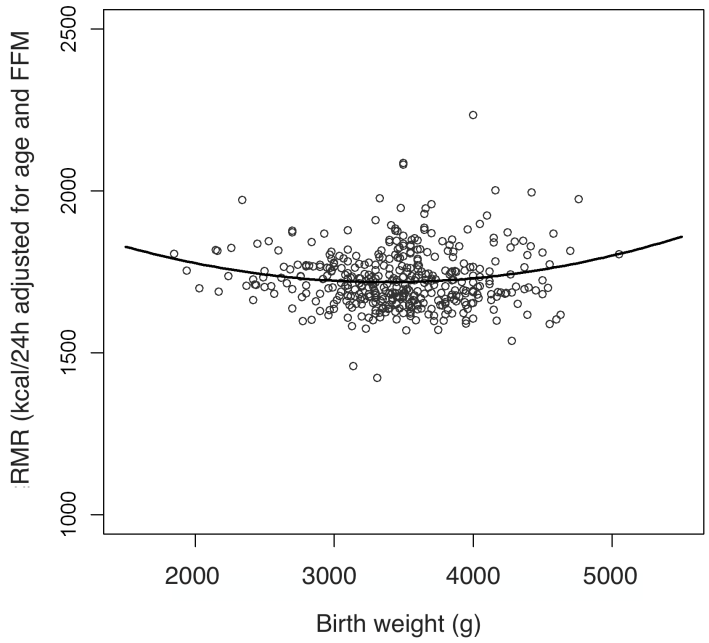
RMR: Resting metabolic rate.

Figure 9. The association between birth weight and age-adjusted RMR in women.



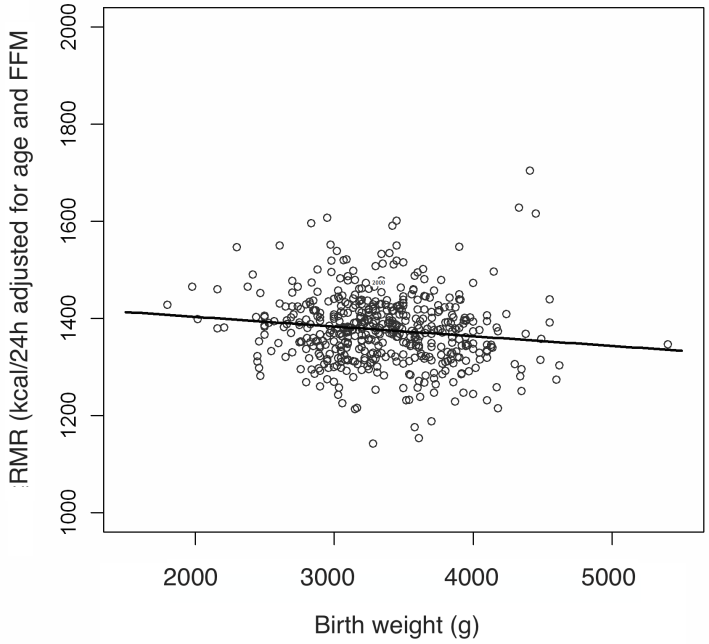
RMR: Resting metabolic rate.

Figure 10. The association between birth weight and age- and FFM-adjusted RMR in men.



RMR: Resting metabolic rate; FFM: Fat-free mass.

Figure 11. The association between birth weight and age- and FFM-adjusted RMR in women.



RMR: Resting metabolic rate; FFM: Fat-free mass.

5.1.1 Additional analysis applying methodology of study IV

This analysis included 858 individuals and focused on the associations between adult body composition and conditional relative weight gain and linear growth. FFM was positively associated with all measurements of birth size and conditional growth, most strongly so with conditional relative weight gain between 11 years and adulthood where one SD of this variable was associated with a 4.1 kg (95% CI 3.9; 4.3) increase in FFM (**table 3**). The influence of relative weight gain during this period was even stronger on FM, where every SD of the conditional variable was associated with an estimated 8.6 kg (95% CI 8.4; 8.7) increase in FM (**table 4**). Interestingly though, body fat percent was only positively associated with conditional relative weight gain after age 2 years, whereas it was inversely associated with birth length and all linear growth measurements, except for the interval between ages 2 and 11 years. The most pronounced effects were found after age 11 years, where one SD of relative weight gain was associated with 5.5% (95% CI 5.3; 5.7) higher body fat percent and one SD of linear growth was associated with 0.7% (95% CI 0.5; 1.0) lower percent body fat (**table 5**).

Table 3. Estimated change in FFM (kg) per unit predictor variable

Predictor variable	**B**	**95% CI**		**p**
(Constant)	82.6	78.4	86.7	<0.001
Sex (0 = male, 1 = female)	-17.2	-17.5	-16.8	<0.001
Age (years)	-0.01	-0.1	0.1	0.85
Birth weight conditioned on birth length (SD)	0.5	0.3	0.6	<0.001
Conditional relative weight gain 0 – 6m (SD)	0.6	0.4	0.8	<0.001
Conditional relative weight gain 6m – 2y (SD)	0.8	0.6	1.0	<0.001
Conditional relative weight gain 2 – 11y (SD)	0.7	0.5	0.9	<0.001
Conditional relative weight gain 11y – adulthood (SD)	4.1	3.9	4.3	<0.001
Birth length (SD)	1.7	1.6	1.9	<0.001
Linear growth 0 – 6m (SD)	1.5	1.3	1.6	<0.001
Linear growth 6m – 2y (SD)	1.7	1.5	1.9	<0.001
Linear growth 2y – 11y (SD)	2.0	1.9	2.2	<0.001
Linear growth 11y – adulthood (SD)	2.9	2.7	3.1	<0.001

B: Regression coefficient; CI: Confidence interval; SD: Standard deviation; m: months; y: years.

Table 4. Estimated change in FM (kg) per unit predictor variable.

Predictor variable	B	95% CI		p
(Constant)	12.2	8.2	16.1	<0.001
Sex (0 = male, 1 = female)	4.6	4.2	4.9	<0.001
Age (years)	0.1	0.0	0.1	0.04
Birth weight conditioned on birth length (SD)	0.7	0.5	0.8	<0.001
Conditional relative weight gain 0 – 6m (SD)	0.2	0.0	0.4	0.02
Conditional relative weight gain 6m – 2y (SD)	0.4	0.2	0.6	<0.001
Conditional relative weight gain 2 – 11y (SD)	2.0	1.8	2.2	<0.001
Conditional relative weight gain 11y – adulthood (SD)	8.6	8.4	8.7	<0.001
Birth length (SD)	0.4	0.2	0.5	<0.001
Linear growth 0 – 6m (SD)	0.0	-0.2	0.2	0.83
Linear growth 6m – 2y (SD)	0.1	-0.1	0.3	0.28
Linear growth 2y – 11y (SD)	0.7	0.6	0.9	<0.001
Linear growth 11y – adulthood (SD)	0.2	0.1	0.4	0.01

B: Regression coefficient; CI: Confidence interval; SD: Standard deviation; m: months; y: years.

Table 5. Estimated change in body fat % per unit predictor variable.

Predictor variable	B	95% CI		p
(Constant)	8.6	3.6	13.5	0,001
Sex (0 = male, 1 = female)	10.0	9.6	10.5	<0.001
Age (years)	0.1	0.003	0.2	0.04
Birth weight conditioned on birth length (SD)	0.2	-0.02	0.4	0.07
Conditional relative weight gain 0 – 6m (SD)	-0.03	-0.3	0.2	0.78
Conditional relative weight gain 6m – 2y (SD)	0.1	-0.2	0.3	0.67
Conditional relative weight gain 2 – 11y (SD)	1.5	1.3	1.7	<0.001
Conditional relative weight gain 11y – adulthood (SD)	5.5	5.3	5.7	<0.001
Birth length (SD)	-0.3	-0.5	-0.1	0.002
Linear growth 0 – 6m (SD)	-0.5	-0.7	-0.2	<0.001
Linear growth 6m – 2y (SD)	-0.5	-0.8	-0.3	<0.001
Linear growth 2y – 11y (SD)	-0.2	-0.4	0.1	0.15
Linear growth 11y – adulthood (SD)	-0.7	-1.0	-0.5	<0.001

B: Regression coefficient; CI: Confidence interval; SD: Standard deviation; m: months; y: years.

5.2 Childhood growth and NAFLD

The mean age of the 646 male and 941 female study participants was 61.6 years (SD 2.8 and 3.0, respectively). Mean liver fat percent was 4.2% (interquartile range 2.5; 6.9) among men and 3.0% (interquartile range 1.9; 5.3) among women. NAFLD, as diagnosed by the NAFLD liver fat score, was present among 43.0% of the men and 22.5% of the women. The prevalence was even higher when defining NAFLD according to FLI: 50.4% among men and 32.6% among women, respectively. The childhood and adult characteristics of the study population are described in **tables 6** and **7**, respectively.

Table 6. Childhood characteristics of participants in study II.

	Men (n=646)		**Women (n=941)**	
Measurement	**Mean / %**	**SD**	**Mean / %**	**SD**
Birth				
Length (cm)	50.6	2.0	50.0	1.8
Weight (g)	3463	482	3358	463
Ponderal index (kg/m^3)	26.6	2.3	26.7	2.2
Gestational age (days)	280	11	281	11
Age 2 years				
Height (cm)	86.7	3.0	85.6	3.0
Weight (kg)	12.4	1.1	11.9	1.1
Body mass index (kg/m^2)	16.7	1.2	16.4	1.2
Age 7 years				
Height (cm)	121.0	4.7	120.1	4.7
Weight (kg)	22.5	2.6	22.2	2.9
Body mass index (kg/m^2)	15.5	1.1	15.5	1.3
Age 11 years				
Height (cm)	141.6	5.9	141.7	6.6
Weight (kg)	33.8	4.5	34.3	5.7
Body mass index (kg/m^2)	16.8	1.5	17.0	1.9

SD: Standard deviation.

