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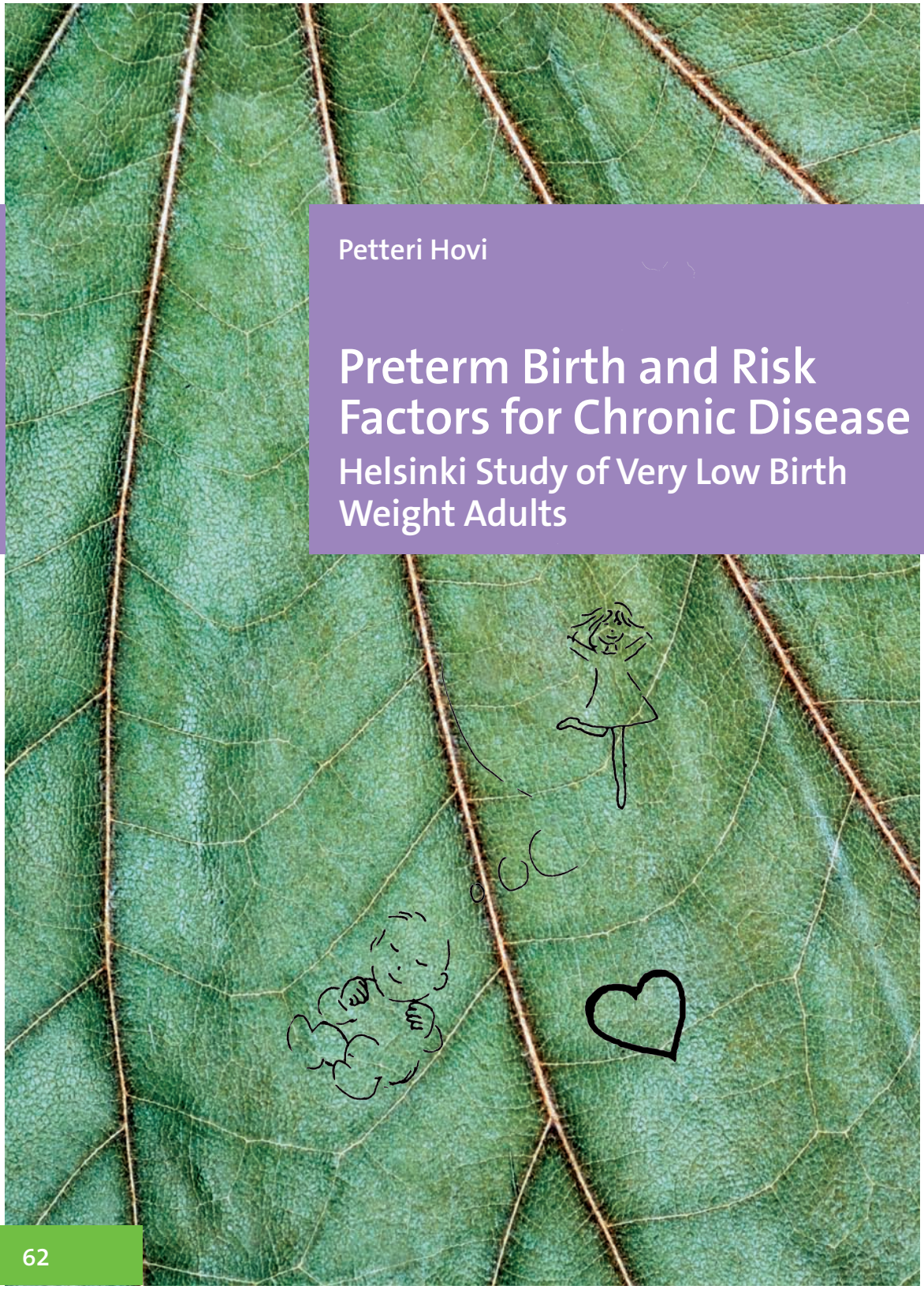

RESEARCH

Petteri Hovi

Preterm Birth and Risk Factors for Chronic Disease

Helsinki Study of Very Low Birth Weight Adults

62

From the Pediatric Graduate School and the Clinical Graduate School in Pediatrics and Obstetrics / Gynecology, Children's Hospital, University of Helsinki and Helsinki University Central Hospital

RESEARCH 62

Petteri Hovi

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Helsinki Study of Very Low Birth Weight Adults

ACADEMIC DISSERTATION

To be publicly discussed, with permission of the Faculty of Medicine, University of Helsinki, at Children's Hospital, Niilo Hallman Auditorium, on June 17th, 2011, at 12 noon.

University of Helsinki

National Institute for Health and Welfare, Helsinki
and the Children's Hospital, University of Helsinki
and Helsinki University Central Hospital, Helsinki

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Dedicated to my family

Summary

Petteri Hovi. Preterm Birth and Risk Factors for Chronic Disease. Helsinki Study of Very Low Birth Weight Adults. National Institute for Health and Welfare (THL), Research 62. 126 pages. Helsinki, Finland 2011.
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Background: The improved prognosis of early preterm birth has created a generation of surviving very low birth weight (< 1500 g, VLBW) infants whose health risks in adulthood are poorly known. Of every 1000 live-born infants in Finland, about 8 are born at VLBW. Variation in birth weight, even within the normal range, relates to considerable variation in the risk for several common adult disorders, including cardiovascular disease and osteoporosis. Small preterm infants frequently exhibit severe postnatal or prenatal growth retardation, or both. Much reason for concern thus exists, regarding adverse health effects in surviving small preterm infants' later lives. We studied young adults, aiming at exploring whether VLBW birth and postnatal events after such a birth are associated with higher levels of risk factors for cardiovascular disease or osteoporosis.

Subjects and Methods: A follow-up study for VLBW infants began in 1978; by the end of 1985, 335 VLBW survivors at Helsinki University Central Hospital participated in the follow-up. Their gestational ages ranged from 24 to 35 weeks, mean 29.2 and standard deviation 2.2 weeks. In 2004, we invited for a clinic visit 255 subjects, aged 18 to 27, who still lived in the greater Helsinki area. From the same birth hospitals, we also invited 314 term-born controls of similar age and sex. These two study groups underwent measurements of body size and composition, function of brachial arterial endothelium (flow-mediated dilatation, FMD) and carotid artery intima-media thickness (cIMT) by ultrasound. In addition, we measured plasma lipid concentrations, ambulatory blood pressure, fasting insulin, glucose tolerance and, by dual-energy x-ray densitometry, bone-mineral density.

Results: 172 control and 166 VLBW participants underwent lipid measurements and a glucose tolerance test. VLBW adults' fasting insulin (adjusted for body mass index) was 12.6% (95% confidence interval, 0.8 to 25.8) higher than that of the controls. The glucose and insulin concentrations 120 minutes after 75 g glucose ingestion showed similar differences (N=332) (I).

VLBW adults had 3.9 mmHg (1.3 to 6.4) higher office systolic blood pressure, 3.5 mmHg (1.7 to 5.2) higher office diastolic blood pressure (I), and, when adjusted for body mass index and height, 3.1 mmHg (0.5 to 5.5) higher 24-hour mean systolic blood pressure (N=238) (II).

VLBW birth was associated neither with HDL- or total cholesterol nor triglyceride concentrations (N=332) (I), nor was it associated with a low FMD or a high cIMT (N=160) (III).

VLBW adults had 0.51-unit (0.28 to 0.75) lower lumbar spine Z scores and 0.56-unit (0.34 to 0.78) lower femoral neck Z scores (N=283). Adjustments for size attenuated the differences, but only partially (IV).

Conclusions: These results imply that those born at VLBW, although mostly healthy as young adults, already bear several risk factors for chronic adult disease. The significantly higher fasting insulin level in adults with VLBW suggests increased insulin resistance. The higher blood pressure in young adults born at VLBW may indicate they later are at risk for hypertension, although their unaffected endothelial function may be evidence for some form of protection from cardiovascular disease. Lower bone mineral density around the age of peak bone mass may suggest increased risk for later osteoporotic fractures.

Because cardiovascular disease and osteoporosis are frequent, and their prevention is relatively cheap and safe, one should focus on prevention now. When initiated early, preventive measures are likely to have sufficient time to be effective in preventing or postponing the onset of chronic disease.

Keywords

Infant, Very low birth weight; Infant, newborn; Infant, premature; Adolescent; Adult; Young adult; Infant, small for gestational age; Finland; Socioeconomic factors; Cohort studies; Case-control studies; Follow-up studies; Blood glucose; Glucose tolerance test; Insulin; Lipids; Blood pressure; Blood pressure monitoring, Ambulatory; Hypertension; Glucose metabolism disorders; Brachial artery reactivity; Carotid intima-media thickness; Elasticity; Bone density; Cardiovascular risk factors

Tiivistelmä

Petteri Hovi. Preterm Birth and Risk Factors for Chronic Disease. Helsinki Study of Very Low Birth Weight Adults [Ennenaikainen syntymä ja pitkäaikaissairauksien riskitekijät. Pikkukeskosen terveys aikuisiässä -tutkimus]. Terveyden ja hyvinvoinnin laitos (THL), Tutkimus 62. 126 sivua. Helsinki 2011.
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Taustaa: Suomessa noin 6 % ikäluokasta syntyy keskosena (< 2500 g) ja noin 1 % pienenä keskosena (< 1500 g). Ensimmäiset nykyaikaisen tehohoidon ansiosta selvinneet pienten keskosten sukupolvet ovat nyt tulossa aikuisikään. Tavalliset sairaudet, kuten sydän- ja verisuonitaudit ja osteoporoosi, ovat yhteydessä alhaisempaan syntymäpainoon; tutkimukset on tehty pääosin täysiaikaisena syntyneiden joukossa. Ennenaikainen syntymä merkitsee kohdunsisäiseen kasvamiseen verrattuna voimakkaasti poikkeavia olosuhteita; kasvuhäiriötä ennen ja jälkeen syntymän ja infektiosairauksia imeväisiässä. On mahdollista, että pieniä keskosia odottavat merkittävät terveysuhkat heidän aikuistuessaan. Tämän tutkimuksen tavoitteena on tutkia pienten keskosten terveyttä keskittyen sydän- ja verisuonitautien ja osteoporoosin vaaratekijöihin.

Aineisto ja menetelmät: Pienten keskosten seurantatutkimus aloitettiin HYKS:n Lastenklinikalla vuonna 1978. Vuoden 1985 loppuun mennessä seurantaan oli otettu 335 henkiin jäänyttä pientä keskosta. Raskausviikkojen lukumäärä vaihteli 24 ja 35 välillä, keskiarvo oli 29,2 ja keskipoikkeama 2,2 viikkoa. Kutsuimme tutkimuskäynnille nuoreen aikuisikään päässeistä pikkukeskosista 255, jotka asuivat Helsingin tuntumassa. Tutkittavien ikä oli 18 ja 27 vuoden välillä. Kutsuimme myös 314 täysiaikaisena syntynyttä verrokkia, jotka olivat samaan aikaan samassa sairaalassa syntyneitä ja olivat samaa sukupuolta. Joihinkin tutkimuksiin pyysimme vain osan tutkittavista. Mittasimme 332 tutkittavalta verenpaineen, painon, pituuden, sekä plasman HDL- ja totaalikolesterolin. Lisäksi teimme 75 gramman glukoosirasituksen paastotilanteen ja kahden tunnin glukoosi- ja insuliininäyttein. Mittasimme 24 tunnin keskiverenpaineen 238:lta ja luun mineraalitiheyden ja 284:lta kehon koostumuksen kaksienergiaisella röntgenabsorptiometrialla. Sadaltakuudeltakymmeneltä arvioimme ultraäänellä olkavarren valtimon endoteelin toiminnan (flow-mediated dilatation, FMD) ja kaulavaltimon intimamediakerroksen paksuuden.

Tulokset: Glukoosirasituksessa ja lipidien mittauksessa kävi 166 entistä pikkukeskosta ja 172 verrokkia. Havaitsimme, että pieninä keskosina syntyneillä nuorilla aikuisilla oli verrokkeihin nähden 12,6 % korkeampi paastoinsuliini, (95 % luot-

tamusväli, 0,8–25,8) ja myös heikompi glukoosinsieto. Pienten keskosten tutkimuskäynnillä mitattu systolinen verenpaine oli 3,9 mmHg korkeampi (1,3–6,4) ja diastolinen paine 3,5 mmHg (1,7–5,2) korkeampi. Vuorokausiseurannan keskimääräinen systolinen paine oli myös korkeampi entisillä pienillä keskosilla: painoindeksillä ja pituudella vakioituna ero oli 3,1 mmHg (0,5–5,5). Kolesteroleissa, triglyserideissä, endoteelifunktiossa tai intimamediapaksuudessa ei ollut eroa.

Pikkukeskosilla oli 0,51 yksikköä alhaisempi lannerangan Z-arvo (95 % luottamusväli, 0,28 – 0,75) ja 0,56 yksikköä alhaisempi reisiluun kaulan Z-arvo (0,34–0,78).

Johtopäätökset: Pienet keskoset ovat enimmäkseen terveitä nuorena aikuisena, mutta tutkimuksemme osoittaa heillä olevan kroonisten sairauksien riskistekijöitä. Korkeampi paastoinsuliinipitoisuus on merkki korkeammasta insuliiniresistenssistä. Nyt havaittu normaali, mutta verrokkeihin nähden korkeampi verenpaine voi olla merkki verenpainetautiriskistä, mutta verrokkeihin nähden yhtä hyvä valtimoendoteelin toiminta puhuu lisääntynyttä sydän- ja verisuonitautiriskiä vastaan. Alhainen luustontiheys iässä, jolloin sen pitäisi olla huipussaan, voi olla merkki luukadosta johtuvien luunmurtumien vaarasta. Koska tutkimamme sairaudet ovat yleisiä ja koska niiden ennaltaehkäisy on halpaa ja turvallista, nyt on otollinen aika ennaltaehkäisyn ja sen vaikutusten tutkimisen aloittamiselle. Varhainen aloitus parantaa ennaltaehkäisyn tuloksia.

Avainsanat

Pienet keskoset; Imeväiset; Vastasyntyneet; Nuori, Nuori aikuinen, Pienet vastasyntyneet; Suomi; Sosioekonomiset tekijät; Kohorttitutkimukset; Tapausverrokkitutkimukset; Seurantatutkimukset; Verensokeri; Glukoosirasituskoe; Insuliini; Lipidit; Verenpaine; Verenpaineen pitkäaikaisseuranta; Verenpainetauti; Glukoosiaineenvaihdunnan häiriöt; Olkavarsivaltimon reaktiviteetti; Kaulavaltimot, sisäkalvo, keskikalvo; Kimmoisuus; Luuntiheys; Sydän- ja verisuonitautien riskitekijät

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Original publications

This thesis is based on four original publications; they are referred to by Roman numerals.

I **Glucose regulation in young adults with very low birth weight**
Petteri Hovi, Sture Andersson, Johan G Eriksson, Anna-Liisa Järvenpää, Sonja Strang-Karlsson, Outi Mäkitie, and Eero Kajantie.
New England Journal of Medicine, 2007; 356(20): 2053-2063.

II **Ambulatory blood pressure in young adults with very low birth weight**
Petteri Hovi, Sture Andersson, Katri Räikkönen, Sonja Strang-Karlsson, Anna-Liisa Järvenpää, Johan G Eriksson, Anu-Katriina Pesonen, Kati Heinonen, Riikka Pyhälä-Neuvonen, and Eero Kajantie.
Journal of Pediatrics, 2010; 156(1): 54-59.

III **Intima-media thickness and flow-mediated dilatation in the Helsinki Study of Very Low Birth Weight Adults**
Petteri Hovi, Maila Turanlahti, Sonja Strang-Karlsson, Karoliina Wehkalampi, Anna-Liisa Järvenpää, Johan G Eriksson, Eero Kajantie, and Sture Andersson.
Pediatrics 2011; 127(2): e304-311. [Erratum appears in Pediatrics 2011; 127(3): 599].

IV **Decreased bone mineral density in adults born with very low birth weight:A cohort study**
Petteri Hovi, Sture Andersson, Anna-Liisa Järvenpää, Johan G. Eriksson, Sonja Strang-Karlsson, Eero Kajantie, and Outi Mäkitie.
PLoS Medicine 2009; 6(8):e1000135.

Abbreviations

ADA	American Diabetes Association
AGA	Appropriate for gestational age
BMAD	Bone mineral apparent density
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BPD	Bronchopulmonary dysplasia
BW	Birth weight
CI	Confidence interval
CP	Cerebral palsy
CV	Coefficient of variance
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DOHaD	Developmental origins of health and disease
DXA	Dual X-ray absorptiometry
E_{inc}	Incremental elastic modulus
FMD	Flow-mediated dilatation
GA	Gestational age
HbA1C%	Glycosylated hemoglobin
HOMA-IR	Homeostasis model assessment insulin-resistance index
HR	Hazard ratio
HeSVA	Helsinki Study of Very Low Birth Weight Adults
IMT	Intima-media thickness
LGA	Large for gestational age
NICU	Neonatal intensive care unit
ROP	Retinopathy of prematurity
SBP	Systolic blood pressure
SD	Standard deviation
SDS	Standard deviation score
SES	Socio-economic status
SGA	Small for gestational age
VLBW	Very low birth weight
VLGA	Very low gestational age
WHO	World Health Organization

Introduction

Unfavourable inherited characteristics and unhealthy life-style result in an increased risk for chronic disease. However, various paths leading to osteoporosis or cardiovascular disease have their origins in early circumstances during fetal life. Such an idea of early circumstances affecting long-term health gained emphasis a few decades ago (Barker 1994, 1995). Since then, research in a multitude of settings in different parts of the world has provided evidence of an inverse relationship between birth weight and later cardiovascular disease. The epidemiology of osteoporosis shows similar findings.