No significant associations were demonstrated between birth anthropometrics and presence of NAFLD, according to the NAFLD liver score (**figure 12**). BMI and weight at 1 year of age, as well as weight at 2 years, adjusted for sex, age, and gestational age,

were all inversely associated with the dichotomous NAFLD outcome. After stratification by sex and additional adjustment for adult BMI, these inverse associations remained for both men and women. Additionally, in men, the model adjusted for adult BMI revealed several other inverse associations. For example, all measurements of BMI between ages 1 and 11 years were inversely associated with the dichotomous NAFLD outcome.

In the combined models, with adjustments for sex, age, and gestational age, liver fat content was significantly inversely associated with weight at ages 1, 2 and 3 years, height at 2 and 5 years, and BMI at 3 years (**figure 13**). In women, a one SD increase of birth weight was associated with an estimated relative decrease of liver fat content by 5.4% (95% CI 1.5; 9.2) after additional adjustment for adult BMI, which corresponds to a relative decrease of 11.5 % (95% CI 3.2; 18.9, p 0.01) per kg birth weight. Except for birth weight in men, all measurements of weight and BMI were inversely associated with the outcome in both sexes, as well as height at age 7 years in women. In both figure 12 and 13, the mean values and 95% CIs at ages 3, 4, 5 and 6 years are based on fewer observation than for the other years, as detailed in the statistics section.

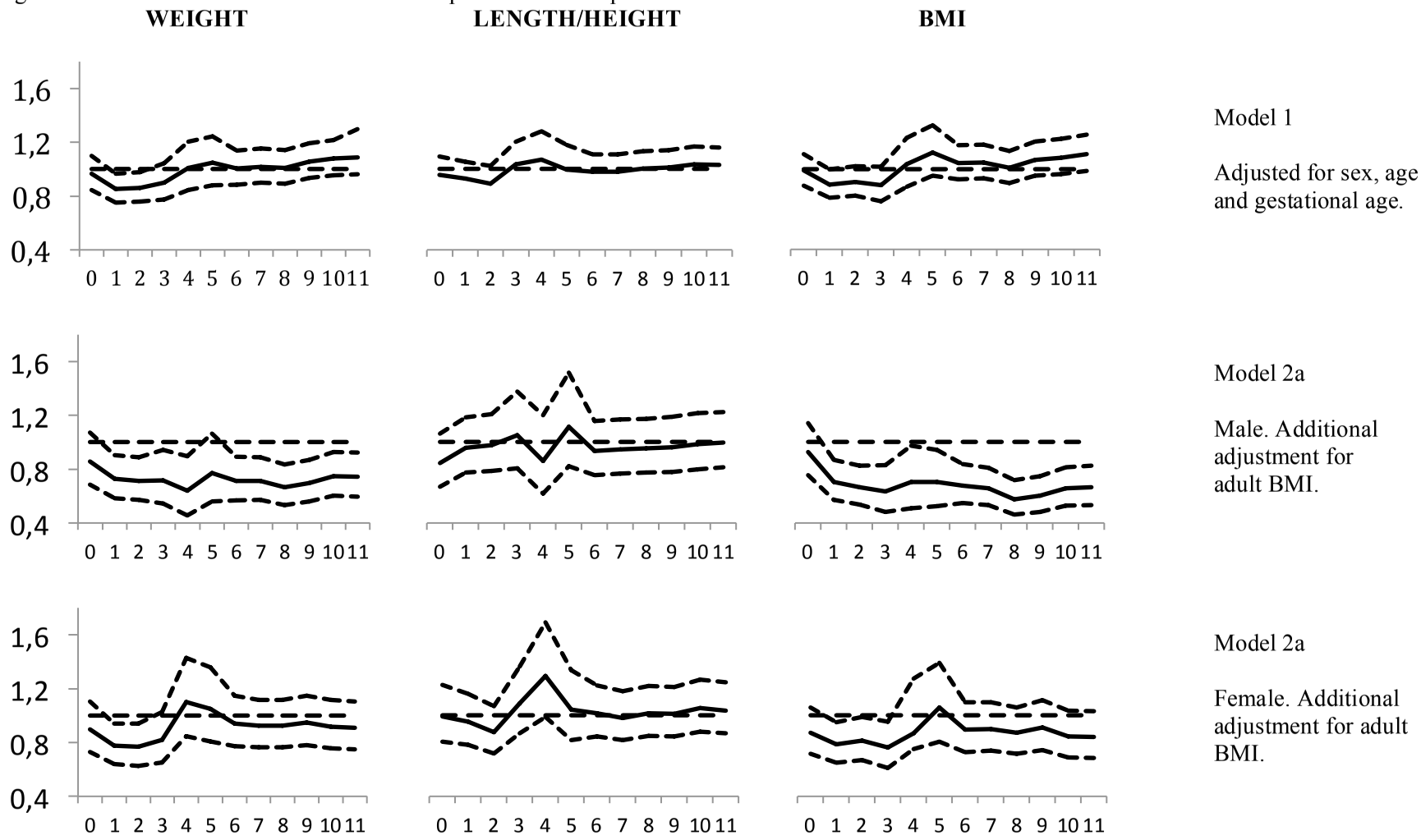
Conditional weight gain between birth and 2 years of age, adjusted for age, sex, and gestational age, was inversely associated with the dichotomous NAFLD outcome in both men and women (**table 8**). Conditional height gain was not significantly associated with NAFLD in either sex. In men, conditional BMI gain between birth and age 7 years, and conditional BMI gain between ages 2 and 11 years, were inversely associated with NAFLD. In women, conditional weight and BMI gain were inversely associated with liver fat content (**table 9**). In men, inverse associations were demonstrated for conditional weight and BMI gain between ages 2 and 7 years, and for conditional BMI gain between ages 2 and 11 years.

Table 7. Adult characteristics of participants in study II.

Measurement	Men (n=646)		Women (n=941)	
	Mean / %	SD / Quartiles	Mean / %	SD / Quartiles
Age (years)	61.6	2.8	61.6	3.0
Height (cm)	176.7	6.0	163.4	5.7
Weight (kg)	85.2	12.7	73.1	12.4
Body mass index (kg/m^2)	27.3	3.7	27.4	4.4
Waist circumference (cm)	99.9	10.8	90.3	11.8
Systolic blood pressure (mmHg)	146.4	19.7	144.1	21.0
Diastolic blood pressure (mmHg)	90.2	10.7	87.6	10.2
Fasting plasma glucose (mmol/l)[1]	5.7	5.4; 6.3	5.4	5.0; 5.8
HDL cholesterol, mmol/l[1]	1.4	1.2; 1.6	1.7	1.4; 2.0
Triglycerides, mmol/l[1]	1.3	1.0; 1.9	1.3	1.0; 1.7
High waist circumference (%)[2]	70.3		80.0	
Elevated blood pressure (%)[3]	86.7		82.5	
Elevated fasting glucose (%)[4]	62.1		61.1	
Reduced HDL-cholesterol (%)[5]	8.4		15.1	
Hypertriglyceridemia (%)[6]	32.3		26.2	
Presence of metabolic syndrome	56.7		45.9	
Presence of diabetes (%)	17.6		11.1	
ALT (U/l)[a]	16.0	12.0; 22.0	13.0	9.0; 17.0
AST (U/l) [a]	27.0	22.0; 33.0	23.0	19.0; 28.0
Fasting insulin (pmol/l)[1]	9.2	6.1; 14.5	7.7	5.3; 11.4
NAFLD (liver fat score) (%)	43.0		22.5	
NAFLD (FLI) (%)	50.4		32.6	
Algorithm-based liver fat%[1,7]	4.2	2.5; 6.9	3.0	1.9; 5.3