Later, in various species, experiments including low-energy or low-protein diets for pregnant dams or partial cessation of blood supply to the pregnant dam uteri induced long-term health effects, including obesity, diabetes, and hypertension (McMillen and Robinson 2005). Interventions in animals were originally aimed at mimicking intrauterine circumstances encountered by human infants in the epidemiological studies. These infants were born at a low birth weight, mostly at term. However, those interventions actually might better mimic the extrauterine life of preterm infants; or more specifically, the life of very low birth weight (VLBW, < 1500 g) infants. Recent findings show that VLBW birth associates with increased risk for a higher blood pressure and higher insulin resistance. The overall risk-factor status for cardiovascular disease and osteoporosis in young adults born at VLBW is, however, unknown.

Development of perinatal care in recent decades has improved the prognosis of VLBW infants markedly. This thesis presents results regarding the health of adults belonging to the first surviving VLBW generation. Note that the literature review, however, also includes risk factor data on those born preterm but not at VLBW. The thesis focuses on risk factors for cardiovascular disease and osteoporosis.

1 Review of the literature

1.1 Long-term consequences of severely preterm birth

Definitions and epidemiology

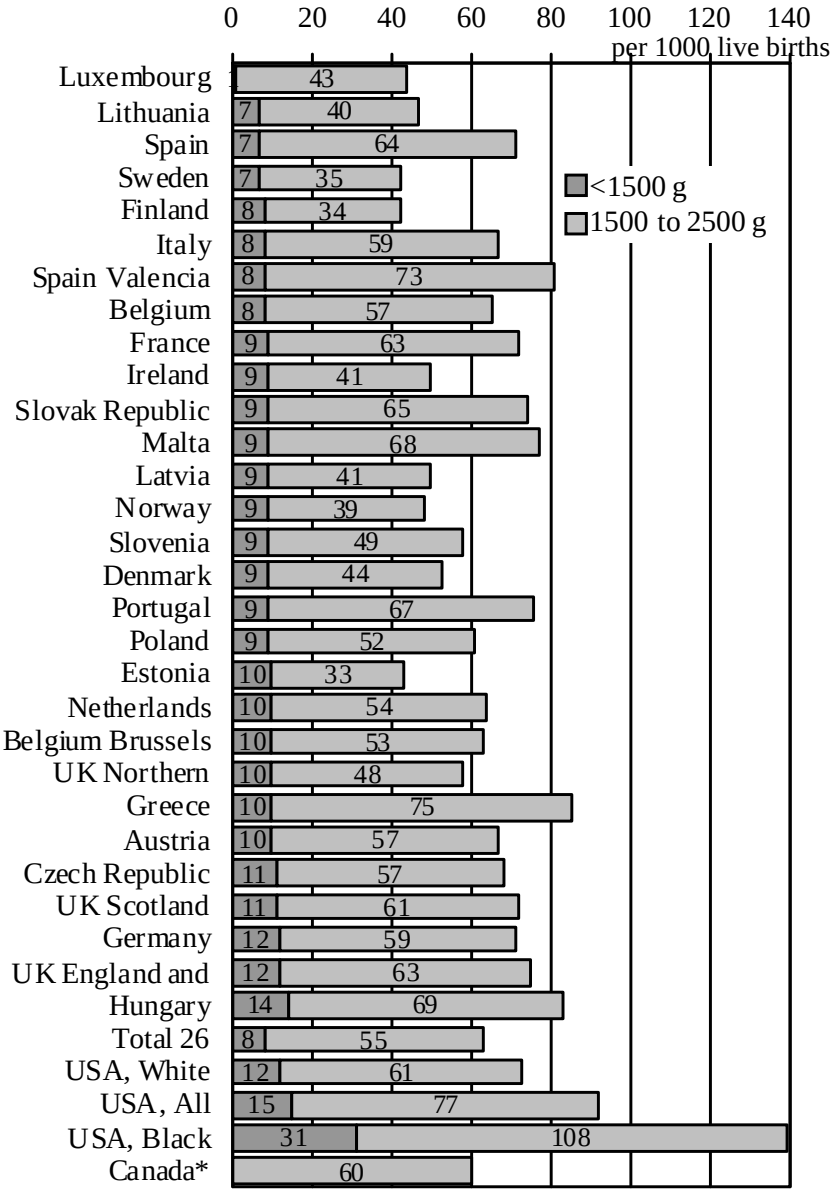
In Finland, 56 neonates per thousand live-born infants are born preterm: before completing 37 gestational weeks. In most European countries, the proportion of preterm births is the same or slightly higher, whereas in the US it is considerably higher, 127, and in South Africa, 175 (Euro-Peristat 2008; National Center for Health Statistics 2008a; Beck et al. 2010). The financial burden arising from preterm birth is marked. Average first-year medical cost for a preterm baby was $32,000 in the US in 2005, whereas cost for a baby born at term was $3,300 (National Center for Health Statistics 2008a). Of all neonatal mortality, preterm birth accounts for 28% world-wide and in Europe for 44%. This translates to 116,000 annual deaths or about 4 deaths per thousand live births in Europe in 2000 (World Health Organization 2005). The probability of surviving and being healthy decreases with decreasing gestational age (GA) and with decreasing birth weight (BW). Estimation of GA according to date of last menstruation has its limits. Both GA and BW are valid and reliable proxies of maturity at birth and are in common use for categorizing preterm infants. The aforementioned sources utilize the following definitions:

Neonatal period	Postnatal days 0 to 27
Preterm birth	Gestational age less than 37 weeks
Very low gestational age (VLGA)	Gestational age less than 32 weeks
Very low birth weight (VLBW)	Birth weight less than 1500 g
Small for gestational age (SGA)	Birth weight standard deviation score (SDS) less than -2.0*
Appropriate for gestational age (AGA)	Birth weight SDS from -2.0 to +2.0*
Large for gestational age (LGA)	Birth weight SDS above +2.0*

*10th and 90th percentiles are alternative limits for SGA/AGA/LGA.

Especially before the era of ultrasound's being widely used during pregnancy, BW limits were preferred, and VLBW infants served as the group of specific interest. In contrast, inclusion in more recent studies is often determined by GA. VLGA defines a group with gestational age less than 32 weeks, and this group largely overlaps with

Figure 1. Number of infants at birth weight under 1500 g and under 2500 g.



* Population data from Canada on VLBW births are not available.

Modified, with permission, from European Perinatal Health Report (Euro-Peristat 2008) with additional data form North America (National Center for Health Statistics 2007; Public Health Agency of Canada 2008).

a group with VLBW: Of all VLBW infants, 87% were born at a VLGA as well. On the other hand, of those born at VLGA, 79% were also VLBW (National Institute for Health and Welfare 2009). Despite this overlap, comparison of either VLBW or VLGA subjects with term born subjects answers, of course, different questions: A VLGA vs. term group comparison measures more purely the effect of immaturity at birth, whereas a VLBW vs. term group comparison measures the mixed effect of immaturity and growth failure. Later parts of this review attempt to cover studies with VLBW as well as those with VLGA participants, whereas study questions were formulated to fit an existing VLBW study. Many of the reports on elderly people only include data stratified by preterm/term delivery without more detailed analysis of degree of immaturity. Therefore, when it comes to questions requiring an already completed follow-up until old age, parts of this review focus on the whole range of preterm birth.

VLBW birth currently occurs in 8 per thousand live births in Finland. In other European countries, the rate of VLBW births is the same or slightly higher (Figure 1), and in the US it is 15 (Euro-Peristat 2008; National Center for Health Statistics 2008b). That aetiology and risk factors for VLBW delivery are numerous (Table 1) complicates the interpretation of data from VLBW follow-up studies. Another challenge for data interpretation is selection by survival, which varies by time and location. Survival of VLBW infants has markedly improved (Figure 2) with between-country variation in mortality and in the history of its development. Some of this may be explained by financial input into education, women's empowerment, wealth and environment, but especially into the health care system (World Health Organization 2005). Regarding the Finnish health care system during the 1970's, more efforts were made to improve survival and long-term health by introducing intensive care for VLBW infants. This thesis is based on VLBW infants who received treatment at the neonatal intensive care unit (NICU) at the Helsinki University Central Hospital. During 1978 and 1979, overall 6-year mortality of infants treated in that unit was 24% for those with birth weight 1001 to 1500 g and 44% for those weighing 1000 g or less, and 89% of deaths occurred in the neonatal period (Järvenpää and Granström 1987). Neonatal mortality of VLBW infants in the late 1970's in the Helsinki area was thus close to that in the USA (Figure 2).

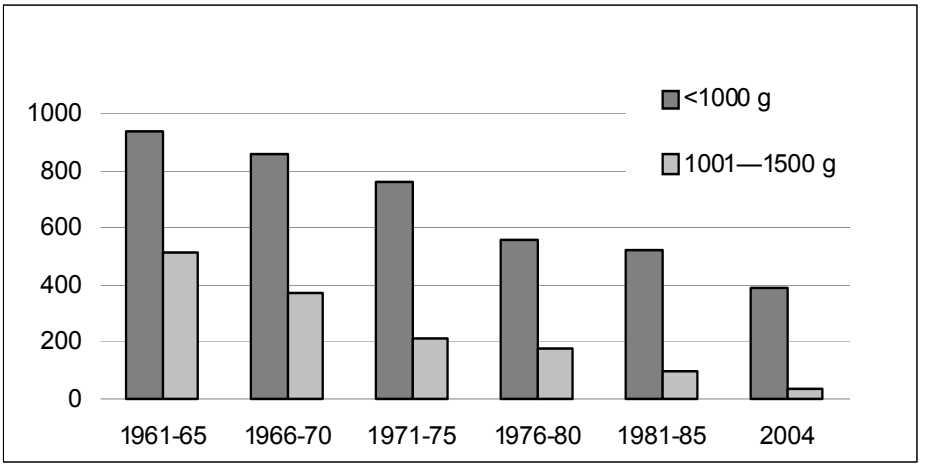
During the three most recent decades, a gradual decrease in neonatal mortality has continued: in Finland, the number of neonatal deaths per live-born infants in 2004 at birth weights from 1000 to 1500 g was 11/269 (4.1%) and for those under 1000 g, 66/175 (38%) (National Research and Development Centre for Welfare and Health, Finland (STAKES) 2005; Euro-Peristat 2008). Apparently, similarity with values in the USA persists (Figure 2).

Table 1. Risk factors for VLBW/VLGA birth (< 1500 g or < 32 weeks) or preterm (< 37 weeks) birth, as presented in the literature.

Risk factors for VLBW or VLGA birth*	Risk factors for preterm birth
History of preterm delivery	All those in the left column plus
Smoking	Multiple gestations
Low socioeconomic status based on occupation	Psychosocial stress
	Afro-American race
Maternal or paternal unemployment	Poor access to prenatal care
Single-room residence	Poor weight gain during pregnancy
Short stature	Physically constraining work
First pregnancy	Anaemia
Age < 20 or ≥ 35	Bacterial vaginosis
Previous abortions	Bacteriuria
Unmarried	Pyelonephritis
Parents not cohabiting	Low prepregnancy weight
Infections	

(Ancel et al. 1999; Grimmer et al. 2002; Lockwood 2002; Scott et al. 2003; Kyrklund-Blomberg et al. 2005; Morken et al. 2005; Muglia and Katz 2010)
*Note that all risk factors in the right column may also apply to the left column despite lack of published data

Figure 2. Neonatal death rates per 1000 live births in the USA



Data from US Congress and Office of Technology Assessment (1987). Data for the year 2004 from Mathews and MacDorman (2007).

Evolution of neonatal care for VLBW/VLGA infants

Perinatal death is obviously the first concern regarding an imminent preterm delivery. Other concerns, however, exist. Stewart et al. wrote (1981) that perinatal care of VLBW/VLGA infants had been evolving in phases: (i) The period before mortality reduction, occurring in the western industrialized countries during the 1940's and 1950's; (ii) Period of increasing knowledge of neonatal diseases and their treatment, during the late 1950's and early 1960's; (iii) Period of improvement of healthy survival, from the early 1960's onward; and finally, (iv) Period of increasing diagnostic and prophylactic skills. The goals for modern perinatal care of VLBW/VLGA infants could be stated as

1. Short-term survival
2. Healthy survival
3. Long-term survival and integration into society

The follow-up studies initiated in the 1970's and 80's reported improving survival (US Congress and Office of Technology Assessment 1987; Lee et al. 1995; Philip 2005). Mortality rates of VLBW/VLGA infants decreased rapidly, probably because of improved technologies reducing the volume needed for crucial blood samples, improved intravenous nutrition, mechanical ventilation, and enhanced phototherapy. Unfortunately, due to a constant proportion of various handicaps typical of VLBW/VLGA children, the absolute numbers of surviving handicapped children increased.

Then perinatal therapy developed further, improving healthy survival, and success in the second goal, began to approach: in a meta-analysis of 106 follow-up studies of VLBW and other severely preterm infants (Escobar et al. 1991), 49 of these studies with more than 24 months of follow-up, reported a decrease in prevalence of any disabilities from around 30% in the period 1960 to 1977 to 21% from 1978 to 1986. Prevalence of cerebral palsy (CP), however, remained persistently at 8%. In Turku, Finland, recent data from the Pipari Study Group describe a regional cohort of 182 VLBW infants born between 2001 and 2006 and assessed at the age of 2 years: only 10% had neurodevelopmental impairments, whereas CP prevalence was as high as 7.1% (Münck et al. 2010). A European VLBW-database study, including live births in 16 centres in 9 countries, expressed a decreasing trend for CP prevalence as well; it dropped from 6.1% in 1980 to 4.0% in 1996 (Platt et al. 2007).

Long-term survival and integration into society, the third goal, includes improving physical and mental conditions and reducing long-term morbidity and mortality. This should facilitate development of independence and full membership of society during the first few decades of life. A health status forecast for the middle-aged and elderly VLBW subjects is the main focus of this thesis. In general,

early life events – those emerging during fetal life, infancy, and childhood – can have permanent long-term consequences and lead to disease in adulthood. This research area began attracting increasing interest because of the work by David Barker (1994, 1995). Currently, this area is referred to as the Developmental Origins of Health and Disease (DOHaD, see the DOHaD Society's website at www.dohadsoc.org).

The Developmental Origins of Health and Disease theory

A widely accepted idea within many human sciences including psychology is that circumstances and phenomena early in life may have sequelae in adulthood. These early phenomena must to occur in one specific period, a "time window". "The figures behave as if the expectation of life [mortality] was determined by the conditions which existed during the child's earlier years" (Kermack et al. 1934). This quote is from a *Lancet* article showing that relative mortality in the UK was more dependent on the decade of birth than on the decade of death. The authors proposed that, rather than present circumstances, it was the early circumstances that explained mortality in the present. Infant mortality rate served as an indicator of those early circumstances. In Northern Norway, county infant mortality from 1896 to 1925 was associated with coronary heart disease mortality in that county 40 to 69 years later (correlation coefficient 0.61 for women and 0.79 for men) (Forsdahl 1977). A further analysis tested which period for infant mortality would best correlate with mortality. By shifting the period from around the time of birth towards older age, the correlation gradually tapered off, although still reaching 0.26 at age 60 to 69. The author speculated: "Some form of permanent damage caused by a nutritional deficit may be involved" (Forsdahl 1977).

A long time ago, nutritional manipulation during fetal life showed considerable late effects; experience came from farm animals and, from scientific experiments. For example, one study aimed at efficient production of marketable mutton (Curll et al. 1975). More recent experiments in sheep and in other species have supported the idea of long lasting health consequences of interventions during pregnancy; this area has been extensively reviewed (McMillen and Robinson 2005; Nuyt 2008). These experiments have applied various interventions to cause late unhealthy effects and often a low offspring birth weight as well (Table 2).

David Barker and his colleagues (1994, 1995) applied such epidemiologic and animal data to human medicine. Their message was that poor nutrition and poor health in girls and women lead to permanent changes in their children's fetal physiology and metabolism and subsequently to diseases such as coronary heart disease and stroke. The fetal environment in large historical birth cohorts was measured by means of proxies such as birth weight. These and subsequent studies showed that those who are small or thin at birth have, as adults, higher

cardiovascular disease incidence and mortality (Barker et al. 1989; Osmond et al. 1993; Forsén et al. 1997; Rich-Edwards et al. 1997). They had higher blood pressure and increased rates of hypertension (Barker and Osmond 1988; Barker 1992; Huxley et al. 2000; Järvelin et al. 2004; Mzayek et al. 2004; Johansson et al. 2005; Eriksson et al. 2007) and impaired glucose regulation as well (Hales et al. 1991; Robinson et al. 1992; Barker et al. 2002). For a wider view of the DOHaD research field, excellent reviews are available, including valuable epidemiological and experimental data (Hales and Barker 2001; McMillen and Robinson 2005; Gluckman et al. 2008; Whincup et al. 2008).

Table 2. Typical models of animal research in the area of Developmental Origins of Health and Disease –area.

Interventions in utero, time from preconception to weaning
Energy restriction
Protein restriction
Uterine artery ligation
Glucocorticoid exposure
Combination of intrauterine nutrient restriction and extrauterine overnutrition
Later life outcomes
High blood pressure
Lower nephron number
High blood glucose
Low beta-cell mass
Increased insulin resistance

(Symonds and Gardner 2006; Nuyt 2008; Simmons 2009)

Gluckman and Hanson (2005) further developed the "Barker hypothesis" or the idea of "programming", and introduced the term "induced phenotype". In their explanatory model, a pregnant mother transfers environmental information to her fetus, which then adapts to be as prepared as possible for postnatal life. Such adaptation can be advantageous when occurring but later can prove hazardous. Hanson and Gluckman extended their explanatory argumentation into evolutionary aspects. An ability to adapt in utero is advantageous for a species. For example, increased risk for cardiovascular disease much later is a low price for improving short-term survival.

In humans, any trials limiting nutrition or oxygen supply to a fetus are unethical. During World War II, parts of the Netherlands experienced, however, a short period of extremely limited food supply, and a number of studies on the health of their offspring demonstrate the effects of nutrient depletion during the three trimesters of pregnancy, as summarized by Roseboom et al. (2006). Although neither blood

pressure (Roseboom et al. 1999) nor carotid artery compliance in adulthood (Painter et al. 2007) was affected by any period of fetal exposure, exposure in early gestation was linked to a greater increase in blood pressure in a standardized social stress test (Painter et al. 2006). Early gestation exposure was also linked to a preference for fatty foods (Lussana et al. 2008), and to higher LDL:HDL cholesterol ratios (Roseboom et al. 2000a) and, most importantly, to coronary heart disease (Roseboom et al. 2000b). Exposure in mid-gestation was associated with microalbuminuria (Painter et al. 2005). Exposure in any trimester was associated with glucose intolerance (Ravelli et al. 1998; de Rooij et al. 2006).

Among other studies on famine exposure, one has a relatively novel approach: At a marketplace in Nigeria in 2009, a mainly Swedish research group contacted and thereafter evaluated 1,399 adults (Hult et al. 2010). As an early-exposure group, they defined those who had experienced the disastrous famine of the Biafran war (1968 to 1970) either during fetal life or during infancy. As compared to those who were children during the famine or who then had not yet been born, the exposed had about 50% increased odds for overweight and for impaired glucose tolerance (plasma glucose 7.8 to 11.0 mmol/l), and had a 7 mmHg higher systolic pressure and three-fold higher odds for hypertension.

Could recall bias, publication bias, or socioeconomic confounding explain these findings? Although critical arguments against the DOHaD hypothesis do exist (Kramer and Joseph 1996; Huxley et al. 2002; Huxley 2006), the idea of long-term consequences of being born at a low weight is now widely accepted as seen in paediatric textbooks and world-wide action policies (National Institute of Child Health and Development 2003; The United Nations Children's Fund and World Health Organization 2004; World Health Organization 2006; McMillan et al. 2006; European Commission 2007).

DOHaD in preterm infants

Gluckman and Hanson (2005) propose preterm birth to be itself a form of adaptation. Although mainly concentrating on aspects concerning the whole range of birth weights in the population, and mostly on term births, they cover preterm infants as well with their mechanistic approach: Prenatal influences such as poor nutrition or redistribution of blood supply may induce a phenotype vulnerable to later disease (quite similarly to term infants who are thin or small). Postnatal influences, including a suboptimal supply of protein and energy and an altered hormonal milieu, may also contribute to disease risk. For additional potential inductors of a vulnerable later phenotype in former VLBW infants see Figure 3. Some of these inductors, in fact, resemble interventions and exposures in experimental research, although those typically were initially aimed at explaining epidemiological findings in mostly term-born populations (Table 2).

1.2 Cardiovascular disease and osteoporosis as major causes of death and disability

The DOHaD idea originated from the field of cardiovascular disease but now includes a wide range of diseases attracting large-scale multidisciplinary research activity. All these areas may be relevant to VLBW/VLGA subjects. This thesis, however, focuses only on risk factors for cardiovascular disease and osteoporosis (Figure 3). These diseases show a high incidence and high significance in most populations, they are responsive to prevention, and their risk factors are well known.

Cardiovascular disease

For the purposes of this thesis, a suitable definition for cardiovascular disease includes:

1. Ischaemic heart disease
2. Cardiac failure
3. Peripheral arterial disease
4. Stroke

Of the 56 million deaths world wide in 2001, cerebrovascular disease and ischemic heart disease accounted for 10.3 million, making cardiovascular disease one of the four major causes of death in various settings (Lopez et al. 2006).

Risk factors for cardiovascular disease tend to cluster, and the metabolic syndrome is a combination of all these factors. Its exact definition varies depending on the intended purpose of the term (Alberti et al. 2005, 2009; Grundy et al. 2005). In this thesis, the main components of the metabolic syndrome serve as the main outcomes:

1. Abnormal adiposity
2. Lipid disturbances
3. Impaired glucose regulation
4. High blood pressure

High blood pressure tracks over decades (Strandberg et al. 2001, 2002). Whether the risk factors in young and middle-aged adults work in linear fashion also throughout their normal ranges or whether true thresholds exist for their effects has been under extensive debate. Many studies (Port et al. 2000; Strandberg et al. 2001) support the suggestion that blood pressure becomes harmful only when exceeding some threshold, although counterarguments exist (Marschner et al. 2007). A linear relation gains support from studies including a meta-analysis of one million subjects with age-stratified analysis (Law and Wald 2002; Lewington et al. 2002).

A clear risk factor for coronary heart disease in the Framingham Heart Study was total cholesterol, coupled with increasing mortality without any clear cut-offs (Kannel et al. 1964). The prediction value of fasting insulin was evident in a linear

model in one study (Lakka et al. 2002) and in both a linear and a categorical model in a meta-analysis (Hu et al. 2004). Results were similar for ambulatory blood pressure in two follow-up studies (Clement et al. 2003; Hansen et al. 2006).

The risk factors listed above predict atherosclerosis, whereas direct evaluation of the morbid tissue itself, the vascular wall, gives insight into the ongoing disease process. Ultrasonography is a noninvasive way to investigate the structure and function of artery walls. Intima-media thickness of the carotid artery (cIMT) (Nichols et al. 1999; O'Leary et al. 1999) and flow-mediated dilatation (FMD) of the brachial artery predict cardiovascular events (Celermajer et al. 1994; Corretti et al. 2002; Gokce et al. 2002; Chan et al. 2003; Lorenz et al. 2006). Endothelial dysfunction has been proposed as a key phenomenon leading to a cascade of events ending in cardiovascular disease (Ross 1993).

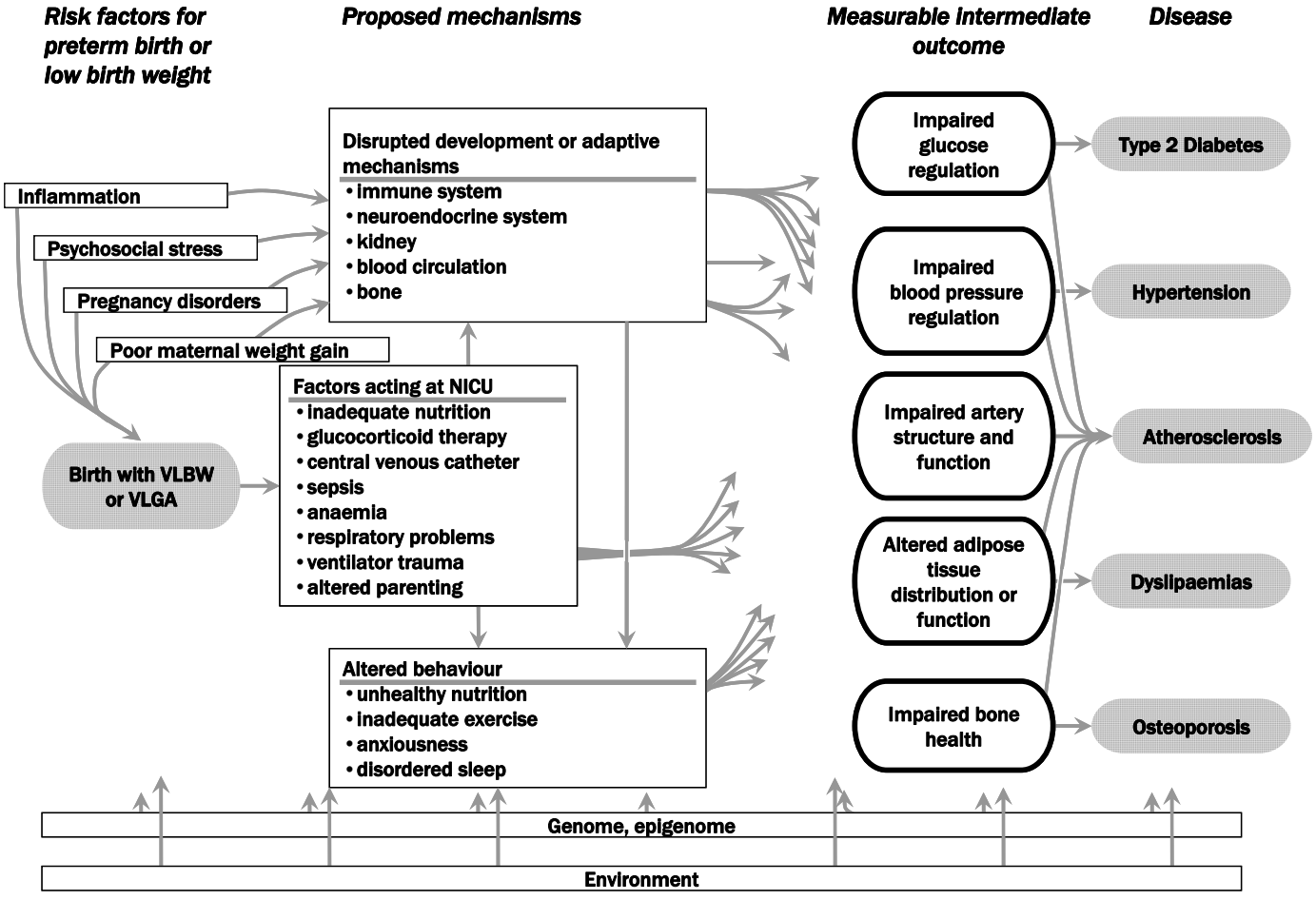
Osteoporosis

Osteoporosis is a disease of bone fragility caused by microarchitectural deterioration and low bone mass (Kanis et al. 1994). Bone mineral density (BMD) predicts fractures in a linear fashion (Johnell et al. 2005). Although true fracture risk depends on other aspects as well, an expert panel of the World Health Organization defined osteoporosis as lumbar spine bone-mineral density below an arbitrary threshold of 2.5 standard deviations below the mean for a healthy young adult population of the same sex and ethnic origin (Kanis et al. 1994). This definition is still in use.

In 1997 in Finland, incidence of osteoporosis was 450 per 100,000 individuals per year (Kannus et al. 1999). In the USA, annually 1.5 million individuals experience an osteoporotic bone fracture, which translates to a health care-bill of more than $6 billion (Orsini et al. 2005). Hip fractures, most commonly due to osteoporosis, have more than doubled in two decades, and ageing explains only half this increase. Medication against osteoporosis is effective, and according to a meta-analysis, it reduces mortality (Bolland et al. 2010). This could imply that osteoporosis contributes to death independently from its co-morbidities. Bone mineral density shows strong tracking as well; a value measured at age 25 was correlated with that individual's value measured at age 44 (R=0.93) (Emaus et al. 2005). Bone mineral density thus serves as one of the main outcomes in this thesis.

What has recently become increasingly clear is the bi-directional cross talk between bone and glucose metabolism (Kanazawa et al. 2009; Lieben et al. 2009). In this crosstalk, adipocyte-derived leptin and osteoblast-derived osteocalcin appear to play important roles. While much remains unknown about the exact mechanisms of this link, these data highlight the relevance of skeletal studies also from the perspective of glucose metabolism and risk factors for cardiovascular disease.

Figure 3. Developmental origins of health and disease in preterm infants.



1.3 Mechanisms – potential pathways linking VLBW/VLGA birth to cardiovascular disease and osteoporosis

Before going into the epidemiological association of VLBW/VLGA and later chronic disease, the following explains some theories of the mechanisms of multiple simultaneous pathways (Figure 3). To introduce some of these theories, the following text refers to cohort studies characterized in Table 3 (Page 34), and presentation of cardiovascular risk outcomes in these studies follows on page 33. Firstly, VLBW or VLGA birth and cardiovascular disease may share aetiological factors. Secondly, some sequelae of VLBW/VLGA birth – several included in a review by Eichenwald and Stark (2008) – may also be mediating factors leading to disease.

Inflammation

In another review (Lockwood 2002), the author considered that for half of all preterm births, their cause is infection. Infections in neonates easily become systemic, spreading through the body via the blood circulation. Infective agents and inflammatory processes may cause damage to arterial walls (Libby et al. 1997). These processes ultimately lead to atherosclerosis (Pesonen 2004).

Vasculature

Arterial wall endothelium is an active organ, and its dysfunction plays a crucial role in the atherosclerotic process (Ross 1993). Early consequences may be linked to later cardiovascular disease via endothelial dysfunction, poor elastic properties of large vessels and small diameters of arteries, as suggested by comprehensive reviews (Martyn and Greenwald 2001; Ligi et al. 2010; Norman 2010).

VLBW/VLGA infants often require a central venous access because of complex parenteral nutrition. A large proportion need an arterial catheter for monitoring. During the late 70's and early 80's, bloodstream access was commonly reached through an arterial line via the umbilicus. Such catheters, however, could cause aortal thrombi and therefore alter renal haemodynamics later (Glickstein et al. 1994). An umbilical artery catheter in the "high" position with its tip superior to the level of the renal arteries may induce turbulence and increased resistance in the renal arteries. This may influence bloodpressure-regulating systems and cause hypertension even in the absence of vascular thrombosis (Cleary et al. 1996).

Among VLBW/VLGA fetuses and infants, anaemia, acidocis, hypoxia, and hyperoxia occur frequently. Oxidative stress occurs when production of reactive oxygen species exceeds the endogenous antioxidant defence and is involved in both the aetiology and complications of prematurity (Woods 2001; O'Donovan and

Fernandes 2004). Oxidative stress plays one of the major roles in the process leading to atherosclerosis (Li and Shah 2004; Paravicini and Touyz 2006).

Organ development

Long-term effects of VLBW/VLGA birth can be mediated by failures of organ growth and development. For example, in children born at VLGA, renal volume was small (Rakow et al. 2008). Normally, all glomeruli are formed before birth at term (Haycock 1998). Similarly, the number of pancreatic beta cells is largely determined during the third trimester and neonatal period (Fowden and Hill 2001).

Hormonal balance

Programming of endocrine axes is one of the key candidate mechanisms to link early life events with health in later life (Kajantie 2006). After birth, placental and maternal hormones (through the placenta) are no longer available to the preterm infant. Alterations in endocrine systems may both underlie preterm birth or be a consequence of it. The hypothalamus-pituitary-adrenal cortex axis may play key roles both in regulation of parturition and in programming of cardiovascular disease (Kamel 2010) and may serve as a mechanism linking maternal stress with preterm birth. As to this axis among preterm infants, a frequent characteristic is a low cortisol concentration shortly after birth (Watterberg and Scott 1995). However, in later life, late preterm birth (GA between 34 and 37) has been found to be unrelated to altered resting levels of plasma cortisol (Rosmalen et al. 2005).

Some studies report preterm/VLBW/VLGA adults as differing from controls in sympathetic drive. Their heart rate, a rough measure of balance within the autonomous nerve system, was higher than that of the controls in one study (Phillips and Barker 1997) but was not higher in four other studies (Siewert-Delle and Ljungman 1998; Kistner et al. 2000; Edstedt Bonamy et al. 2005; Keijzer-Veen et al. 2010). Unfortunately, such data were missing from many studies with blood pressure results. A rise in blood pressure after psychological stressors did not associate with a lower gestational age (Ward et al. 2004). As compared to term-born children, preterm-born ten-year-old children have exhibited, both at rest and after completing mathematical tasks, a higher pulse rate and higher urinary catecholamines (Johansson et al. 2007).

Behaviour

NICUs in the 60's were busy; they lacked diurnal variation of illumination, and stressful procedures were inevitable (Blackburn 1998). In addition, parents were not allowed to participate very much in NICU care (Philip 2005). Possibly related to this, preterm children have had sleep disorders and behavioural differences including anxiety and attention-deficit-hyperactivity-disorder (Bhutta et al. 2002;

Rosen et al. 2003; Saigal et al. 2003). These disorders, in turn, may indicate an increased risk for later cardiovascular disease (Hemingway and Marmot 1999; Bradley and Floras 2009).

In addition, the daily nutrition pattern during hospitalization differed considerably from nutrition in utero. This may have long-lasting effects on lifestyle and behaviour, including food preferences and satiety control. Infants born small drink more milk than do normal birth weight babies (Ounsted and Sleigh 1975) and in childhood are more impulsive in a snack-delay test (Silveira et al. 2009). As young women, they prefer food rich in carbohydrates (Barbieri et al. 2009). In the Dutch Famine Study, carbohydrate intake was unaffected by any exposure to the famine, but those exposed in early fetal life preferred fatty foods as adults (Lussana et al. 2008). Although food preferences develop during fetal life and infancy, a search in Medline® provides only a few studies of preterm infants' macronutrient preferences in childhood or later.

Young adults with BW < 1000 g have a weaker handgrip, and they less regularly participate in sports activities (38% vs. 59%) (Saigal et al. 2007). Motor performance is affected in adolescents with BW < 800 g (Rogers et al. 2005). In a study investigating adults who as fetuses had been at risk for preterm birth, those who actually were born preterm, with a median GA of 34 weeks, had similar exercise levels as those who were full term (Dalziel et al. 2007). An activity subdomain score in a health and illness profile indicated that VLBW adolescents were physically less active than were controls (Hack et al. 2007). Other studies in Table 3 did not report data on exercise. Hypertension, type 2 diabetes, and osteoporosis are associated with lower levels of physical activity, and evidence is strong that increasing physical activity is effective in preventing these conditions (Kohrt et al. 2004; Pescatello et al. 2004; Orozco et al. 2008). Exercise promotion is therefore wise for anybody at risk for cardiovascular disease, especially if the current amount of exercise is inadequate.