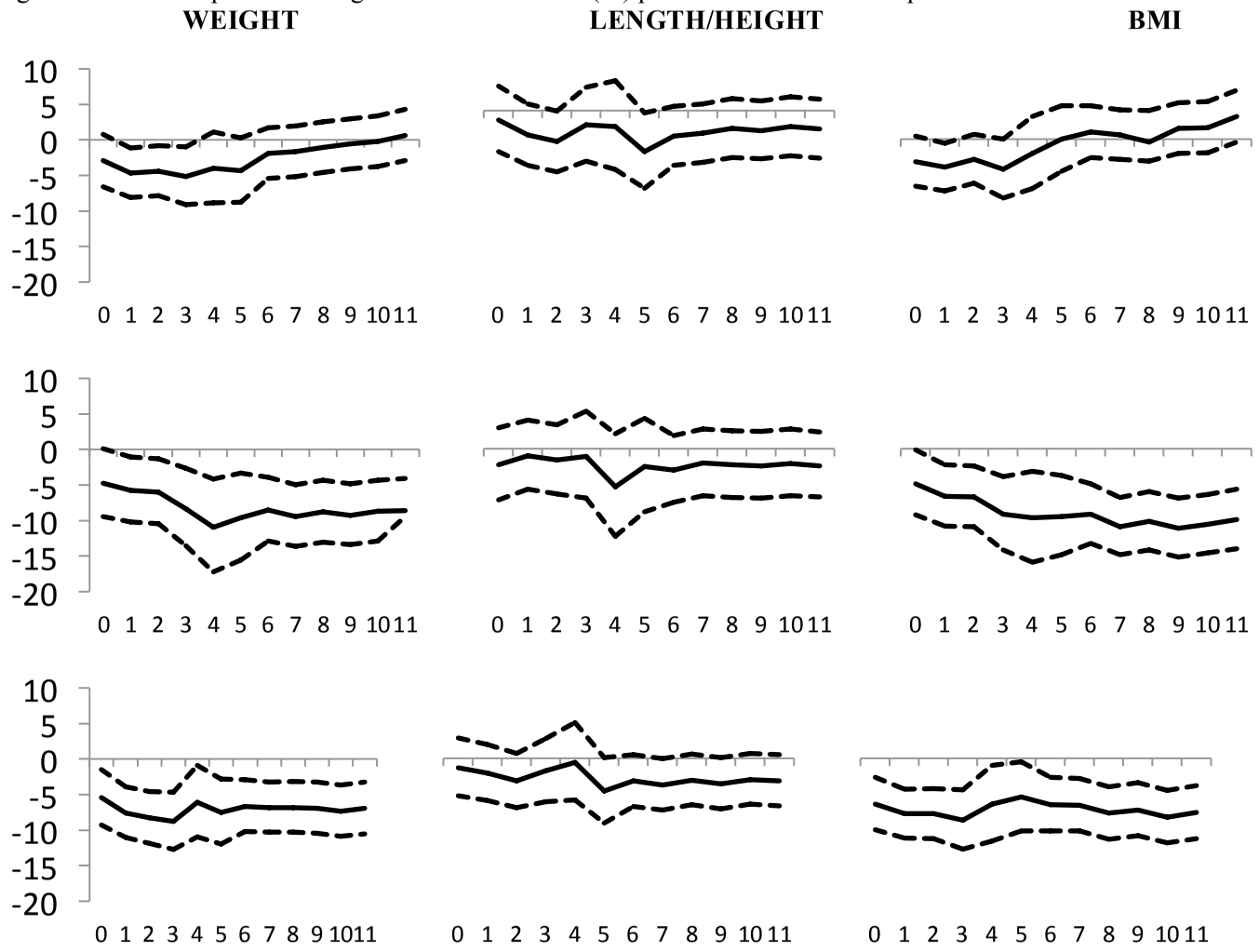
SD: Standard deviation; HDL: high density lipoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; NAFLD: Non-alcoholic fatty liver disease; FLI: Fatty Liver Index. [1]Median values and interquartile ranges presented due to skewedness. [2–6]2009 harmonized criteria for diagnosis of the metabolic syndrome [2]Waist circumference ≥ 94 cm in men, ≥ 80 cm in women). [3]Systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg and/or antihypertensive medication. [4]Fasting plasma glucose (≥ 5.6 mmol/l), alternatively diabetes medication [5]Reduced high density lipoprotein cholesterol (HDL-C) (≤ 1.0 mmol/l in men, ≤ 1.3 mmol/l in women), alternatively drug treatment for reduced HDL-C [6]Serum triglycerides (≥ 1.7 mmol/l), alternatively drug treatment for elevated triglycerides [7]Liver fat percent estimated using the NAFLD liver fat equation.

Figure 12: Odds ratio and 95% CI for NAFLD per SD of anthropometric measurement



Y-axis: Odds ratio; X-axis: Age. Solid lines: Odds ratio; Broken lines: 95% CI.

Figure 13: Relative percent change in liver fat content (%) per SD childhood anthropometric.



Y-axis: Relative percent change; X-axis: Age; Solid lines: percent change; broken lines: 95% CI.

Table 8. Odds ratio of a positive NAFLD score per SD of conditional growth variable.

			Growth 0–2 y	Growth 2–7 y	Growth 7–11 y	Growth 2–11 y
Weight	*Model 1*[1]	**OR**	*0.88*	*1.18*	1.12	-
		95%CI	*0.78; 0.99*	*1.05; 1.33*	0.99; 1.25	-
		p	*0.03*	*0.01*	0.07	-
	Model 2[2]*, male*	**OR**	*0.77*	0.89	1.00	-
		95%CI	*0.63; 0.94*	0.72; 1.09	0.82; 1.21	-
		p	*0.01*	0.25	0.98	-
	Model 2[2]*, female*	**OR**	*0.79*	1.14	0.91	-
		95%CI	*0.65; 0.96*	0.94; 1.37	0.75; 1.10	-
		p	*0.02*	0.18	0.31	-
Length/ height	*Model 1*[1]	**OR**	0.91	1.08	1.09	-
		95%CI	0.81; 1.03	0.96; 1.22	0.97; 1.23	-
		p	0.14	0.19	0.15	-
	Model 2[2]*, male*	**OR**	1.02	0.95	1.09	-
		95%CI	0.84; 1.25	0.78; 1.16	0.90; 1.32	-
		p	0.83	0.61	0.38	-
	Model 2[2]*, female*	**OR**	0.87	1.11	1.09	-
		95%CI	0.72; 1.06	0.92; 1.33	0.90; 1.31	-
		p	0.16	0.27	0.38	-
BMI	*Model 1*[1]	**OR**	0.91	*1.14*	1.10	*1.17*
		95%CI	0.81; 1.03	*1.01; 1.28*	0.98; 1.24	*1.04; 1.32*
		p	0.12	*0.04*	0.10	*0.01*
	Model 2[2]*, male*	**OR**	*0.69*	*0.81*	0.92	*0.80*
		95%CI	*0.56; 0.84*	*0.66; 0.99*	0.75; 1.12	*0.65; 0.98*
		p	*<0.001*	*0.04*	0.40	*0.03*
	Model 2[2]*, female*	**OR**	0.84	1.03	0.86	0.92
		95%CI	0.70; 1.02	0.85; 1.24	0.71; 1.04	0.75; 1.11
		p	0.08	0.77	0.12	0.37

y: years; OR: Odds ratio; CI: Confidence interval; BMI: Body mass index. Significant associations italicized for clarity. [1]Adjusted for sex, age, and gestational age; [2]additionally adjusted for adult BMI.

Table 9. Relative % change in liver fat content (%) per SD of conditional growth variable.

Measurement			Growth 0–2 y	Growth 2–7 y	Growth 7–11 y	Growth 2–11 y
Weight	*Model 1*[1]	%	-3.3	2.1	3.7	-
		95%CI	-6.7; 0.1	-1.4; 5.9	0.1; 7.3	-
		p	0.06	0.23	0.04	-
	Model 2[2], *male*	%	-4.2	*-6.6*	-0.7	-
		95%CI	-8.4; 0.2	*-10.8; -2.1*	-5.2; 3.9	-
		p	0.06	*0.004*	0.75	-
	Model 2[2], *female*	%	*-6.8*	-1.6	-2.2	-
		95%CI	*-10.1; -3.1*	-5.4; 2.3	-5.8; 1.6	-
		p	*<0.001*	0.33	0.25	-
			-3.3	2.1	3.7	
Length/ height	*Model 1*[1]	%	-3.3	0	0.3	-
		95%CI	-6.6; 0.1	-3.4; 3.6	-3.1; 3.9	-
		p	0.06	0.99	0.85	-
	Model 2[2], *male*	%	-1.0	-1.1	-1.5	-
		95%CI	-5.4; 3.7	-5.5; 3.6	-5.8; 2.9	-
		p	0.67	0.64	0.50	-
	Model 2[2], *female*	%	-2.8	-2.3	0.2	-
		95%CI	-6.4; 0.9	-5.9; 1.4	-3.5; 4.0	-
		p	0.14	0.22	0.93	-
BMI	*Model 1*[1]	%	-2.0	2.9	*4.0*	*4.9*
		95%CI	-5.4; 1.5	-0.6; 6.5	*0.4; 7.6*	*1.4. 8.7*
		p	0.25	0.11	*0.03*	*0.01*
	Model 2[2], *male*	%	*-5.5*	*-8.3*	-1.5	*-7.2*
		95%CI	*-9.7; -1.2*	*-12.4. -4.1*	-5.9; 3.1	*-11.4; -2.8*
		p	*0.01*	*<0.001*	0.53	*0.002*
	Model 2[2], *female*	%	-6.3	-2.0	-3.6	-4.1
		95%CI	-9.8; -2.7	-5.7; 1.8	-7.2; 0.1	-7.7; -0.3
		p	0.001	0.30	0.06	0.04

y: years; OR: Odds ratio; CI: Confidence interval; BMI: Body mass index. Significant associations italicized for clarity. [1]Adjusted for sex, age, and gestational age; [2]additionally adjusted for adult BMI.

Figure 14 and **table 10** show the combined influence of BMI at age 2 years and adult BMI on the prevalence of NAFLD, defined by the NAFLD liver fat score. The model is adjusted for sex and age. The OR of a positive NAFLD score was 18.5 (95% CI 10.1; 33.6) among those who belonged to the smallest BMI tertile at age 2 years and subsequently were obese in adulthood compared to individuals of the same BMI tertile at age 2 years who were lean or normal weight as adults.

Figure 14. Odds ratios and 95% confidence intervals for a positive NAFLD score according to BMI group in adulthood and BMI tertile at age 2 years.