Fortunately, not all habits of adults with VLBW/VLGA turn out to be harmful. An example is their relatively low use of alcohol and tobacco. ELBW teens showed less alcohol consumption than did controls (Saigal et al. 2003). Hack and co-workers were the first to show decreased risk-taking in VLBW adults compared with levels in controls. Their VLBW adults used less alcohol and marijuana and had lower rates of sexual intercourse, pregnancy, and childbirth, and fewer contacts with the police (Hack et al. 2002). In other studies, as compared to controls, VLBW adults use less illicit drugs and alcohol (Cooke 2004), but in other studies, rates are similar (Bjerager et al. 1995). In some studies, VLBW adults smoke as often as controls do (Hack et al. 2002; Cooke 2004), whereas in the Netherlands, VLGA/VLBW adults report less smoking, drinking, illicit drug use, and criminal activity than does the general Dutch population on average at the same age (Hille et

al. 2008) (Table 3). In moderately preterm adults, as well, smoking and illicit drug use have been less common than in term borns (Dalziel et al. 2007), and register studies from the Nordic countries report equal rates of criminal activity and drug-related hospital admission in preterm and in term-born adults (Lindstrom et al. 2007; Moster et al. 2008).

The mechanisms of links between VLBW/VLGA birth and osteoporosis

In a term newborn, 80% of calcium accumulates during the third trimester (Kovacs and Kronenberg 2006). During the corresponding period, infants with VLBW or VLGA receive neonatal care outside the womb. They lack the influence of maternal and placental regulating hormones and the physical forces mediated by their mother that should be acting on their developing skeletons. One hormone-replacement trial supported the importance of estradiol and progesterone in bone mineral accretion during infancy (Trotter et al. 1999). Later, bone mineralization in preterm infants may also fail because of low amounts of ingested vitamin D or calcium, or lack of weight-bearing exercise (Slemenda et al. 1991; Cooper et al. 1995).

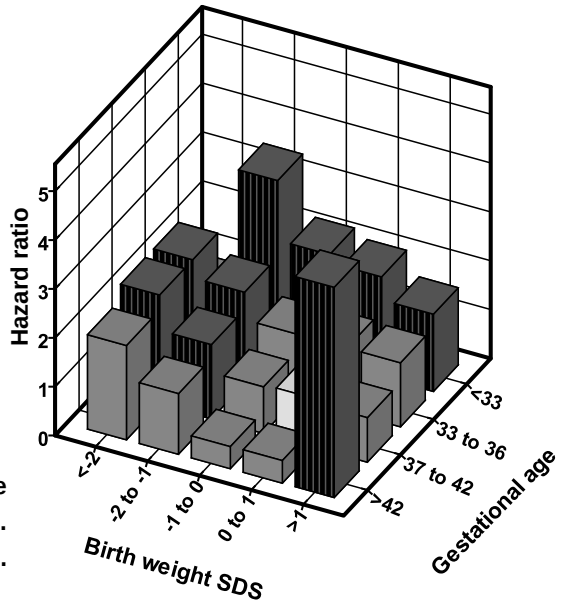
Common genetic or environmental factors

If the association of preterm birth and cardiovascular mortality were due to a common genetic background for these conditions, those having a premature baby should be at greater risk for cardiovascular disease themselves. Such an association in fathers of preterm offspring would support the theory that the mechanisms of the linkage would be genes, and not fetal experience. In a study of 3706 live births in Helsinki from 1954 to 1963 by Smith et al. (2000), preterm birth (<37 weeks) associated with a hazard ratio (HR) of 2.06 (1.22 to 3.47) for the mother's own cardiovascular mortality. A history of experiencing a preterm delivery meant no increased risk for smoking-related cancers in the mother, which could imply, the authors suggest, a minor role for smoking as a confounder in the reported cardiovascular-disease association. In a more recent study that included all children born in Sweden between 1973 and 1980, preterm birth associated with increased risk for cardiovascular mortality, with a HR of 2.5 (2.1 to 2.9) among mothers. Among fathers, however, the respective HR was 1.2 (1.1 to 1.3) (Smith et al. 2005). One interpretation of the marked difference between these risks is that common genetic background plays only a minor role.

1.4 Epidemiology: Preterm/VLBW/VLGA birth and chronic disease risk factors

Studies incorporating the entire distribution of GA provide important information about how preterm birth associates with many outcomes in adulthood. Diabetes and hypertension were related to shorter duration of gestation in a linear fashion (Järvelin et al. 2004; Johansson et al. 2005; Lawlor et al. 2006; Kaijser et al. 2009). For diabetes, this was clear also after accounting for size for gestation by stratification (Figure 4) (Kaijser et al. 2009). Ability to stratify is one obvious strength of these large epidemiological studies. One of their limits, however, is that the cohorts were born a long time ago. This thesis summarises findings from three types of studies: ones weight-limited, such as VLBW; ones gestational-age limited, such as VLGA; and whole-distribution studies. These three study types answer different questions. The studies also have various outcomes, studies on blood pressure being most abundant; they thus receive the largest coverage, here. Literature search methods are in the Appendix (Page 123).

Figure 4. Disentangling the effects of low gestational age and low birth weight on type two diabetes.



Referent group

For difference from the referent group, P < 0.05. Data from Kaijser et al. (2009).

Table 3. Profiles of follow-up studies (i).

Cohort name or area	Auckland Steroid Trial, New Zealand	Edinburgh, UK	Cambridge, UK, with four other units
References, main findings on cardiovascular-disease risk factors / Additional references	Dalziel et al. 2007: Higher blood pressure, higher insulin AUC in OGTT, similar cortisol and total cholesterol	Irving et al. 2000: Higher blood pressure and insulin, similar lipids / Belton et al. 1986; Irving et al. 2004	Singhal et al. 2001b: Similar FMD, blood pressure. Singhal et al. 2003: Glucose regulation findings
Case recruitment	Expected GA 24—36 at the National Women's Hospital	< 2000 g, born in the Simpson Memorial Maternity Pavilion	< 1850 g babies admitted to neonatal units
Control recruitment	Expected GA 24—36 but were born at term	Same hospital, matched for sex, birth order and fathers SES	From schools at age 13—16 yrs
GA, wks (SD) (range)	Median, 34.1	33.4 (2.3) ()	31.0 (2.7) ()
Birth years	1969—74	1973—75	1982—85
Survival; participation (of cases)	81%; 44%	No report; 75% of contacted. All these had agreed at NICU	No report; 23%
Cases + controls at age (yrs)	311 + 147 at age 30	34 + 27 at age 24	216 + 61 at age 13—16
Excluded disabled	No report	No report	Major congenital anomalies
Sociodemographics	Similar	Matched for SES	Similar
Gestational hypertension	11% vs. 2%	No report	No report
Preeclampsia	No report	No report	No report
Smoking during pregnancy	No report	No report	No report
Antenatal glucocorticoids	51% vs. 44%	No report	No report
Current smoker	43% vs. 63%	Accounted for	0% vs. 0%

Footnotes are on the page following Table 3.

Table 3 continued (ii).

Cohort name or area	Stockholm, Sweden	Uppsala, Sweden	Trondheim, Norway
References, main findings on cardiovascular-disease risk factors / Additional references	Kistner et al. 2000, 2005: Higher ambulatory blood pressure during day	Edstedt Bonamy et al. 2005: Higher blood pressure and peripheral vascular resistance, similar pulse wave velocity and aortic and carotid stiffness	Indredavik Evensen et al. 2009: Higher blood pressure, similar endothelial function / Indredavik et al. 2004
Case recruitment	GA<32 babies admitted to St Göran's Children's Hospital	GA≤34 , born in Uppsala, all girls	VLBW infants admitted to the University Hospital in Trondheim
Control recruitment	Healthy female volunteers	Healthy female volunteers	Random sample recruitment from all pregnant mothers in region
GA, wks (SD) (range)	30 () (28—32)	29.1 (2.9) (23 to 34)	28 (2.7) (24—35)
Birth years	1970—74	1982—86	1986—88
Survival; participation (of cases)	No report; 60%	No report; 57%	77%; 54%
Cases + controls at age (yrs)	15 + 17 at age 26	34 + 32 at age 16.5	37 + 63 at age 18
Excluded disabled	No report	No one	One with trisomy 21
Sociodemographics	No report	No report	Parents' education shorter, lower SES, higher income, all NS
Gestational hypertension	No report	No report	No report
Preeclampsia	No report	12% vs. 0%	No report
Smoking during pregnancy	No report	10% vs. 5%	No report
Antenatal glucocorticoids	No report	2% vs. 0%	No report
Current smoker	NS	2% vs. 2%	31% vs. 29%

Footnotes are on the page following Table 3.

Table 3 continued (iii).

Cohort name or area	POPS-19, The Netherlands	POPS substudy, Rotterdam	POPS substudy, Amsterdam
References, main findings on cardiovascular-disease risk factors / Additional references	Keijzer-Veen et al. 2005, 2010: Blood pressure; Finken et al. 2006a, 2006b: Insulin, cIMT, and lipids / Verloove-Vanhorick et al. 1986; Hille et al. 2008;Weisglas-Kuperus et al. 2009	Keijzer-Veen et al. 2010: Higher blood pressure	Rotteveel et al. 2008a: Higher blood pressure, lower insulin sensitivity; Rotteveel et al. 2008b: Lipids, mixed meal
Case recruitment	VLGA / VLBW, the Netherlands	VLGA, starting from extremes of BW SDS. Rotterdam area	(VLGA / VLBW) and (BW SDS 0.0—2.0), Amsterdam.
Control recruitment	No controls at 19.3 yrs	Healthy volunteers at 20.7 yrs, flyers to medical students	Healthy volunteers, notice at medical faculty
GA,wks (SD) (range)	29.7 (1.5) (VLGA) 33.9 (1.6) (32 to 39)	30.6 (1.1) (SGA) 29.5 (1.4) (AGA)	28.9 (1.4) ()
Birth years	1983	1983	1983
Survival; participation (of cases)	76% (all) and 69% (VLGA); 62	No report; no report	No report; 40% (=0.64*0.62)
Cases + controls at age (yrs)	588 + 0 at age 19	50 + 30 at age 21	29+30 at age 22
Excluded disabled	No report	No report	5 seriously ill or pregnant
Sociodemographics	89% Caucasian	No report	No report
Gestational hypertension	Not associated with offspring blood pressure	62 (SGA) and 7 (AGA), unrelated to BP	No report
Preeclampsia	No report	No report	No report
Smoking during pregnancy	30%, not associated with BP	No report	No report
Antenatal glucocorticoids	No report	10% (SGA) and 28% (AGA)	No report
Current smoker	34% vs. 43% in population	No report	No report

Footnotes are on the page following Table 3.

Table 3 continued (iv).

Cohort name or area	Merceyside, UK	Melbourne, Australia	Cleveland, Ohio, USA
References, main findings on cardiovascular-disease risk factors / Additional references	Pharoah et al. 1998: Higher blood pressure / Pharoah et al. 1994; Stevenson et al. 2001	Doyle et al. 2003: Higher ambulatory blood pressure, day and night / Kitchen et al. 1982a, 1982b	Hack et al. 2005: Higher blood pressure, among men, only when adjusted for current weight and height/ Hack et al. 2002, 2003
Case recruitment	VLBW births within geographical, at 3 years	VLBW births (consecutive) at Royal Women's Hospital	VLBW, admitted to Rainbow Babies and Children's Hospital
Control recruitment	From same school with age and sex –matching	From the same hospital in the newborn period	From schools at age 8 years, matching the catchment areas
GA,wks (SD) (range)	30.7 ()(26 to 37)	28.8 (2.0) (24 to 30)	29.6 (2.2) ()
Birth years	1980—81	1977—82	1977—79
Survival; participation (of cases)	55%; 93%	53%; 74%	64%; 76% vs. 64%
Cases + controls at age (yrs)	128 + 128 at age 15	156 + 38 at age 18.6	195 + 108 at age 20.1
Excluded disabled (n)	47 twins, 34 disabled	3 disabled	25 neurosensory impairment, 12 pregnant
Sociodemographics	SES of controls higher (NS)	No report	54% vs. 53% Afro-American 17% vs. 10% less than high school
Gestational hypertension	No report	Hypertension, 24% vs. 3%	No report
Preeclampsia	No report	No report	10% vs. no report
Smoking during pregnancy	(Ever-smoker mothers 69% vs 47%)	No report	No report
Antenatal glucocorticoids	No report	53%	0%
Current smoker	16% vs. 4%	No report	Men: 57% vs. 59%. Women: 40% vs. 48%

Footnotes are on the page following Table 3.

Table 3 continued (v).

Cohort name or area	Providence, Rhode Island, USA	Ontario, Canada	British Columbia, Canada
References, main findings on cardiovascular-disease risk factors / Additional references.	Vohr et al. 2010: Higher blood pressure / Ment et al. 1994	Saigal et al. 2007: Less exercise / Saigal et al. 1991; Saigal et al. 2006; Saigal et al. 2007	Rogers et al. 2005: Aerobic capacity, strength, activity / Grunau et al. 2004
Case recruitment	< 1250 g, from three tertiary centres, indomethasin trial	< 1000 g babies in an area in Ontario	≤ 800 g babies admitted to a provincial NICU
Control recruitment	From a tele-marketing list frequency-matched on zip-code, age, gender and race	From schools near the study centre, at 8 yrs of age –social class matching	Recruitment age 3 years from health units and recreation centers
GA,wks (SD) (range)	27.9 (2) ()	27.1 (2.3) ()	25.8 () (23 to 29)
Birth years	1989—92	1977—82	1981—86
Survival; participation (of cases)	88%; 68%	45%; 94%	39%; 67%
Cases + controls at age (yrs)	296 + 95 at age 16	147 + 131 at age 21— 27	53 +31 at age 17
Excluded disabled (n)	74 with IVH	No one	19 with neurosensory impairment
Sociodemographics	Predominantly Caucasian 75%	Mothers were younger, otherwise similar to the controls, Caucasian 95%	Mothers' education 12.3 vs. 14.2 years
Gestational hypertension	Together with preeclampsia, 11%	15%	No report
Preeclampsia	No report	No report	No report
Smoking during pregnancy	No report	(Maternal smoking 30%)	No report
Antenatal glucocorticoids	36%	47%	No report
Current smoker	No report	No report	No report

Footnotes are on the page following Table 3.

Footnotes for Table 3.
AGA, appropriate for gestational age; AUC, area under the curve; CVD, cardiovascular disease; FMD, flow-mediated dilatation; OGTT, oral glucose tolerance test; NICU, neonatal intensive care unt; No report, information was not reported or unfound; NS, nonsignificant; SGA, small for gestational age; SES, socio-economic status; vs, comparison of the cases *versus* the controls.

Coronary heart disease and stroke

Infants included in most VLBW/VLGA follow-up studies (Table 3) have currently reached the age of 20 to 30. Only after several more decades, will their clinical signs and symptoms of coronary heart disease and stroke start to emerge. In Sweden, however, researchers have already been able to retrieve such diagnoses from registers for people who survived preterm birth during the period 1925 to 1949 (Kaijser et al. 2008). That study included 986 VLGA infants, and their HR for diagnosed ischaemic heart disease was 0.91 (95% CI, 0.72 to 1.16). In another Swedish study, ischaemic heart disease mortality was not higher among those with GA < 36 weeks (Koupil et al. 2005). However, this preterm group had 3-fold higher stroke mortality.

Adiposity, body composition

VLBW/VLGA adults are lighter and shorter than their peers born at term (Table 4). In one study, men with VLBW had 2.6 kg/m^2 (95% CI, 1.3 to 3.8) lower BMI (Hack et al. 2003), whereas in another study, male conscripts with VLGA had only 0.2 kg/m^2 (0.0 to 0.4) lower BMI (Johansson et al. 2005). Men and women with VLBW/VLGA show, in other studies, BMI levels similar to those of their term born peers (Table 4). Instead of using only BMI, which reflects total body mass, it is interesting to evaluate separately fat mass and fat-free mass. VLBW subjects in prepuberty (Wang et al. 2007) and in adolescence (Weiler et al. 2002), had lower fat-free mass than did their term-born peers.

Table 4. Body composition in adolescents and adults born with VLBW/VLGA, as compared to controls.

Reference	Cases are	Age	Height mean (SD) (cm)	Height difference (95% CI) (cm)	Weight mean (SD) (kg)	Weight difference (95% CI) (kg)	BMI mean (SD) (kg/m^2)	BMI difference (95% CI) (kg/m^2)
Men								
Saigal et al. 2006	<1000 g	24.0	170.6 (9.5)	-7.2 (-10.3 -4.1)	70.7 (14.9)	-6.5 (-11.7 -1.2)	24.2 (4.6)	-0.15 (-1.8 1.5)
Rogers et al. 2005	≤800 g	17.3	172.0	-10.2 P<.001	64.7	-9.4 P<.01	21.9	NS
Hack et al. 2003	VLBW	20.1	173.7 (7.9)	-3.1 (-5.2 -1.1)	69.2 (13.9)	-10.5 (-14.8 -6.2)	22.9 (4.2)	-2.6 (-3.8 -1.3)
Rotteveel et al. 2008a	VLGA	22.0	183.1 (8.9)	negative NS	77.0 (16.8)	positive NS	22.8 (3.4)	positive NS
Women								
Saigal et al. 2006	<1000 g	24.0	158.3(6.8)	-6.2(-8.3 -4.0)	60.1 (13.1)	-7.1 (-11.8 -1.2)	24.0 (5.6)	-0.7 (-2.5 1.0)
Rogers et al. 2005	≤800 g	17.3	160.1	-7.9 P<.001	61.0	-5.3 P<.01	23.9	NS
Hack et al. 2003	VLBW	20.1	161.7 (7.3)	-1.2 (-3.2 0.9)	64.9 (16.7)	-2.0 (-6.9 2.8)	24.7 (5.2)	-0.5 (-2.1 1.0)
Rotteveel et al. 2008a	VLGA	22.0	169.6 (7.9)	negative n.s	61.2 (9.7)	negative NS	21.2 (2.1)	neg NS
Edtedt Bonamy et al. 2005	GA≤34	16.5	163 (5.7)	-3.0 (-5.9 -0.1)	58.0 (12.6)	+1.0 (-4.1 6.1)	22.0 (4.0)	+1.0 (-0.7 2.7)
Kistner et al. 2000, 2005	VLGA	26.0	165.3 (7.8)	-3.0 (-7.9 1.5)	63.9 (9.3)	-4.0 (-10.4 2.4)	23.4 (2.9)	-0.5 (-2.6 1.6)*
Men and women								
Indredavik et al.2009	VLBW	18.2	169.6 (7.2)	-3.6 (-6.5 -0.7)	64.2 (10.2)	-5.6 (-10.2 -1.0)	22.2 (3.0)	-1.0 (-2.3 0.3)*
Irving et al. 2000	<2000 g	24.3	167.0 (9)	-1.0 (-5.9 3.9)	66.9 (12.7)	+2.0 (-4.2 8.2)	No report	No report

CI, confidence interval; No report, information was not reported or unfound.; NS, nonsignificant

* Calculated from published metadata.

Waist circumference reflects central adiposity. Waist circumference was 4 cm larger, but BMI was similar, in postpubertal girls with GA < 34 when compared to measurements of healthy volunteers (Edstedt Bonamy et al. 2005). In another study, with its control group appropriately based on the local population, the danger of selection bias should thus be lower but the results were similar: VLBW young adults had relatively thicker subscapular skinfolds, indicating more central fat distribution (Indredavik Evensen et al. 2009).

Overall, despite tiny differences in adult BMI, a more central fat distribution can be suspected in VLBW/VLGA generations who have reached adulthood. Recently, preterm infant nutrition has changed growth trajectories, and methods for determining body composition have developed. In 2003, magnetic resonance images at term showed that, as compared with term-born neonates, VLGA infants did have more intra-abdominal and less subcutaneous adipose tissue (Uthaya et al. 2005).

Lipid regulation

Preterm birth or lower gestational age is unrelated to serum lipids in a number of studies of young adults, and some of these studies include more than 300 participants (Irving et al. 2000; Finken et al. 2006b; Dalziel et al. 2007; Rotteveel et al. 2008a; Cooper et al. 2009). Some exceptions to this negative finding exist: GA has been inversely correlated with total cholesterol (Cooper et al. 2009), and in another study, with triglycerides (Morley et al. 2000). Morley and colleagues studied 422 children aged 11 to 15 years; those 20 born with BW < 2500 g had higher HDL cholesterol. We can conclude that HDL-, LDL-, or total cholesterol, or triglyceride measurements in preterm-born adults show, thus far, no clear signs of disturbed lipid metabolism. Studies on subgroups or on lipid metabolism characteristics in more detail are unavailable.

Blood pressure

In their extensive overview concentrating on effects of various perinatal characteristics on systolic blood pressure, Huxley and colleagues (2000) suggested no consistent effect of low gestational age on systolic blood pressure. Despite that conclusion, such an effect may exist, especially regarding preterm subjects. Only seven studies in that review included preterm subjects (Martyn et al. 1995; Campbell et al. 1996; Zureik et al. 1996; Ley et al. 1997; Nilsson et al. 1997; Siewert-Delle and Ljungman 1998; Mi et al. 2000). Secondly, a high positive correlation between GA and BW makes a BW-adjusted effect of GA uninformative. For proper interpretation of the data, the crude association of GA and blood pressure is important as well. Only three studies estimated this crude association: it was either negative (Siewert-Delle and Ljungman 1998), missing (Mi et al. 2000), or positive (Martyn et al. 1995).

Table 5. Studies including adolescents and adults born prematurely. Effect of lower gestational age on blood pressure or hypertension.

First author, project of origin	Case GA	Birth years	Age	Cases*	Controls	SBP higher	SBP higher, mmHg †	DBP higher, mmHg †
Leon et al. 1996, Uppsala Academic Hospital, only men	≤37	1920—24	50	61	442	Yes	3.1	1.1
Siewert-Delle and Ljungman 1998, Göteborg, only men	≤37	1926—27	49	44	336	No	3 (-3.4 9.4) ‡	0 (-4.1 4.1) ‡
Edstedt Bonamy et al. 2008b, Swedish registers	≤32	1925—49	38—82	947	3174	No	Hazard ratio 1.0	No report
Martyn et al. 1995, hospital-based, Sheffield, UK	<38	1939—40	50	28 (81)	308	Opposite	-8.0	No report
Barker et al. 1990, Preston, Lancashire, UK	≤37	1935—43	46—54	(89)	449	No	Not higher	Not higher
Cooper et al. 2009, England Scotland, and Wales	<37	1958	44—45	143	1075	Yes	No report	2.4 (1.0 3.8) §
Järvelin et al. 2004, Northern Finland Birth Cohort	<37	1966	31	273	4356	Yes	2.8 (0.9 4.7) per -10 wks	1.1(-0.5 2.8) per -10 weeks
Leon et al. 2000, Swedish birth register, only men	35 to 38	1973—76	17—19	12135 (82)	45637	Yes	0.9, P<0.001¶	No report
Johansson et al. 2005, Swedish birth register, only men	<29	1973—81	18	162	275895	Yes	3 (1.3 4.7) ‡††	No report
Barros and Victora 1999 Pelotas, Brazil	<37	1982	14—15	44 (62)	770	No	0.2 (-3.2 3.5)	0.1 (-2.9 3.1)
Lazdam et al. 2010, 19% received antenatal steroid	<37	1982—85	24.5	52 (51**)	38	Yes	6.7 (2.2 12.2)‡	5.5 (2.6 8.4) ‡

Footnotes on the next page.

Footnotes for Table 5

* Number of cases (percentage of intended)

† Difference in mmHg. (95% confidence interval displayed if available)

‡ Calculated from aggregated data

§ Given difference is BMI adjusted; it was unaffected by preeclampsia or by father's or subject's own occupation

¶ for trend

** Of 927 in a previous study, 140 had agreed to be contacted later; 140 served as the number of intended

†† Odds ratio for hypertension 1.4 (95% confidence interval, 1.2 to 1.7)

I systematically searched the literature, in June 2010, as regards the crude effect of GA below some threshold on blood pressure in adolescence or adulthood, or as to any linear effect of GA among preterm participants on that pressure. In 24 studies, number of preterm subjects was sufficient. In nine of those studies, subjects were born several decades previously and the comparisons were often between all of those preterm born versus those term born (Table 5). Thirteen studies on effects of more extreme prematurity are in Table 6, but two studies on Swedish military conscripts are included in Table 5; one because of births occurring long ago (Edstedt Bonamy et al. 2008b) and the other for comparison (Johansson et al. 2005). Of the eleven studies, in six (Leon et al. 1996, 2000; Järvelin et al. 2004; Johansson et al. 2005; Cooper et al. 2009; Lazdam et al. 2010), preterm birth did associate with higher blood pressure, either systolic or diastolic. Of these six, two also report that socioeconomic factors fail to explain the difference (Järvelin et al. 2004; Johansson et al. 2005). Five studies found that preterm birth was not associated with higher blood pressure (Barker et al. 1990; Martyn et al. 1995; Siewert-Delle and Ljungman 1998; Barros and Victora 1999; Edstedt Bonamy et al. 2008b).

Based on the studies in Table 5, a trend toward preterm birth as associating with higher blood pressure seems more likely in cohorts born more recently. A cohort in Pelotas, Brazil, born in 1982, is an exception, with no effect of preterm birth on blood pressure (Barros and Victora 1999). One explanation for these findings is selective mortality, the timing and extent of which depends on country and setting: before the breakthroughs in perinatology, selection by early mortality left only the healthiest, least impaired preterm subjects alive for participation, and no association between preterm birth and later blood pressure emerged.

In severely preterm adults, an elevated blood pressure was first reported by Pharoah et al. (1998) and by Irving et al. (2000) followed by others (Table 6). As compared to my systematic search focused on blood pressure and preterm birth, a recent review (Norman 2010), appears to include a set of studies nearly identical.

Table 6. Blood pressure in adolescents and adults born preterm/VLBW/VLGA.

Reference	GA	Case definition	Birth year	Cases + controls	SBP difference, mean (95% CI)		DBP difference, mean (95% CI)
					Crude	Height adjusted	
Dalziel et al. 2007	34.1	GA<37	1969—74	311 + 147	3.5 (1.0 6.1)	3.3 (1.0 5.7)	No report
Irving et al. 2000	33.4	<2000 g	1975	34 + 27	7, P<.001	No report	5, P<0.05
Singhal et al. 2001b	31.0	<1850 g	1982—85	216 + 61	-0.5 (-2.7 1.7)	No report	0 (-2.4 2.4)
Edstedt Bonamy et al. 2005	29.1	GA≤34	1982—89	34 + 32	No report	5.7, P<0.001	2.7 P<0.001
Kistner et al. 2000; Kistner et al. 2005	30.0	VLGA	1970—74	15 + 17 all women	Office: 13 (5.6 20.4)* Daytime: 7†, P=0.03	No report	Office: 5 (-0.4 10.4) Daytime: 77 vs. 74†, NS
Keijzer-Veen et al. 2010	29.5	VLGA	1983	29 + 30	Office: 8.4 (4.1 12.7) Daytime: 4.2 (0.4 8.0)	No report	Office: 2.0 (-1.9 5.9) Daytime: 0.5 (-2.4 3.4)
Rotteveel et al. 2008a	28.9	VLBW /VLGA	1983	29 + 30	13.9 (7.6 20.1)	15.0 (8.8 21.2)	6.9 (3.0 10.8)
Pharoah et al. 1998.	30.7	VLBW	1980—71	128 + 128	3.2 (0.4 6.0)	No report	1.1 (–0.7 2.9)
Doyle et al. 2003	28.8	VLBW	1977—82	156 + 38	Office: 8.6 (3.4 13.9) 24-h: 4.7 (1.4 8.0)	No report	Office: 4.3 (1.0 7.6) 24-h: 1.1 (-1.2 3.5)
Hack et al. 2005	29.8	VLBW	1977—79	195 + 108	Men: -0.8 (-2.2 3.8) Women: 3.4 (0.3 6.5) All: 1.9 (-0.2 4.1)	3.2 (0.1 6.2) 3.8 (0.8 6.8) 3.5 (1.4 5.6)	0.6 (-1.8 3.0) 0.5 (-2.0 3.0) 0.4 (-1.4 2.1)
Indredavik Evensen et al. 2009	28.0	VLBW	1986—88	37 + 63	6.5 (2.5 10.5)*	P<0.05	5.6 (1.8 9.4)*
Rogers et al. 2005	25.8	<800 g	1981—86	53 + 31	NS No data shown	No report	
Vohr et al. 2010	27.9	<1250 g	1989—92	296 + 95	4 (P=0.003)	5.9 (0.001)	2.1 (P=0.05)

NS, nonsignificant; No report, information was not reported or unfound.

* Crude difference and 95% CI calculated from aggregate data

† Figures are medians

Overall, these studies show a trend towards higher blood pressure in preterm subjects. Exceptions to this finding do have another outcome as their main focus, and their study subjects do not match very well those in other studies: children with BW < 1850 g (Singhal et al. 2001a), adolescents with BW < 800 g (Rogers et al. 2005).

Could the higher blood pressure in VLBW/VLGA adults be caused by their lower socioeconomic status (SES)? After adjustment for SES in large studies on Swedish military conscripts, effect of preterm birth remained unchanged (Leon et al. 2000; Johansson et al. 2005). In 6 of the 13 studies in Table 6, data on possible confounding by SES were missing (Kistner et al. 2000, 2005; Doyle et al. 2003; Edstedt Bonamy et al. 2005; Rogers et al. 2005; Rotteveel et al. 2008b; Keijzer-Veen et al. 2010). Most of these tended to be the smallest studies, and they reported the largest unadjusted effect sizes. The seven remaining studies applied SES information in variable ways: by recruitment of socioeconomically equal groups and reporting a SES-adjusted effect size (1.9 mmHg) (Hack et al. 2005); by matching (Irving et al. 2000; Vohr et al. 2010); or by solely reporting that SES differences were statistically nonsignificant (Pharoah et al. 1998; Singhal et al. 2001a; Dalziel et al. 2007; Indredavik Evensen et al. 2009). However, a comparison of adjusted and unadjusted effect estimates would help rule out confounding. In short, estimates of higher blood pressure in VLBW/VLGA adults are likely to be in part due to confounding by SES.

As adults, those who were born preterm tend to be short in height. Should height be in the model when estimating blood pressure differences from normal-sized term-born subjects? A great body height is related to high blood pressure in animals (as in giraffes: see Goetz et al. 1960). For humans, this is true for children, adolescents, and young adults (Voors et al. 1982). The short stature of VLBW/VLGA adults thus suggests that their blood pressure should be low, instead of high. In addition, including shorter height as a covariate raises or leaves unchanged the effect size of VLBW/VLGA birth (Edstedt Bonamy et al. 2005; Hack et al. 2005; Rotteveel et al. 2008b) (Table 6). The studies showing that blood pressure predicts cardiovascular disease do not include height in their analysis (Lewington et al. 2002). Whether the important pressure for young adults would be the absolute one or be the one adjusted for size is currently unknown. It is therefore rational to report primary comparisons with and without size adjustment.

Selection by increasing survival by time could explain the increase in the blood pressure difference between VLBW/VLGA and term born young adults. Table 5 shows that the more recent the date of birth of the preterm participants (therefore ones with better survival), the higher the blood pressure difference as compared to that of the term-born participants. The findings among more extreme cases of prematurity are in line with this trend (Table 6).

Table 7. Blood pressure in former preterm/VLBW/VLGA infants, assessing men and women separately.

First author	Cases+ Controls	Case definition	SBP difference, mean (95% CI) Men	Women	Sex difference in VLBW effect
Cooper et al. 2009	143 + 1075	GA<37	1.5 (-0.4 3.4)	4.2 (2.3 6.1)	Similar*, P_{int}=0.11
Järvelin et al. 2004	273 + 4356	GA<37	1.0 (-1.2 3.2) †	2.7 (0.6 4.8) †	Different*, P_{int} <0.05
Rotteveel et al. 2008a	29 + 30	GA<32	19 (9.5 20.5) †	9 (1.0 17.0) †	No report
Doyle et al. 2003	156 + 38	VLBW	8.6 (1.2 15.9)	9.5 (2.2 16.8)	Similar
Hack et al. 2005	195 + 108	VLBW	0.8 (-2.2 3.8)	3.4 (0.3 6.5)	Similar

P_{int} , P value for sex × preterm or sex × VLBW interaction; No report, information was not reported or unfound.

* Interaction tested in a linear model with gestational age (GA) as a continuous variable

† Crude effect with 95% confidence interval calculated from aggregate data

Studies with results only for men show that preterm birth with GA of between 35 and 38 weeks is associated with a mild blood pressure increase (Leon et al. 2000), and this difference from controls increases with more extreme prematurity; GA < 29 weeks was associated with the largest blood pressure increase (Johansson et al. 2005). This increase is often more pronounced in women (Table 7). An interaction analysis tests the statistical significance of an effect difference in men and women: a sex × predictor product term, such as sex × VLBW birth, is included in a model predicting higher blood pressure, also with main-effect terms sex and the predictor as explaining variables (Armitage et al. 2002). Regarding sex difference in the effect of preterm/VLBW/VLGA birth on later blood pressure, only two studies report interaction tests (Doyle et al. 2003; Hack et al. 2005). In addition, two studies report such test results in another, related model with GA as a continuous variable (Järvelin et al. 2004; Cooper et al. 2009). Only in one study did the effect of preterm birth differ between men and women according to interaction testing (Järvelin et al. 2004). This study was relatively large, and other studies may have lacked the power to show the difference. In short, both men and women born preterm or with VLBW/VLGA are at risk for hypertension, the risk being even greater for women than for men.

Glucose regulation

Because blood pressure measurement equipment is easily accessible, it has been widely in use. Fewer studies exist on glucose regulation. A GA < 38 weeks in 42 men was unrelated to insulin sensitivity index at ages 69 to 73 years in a study of 308 men born between 1920 and 24 in Uppsala, Sweden (McKeigue et al. 1998). However, a large study combining birth data from four large birth hospitals from 1925 to 1949 with data from nationwide hospital registers from 1987 to 2006 showed that both short GA and low BW SDS were associated with a higher hazard for type 2 diabetes (Kaijser et al. 2009). Short gestation was related to a higher HR for diabetes also when studied in strata by birth weight SDS (Figure 4). Table 8 shows that those at the lowest extremes of birth weight and gestational age have a higher risk for hospitalization related to a diagnosis of diabetes in later life. The table also shows current evidence on glucose-regulation related outcomes in preterm-born adolescents and adults (one study in children included). Most of the impaired glucose regulation findings were not confounded by low SES (Irving et al. 2000; Lawlor et al. 2006; Thomas et al. 2007; Kaijser et al. 2009). One study reported similar SES in their groups (Dalziel et al. 2007), and another study did not account for SES (Rotteveel et al. 2008b). Data on VLGA children thus suggest that their insulin resistance is higher. In young adults born with a BW < 2000 g, insulin resistance was higher than in control subjects (Irving et al. 2000). In pubertal children with BW < 1850 g, insulin resistance was not higher in a descriptive report

Table 8. Findings regarding insulin resistance or glucose intolerance in adolescents and adults born preterm/VLBW/VLGA.