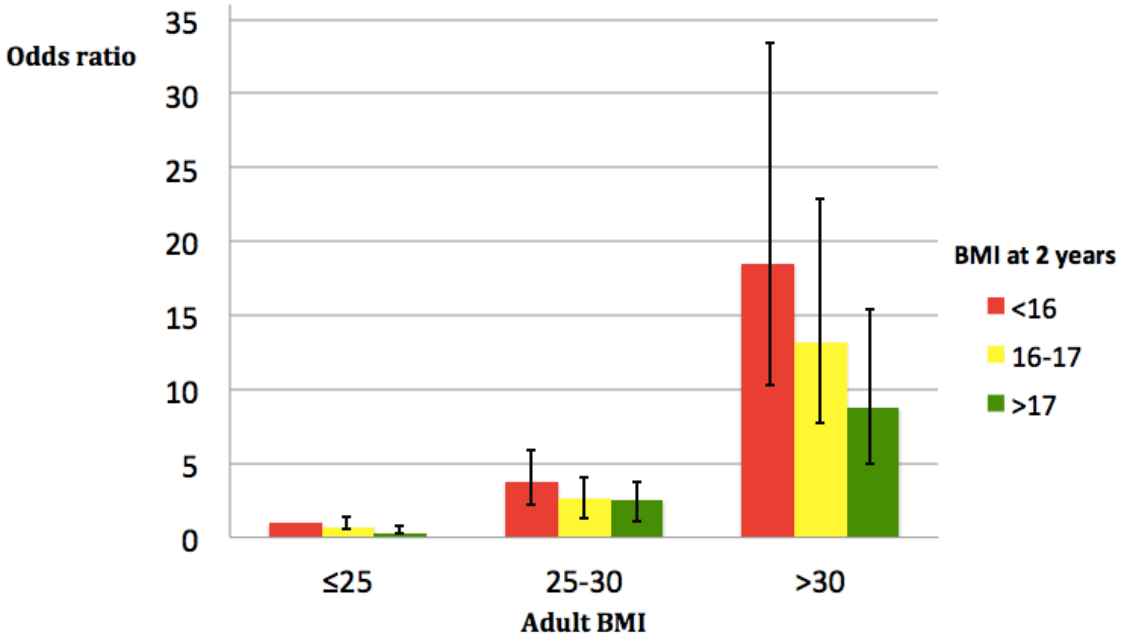


Table 10. Prevalence, odds ratios and 95% confidence intervals for a positive NAFLD score according to BMI group in adulthood and BMI tertile at age 2 years.

		Adult BMI								
		< 25			25–30			>30		
		OR	95% CI	%[1]	OR	95% CI	%[1]	OR	95% CI	%[1]
BMI 2y	**<16**	1.0	-	12.1	3.7	2.2; 6.1	32.4	18.5	10.1; 33.6	67.6
	16–17	0.7	0.4; 1.4	9.4	2.6	1.6; 4.4	28.6	13.2	7.5; 23.2	60.8
	>17	0.3	0.1; 0.8	3.5	2.5	1.5; 4.2	29.3	8.8	5.0; 15.2	51.8

BMI: Body mass index: [1]Percentages represent the proportion of individuals within the BMI group with NAFLD diagnosis according to the NAFLD liver fat score.

5.3 Fructose intake and NAFLD

Table 11 shows the characteristics of the participants in study III, according to quartiles of fructose intake. Prevalence of NAFLD, according to FLI, was 44%. The corresponding number for the NAFLD liver fat score was 32%. Compared to individuals belonging to the lowest quartile of fructose intake, those belonging to the highest quartile were more likely to be women than men, less likely to be smokers or physically inactive, and had higher educational attainment.

Fructose intake was inversely associated with NAFLD diagnosis according to both algorithm scores, when adjusting for age, sex, and energy intake (model 1) (**table 12**). After further adjustments for leisure-time physical activity and smoking (model 2), as well as total intake of fat, fiber, alcohol, and vitamin E (model 3), the inverse association only remained for the FLI. The OR for NAFLD according to FLI in the fully adjusted model was 0.68 (95% CI 0.47; 0.97, p for trend <0.05) for individuals belonging to the quartile with the highest intake of fructose compared to the lowest quartile.

Table 11. Characteristics of participants in study III.

Characteristics	Fructose intake quartiles (range, g/d)								P^1
	Q1 (2.2–15.3)		Q2 (15.3–21.9)		Q3 (21.9–29.2)		Q4 (29.2–88.0)		
n	403		403		402		403		
	Mean / %	SEM	Mean / %	SEM	Mean / %	SEM	Mean / %	SEM	
Fructose (g/d)	10.6	±1.0	18.6	±1.0	25.2	±1.0	38.1	±1.0	
Women (%)	41		55		67		76		< 0.001
Age (y)	61.6	±0.2	61.7	±0.2	61.5	±0.2	61.6	±0.2	0.91
Educational attainment (y)	11.4	±0.2	12.0	±0.2	12.4	±0.2	12.6	±0.2	< 0.001
Current smokers (%)	38		17		18		13		< 0.001
Physically inactive participants (%)[2]	16		9		9		10		< 0.01
BMI (kg/m^2)	27.7	±0.2	27.8	±0.2	27.4	±0.2	27.5	±0.2	0.35
Waist circumference (cm)	95.7	±0.6	95.4	±0.6	93.9	±0.6	94.2	±0.6	< 0.05
Diabetics (%)	17		14		12		13		0.36
Metabolic syndrome (%)	54		54		47		49		0.08
NAFLD (FLI) (%)	48		44		38		34		< 0.001
NAFLD (NAFLD-score) (%)	35		32		29		28		0.06
Energy intake (kJ/d)	8970	±160	9230	±160	9420	±160	9110	±160	0.07
Fiber (g/d)	22.8	±0.4	26.1	±0.4	28.1	±0.4	32.4	±0.4	< 0.001
Total fat (g/d)	82.2	±0.5	76.9	±0.5	73.6	±0.5	66.3	±0.5	< 0.001
Alcohol (g/d)	13.9	±0.6	14.5	±0.6	13.2	±0.6	12.1	±0.6	0.22
Vitamin E (alphatocopherol equivalents; mg/d)	12.2	±0.2	13.2	±0.1	13.4	±0.1	13.3	±0.2	< 0.001

BMI: body mass index; FLI: fatty liver index; HDL: high-density lipoprotein; NAFLD: non alcoholic fatty liver disease; Q: quartile; SEM: standard error of mean. [1]P-value for trend obtained from linear regression for continuous variables and from logistic regression for binary variables. P-values were adjusted for age and sex. For nutrient intakes, P-values were additionally adjusted for energy intake. [2]Leisure-time physical activity (brisk walk or comparable) less than 3 times weekly.

Table 12. Odds ratio for NAFLD (according to NAFLD liver fat score and FLI) by quartiles of fructose intake.

	Energy-adjusted fructose intake quartiles (g/d)								
	Q1 (2.2 – 15.3 g/d)	Q2 (15.3 – 21.9 g/d)		Q3 (21.9 – 29.2 g/d)		Q4 (29.2 – 88.0 g/d)			
Model	reference	OR	95% CI	OR	95% CI	OR	95% CI	P-trend[1]	P-LRT[2]
Positive FLI (%)	51	45		37		32			
Crude[3]	1	0.80	0.60, 1.05	0.57	0.43, 0.76	0.46	0.34, 0.61	< 0.001	
Model 1[4]	1	0.87	0.65, 1.15	0.67	0.50, 0.90	0.56	0.42, 0.75	< 0.001	< 0.001
Model 2[5]	1	0.94	0.71, 1.26	0.74	0.55, 1.00	0.62	0.46, 0.84	< 0.001	< 0.01
Model 3[6]	1	0.97	0.72, 1.31	0.78	0.57, 1.07	0.68	0.47, 0.97	<0.05	0.09
Positive NAFLD score (%)	39	34		28		26			
Crude	1	0.81	0.61, 1.08	0.62	0.46, 0.83	0.54	0.40, 0.73	<0.001	
Model 1	1	0.91	0.68, 1.22	0.77	0.57, 1.04	0.72	0.53, 0.99	<0.001	0.15
Model 2	1	0.95	0.70, 1.28	0.81	0.59, 1.11	0.75	0.54, 1.04	0.11	0.27
Model 3	1	0.99	0.72, 1.35	0.87	0.62, 1.22	0.88	0.60, 1.29	0.80	0.81

OR: Odds ratio; CI: Confidence interval; Q: Quartile; LRT: Likelihood-ratio test; FLI: Fatty liver index; NAFLD: Non-alcoholic fatty liver disease. [1]P-values for trend obtained from logistic regression with energy-adjusted fructose intake as continuous variable. [2]P-value for likelihood-ratio test. [3]Unadjusted model. [4]Adjusted for age, sex, and energy intake. [5]Additionally adjusted for smoking and leisure-time physical activity. [6]Additionally adjusted intake of alcohol, fiber, vitamin E, and total fat.

5.4 Childhood growth and hypertension: amplification with age

Childhood and adult characteristics of the 1036 study participants are found in **tables 13** and **14**. The proportion of participants using antihypertensive medication was 30.3% and 42.2%, at the first and second clinic visit, respectively. 61.9% and 62.8% had blood pressure values within the hypertensive range, respectively.

Systolic blood pressure at the first clinic visit was inversely associated with birth length and birth weight conditioned on birth length. For every SD increase in these variables, systolic blood pressure decreased 1.1 mmHg (95% CI 0; 2.2) and 1.4 mmHg (95% CI 0.3; 2.5), respectively (**table 15**). Conversely, a positive association was demonstrated between relative weight gain after age 11 years. One SD of this conditional variable was associated with 3.8 mmHg (95% CI 2.2; 5.1) higher systolic blood pressure. Several inverse associations were found between systolic blood pressure at the time of the second clinic visit and the childhood conditional growth variables (**table 15**). For example, both conditional relative weight gain and linear growth between ages 2 and 11 years were inversely associated with the outcome, both before and after adjustment for systolic blood pressure at the time of the first clinic visit. Relative weight gain after age 11 years stayed positively associated with the outcome in all models, albeit attenuated to 1.1 mmHg (95% CI 0.1; 2.1, p = 0.04) per SD of the conditional variable in the fully adjusted model. Birth length and birth weight conditioned on birth length were both associated with an odds ratio of 0.85 (95% CIs 0.75; 0.98 and 0.74; 0.98, respectively, p = 0.02 for both associations) for hypertension at the first clinic visit, per SD of conditional variable (**table 15**). One SD of conditional relative weight gain after age 11 years was associated with an odds ratio of 1.79 (95% CI 1.51, 2.11, p <0.001) for hypertension. At the time of the second clinic visit, an inverse association was demonstrated for linear growth between ages 2 and 11 years with an odds ratio of 0.61 (95% CI 0.4; 0.81, p = 0.001) for hypertension per SD of the conditional variable (**table 15**).

Table 13. Childhood characteristics of participants in study IV.

	Female (n=574)		**Male (n=462)**	
	Mean/ Median/%	SD/ IQR	Mean/ Median/%	SD /IQR
Birth weight (g)	3365	459	3481	487
Birth length (cm)	50.1	1.8	50.7	2.0
Weight 6 months (kg)	7.4	0.8	7.9	0.8
Length 6 months (cm)	66.3	2.2	67.9	2.3
Weight 2 years (kg)	12.0	1.1	12.5	1.1
Height 2 years (cm)	85.8	3.0	86.8	3.0
Weight 11 years (kg)	34.4	5.6	33.7	4.4
Height 11 years (cm)	141.7	6.4	141.7	5.7
Childhood SES (low / medium / high, %)	15.1 / 22.4 / 62.5		18.7 / 22.3 / 59.0	

SD: Standard deviation. IQR: Interquartile range; SES: Socioeconomic status.

Table 14. Adult characteristics of participants in study IV.

	Female (n=574)		**Male (n=462)**	
	Mean/ Median/%	SD/ IQR	Mean/ Median/%	SD /IQR
First clinic visit (2001–04)				
Age (years)	61.5	3.0	61.4	2.7
Weight (kg)	72.3	12.5	84.6	11.9
Height (cm)	163.5	5.7	176.9	5.9
Daily sodium intake (g)[1]	3.0	2.4; 3.6	3.6	2.9; 4.5
Systolic blood pressure (mmHg)	141.8	20.2	144.6	18.4
Diastolic blood pressure (mmHg)	86.9	10.0	89.8	9.9
Second clinic visit (2006–08)				
Age (years)	66.6	2.9	66.2	2.7
Weight (kg)	72.0	13.5	83.2	12.0
Height (cm)	162.8	5.7	176.4	6.0
Daily sodium intake (g)[1]	3.0	2.5; 3.6	3.7	2.9; 4.5
Systolic blood pressure (mmHg)	143.5	20	146.2	19.9
Diastolic blood pressure (mmHg)	89.4	11.1	90.4	10.9

SD: Standard deviation. IQR: Interquartile range; SES: Socioeconomic status.
[1]Median and interquartile range

Table 15. Estimated change in systolic blood pressure per unit predictor variable.

	Clinic visit 1			Clinic visit 2, Model 1			Clinic visit 2, Model 2		
Predictor variable	**B**	**95% CI**		**B**	**95% CI**		**B**	**95% CI**	
(Constant)	**84.5**	**59.3**	**109.7**	**96.2**	**66.5**	**125.9**	**58.9**	**34.0**	**83.9**
Sex (0 = male, 1 = female)	**-3.8**	**-6.1**	**-1.4**	**-4.1**	**-6.6**	**-1.5**	-1.8	-3.9	0.3
Age (years)	**1.0**	**0.6**	**1.4**	**0.7**	**0.3**	**1.1**	0.0	-0.3	0.4
Birth weight conditioned on birth length (SD)	**-1.1**	**-2.2**	**0.0**	-0.7	-1.9	0.5	0.0	-1.0	1.0
Conditional relative weight gain 0 – 6m (SD)	-0.6	-1.7	0.5	0.2	-1.0	1.4	0.6	-0.4	1.6
Conditional relative weight gain 6m – 2y (SD)	-0.8	-1.9	0.3	**-1.2**	**-2.4**	**-0.1**	-0.7	-1.7	0.2
Conditional relative weight gain 2 – 11y (SD)	0.0	-1.2	1.2	-1.2	-2.5	0.1	**-1.2**	**-2.2**	**-0.1**
Conditional relative weight gain 11y – adulthood (SD)	**3.8**	**2.5**	**5.1**	**3.2**	**2.0**	**4.4**	**1.1**	**0.1**	**2.1**
Birth length (SD)	**-1.4**	**-2.5**	**-0.3**	**-1.7**	**-3.0**	**-0.5**	-0.7	-1.8	0.3
Linear growth 0 – 6m (SD)	-0.8	-1.9	0.3	**-1.4**	**-2.6**	**-0.3**	**-1.0**	**-2.0**	**0.0**
Linear growth 6m – 2y (SD)	-1.1	-2.2	0.0	-0.1	-1.3	1.2	0.6	-0.4	1.6
Linear growth 2y – 11y (SD)	-0.6	-1.8	0.6	**-1.7**	**-3.0**	**-0.4**	**-1.3**	**-2.4**	**-0.3**
Linear growth 11y – adulthood (SD)	-0.8	-1.9	0.3	-1.1	-2.3	0.1	-0.5	-1.5	0.5
Antihypertensive medication (0 = no, 1 = yes)	**6.2**	**3.7**	**8.7**	-0.3	-2.7	2.2	0.6	-1.4	2.6
Daily sodium intake (g) (logarithmized)	**-3.9**	**-7.1**	**-0.6**	-3.3	-7.1	0.4	-2.3	-5.4	0.8
Childhood SES (low, medium, high)	**1.8**	**0.3**	**3.3**	**1.7**	**0.1**	**3.3**	0.4	-0.9	1.7
Time between visits (in years)				0.8	-0.6	2.3	0.6	-0.6	1.8
10 mmHg of systolic BP at first clinic visit							**5.9**	**5.3**	**6.4**

CI: Confidence interval, SD: Standard deviation. SES: Socioeconomic status. BP: Blood pressure. All predictor variables in each model entered simultaneously. Associations with significance level <0.05 bolded for clarity.

Table 16. Odds ratio for hypertension per unit predictor variable.

	Clinic visit 1			Clinic visit 2		
Predictor variable	**OR**	**95% CI**		**OR**	**95% CI**	
Constant	0.04			0.01		
Sex (0 = male, 1 = female)	**0.74**	**0.56**	**0.98**	1.28	0.76	2.18
Age (years)	**1.07**	**1.02**	**1.12**	0.97	0.88	1.07
Birth weight conditioned on birth length (SD)	**0.85**	**0.75**	**0.98**	1.08	0.85	1.38
Conditional relative weight gain 0 – 6m (SD)	0.95	0.83	1.08	1.11	0.86	1.42
Conditional relative weight gain 6m – 2y (SD)	0.92	0.81	1.04	1.10	0.87	1.39
Conditional relative weight gain 2 – 11y (SD)	0.94	0.82	1.09	0.94	0.72	1.22
Conditional relative weight gain 11y – adulthood (SD)	**1.79**	**1.51**	**2.11**	0.95	0.67	1.36
Birth length (SD)	**0.85**	**0.74**	**0.98**	1.03	0.79	1.33
Linear growth 0 – 6m (SD)	0.88	0.77	1.00	0.94	0.72	1.23
Linear growth 6m – 2y (SD)	0.89	0.78	1.01	0.82	0.64	1.05
Linear growth 2y – 11y (SD)	1.02	0.89	1.18	**0.61**	**0.45**	**0.81**
Linear growth 11y – adulthood (SD)	0.96	0.84	1.10	0.90	0.71	1.13
Childhood SES (low, medium, high)	1.14	0.96	1.35	1.22	0.89	1.66
Daily sodium intake (g) (logarithmized)	0.92	0.83	1.02	1.01	0.83	1.24
Diastolic BP at first visit (mmHg)				**1.04**	**1.00**	**1.10**
Systolic BP at first visit (mmHg)				1.02	0.99	1.05
Time between visits (years)				1.12	0.85	1.49

OR: Odds ratio; CI: Confidence interval; m: months; y: years; BP: blood pressure. Associations with significance level <0.05 bolded for clarity.

5.5 Regional differences in birth size

Characteristics of the study participants are described in **table 17**. The Helsinki Birth Cohort Study subjects born 1937–44 comprised 11808 individuals. The corresponding number for the Åland cohort was 1697 births. Mean birth weight on the Åland Islands was 3499 grams, 87 grams (95% CI 62; 111) more than for those born in Helsinki. Mean birth length was 50.7 cm, 0.4 cm (0.3; 0.5) more than in Helsinki. Ålandic mothers were on average 6 months (95% CI 3.6; 9.6 months) younger than their Helsinki peers with a mean age of 27.9 years (SD 5.9). Babies born to unmarried mothers on the Åland Islands were 291 grams (95% CI 123; 459) lighter than those born to married mothers, on average. The corresponding average weight difference in Helsinki was 111 grams (95% CI 79; 153). **Table 18** shows the associations between predictor variables and birth weight for both cohorts combined as well as stratified.

Table 17. Characteristics of the participants in study V.

	Helsinki n = 11808		**Åland** n = 1697	
	Mean (SD) / %	range	Mean (SD) / %	range
Maternal characteristics				
Maternal age (years)	28.5 (5.5)	15–48	27.9 (5.9)	15–45
Marital status (%)				
- Married	95.1		94.7	
- Unmarried	4.4		2.2	
- Unknown/other	0.4		3.1	
Offspring characteristics				
Female (%)	47.6		48.3	
Birth weight (g)	3412 (479)	1260–5640	3499 (508)	1100–5500
Birth length (cm)	50.3 (1.9)	41–59	50.7 (2.1)	34–59

SD: Standard deviation

Table 18. Associations between predictor variables and birth weight.