Subject	Reference	Age	N	Case definition	Insulin resistance	Glucose intolerance	Main result on insulin resistance and glucose intolerance (95% CI)
Diabetes	Lammi et al. 2009	15—39	710	(Linear)		No, Yes	GA not associated with diabetes/ If < 4.2kg, 1kg lower BW doubles risk
Diabetes	Lawlor et al. 2006	50	? + 5793	GA<37		Yes	OR for diabetes 2.1 (1.3 to 3.7)
HbA1C% ≥ 6	Thomas et al. 2007	45	540 + 6978	GA<38		Yes	OR for HbA1C ≥ 6 was 1.4 (1.0 to 2.1)
HbA1C%	Cooper et al. 2009	44—45	3764	(Linear)		No, Yes	High and low GA associated with HbA1C in women, but not in men
OGTT	Dalziel et al. 2007	30	311 + 147	GA<37	Yes	No	Insulin AUC higher. Fasting insulin, fasting glucose, and glucose AUC NS
IVGTT	Willemsen et al. 2009	18—24	169 +136	GA<36	No		Insulin sensitivity similar (note pathology among term-born group, see text)
Diabetes	Kaijser et al. 2009	38—81	986 + 5439	VLGA		Yes	Hazard ratio for diabetes 1.67 (1.33 to 2.11)
IVGTT	Hofman et al. 2004	4—10	38 + 22	VLGA	Yes, No	No	Insulin sensitivity lower. Fasting insulin and glucose disposal index NS
Clamp	Rotteveel et al. 2008b	22	29 + 30	VLGA	Yes		Mi-value 6.6 (2.3 to 11.0) lower (standard deviation among controls was 10).
Fasting insulin	Irving et al. 2000	24.3	34 + 27	BW<2000	Yes		Fasting insulin was 0.3 mmol/L higher, P < 0.001
Fasting insulin	Singhal et al. 2003	13—16	216 + 61	BW<1850	No	No	Fasting insulin, 32-33 split pro insulin, and glucose similar

AUC, area under the curve; CI, confidence interval; GA gestational age; HbA1C%, glycosylated haemoglobin; IR, insulin resistance; NS, nonsignificant; OR, odds ratio; Linear, linear analysis; OGTT, oral glucose tolerance test; Mi value, glucose disposal (mg/kg per min) per insulin levels (pmol/L) × 100.

of a randomized controlled trial with a relatively low follow-up rate (Singhal et al. 2003). In the only other study that reported similar insulin resistance in preterm and comparison subjects, those comparison subjects might insufficiently represent the whole population; they were either hospitalized or were being investigated for SGA or for short stature or might also have been recruited by advertisements (Willemsen et al. 2009) (Table 8). In sum, preterm/VLGA/VLBW children seem to develop more insulin resistance, and possibly this leads to glucose intolerance and diabetes.

Vascular structure and function

Most studies find neither arterial stiffness nor endothelial dysfunction in preterm-born subjects (Table 9). Among the 184 VLGA participants in the POPS-19 study, gestational age failed to predict cIMT at age 19 (Finken et al. 2006b), but that study lacks term-born control subjects. In another study, of 109 young adults born preterm with a mean GA of 30 weeks, cIMT was higher than among those born at term (Lazdam et al. 2010).

At ages 23 to 30 years, retinal vasculature was evaluated in 47 female volunteers (Kistner et al. 2002). Those recruited in a preterm group with mean GA of 30 weeks, had fewer branching points in their retinal arterioles. The authors speculate that vascular beds in other locations as well, such as the brain, heart, and kidney, could be permanently affected in preterm infants. Smaller vessel diameters have also been reported: One cohort of six-year-olds had a mean retinal arteriole diameter of 166 µm (95% CI, 164 to 167). In comparison to the rest of the cohort, this diameter in the 112 preterm born was shorter by 2 µm, and in the 23 with BW < 2000 g, it was shorter by 9 µm (Mitchell et al. 2008). The brachial artery, a medium-sized artery, was narrower in preterm born subjects (Singhal et al. 2001a). In arteriography patients, narrow coronaries contribute to an increased risk for atherosclerotic lesions (Nwasokwa et al. 1996). Speculatively, preterm subjects may have narrow coronaries that contribute to a risk for myocardial infarction (Norman 2008).

Table 9. Findings regarding arterial stiffness or endothelial function in former preterm and VLBW infants. Studies of neonates not included.

Reference	Age	Cases + Controls	GA, mean or range	Stiffness		Endothelial function	
				Higher in preterm infants Yes / No	Location	Lower in preterm infants Yes / No	Method
Oren et al. 2003	28	26 + 396	34	No	Aorta		
Lazdam et al. 2010	25	52 + 38	<37	Yes	Carotid artery	No	FMD
Indredavik Evensen et al. 2009	18	37 + 63	24—35			No	FMD
Edstedt Bonamy et al. 2005	17	46	<34	Opposite No	Aorta Brachial artery	No	Laser Doppler
Rossi et al. 2006	14	25 + 41	34	Yes	Aorta		
Singhal et al. 2001b	13—16	216 + 61	31			No	FMD*
Cheung et al. 2004	6—13	51 + 35	<37, AGA	No	Brachial artery		
Edstedt Bonamy et al. 2007, 2008a	7—12	60	<30	No	Carotid artery	No	Laser Doppler
Mikkola et al. 2007	5	47 + 13	28 (VLBW)			No	Laser Doppler
Norman and Martin 2003	3 mo	35 + 19	29			No	Laser Doppler

* absolute dilatation adjusted by basal diameter

Bone health

In some paediatric patients, prior to the influence of modern perinatal care, a history of VLBW birth with a specific habitus was obvious: a typical flattened head shape with a short biparietal in relation to frontooccipital diameter. Studies reveal that 26% of variation in VLBW newborn head shape is due to poor bone mineralization (Pohlandt 1994a). The mean BMD in adults born at all degrees of prematurity did not differ from that in the comparison subjects; whereas in VLBW/VLGA subjects BMD was lower (Table 10). A report of the Northern Finland Birth Cohort 1966 at age 31 included BMC and BMD in two sites in the radial bone. BMC in the distal radial bone was low in 13 of the 83 preterm born, instead of being low in predicted 8 (P = 0.07) (Laitinen et al. 2005).

Promotion of bone mineralization is possible by adequate calcium and phosphorous supplementation during infancy (Pohlandt 1994b; Backström et al. 1999). When a number of bone mineral studies in preterm subjects were initiated (Fewtrell et al. 1999; Jones et al. 2001; Weiler et al. 2002), intakes of calcium and phosphorous were below modern recommendations (Committee on Nutrition 1985; Kashyap 2007), reducing their generalizability to subjects born recently (Table 10).

Adults born at VLBW/VLGA are on average shorter than their peers born at term. Whether the low BMD in VLBW/VLGA subjects is adequate for their smaller size is unclear. Not all analyses have adjusted for current body size (Fewtrell et al. 2009). The differences in BMC or BMD often become attenuated when accounting for size by height adjustment (Fewtrell et al. 1999; Ichiba et al. 2000; Weiler et al. 2002; Dalziel et al. 2007). This attenuation may also be only partial (Wang et al. 2007). One study in neonates accounted for size by measuring BMD at a standard achieved bodyweight (5 kg); those born preterm had a clearly lower BMD (Kurl et al. 2000).

1.5 The role of aetiology and the role of growth as mediators of cardiovascular risk in VLBW/VLGA subjects

Preterm birth is a heterogeneous condition; its causes can broadly be divided into iatrogenic (a life-threatening condition necessitating preterm delivery), infectious, or idiopathic, the distinction between the latter two being difficult to make on an individual level. Whether the long-term outcomes of preterm birth differ by its aetiology has been neglected, although some studies have assessed the effects of being born preterm and SGA, and others have taken into account pre-eclampsia and/or gestational hypertension.

Table 10. Bone mineral density in preterm/VLBW/VLGA subjects. Effect of size adjustment.*

Reference	Age, years	Cases + controls	Case definition	Ca+P†	Whether BMD was lower in cases		
					Lumbar spine	Femoral neck	Total body
Kurl et al. 2000	Corrected age 3 months	58 + 17	GA<37	Yes	Yes / Yes		
Ganpule et al. 2006	6	84 + 614	GA<37	No report	No		No
Kurl et al. 1998	6—7	38 vs. ref	GA<37	No report	No		
Zamora et al. 2001	8	25 + 50	GA<37	No report	No	Yes / Yes	
Hamed et al. 1993	20—23	17 + 172	GA<37	No report	No	No	
Schlüssel et al. 2010	23—24	30 + 466	GA<37	No report	No	No	
Dalziel et al. 2007	30	174	Linear	No report	No	No	No
Jones et al. 2001	7—9	46 + 40	VLGA	No	No	Yes / No	
Ichiba et al. 2000	At term	21+ 6	VLBW	Yes	Yes / Yes		
Fewtrell et al. 1999	8—12	244 + 95	BW<1850	No	Yes / No	Yes / No	Yes / No
Weiler et al. 2002	16—19	25 + 25	VLBW	No	Yes / No	Yes / No	Yes / No
Fewtrell et al. 2009	20	201 vs. ref	BW<1850	No	Yes / ?		
Wang et al. 2007	7	83 + 36	VLBW	No report	Yes / Yes		Yes / Yes

No report, information was not represented or was unfound.

*In columns for lumbar spine, femoral neck, and total body, “Yes” indicates a lower BMD. The result with size adjustment comes after the slash (/).

† Ca+P suppl Yes= supplemental calcium and phosphorous given in the NICU.

Pregnancy disorders

In general, gestational hypertension and preeclampsia each includes gestational blood pressure elevation after midpregnancy; in pre-eclampsia, this is accompanied by proteinuria (National High Blood Pressure Education Program Working Group 2000).

Not all studies on VLBW/VLGA adults report pregnancy disorders or their influence upon the associations on which they focus (Table 3). One study reported that preeclampsia did not confound the relation between preterm birth and higher glycosylated haemoglobin (HbA1C%) at 45 years (Thomas et al. 2007). Although three VLBW and VLGA studies included no VLBW/VLGA effect adjusted for preeclampsia (Hack et al. 2005) or for pregnancy hypertension (Doyle et al. 2003; Keijzer-Veen et al. 2010), these disorders were unrelated to offspring blood pressure. Even after excluding those exposed to pregnancy hypertension, preterm birth was associated with higher blood pressure in adulthood (Dalziel et al. 2007). Such exclusion was not reported in a recent study on adolescents born at BW < 1250 g, in which preeclampsia and gestational hypertension had a six-mmHg increasing effect on systolic pressure at age 16 (Vohr et al. 2010). The POPS-19 study covered 588 19-year-olds born at either VLBW or VLGA: Hypertensive pregnancy had no effect on offspring blood pressure (Keijzer-Veen et al. 2005). Maternal preeclampsia and hypertension both associated with higher blood pressure in the prepubertal offspring. Adjustment for GA and BW attenuated the offspring blood pressure effect of maternal preeclampsia but not the effect of gestational hypertension (Geelhoed et al. 2010).

In a study among young adults born preterm, those born after a hypertensive gestation had higher cIMT and lower FMD than did those born after a normotensive pregnancy. This latter group, in turn, showed greater aortic stiffness (Lazdam et al. 2010). Preeclampsia was not associated with blood pressure, stiffness or endothelial function in a study of 34 preterm-born (GA ≤ 34) adolescent girls (Edstedt Bonamy et al. 2005). A history of preterm premature rupture of the membranes was associated with endothelial dysfunction in childhood (Liljedahl et al. 2008). Other early exposures in the POPS-19 study (smoking during pregnancy, asphyxia indicated by cardiotocography, neonatal glucococorticoids or respiratory distress syndrome) showed no influence on current blood pressure (Keijzer-Veen et al. 2005).

Preterm birth and effects of intrauterine growth

By definition, relative size at birth is smaller among those who are more mature within a BW-limited cohort, such as one born at VLBW (Arnold et al. 1991). In contrast, in a GA-limited cohort, relative size at birth is less likely to depend on

maturity. Among a VLGA group, being SGA contrasts with being AGA by indicating a more difficult starting point for extrauterine life. However, SGA among those with VLBW defines a group sharing comparable perinatal experiences with the AGA group. One reflector of these experiences is growth during the period corresponding to the third trimester. The typical slow growth of a VLBW subject who also is AGA results at the age of 34 to 37 postmenstrual weeks in a body weight SDS that is < -2.0, not very different from the typical weight of a peer born SGA at a postmenstrual age of 34 to 37 weeks.

What are the effects of being SGA on glucose regulation? Among those born at VLGA, being born SGA was associated with an increased risk for diabetes, with a HR of 3.4 (95% CI, 1.9 to 6.1) (Kaijser et al. 2009). However, SGA and BW SDS were unrelated to insulin sensitivity among one group of 57 VLGA/VLBW adults (Rotteveel et al. 2008b) and among one group of 37 VLGA children (Regan et al. 2006).

SGA among VLBW adults associated with hypertension in one study (Indredavik Evensen et al. 2009). However, in other studies among adults born at VLBW (Doyle et al. 2003; Hack et al. 2005), at BW < 2000 g (Irving et al. 2000) or at VLGA (Keijzer-Veen et al. 2005; Rotteveel et al. 2008b; Keijzer-Veen et al. 2010), a lower BW SDS was unrelated to blood pressure.

Associations of postnatal nutrition and growth with later cardiovascular risk factors

Early weight measurements of preterm infants offer a unique opportunity to investigate the time-window aspect in the DOHaD context (Page 23). Poor conditions are related to poor weight gain, although natural variation may be partially masked because weight is certainly one of the key variables that clinicians try to optimize during NICU care.

Weight SDS at term is comparable across individuals and cohorts regardless of degree of immaturity at birth, and it adds to intrauterine growth the growth from birth to term. Weight SDS at term as such seems not to be associated with systolic or diastolic pressures (Hack et al. 2005). Change in weight SDS from birth to term indicates weight growth during the time most term babies spend in utero. Rapid weight gain before term is not associated with blood pressure but in some studies relates to insulin resistance (Table 11 and 12).

In an extensive series of randomized controlled nutrition trials by Alan Lucas and colleagues, working in the 1980's and 90's in Cambridge, UK, descriptive reports on subjects with BW < 1850 g show that rapid early infant growth during the first two postnatal weeks was associated with a lower FMD in their childhood (Singhal et al. 2004). Although birth-to-term weight gain had no influence on glucose and

insulin, it was directly related to proinsulin and to 32-33 split proinsulin. Later fasting insulin in childhood was negatively associated with weight gain during infancy (Singhal et al. 2003), whereas with weight gain in childhood the association was positive (Fewtrell et al. 2000). In the POPS cohort, blood pressure was associated with weight at 12 months corrected age, but not with weights before that (Rotteveel et al. 2008b). However, weight at 3 months corrected age was positively associated with fasting insulin (Finken et al. 2006a). Within this study, weight gain during late infancy was positively associated with cIMT in young adulthood (Finken et al. 2006b). Another study, one investigating boys and girls at age 6, observed a weak positive effect of growth in infancy on systolic blood pressure (Belfort et al. 2010). The reason for this effect, however, could be that taller children do have higher blood pressure.

Findings of adverse effects of weight gain during late infancy and childhood need to be interpreted with caution. This analysis becomes trickier with an increasing age range because of the correlation between weights in childhood and in adulthood. For example, in subjects with BW < 1250 g, each 100 g more weight gained from birth to 3 years associated with an 8.5 mmHg higher systolic pressure at age 16 (Vohr et al. 2010). Correlation is obvious between that weight gain and weight at age 16, and may explain these findings.

Effect of infant nutrition: descriptive and experimental studies

Growth regulates nutrient intake and vice versa. One systematic review shows that fortifying the nutrition of preterm babies improves growth and bone mineral aggregation (Kuschel and Harding 2009). A descriptive infant nutrition study on 37 VLGA subjects studied at age 4 to 10 years by Regan et al. (2006) showed no association of neonatal macronutrient intakes with childhood insulin sensitivity. However, as compared with term controls, VLGA children had lower insulin sensitivity. In that study, the mean daily amount of protein administered to VLGA neonates was 2.3 g/kg (SD 0.3), which indicates a large portion falling below recommendations (about 3.0 g/kg) (Klein 2002).

Table 11. Infant weight gain in VLBW and other preterm cohorts.

Reference	Definition	Birth	Sex	Weight SDS at birth, mean (SD)	SDS at term, mean (SD)	SDS at 12 months post term, mean (SD)
Bazaes et al. 2004	VLBW	1994—96	Both	-0.9 (0.8)	- 0.7 (1.2)	-0.7 (1.0)
Belfort et al. 2010	GA<37	1985—86	Both	(38% SGA)	-0.6	-0.7
Hack et al. 2003	VLBW	1977—79	Boys	-0.7 (1.3)	-1.7 (1.3)	-1.7 (1.5)*
			Girls	-1.1 (1.1)	-2.0 (1.0)	-1.1 (1.4)*
Euser et al. 2005	VLGA, AGA	1983	Both	-0.1 (1.0)	-0.9 (1.3) †	-1.0 (1.2)
Finken et al. 2006a	VLGA / VLBW	1983	Both	−0.1 (1.0)	-0.9 (1.3) †	-1.0 (1.2)
Saigal et al. 2006	ELBW	1977—82	Boys	-0.7 (1.0)		-2.5 (1.5)
			Girls	-0.7 (1.0)		-2.0 (1.4)
Lucas and Morley 1994	BW<1850 g	1982—85	Both	-1.0	-2.3‡	

SDS, standard deviation score

* age 8 months post term

† age 3 months post term, studies share the same participants

‡ at discharge

Table 12. Among preterm infants, effects of postnatal weight gain on later cardiovascular health.

References	GA mean (SD) (range)	Inclusion	Birth year	N	Age, yrs	Associations of weight gain		
						Birth to term	Infancy	Childhood
Bazaes et al. 2004 AGA	29.2 (2.1)	VLBW	1994—96	60	5—7	Positive with insulin resistance (only crude)*		
Willemsen et al. 2009	32 (2.2) (27—36)	GA<37	1981—89	305	18—24	Positive with insulin secretion (only crude); Insulin sensitivity NS	Positive with insulin secretion (only crude); Insulin sensitivity NS	
Belfort et al. 2010.	34 ( ) (25—37)	BW<2500 and GA<37	1985—86	911	6.5		Positive with blood pressure (no height adjustment)	
Hack et al. 2005	29.6 (2.2) ()	VLBW	1977—79	195	20.1	(Blood pressure NS) BW not in model		
Fewtrell et al. 2000*	31.1 (2.7) (25-39)	BW<1850	1982—85	385	9—12	NS with glucose and insulin	Negative with fasting insulin	Positive with fasting insulin
Singhal et al. 2003*, Singhal et al. 2001a*	31.1 (2.7) (25-39)	BW<1850	1982—85	216	13—16	Positive with 32-33 split proinsulin NS with blood pressure	NS with 32-33 split proinsulin, NS blood pressure	NS with 32-33 split proinsulin, NS with blood pressure
Regan et al. 2006	27.7 (2.4) ()	VLGA	No report	37	4—10	NS with insulin resistance	Positive with insulin resistance	Positive with insulin resistance

NS, nonsignificant

* Studies share the same participants

While summarizing randomized controlled nutrition studies by Alan Lucas' group, I concentrate on preterm infants otherwise, but include one study on term born SGA subjects: In 1993 to 1995, the group conducted a trial involving term SGA infants who were originally on standard formula (Fewtrell et al. 2001). Those infants who were thereafter randomized to enriched formula were at age 7 years slightly taller and heavier than those who were randomized to standard formula (Singhal et al. 2007). Even after adjustment for this difference in body size, they also had as 7-year-olds 3.5 mmHg (95% CI, 0.7 to 6.2) higher diastolic pressure than did those on standard formula. For systolic pressure, the difference was 2.0 mmHg (-1.3 to 5.3). It is notable that these infants received the enriched formula for 9 months.

The median duration of a randomized diet was 30 days in another study by the same researchers. It involved infants with BW < 1850 g. The infants were on this diet for the length of their hospital stay or until they reached a weight of 2000 g. The diet consisted of banked breast milk (1.1 g protein /100ml), standard formula (1.5 g/100ml), or preterm formula (2.0 g/100ml) (Lucas and Morley 1994). In those 758 preterm infants who underwent blood pressure measurements at age 8 years, the preterm formula had no effect on blood pressure. It also had no influence at 13 to 16 years on arterial endothelial vasodilatory function as measured by FMD (Singhal et al. 2004) or on fasting insulin. The 32-33 split pro-insulin concentration, however, was higher for preterm infants receiving nutrient enrichments than for those without but was similar to that of the participants born at term (Singhal et al. 2003). Post hoc, at 13 to 16 years, the group who had received banked breast milk had the lowest diastolic blood pressure (Singhal et al. 2001b).

The fact that nutrition enrichment was unrelated to blood pressure and fasting insulin in adolescents in these studies may depend on the short duration of this intervention. Furthermore, the number of subjects in individual diet categories ranged between 60 and 150, a number perhaps insufficient. Therefore, researchers should aim at discovering the potential effects of infant nutrition on the cardiovascular prognosis of the preterm infant.

1.6 Summary

1. About one in each one hundred live-born neonates is born at a VLBW.
2. Cardiovascular disease and osteoporosis are concerns at population level. Cardiovascular disease is among the four most important causes of death worldwide.
3. Those born at VLBW have higher blood pressure than do those born at term. It is likely that the difference is sufficiently large to have significance both in men and in women.
4. Impairments in glucose regulation in VLBW subjects are likely, because insulin resistance occurs in VLGA children and in adults with BW < 2000 g. Some studies show glucose intolerance in adults born preterm. Whether it exists in VLBW adults is unknown.
5. High cIMT, arterial stiffness, or endothelial dysfunction are uncommon features in preterm subjects at young ages. In adult VLBW subjects, the occurrence of these outcomes is unknown.
6. VLBW subjects in childhood or prepuberty have lower bone mineral density. Whether they manage to recover normal bone mineral density in young adulthood is unknown. Some suggest that the effect of preterm birth on the bones is due to smaller body size. When studying BMD in adults with VLBW, considering the effect of body size is important.
7. Some data suggest that among VLBW subjects, rapid weight gain
   7.1. according to one study during the first two postnatal weeks relates to endothelial dysfunction
   7.2. from birth to term relates to insulin resistance
   7.3. during the period of infancy after term lacks any clear effect on blood pressure or on glucose regulation

2 Aims

The primary aim was to evaluate the health of very-low-birth-weight (VLBW) adults and compare it with that of term-born control subjects. The main hypothesis was that, for cardiovascular disease and osteoporosis, VLBW adults have more risk factors:

1. higher office and ambulatory blood pressure
2. higher insulin resistance, lower glucose tolerance
3. higher triglycerides, higher total cholesterol, lower HDL cholesterol
4. more adipose tissue or its more central distribution in the body
5. impaired vascular vasodilatative function in the right brachial artery
6. thicker intima-media layer in the right carotid artery
7. lower bone mineral density in the lumbar spine, the femoral neck, and the whole body

A secondary aim was to discover whether the risk factors that possibly emerge are, at least partially, attributable to

8. higher incidence of parental cardiovascular disease
9. poor maternal health or smoking during pregnancy
10. lower family socioeconomic status
11. VLBW subject's current body size and composition
12. their unhealthy life style, including smoking, infrequent exercise

Another secondary aim was to assess how the outcomes relate to

13. poor fetal growth
14. neonatal morbidity and abnormalities in early infant growth

3 Subjects and methods

3.1 Cohort of very low birth weight infants

In 2004 we invited young adults belonging to a pre-existing cohort of VLBW subjects (Järvenpää and Granström 1987; Järvenpää et al. 1991). During 1978 to 1985, Dr Järvenpää began a follow-up study including a total of 474 VLBW infants admitted to the NICU of Childrens's Hospital at Helsinki University Central Hospital. The province of Uusimaa had centralized all VLBW neonatal care into this tertiary centre. Of the original subjects, 335 (71%) survived until NICU discharge. Information in the research documents included gestational age as assessed by last menstruation date or by Dubovitz score (Järvenpää A-L, personal communication). Structured data collection and clinic visits at 4, 9, and 15 months postnatal age included a doctor's statement as to any cerebral palsy and as to overall cognitive outcome. Members of the cohort with BW < 1000 g showed normal neurodevelopment in the majority of survivors (Järvenpää et al. 1991).

The Population Register Centre of Finland provides the regular home address for residents in Finland at an accuracy of 99% (Statistics Finland 2010b), and the vitality register is credible (Statistics Finland 2010a). Through this data, we traced the subjects. Because we aimed at having 140 per group in our main analysis, and because we planned a quite laborious set of clinic visits, we chose to invite only those 255 adults with VLBW residing within 110 km of our study clinic in Helsinki. A high participation rate among those whom we would invite was one of our main aims when planning the protocol. However, we invited all the subjects regardless of their known disabilities.

3.2 Cohort of subjects born at term

For each VLBW subject we chose a control subject from records of consecutive births at the five birth hospitals serving the area. A suitable control subject was born at term and after the VLBW subject in the same hospital, was not SGA (BW SDS < -2.0), was of the same sex, and currently resided within 110 km of Helsinki. We invited more control than VLBW subjects, and more men than women because we aimed at sets of VLBW and control participants of similar sex and age distributions.

3.3 Invitation to the study

Our group contacted the public media to promote the subject of life course medicine and the fate of preterm infants. Finland's leading daily newspaper dedicated a page to these subjects (*Helsingin Sanomat*, April 13th, 2004). To the VLBW subjects, we wrote letters otherwise similar to those we wrote to term-born subjects, except for

the introductory lines. After 1 or 2 weeks, we contacted all the young adults by telephone and if they agreed, we scheduled a visit. The researchers and personnel were unaware of birth status and other background information of those invited.

3.4 Gathering the data

From hospital records, we gathered information on pregnancy, including the mothers' health and smoking during pregnancy. Other information included anthropometry at birth and data on neonatal care and on later growth. When GA data from many sources did not match, we chose the data in the original research files that were updated during the NICU stay. We also gathered child-welfare clinic data on infant growth. We used the data in the original research files, which defined bronchopulmonary dysplasia as need for supplementary oxygen at postnatal day 28 and a typical chest x-ray (Northway et al. 1967). We defined maternal preeclampsia as blood pressure exceeding 140/90 mmHg on more than one occasion after mid-pregnancy, together with proteinuria of 0.3g/24 h or more or a positive dip-stick and without a history of hypertension medication before pregnancy or during the first trimester (National High Blood Pressure Education Program Working Group 2000). For gestational hypertension, we used the same blood-pressure criteria but without the proteinuria.

3.5 Questionnaire

As attachments in the invitation letter to the young adults was information about the study and a health questionnaire. The questions concerned current education, diagnosis of cerebral palsy, current medication, leisure-time exercise frequency and duration, parental diagnosis of type 2 diabetes, hypertension, myocardial infarction, or stroke. Participants had an opportunity to complete the questionnaire during their visit. In order to achieve complete and correct data, we encouraged the young adults to check questionable issues with their parents, if necessary.

3.6 Clinical measurements

We planned a study protocol with a very wide range of measurements. This thesis concentrates only on those related to risk for osteoporosis, type 2 diabetes or cardiovascular disease. The protocol aimed at reducing any possibility of measurements affecting each other. The participants had to spend a total of about 8 hours at our study facilities during the 3 days of attendance. We provided no monetary compensation other than travel costs. We offered a detailed individual report comprising the participant's core meaningful data measured at our clinic, including body–composition measurements. After an opportunity to consult the research nurses and doctors, the invitees gave their written informed consent.

The participants fasted overnight before they attended the clinic. After a 10-minute rest, we measured blood pressure two or three times at one-minute intervals with an automatic sphygmomanometer (Omron HEM-773-E, Omron Healthcare Europe, Hoofddorp, The Netherlands). Of two successful measurements per participant, we calculated the mean.

After we had drawn a fasting blood sample, each participant underwent a standard 75-g oral glucose tolerance test, and we drew a blood sample for glucose and insulin at 120 minutes. All samples were frozen. A hospital laboratory measured glucose concentrations with a spectrophotometric hexokinase and glucose-6-phosphate dehydrogenase assay (Glukoquant glucose/hexokinase; Roche Diagnostics, Mannheim, Germany) with a Hitachi Modular automatic analyzer (Hitachi Ltd, Tokyo, Japan). At a glucose concentration of 4.7 mmol/L (84.7 mg/dL), the interassay coefficient of variation (CV) is 2.3% (Kunst et al. 1984). For insulin measurements, the assay was a time-resolved immunofluorometric assay (Perkin Elmer Wallac, Turku, Finland) with a detection limit of 0.5 mU/L (3 pmol/L). The interassay CV was less than 4% in the concentration range of 6 to 104 mU/L (36 to 624 pmol/L) (Toivonen et al. 1986). We calculated the homeostasis model assessment insulin-resistance index (HOMA-IR) by multiplying fasting serum insulin concentration (in mU/L) and fasting plasma glucose concentration (in mmol/L) and dividing it by 22.5 (Matthews et al. 1985). During the oral glucose tolerance test, the participants completed the health questionnaire and completed some more questionnaires (beyond the scope of this thesis).

For fasting serum samples, the laboratory measured lipid levels by enzymatic methods (HDL-C plus, second generation; cholesterol CHOD-PAP; and triglycerides GPO-PAP; Roche Diagnostics) with the Hitachi Modular analyzer; CV range from 2.4 to 4.6%. The laboratory workers were unaware of each individual subjects' birth weight status.

3.7 Measurements at home

By computer, we randomly selected a subgroup for ambulatory blood pressure measurement. We instructed all the participants how to keep a food diary for 3 days and, regarding the subgroup we selected, how to wear an oscillometric SpaceLabs 90207 ambulatory blood pressure monitor for 24 hours (Spacelabs Healthcare, Issaquah, WA, USA) (O'Brien et al. 1991). We programmed this device to measure blood pressure once every 30 minutes during the day and once an hour between 10 pm and 7 am. The participants wrote in a diary their sleep times and, in case they went swimming or took a shower, the periods when not wearing the blood pressure monitor.

After completing the measurements at home, each participant returned the device and the two diaries to the clinic. Together with each participant, a nutritionist

double-checked the data regarding consumed food items and nutritional supplements; with a current version of the Finnish Food Composition Database, we obtained, for each individual, the average daily intake of calcium and vitamin D (National Public Health Institute 2002).

3.8 Separate visits for bone mineral density and ultrasound

We scheduled a DXA scan at the Department of Radiology of the Helsinki University Central Hospital for everyone except anyone who was pregnant. A dual-energy x-ray densitometry device (DiscoveryA, Hologic, Hologic Inc., Bedford, MA, USA) scanned the whole body to obtain bone mineral density, fat percentage, and lean body mass. Lean body mass is the total body mass with the fat mass and bone mass subtracted. Areal BMD gives the amount of bone mineral in grams within the bone area in an anteroposterior projection, divided by the area in cm^2. By dividing BMC in the lumbar spine by the 1.5^{th} power of the bone area, we calculated, for the lumbar spine, a bone mineral apparent density (BMAD), which is a surrogate of true volumetric BMD and, unlike areal BMD, is not correlated with bone area (Carter et al. 1992).

With the aid of computer software, we randomly selected a subgroup for an ultrasonographic evaluation of carotid-artery wall structure (cIMT) and brachial artery endothelial function (FMD). Within a couple of weeks after the first visit, after an 8-hour abstinence from food, coffee, and tobacco, participants in this subgroup attended the Cardiology Unit at the Hospital for Children and Adolescents in the morning hours. They completed a structured questionnaire on their medication and recent illnesses. We used the unit's ultrasound equipment (Versions Vivid 5, Vivid 4, or Vivid-7-Dimension, GE Ultrasound, Horten, Norway) with a linear 10 MHz transducer to obtain longitudinal images of the carotid and brachial arteries.

At end-diastole, for measurement of cIMT and the lumen diameter, we took two images of the right common carotid artery. For measurement of FMD, we first placed a sphygmomanometer on the participant's right forearm but left it uninflated. We took several (average 7.1, SD 2.9) images of the right brachial artery, inflated the cuff to 300 mmHg for 5 minutes, and released it rapidly. At every third end-diastole from 30 to 120 seconds after deflation, we took an image (Corretti et al. 2002). We utilized semiautomatic image analysis software that applies a fuzzy-logic contour-tracer technique (Automated Measurement System, AMS, Chalmers University of Technology, Gothenburg, Sweden) (Wendelhag et al. 1997). We measured cIMT in the carotid and lumen diameters in each artery as the mean of measurements at each pixel width within a 1.0 cm-long sample length. I performed all but one of the scans and analyzed all images. I obtained CV for another group of adults. For cIMT it was 1.2% and for brachial diameter, 1.7%. Although absolute cIMT was a primary outcome, we also calculated an intima-media lumen ratio. FMD

is the maximal percentage increase in brachial artery lumen from the baseline median, and together with cIMT served as the primary outcome variable in the ultrasonographic substudy.

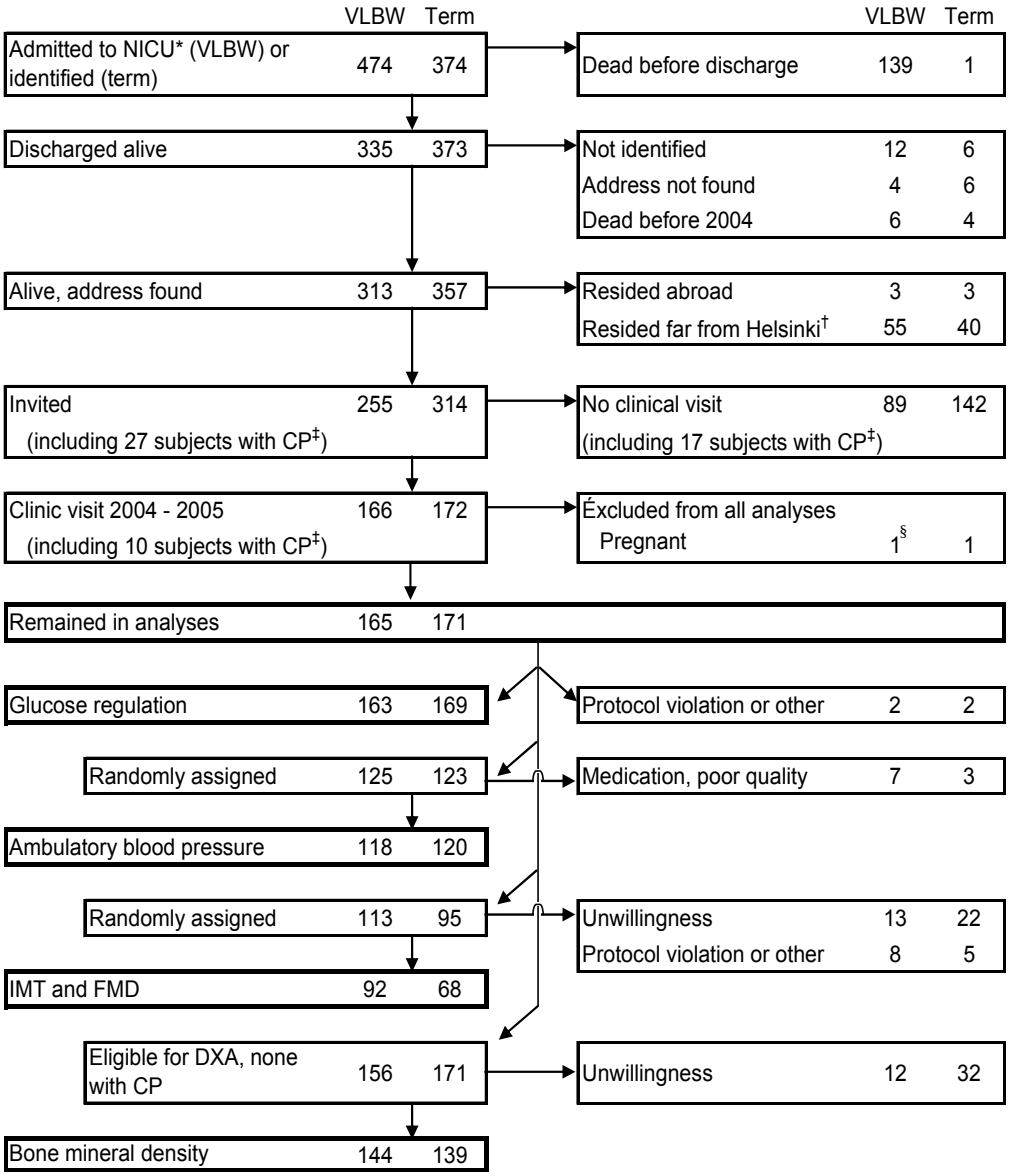
3.9 Statistical methods

A meaningful group difference for each risk factor had to be decided. In elderly hypertensive patients, a risk reduction of 13% for a combined cardiovascular end-point resulted from systolic pressure reductions of 4.0 mmHg (Hansen et al. 2006). In young adults, 4.0 mmHg corresponds to 0.4 SD (Leino et al. 1999). We aimed at not missing any difference of 4.0 mmHg or more. With an alpha level of 0.05 and statistical power of 90%, in two-sided analysis we needed 140 subjects in each group to achieve this. We considered a 0.4 SD-unit difference clinically significant for most other variables as well and used it to calculate required sample sizes. Ambulatory pressures and ultrasonography variables were exceptions; we accepted a power of 80% after reducing the required number of participants. To detect a 3-mmHg difference required 113 participants per group. A 2.0 percent-unit FMD difference or a 50-µm cIMT difference, each corresponding to 0.50 standard deviations (Juonala et al. 2005), required 64 per group. Our main reason for accepting lower power was equipment availability.