	Both cohorts combined		Helsinki		Åland		
Predictor	B	95% CI	B	95% CI	B	95% CI	p for interaction[1]
(constant)	3511	3491; 3531	3516	3495; 3536	3547	3478; 3616	-
Sex (0 = male, 1 = female)	-137	-153; -121	-132	-149; -115	-166	-216; -116	0.15
Married vs. unmarried (0/1)	-123	-164; -83	-111	-153; -70	-291	-459; -123	0.01
Married vs. unknown marital status (0/1)	14	-82; 110	95	-34; 225	-73	-221; 75	
Maternal age (centred age 28 years[2])	8	7; 10	7	6; 9	13	9; 18	0.003
Year of birth 1937[3]	-12	-48; 26	-22	-62; 18	80	-19; 180	0.09
Year of birth 1938[3]	-36	-70; -2	-36	-73; 1	4	-89; 97	
Year of birth 1939[3]	-50	-82; -17	-57	-92; -23	21	-77; 120	
Year of birth 1940[3]	-74	-104; -43	-88	-120; -56	46	-53; 145	
Year of birth 1941[3]	-61	-88; -33	-72	-100; -44	55	-44; 153	
Year of birth 1942[3]	-31	-59; -3	-43	-73; -14	72	-20; 165	
Year of birth 1944[3]	-16	-43; 11	-21	-49; 7	39	-53; 131	
Cohort (0 = H, 1 = Å)	86	61; 112					

B: Regression coefficient; CI: Confidence interval; H: Helsinki; Å: Åland. [1]p-value represents significant F change between a model with and without the interaction term between birth cohort and the row's predictor variable. Only one p-value is presented for marital status, and year of birth, respectively, as these were added simultaneously. [2]Mean maternal age. [3]The year of birth dummy variables all had 1943 as the reference year.

6 DISCUSSION

6.1 Birth weight, body composition and resting metabolic rate

Birth weight was positively associated with fat-free mass (FFM) in both men and women and with fat mass (FM) in men. The most pronounced association between childhood growth and adult body composition was found for relative weight gain between age 11 years and adulthood. One SD of this conditional variable was associated with an estimated 4.1 kg (95% CI 3.9; 4.3) increase of FFM, 8.6 kg (95% CI 8.4; 8.7) increase of FM and 5.5 % (95% CI 5.3; 5.7) increase of body fat percent. Birth length and all measurements of linear growth, except for the interval between 2 and 11 years, were inversely associated with body fat percent. In men, the association between birth weight and resting metabolic rate (RMR) was quadratic, after adjustment for age, FFM and FM. In women, an inverse association was found between birth weight and RMR, after adjustment for age and FFM. This association lost significance after additional adjustment for FM.

A small number of previous studies have demonstrated an inverse association between birth weight and adult RMR (Sipola-Leppänen et al., 2011, Kensara et al., 2006, Eriksson et al., 2002, Weyer et al., 2000). In the studies by Eriksson et al and Sipola-Leppänen et al, RMR, expressed per unit of FFM, was higher in individuals with low birth weight, indicating that these have more metabolically active FFM. In healthy individuals, body mass does not influence specific internal organ metabolism (Later et al., 2008) suggesting that the relatively higher metabolic activity per unit FFM, described in the above studies, might be specific to the muscle mass compartment of the FFM. On the other hand, these findings could also be explained by a smaller amount of total muscle mass in individuals with low birth weight, leading to a larger relative contribution to RMR from more metabolically active compartments of FFM (i.e. internal organs) (Heymsfield et al., 2002).

In the present study, the associations between birth weight and RMR remained significant despite adjustment for FFM in both sexes, as well as after additional adjustment for FM in men, suggesting that the early life origins of resting metabolism are not solely mediated by adult body composition. A low birth weight is associated

with elevated plasma cortisol (Phillips et al., 2000) which might accordingly mediate the association between birth weight and RMR. Additionally, low birth weight has been linked to increased sympathetic tone (Ijzerman et al., 2003) which in turn has been linked to increased resting metabolism in non-obese, healthy adults (Monroe et al., 2001). Two small experimental studies (n = 9 and n = 8, respectively) in humans have demonstrated increased energy expenditure after administration of cortisol, and corticotropin-releasing hormone (CRH), respectively (Brillon et al., 1995, Smith et al., 2001). Although no previous study has demonstrated sex-specific differences in the associations between birth weight and resting metabolism, some studies have demonstrated that the developmental programming of the autonomic nervous system and the HPAA differs between men and women (Kajantie and Räikkönen, 2010). In their review, Kajantie and Räikkönen conclude that early developmental factors seem to be more strongly associated with autonomic nervous system reactivity in women, and with reactivity in peripheral vasculature, and potentially the HPAA, in men. This might in underlie our findings.

6.2 Childhood growth and NAFLD

Non-alcoholic fatty liver disease is the most prevalent cause of chronic liver disease in the Western world. It is closely associated with obesity, type 2 diabetes and the metabolic syndrome as well as with an increased overall mortality, due to liver-related disease and CVD (Musso et al., 2011). To our knowledge, this study represents the first study of the developmental origins of NAFLD in a large epidemiological setting.

NAFLD was defined according to the NAFLD liver fat score (Kotronen et al., 2009), an algorithm score including five readily available variables. NAFLD, which was present in 43% of the male and 20.5% of the female subjects, was inversely associated with several measurements of childhood body size between birth and age 11 years. Similar results were seen for liver fat content, calculated using the NAFLD liver fat equation. The most pronounced association with adult NAFLD was seen for individuals who were lean at 2 years of age and subsequently obese as adults. These had an OR of 18.5 (95% CI 10.1; 33.6) for NAFLD, compared to individuals who remained lean or normal weight in adulthood.

Previous studies featuring the current study population have revealed inverse associations between various measurements of childhood body size and the metabolic syndrome in both normal weight and obese individuals (Salonen et al., 2009a, Salonen et al., 2009b). Accordingly, our findings are expected, considering that NAFLD is a feature of the metabolic syndrome and that the metabolic syndrome, or features thereof, are included in the algorithm tests used to define NAFLD. The metabolic syndrome was present for 56.7% of the male participants, and for 49.5% of the female. This corresponds to findings from the 2007 Fin-D2D survey, featuring Finnish men and women aged 45–74 years, where the prevalence was 60.1% in men and 54.3% in women (Pajunen et al., 2011).

Three studies assessing the influence of childhood growth on later risk of developing NAFLD have recently been published, one from the Avon Longitudinal Study of Parents and Children (ALSPAC) study (Anderson et al., 2014), one from the Western Australian (Raine) cohort (Ayonrinde et al., 2015) and one from the PROGRAM study (Breij et al., 2014). In contrast to our findings, these studies demonstrated positive associations between various phases of early growth and NAFLD, as diagnosed by ultrasound or FLI. Importantly though, the participants of these studies were much younger than those included in the present study, with mean ages of 17.8, 17 and 20.9 years, respectively. Additionally, mean BMI at age 10.5–11.49 in the ALSPAC study was 18.3 kg/m^2 (SD 3.1) and 18.55 kg/m^2 (SD 3.16) in the Raine study compared to 16.9 kg/m^2 (SD 1.7) in the HBCS. These BMI values refer to all ALSPAC and Raine study participants, not only those included in the NAFLD analyses (Warrington et al., 2013). In the HBCS, childhood obesity was very rare. Only 3 boys and 30 girls in study II had BMIs at age 11 years corresponding to values ≥ 25 kg/m^2 (age specific cut-off points ≥ 20.55 kg/m^2 and ≥ 20.74 kg/m^2, respectively) (Cole et al., 2000). This most likely explains the inconsistencies between our findings and those of Andersson, Ayonrinde and Breij. Our main finding, that the highest prevalence of NAFLD was seen in those who were lean at age 2 years and subsequently obese in adulthood, supports the hypothesis that those who developed obesity and NAFLD in our cohort did so after age 11 years. In this group, the prevalence of NAFLD was 67.6% compared to only 3.5% among those who belonged to the largest BMI tertile at age 2 years and were lean or normal weight as adults.

The underlying mechanisms of the association between early growth and later NAFLD are poorly understood. Animal studies have demonstrated that both maternal undernutrition and overnutrition, as well as maternal obesity, are associated with NAFLD in the offspring (Hyatt et al., 2011, Bruce et al., 2009, Mouralidarane et al., 2013, Oben et al., 2010, Pruis et al., 2014). The influence of maternal obesity has also been demonstrated in human studies. Hepatic intracellular fat content, measured by MRI, was positively associated with maternal BMI in two studies of newborn infants (Brumbaugh et al., 2013, Modi et al., 2011). In a recent study from the epidemiological part of the 1934–44 HBCS (n = 13345), a higher maternal BMI during late pregnancy was associated with several disease outcomes in adulthood, most strongly so with type 2 diabetes and cardiovascular disease. (Eriksson et al., 2014). NAFLD, however, was not among the outcomes studied.

6.3 Fructose intake and NAFLD

A high dietary intake of fructose has been suggested to contribute to the development of NAFLD (Vos and Lavine, 2013). In our study, however, NAFLD was least prevalent in the highest quartile of fructose intake. In a model controlling for age, sex, smoking status, physical activity, and various nutrients, the odds ratio for FLI-defined NAFLD was 0.68 (95% CI 0.47; 0.97) in the highest quartile of fructose intake compared to the lowest.

Median fructose intake in the HBCS was 20 g/d. In comparison, fructose doses administered in the animal and human feeding studies that have linked fructose to NAFLD typically vary between 60 and 220 g/d. In our study, only 45 individuals had fructose intakes exceeding 60 g/d. This most likely explains the inconsistencies between our results and those of previous studies. Indeed, the hypothesis of an association between fructose and NAFLD has been called into question, as most previous studies have featured extreme levels of fructose exposure (Chiu et al., 2014). When comparing an isocaloric high-fat diet to an isocaloric high-carbohydrate, the prior increased liver fat content and insulin levels more than the latter (Pietinen et al., 2010). Another study, featuring healthy young men, showed that overfeeding with fat increased liver fat more than overfeeding with fructose (Sobrecases et al., 2010). The increase of intrahepatocellular lipids and liver enzymes seen in hypercaloric studies

might be confounded by, or be a result of, excessive energy intake rather than to the effects of fructose intake (Chiu et al., 2014, Chung et al., 2014).

The potential role of fructose in the pathogenesis of NAFLD is further influenced by its dietary source. A strong association between soft-drink consumption and NAFLD has been demonstrated in previous studies (Assy et al., 2008, Abid et al., 2009). In Finland, the main sources of fructose are table sugar, soft drinks and fruit. Although fructose intake was not separated by source in our study, the proportion of study participants who reported intake of fruit (not including fruit juices) was 54–80% compared to 0–8% for soft drinks (not including artificially sweetened soft drinks). Accordingly, it is possible that the potentially harmful effects of soft drink intake have been overshadowed by the beneficial effects of fruit intake, in our study.

6.4 Childhood growth and hypertension: amplification with age

Although several previous studies have explored the associations between childhood growth and adult hypertension, none have, to our knowledge, assessed whether these associations change over time in adult life. In our longitudinal study of 1036 men and women, examined at mean ages 61.5 and 66.4 years, respectively, we found that several measurements of childhood growth before age 11 years were inversely associated with adult systolic blood pressure at mean age 66.4 years. Some of these associations remained significant, despite adjustment for systolic blood pressure at mean age 61.5 years. Additionally, the presence of hypertension at mean age 66.4 years was inversely associated with linear growth between ages 2 and 11 years. In contrast to this, the only significant associations found with hypertension and systolic blood pressure at mean age 61.5 years were for birth measurements. Conditional relative weight gain between age 11 years and adulthood was positively associated with the presence of hypertension at mean age 61.5 years, as well as with systolic blood pressure at both clinic visits.

Contrary to our findings, previous studies have demonstrated positive associations between early childhood growth and later blood pressure. Importantly though, stronger associations were found for later rather than earlier growth. In a publication from the ALSPAC study, growth after age 17 months was more strongly associated with

systolic blood pressure at age 10 years than growth from birth until 17 months (Jones et al., 2012). A study from Chiolero et al demonstrated that systolic blood pressure at age 15.5 years was more strongly associated with weight change between ages 12.5–15.5 years than with weight change between ages 1 and 12.5 years indicating that blood pressure is most responsive to recent, rather than earlier changes in weight (Chiolero et al., 2012). In a Danish study (n = 1284) of men born 1936–1970, adult systolic blood pressure was more strongly affected by changes in relative body size after age 11 years, compared to changes in earlier childhood (Gamborg et al., 2009).

Whereas previous studies have primarily focused on young individuals, the HBCS consists of men and women born 1934–44 who were 56–70 years old at the time of the first clinical examination in 2001-04. Childhood obesity was very rare among participants in our study. Compared to current Finnish growth standards, the study participants were shorter than current mean attained adult height, 3.8 cm for men and 3.7 cm for women and additionally, shorter and leaner during childhood (Saari et al., 2011). Taking this into account, it is likely that a larger body size during childhood is an indirect sign of a beneficial childhood environment, rather than the early stages of obesity. Given that relative weight gain after the age of 11 years was positively associated with adult systolic blood pressure, it is furthermore likely that the trajectory towards obesity and related conditions began at a later stage for our study participants, compared to what has been demonstrated in more contemporary cohorts. This conclusion is also supported in studies I and II, where conditional relative weight gain after age 11 years was strongly associated with gains in fat mass and body fat percentage and the prevalence of NAFLD was highest among those who were small in early childhood and subsequently obese as adults.

Both conditional relative weight gain and linear growth between ages 2 and 11 years were inversely associated with systolic blood pressure as well as the dichotomous hypertension outcome at mean age 66.4 years, despite adjustment for previous systolic blood pressure as well as diastolic blood pressure, in the logistic regression analysis. No associations, however, were found between conditional growth and the outcome variables at the first clinic visit. Accordingly, it would seem that the beneficial effects of a more rapid than expected childhood growth in our cohort become increasingly apparent with age.

6.5 Regional differences in birth size

We analysed differences in birth size between the Åland Islands and Helsinki during the years 1937–44 as a first step in a potential future analysis of early life origins of Ålandic health. The Åland Islands have lower prevalence of several NCDs compared to the Finnish national mean and additionally one of the highest mean life expectancies in the Nordic countries (Terveyden ja hyvinvoinnin laitos (Finnish National Insititute for Health and Welfare), 2012, NOMESCO (Nordisk Medicinalstatistisk Komité), 2011). The average birth weight on the Åland Islands was 3499 grams (SD 508) and the average length at birth was 50.4 cm (SD 2.1), 87 grams (95% CI 62; 111) and 0.4 cm (95% CI 0.3; 0.5) more than in Helsinki, respectively.

The mean weighted estimate of the relative risk for CHD associated with a one kg increase of birth weight was reported as 0.83 (95% CI 0.80; 0.86) in a recently published meta-analysis (Wang et al., 2014b). The hazard ratio for all-cause mortality has been estimated to 0.94 (95% CI 0.92; 0.97) per kg of birth weight (Risnes et al., 2011). Applying these estimates, the 87 gram difference in birth weight between the Åland cohort and the HBCS would only correspond to a very small relative reduction in the prevalence of CHD and all-cause mortality. The estimated relative CHD risk and relative all-cause mortality hazard ratio would be 0.984 (95% CI 0.980; 0,987) and 0.995 (95% CI 0.993; 0.997), respectively.

In the 2012 report on regional health differences from the Finnish National Institute for Health and Welfare, the Åland Islands were ranked as Finland's healthiest region. This ranking was based on an age-standardized composite index of disease prevalence including seven disease categories which are weighed according to influence on mortality, health care costs, work disability, and quality of life. A higher score represents a higher morbidity and the national mean is set at 100. The Åland Islands received a composite score of 68.9 with significantly lower scores for five of seven disease categories compared to the national mean. In comparison, the Northern Savonia region, in Eastern Finland, received a composite score of 127, the highest in the country.

An indication that the Ålandic population's relative healthiness might have early life origins can be found in historical records. Anthropometric studies on men born on the Åland islands show that the Ålandic population historically have been taller than the mainland Finnish population and even among the tallest people worldwide (Arho, 1934, Sievers, 1927). The Åland population's mean increase in height between 1768 and 1968 was 8.4 cm compared to 4.7 cm for Eastern Finns and 6.0 cm for Western Finns (Eriksson AW, 1980). A beneficial intrauterine and postnatal environment is positively associated with adult height. which in turn is inversely associated with cardiovascular and all-cause mortality (Jousilahti et al., 2000). In 2005–2009, the mean life expectancy at birth was 79.7 years for men born on the Åland Islands, 3.2 years more than for men born in the rest of Finland. Women born on the Åland Islands had a mean life expectancy at birth of 83.1 years, the same as for the rest of the country. In a report from 2001–04, however, the mean life expectancy at birth of Ålandic women was 83.9 years, the highest in the Nordic countries.

No causal conclusions can be drawn from the reported difference in birth weight between the Åland Islands and Helsinki during the years 1937–44. However, our findings, along with historical records of anthropometric differences between the Ålandic population and mainland peers, suggest that a beneficial early life environment might have contributed to Ålandic health and longevity, meriting further studies.

6.6 Strengths and limitations

General considerations

The Helsinki Birth Cohort Study is a longitudinal study with a large sample-size consisting of 13345 individuals born 1934–44, 2003 of whom have taken part in a clinical study which commenced in 2001. 1083 of the study participants attended a follow-up at mean age 66.4 years, the most recent clinic visit included in this thesis (study IV). Since then, the participants have been followed up on additional occasions. Our data set includes detailed records of birth and childhood characteristics as well as an extensive collection of data recorded during the clinical study. The 1697 individuals

born on the Åland Islands between 1937 and 1944 (study V) represent 44% of all births on the islands during these years.

Given the long follow-up time, survivor bias might be a limitation in the HBCS. Only individuals who were alive in 1971, when all residents in Finland received a personal identification number, were included in the epidemiological study and only those still alive in 2001–04 were included in the clinical study. As a small size at birth is associated with premature mortality (Kajantie et al., 2005), the findings of all included studies might be attenuated by the fact that the least healthy individuals had already died before being eligible for inclusion.

Most of the study participants were either born or grew up during the Second World War which might influence the generalizability of our findings. In Helsinki, food shortages most likely influenced both maternal and offspring nutritional status. The Åland Islands, on the other hand, were mostly unaffected by the war (Rotkirch, 1986).

All HBCS participants were born in Helsinki and additionally attended child welfare clinics in the city. Accordingly, they might not be representative of the general population of Helsinki or Finland as a whole. However, the socioeconomic status at birth of the participants was comparable to the contemporary Helsinki population with roughly 60% of the fathers belonging to the labourer category (Salonen et al., 2009c, Rosen R, 1962).

Study-specific considerations

In study I, bioelectrical impedance analysis (BIA) was used in the assessment of body composition. Previous studies have demonstrated that BIA might underestimate body fat percentage, compared to DEXA, when studying men and women from various ethnic backgrounds (Gibson et al., 2008). Accordingly, it has been suggested that population-specific algorithms should be used when studying individuals of different ethnicity (Dehghan and Merchant, 2008, Aleman-Mateo et al., 2010). Given the homogenous ethnicity of the participants in the current study, the algorithms supplied by the manufacturer were used. It is possible that more precise results might have been attained with the use of population-specific algorithms but on the other hand, it is

unlikely that this inaccuracy would vary according to birth weight, suggesting that the main study findings are unaffected by this potential limitation. Furthermore, BIA is a suitable method for large epidemiological studies due to its ease and haste of use, compared to DEXA and other alternative methods of measuring body composition.

Studies II and III quantified liver fat content and defined the presence of NAFLD using algorithm tests. Although these are associated with a certain degree of diagnostic uncertainty, their facility of use make them more suitable for large epidemiological studies than more objective methods, e.g. liver biopsy and imaging techniques. Another potential limitation in studies II and III is related to the exclusion of individuals with daily alcohol intake in excess of 20 g/d based on FFQ data. The potential for underreporting of alcohol intake is a well known issue in questionnaires and interviews, suggesting that a number of individuals with fatty liver disease secondary to alcohol overconsumption might also have been included in the analysis. It is unlikely, however, that this would affect the main findings as there is no reason to believe that the tendency for underreporting would vary according to childhood growth trajectories or fructose intake.

The participants in study IV represent a relatively healthy subsample of the HBCS given that only individuals without type 2 diabetes at first clinic study were included in the follow-up. This might influence the generalizability of the findings. Furthermore, the analyses were based upon blood pressure measurements acquired at the clinic visits. As such, they might not fully reflect the participants' true resting blood pressure. On the other hand, there is no reason to believe that the participants' early growth would influence a potential over-estimation of resting blood pressure.

Data on gestational age was missing from the Åland records for all subjects. Without this information, it is not possible to determine whether a small size at birth is a result of intrauterine growth retardation, short gestation, or a combination of both. Furthermore, a majority of the Åland records lacked information on parity. Birth order is positively associated with birth weight (Swamy et al., 2012) making it a possible confounder for the observed differences in birth weight between the Åland Islands and Helsinki. Comparing all in-wedlock births for the years 1942, 1943 and 1943, a larger proportion were firstborn in the Uusimaa region (in which Helsinki is located)

compared to the Åland Islands, 50–58% and 32–39%, respectively (Central Statistical Office of Finland, 1946, Central Statistical Office of Finland, 1948, Central Statistical Office of Finland, 1943).

6.7 Implications of findings

In our cohort, relative weight gain after age 11 years, i.e. a faster weight gain than would have been expected based on previous body size, was associated with increase in fat mass, body fat percentage and adult systolic blood pressure. Additionally, the prevalence of NAFLD was highest among those who were lean at age 2 years and subsequently obese as adults. The participants were relatively lean and short in childhood which most likely explains inconsistencies with findings from more contemporary longitudinal studies, where growth during earlier periods are also associated with detrimental outcomes. Although the findings might not be directly applicable on children growing up in Finland and other Western countries today, they are still relevant for individuals reaching old age today. Additionally, the findings could potentially also be applicable in certain countries in the developing world, undergoing socioeconomic and nutritional transitions.

We did not find any support for the hypothesis that fructose intake is associated with NAFLD. Instead, those with the highest fructose intake were least likely to suffer from fatty liver according to the algorithm scores applied in the study. Given our results, it is unclear whether general advice to lower fructose intake would be beneficial without also taking the source of fructose into account.

6.8 Potential future studies

We are currently validating the FLI and the NAFLD liver fat score and equation in a small subset of women from the HBCS (n = 42) who have undergone MRS, either once or twice, as part of a study exploring the influence of maternal obesity on later health and frailty. Genome-wide association studies (GWAS) represent another attractive field of research. A recent publication from the Raine study identified specific short nucleotide polymorphisms (SNPs) associated with the presence of

NAFLD (Adams et al., 2013). A similar analysis in the HBCS would be of great interest.

Our findings regarding fructose intake and NAFLD merit further study. Our study was cross-sectional making it difficult to draw any conclusions in regards to causality. Population-based longitudinal studies are needed to further explore these findings.

The findings from study IV indicate that the associations between childhood growth and adult blood pressure become more apparent with increasing age. Follow-up studies are needed to verify this hypothesis.

Study V showed a small but significant difference in birth size between the Åland islands and Helsinki. Register linkage, similar to what has been performed in the HBCS, could offer further insight into the potential developmental origins of Ålandic health and longevity.

7 CONCLUSIONS

1. The association between birth weight and adult resting metabolic rate varies according to sex with an inverse association in women and a quadratic in men. Furthermore, we found that relative weight gain after age 11 years was strongly associated with body fat mass and percentage, whereas linear (height) growth in early childhood and after age 11 years was inversely associated with body fat percentage.

2. Individuals who were small at age 2 years and subsequently obese as adults were at the highest risk of NAFLD. Conversely, all measurements of childhood body size and growth up until age 11 years that achieved statistical significance were inversely associated with NAFLD.

3. Individuals with the highest fructose intake were significantly less likely to suffer from NAFLD. This association stayed significant despite adjustment for sex, age, smoking, physical activity, and intake of fat, alcohol, fiber, and vitamin E.

4. Relative weight gain and linear growth between ages 2 and 11 years were inversely associated with blood pressure at mean age 66.4 years, as well as the presence of hypertension for the latter growth measurement, despite adjustment for previous blood pressure.

5. Babies born on the Åland Islands during 1937–1944 were significantly heavier and taller than those born in Helsinki during the same time period.

8 ACKNOWLEDGEMENTS

This study was conducted at Folkhälsan Research Centre and at the Diabetes Prevention Unit of the Department of Chronic Disease Prevention at the National Institute for Health and Welfare. Many thanks to Professor Pekka Puska, Docent Markku Peltonen and Docent Jaana Lindström for providing excellent research facilities during my time at the Institute.

I would like to express the deepest gratitude to my supervisor Professor Johan Eriksson, whose enthusiasm, support, kindness and vast knowledge have been a great inspiration during my time as a doctoral student. I am impressed by, and very grateful for, Johan's availability – not many supervisors take the time to reply to e-mails from confused doctoral students at 9 pm in the evening. I am also deeply grateful to Docent Eero Kajantie for his valuable insights and support in the role of senior co-author and for his welcoming attitude to new members of the research group.

Warm thanks also go to my official reviewers, Adjunct Professor Harri Niinikoski and Professor Leo Niskanen for the smooth review process and for their helpful comments and suggestions which helped improve the thesis text. I am also grateful to Professor Tom Pettersson for accepting the role of Opponent at my thesis defence.

My deepest gratitude goes to the late Professor David Barker, who sadly passed away in August 2013, aged 75 years. It was indeed a great privilege for a young researcher to meet and work with the man whose early studies lay the foundation of the DOHaD research field. I am also deeply grateful to Professor Clive Osmond, whose kind personality, great expertise and pedagogical approach has helped me take bolder and bolder steps into the world of statistics.

I would also like to express my gratitude to the following:

All of the 13345 participants of the Helsinki Birth Cohort Study without whom none of this would have been possible.

All of my fellow researchers at Folkhälsan Research Centre, the Diabetes Prevention Unit and the Developmental Psychology Research Group. I am happy to have had the privilege of working with you. Thank you for your enthusiasm, passion for research, and for making an expatriate Swede feel welcome.

Study Nurses Paula Nyholm and Terttu Nopanen, both of whom I worked with during my time as study physician for the DORIAN study. Their knowledge, organized approach and great contact with the study participants made working together an absolute pleasure.

Sigrid Rosten, who in the role as data manager has been a great help, always able to answer any and all of my questions. Liisa Saarikoski and Pirjo Saastamoinen for all their help in various administrative issues.

Professors Aldur Eriksson and Johan Fellman for graciously allowing me access to their extensive material on births on the Åland Islands and Professor Peter Nilsson who, together with Professor Eriksson, originally suggested studying Ålandic health from a life-course perspective. Professor Eriksson sadly passed away this April, at the age of 88. I am grateful that I had the privilege of meeting and working with him.

Docent Petteri Hovi and Dr. Minna Salonen for their kind and welcoming personalities and all their help through the years, both relating to general research-related questions and in the case of Minna, in the role of co-author. It has been a privilege working together.

Drs. Paul Blomstedt and Elena Moltchanova for all your help in matters relating to statistical analysis, for great discussions regarding issues both within and outside the field of science, and for your friendship.

Drs. Niina Kaartinen, Noora Kanerva and Mia Perälä and Adjunct Professor Satu Männistö for their helpful insights and suggestions during the times my studies strayed into the field of nutritional science. A special thank you to Noora for her focused and extensive work with our fructose study, which I had the pleasure of co-authoring.

Professor Katri Räikkönen, Docents Sture Andersson, Jari Lahti and Anu-Katriina Pesonen, Drs. Marius Lahti, Silja Martikainen, Maiju Mikkonen, Riikka Pyhälä-Neuvonen, Katri Savolainen, Nadja Schreier and Soile Tuovinen for the many interesting discussions and experiences shared over the years, on meetings, during lunches and on congress trips.

Anna-Maija Luomi for language revision of the Finnish abstract.

My dear friends in Göteborg and Helsinki – thank you for your support and friendship.

My parents-in-law, Maria and Mikael Planting, for their enthusiasm over my research and my wife's grandfather, Clas Hagelstam, for many rewarding scientific discussions over the years.

My Mother Inga-Lisa, Father Jarl and Brother David – thank you for your support and love throughout my life. I am truly blessed to have grown up in a family in which the love of reading, exploring, discussing and learning has always been present.

Lastly, I would like to express my deepest gratitude to my family. Our beloved son Theodor, whose smiles, energy and enthusiasm brightens every day. My wife and best friend Bettina, without whose support, kindness and patience, none of this would have been possible. Thank you for believing in me. I love you.

The research project was funded by grants from the Academy of Finland, the British Heart Foundation, The EU FP7 DORIAN study, the Finnish Cultural Foundation, the Finnish Special Governmental Subsidy for Health Sciences, Finska Läkaresällskapet, the Juho Vainio Foundation, Liv och Hälsa, Samfundet Folkhälsan, the Signe and Ane Gyllenberg Foundation, the Foundation Stiftelsen Dorothea Olivia, Karl Walter och Jarl Walter Perkléns minne and the Wilhelm and Else Stockmann Foundation. All of these contributions are gratefully acknowledged.

Samuel Sandberg

Helsinki, August 2015

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