We analyzed the data with help from the Statistical Package for Social Sciences (SPSS), versions 14 to 17 (SPSS Inc., Chicago, IL, USA). We compared frequencies in groups with Pearson's chi-square test or – when adjustment was needed – with logistic regression. We visually inspected the distribution of each outcome variable to detect deviations from normality and, prior to further analysis, we calculated natural logarithms of current weight and BMI, triglycerides, fasting insulin, and 2-hour glucose. For these variables, we described distributions by geometric means and geometric standard deviations. We estimated and tested crude differences between groups with an unpaired Student's t-test, but usually applied linear regression because of adjustments at least for age and sex.

We fitted logistic and linear regression models to see whether VLBW and term groups differed. We chose predictor variables according to their a priori importance. By comparing difference estimates before and after adding a new variable, we estimated the mediating/confounding effect of that variable. If the effect was small (less than a 10% change), that variable could be omitted from the further models in order to keep them as simple as possible.

Figure 5. Flow chart of the Helsinki Study of Very Low Birth Weight Adults.



cIMT, carotid intima-media thickness; CP, cerebral palsy; DXA, dual X-ray absorptiometry; FMD, flow mediated dilatation; NICU, neonatal intensive care unit; VLBW, very low birth weight.

* Term subjects were identified from the birth-hospital records of each infant.

† Only those residing within 110 km were invited.

‡ (CP) data are from VLBW subjects' clinical visit at 15 months of age.

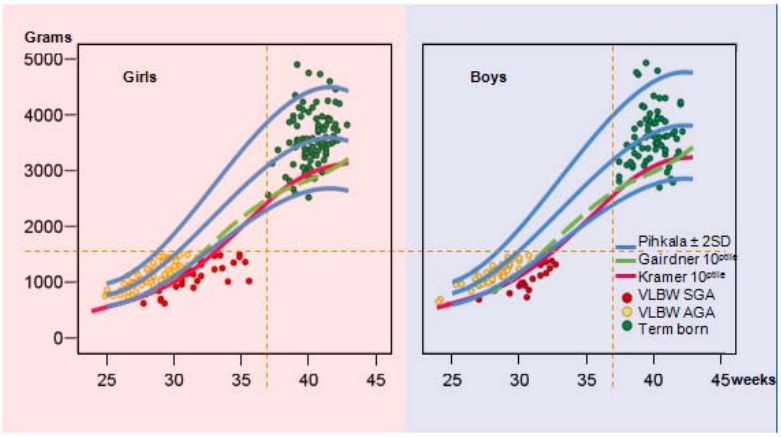
§ The VLBW woman excluded because of pregnancy also had CP.

4 Results and their evaluation

4.1 Formation of study groups and participation (I-IV)

Participation rates at different stages of the study can be calculated from the absolute numbers presented in a flow chart (Figure 5, page 66). Briefly, no dropout as a result of family withdrawal occurred during the NICU stay, but 29.3% of the infants died before hospital discharge. Of those invited in young adulthood, participation rates at the clinic visit were 65.1% among the VLBW subjects and 54.8% among those born at term. Of the 338 participants, 43.3% of the VLBW and 40.6% of the term-born were men. Participants and nonparticipants were otherwise similar in terms of perinatal characteristics, but of the 27 invited with CP at 15 months, only 10 participated. Regarding the 166 VLBW participants, GA ranged from 24 to 35 weeks, as illustrated in Figure 6 and Table 13. That figure compares some SGA limits and illustrates quite similar categorizations of VLBW infants, with larger categorization variations among the late preterm subjects.

Figure 6. Birth weight by gestational age -scatterplot



Dots represent birth weights of participants in the clinical study. The lowest blue line indicates our threshold for being small for gestational age. The red and green curves indicate two alternative thresholds (Gairdner and Pearson 1971; Pihkala et al. 1989; Kramer et al. 2001)

Subgroups in substudies were those 293 who were able to and agreed to undergo DXA, and those 238 and 160, respectively, whom we randomly selected for the ambulatory blood pressure and ultrasonography substudies. Comparison of

participants in each substudy with the remainder of the 338 participants in the clinical study showed that perinatal characteristics were otherwise similar, but among the VLBW ultrasonography participants, gestational age was 0.8 weeks longer and an occurrence of maternal preeclampsia was slightly more frequent.

Our cohort of VLBW infants represented all VLBW infants born in the county of Uusimaa, because of the successful centralization of treatment of VLBW infants during the recruitment period, 1978 – 1985 (Järvenpää A-L 2010, personal communication). The survival rate of 70.7% was comparable to other VLBW cohorts starting recruitment during the same period (Tables 3 and 13). In populations recruited later, during the late 1980's, survival approached 80%.

As mentioned, we chose to measure several outcomes during a single series of visits. Although some of those invited perhaps participated because of the extensive protocol giving information on their own health which would have been otherwise difficult to obtain (such as DXA), a shorter protocol might have resulted in a higher participation rate. Participation rates in other studies with a 2-decade follow-up are quite similar to ours (Tables 3 and 13). Particularly data on participation rates in control groups of other studies is frequently missing, or controls may be gathered by means of advertisements, resulting in a selection effect difficult to evaluate.

Although participants and nonparticipants were in almost all aspects similar, nonparticipation may have caused biased results. However, this would happen only if our major point of interest, a VLBW effect, had differed among the participants and nonparticipants. One possible cause of such an effect-difference could be that a number of the young adults born at VLBW participated because of loyalty towards the health care system or the staff that once provided their neonatal care. Other reasons for participation would thus be more frequent among those born at term. Speculatively, one of the important motivating factors in participation of any young adult could be a personal interest in one's own health. A high proportion of health-oriented participants in the term-born group could thus cause bias towards a healthier outcome among the term-born participants. We did not collect information, however, on health orientation or any possible impact of loyalty on participation. Most VLBW young adults had had no medical follow-up after age six, which could reduce the potential of such a selection-by-loyalty bias.

Young adulthood may not be the ideal invitation age, because a young adult cannot always easily arrange a free day off from work or other duties. As insulin resistance tends to peak in puberty (Amiel et al. 1986), an invitation in the early teens would cause problems regarding different pubertal stages; a postpubertal age such as 17 might be ideal. At that age, only a few regularly are employed.

Table 13. Participant characteristics in the Helsinki Study of VLBW Adults with comparison data from Table 3.

Cohort name or area	Helsinki, Finland	Cleveland, Ohio, USA	Melbourne, Australia
References, main findings on cardiovascular-disease risk factors / Additional references	I,II,III: Higher blood pressure and impaired glucose regulation. Similar cholesterol and triglycerides / Räikkönen et al. 2008; Pyhälä et al. 2009; Kajantie et al. 2010.	Hack et al. 2005: Higher blood pressure, among men, only when adjusted for current weight and height/ Hack et al. 2002m 2003	Doyle et al. 2003: Higher ambulatory blood pressure, day and night / Kitchen et al. 1982a, 1982b
Case recruitment	VLBW, admitted to Childrens Hospital, Helsinki University	VLBW, admitted to Rainbow Babies and Children's Hospital	VLBW births (consecutive) at Royal Women's Hospital.
Control recruitment	From hospital records, same sex and age	From schools at age 8 years, matching the catchment areas	From the same hospital in the newborn period
GA,wks (SD) (range)	29.2 (2.2) (24 to 35)	29.6 (2.2) ()	28.8 (2.0) (24 to 30)
Birth years	1978—1985	1977—79	1977—82
Survival, participation	71%, 65% vs. 55%	64%, 76% vs. 64%	53%, 74%
Cases + controls at age (yrs)	166 + 172 at age 22.4	195 + 108 at age 20.1	156 + 38 at age 18.6
Excluded disabled (n)	10 with cerebral palsy,* 2 pregnant	25 neurosensory impairment, 12 pregnant	3 disabled
Sociodemographics, highest parental education	5.5% vs. 3.6% elementary 35% vs. 49% university	54% vs. 53% Afro-American 17% vs. 10% less than high school	No report
Gestational hypertension	4% vs. 15%	No report	24 vs. 3
Preeclampsia	21% vs. 8%	10% vs. no report	No report
Smoking during pregnancy	19% vs. 16%	No report	No report
Antenatal glucocorticoids	3%	0	53
Current smoker	21.5% vs. 33.7%	Men: 57% vs. 59%. Women: 40% vs. 48%	No report

* data presented with and without exclusion of those with cerebral palsy

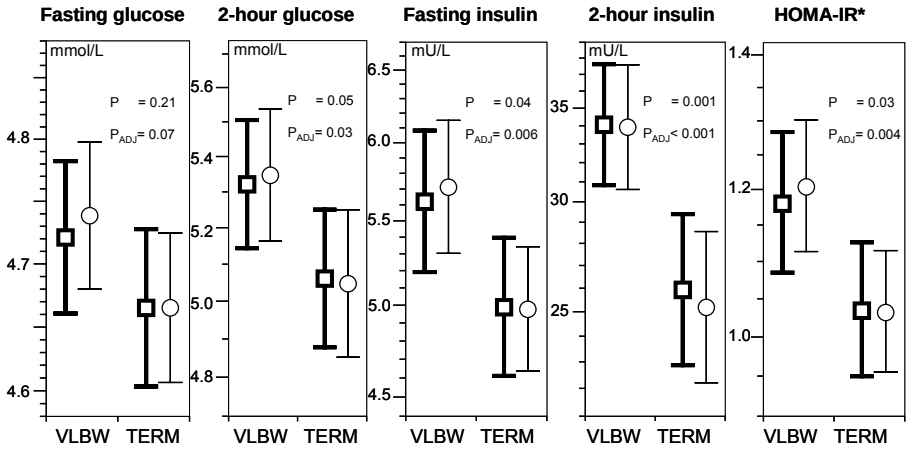
4.2 Associations between VLBW birth and cardiovascular disease and osteoporosis risk factors in young adulthood (I—IV)

For each outcome, we first tested whether the VLBW effect is similar for men and women. This testing revealed that the VLBW effect on diastolic ambulatory pressure differed by gender; the interaction P value (see page 47) was 0.04 for diastolic and 0.10 for systolic ambulatory pressure. Among women, those born at VLBW had a higher diastolic ambulatory pressure, whereas among men, this pressure was, between VLBW and term-born subjects, similar. The VLBW effect was also similar by gender for all other outcomes, allowing presentation of our results for men and women pooled.

Lipid metabolism (I)

After an overnight fast, concentrations of triglycerides and of total-, and HDL-cholesterol in the two groups were equal. Children born SGA at term do have higher total cholesterol in some studies (Tenhola et al. 2000; Mogren et al. 2001), but systematic reviews show that findings on any relationship between birth weight and cholesterol are inconsistent (Lauren et al. 2003; Huxley et al. 2004). In most studies of preterm adults, neither LDL nor total cholesterol, nor triglyceride levels are elevated (Irving et al. 2000; Finken et al. 2006b; Dalziel et al. 2007; Rotteveel et al. 2008a; Cooper et al. 2009), and our results agree.

Figure 7. Glucose regulation in VLBW subjects



Geometric means with 95% confidence intervals. (—□—) unadjusted variables, (—○—) variables adjusted for age, sex, BMI, exercise intensity, parental diabetes, and parental education. Printed with permission; essentially the same figure appears in the *New England Journal of Medicine*, 2007 356(20):2053 (I).

Glucose regulation (I)

Estimates of mean concentrations of all glucose-regulation measurements were higher in the VLBW subjects than in the term born (Figure 7). For fasting plasma glucose, the sex- and age-adjusted difference was 1.0% (95% CI, -0.7 to 2.8), whereas for all the other variables, the difference was statistically significant. For 2-hour glucose, it was 5.3% (0.2 to 10.7) and for fasting insulin, even more. These differences persisted even with further adjustment for exercise intensity, parental diabetes, and parental education (Figure 7, Table 14). As compared with differences in fasting insulin, the HOMA-IR index in all analyses behaved similarly, and the differences in 2-hour insulin were consistently clearer.

The fasting plasma glucose of five VLBW and six term subjects fell within ADA (American Diabetes Association 2006) limits for impaired fasting glucose (≥ 5.6 and < 7 mmol/L) (≥ 100 and < 126 mg/dL). Two hours after a per-oral glucose load, plasma glucose in 10 VLBW and in 8 term-born subjects fell within the limits of impaired glucose tolerance (≥ 7.8 and < 11 mmol/L) (≥ 140 and < 200 mg/dL according to both ADA and WHO (1999) criteria (P = 0.63, Fischer's exact test). One-third of the VLBW subjects had fasting insulin within the range of the highest quartile among the controls (adjusted for age, sex and BMI, P = 0.003). No subject had type II diabetes.

In one population comprising mostly term-born individuals, a history of being born SGA was related to impaired glucose tolerance and type 2 diabetes (Hales et al. 1991). In 2008, a meta-analysis confirmed an inverse relationship between BW and risk for diabetes (Whincup et al. 2008), and other studies have suggested that preterm birth is also an independent predictor of this disorder (Kaijser et al. 2009). In adults born at BW < 2000 g, most of them preterm, fasting insulin was higher (Irving et al. 2000), and in prepubertal children born at VLGA, insulin sensitivity was lower than for control subjects (Hofman et al. 2004; Regan et al. 2006). Our results confirm that a a similar contrast appeared in VLBW adults: insulin resistance higher and glucose tolerance lower. One of the weaknesses of an OGTT is that a large oral dose of carbohydrate is not an ordinary event in daily life. One of OGTT's notable strengths is that it predicts type 2 diabetes well (Nijpels 1998).

Table 14. VLBW vs. term comparison: Glucose regulation, blood pressure, vascular function, and bone health.

Variable	VLBW	Term	Difference, sex and age adjusted	Difference, full model*
Glucose regulation				
Fasting insulin, mU/L	5.61 (1.66)†	5.01 (1.72†)	12.6% (0.8 to 25.8)	16.7% (4.6 to 30.2)
2-hour plasma glucose, mmol/L	5.34 (1.25)†	5.05 (1.27†)	5.3% (0.2 to 10.7)	5.6% (-1.2 to 12.8)
Blood pressure				
Systolic, mmHg	121.6 (12.6)	117.5 (10.8)	3.9 (1.3 to 6.4)	5.4 (2.7 to 8.1)
Diastolic, mmHg	78.7 (8.7)	75.2 (8.0)	3.5 (1.7 to 5.2)	4.5 (2.5 to 6.4)
24-hour blood pressure				
Systolic, mmHg	119.0 (9.3)	117.2 (8.0)	1.8 (-0.4 to 4.0)	3.1 (0.5 to 5.5)
Diastolic, mmHg	70.5 (7.1)	70.0 (5.6)	0.8 (-0.8 to 2.4)	0.9 (-1.0 to 2.8)
Arterial health				
Intima-media thickness, µm	437 (54)	426 (41)	11 (-5 to 26)	10 (-7 to 27)‡
Flow-mediated dilatation, %	6.9 (4.0)	5.8 (3.3)	1.1 (0.0 to 2.2)	1.5 (0.3 to 2.7)‡
Bone health				
Lumbar spine BMD Z score	-0.93 (0.98)	-0.41 (1.05)	-0.51 (-0.75 to -0.28)	-0.26 (-0.51 to -0.01)
Femoral neck BMD Z score	-0.42 (0.85)	0.14 (0.97)	-0.56 (-0.78 to -0.34)	-0.40 (-0.64 to -0.17)

BMD, bone mineral density. For difference estimates, find 95% confidence intervals.

* A full model included; *for fasting insulin,* sex, age, body mass index (BMI), exercise intensity, parental diabetes, and parental education; *for 2-hour plasma glucose*, sex, age, current lean body mass and height, exercise intensity, parental diabetes, and parental education; *for blood pressure*, sex, age, BMI and height, smoking, maternal preeclampsia or gestational hypertension, maternal or paternal hypertension, and parental education; *for arteries*, sex, age, BMI and height; *and for BMD Z scores*, sex, current height, and exercise intensity.

† For fasting insulin and 2-hour plasma glucose, we report a geometric mean and a geometric SD. A geometric SD is the relative change in the original variable that corresponds to an absolute change of 1 SD unit in a logarithm-transformed variable.

‡ Data-analysis after Study III article submission.

Blood pressure (I, II)

Among the 334 subjects attending their first clinic visit, VLBW adults had 3.9 mmHg (95% CI, 1.3 to 6.4) higher office systolic pressure and 3.5 mmHg (1.7 to 5.2) higher office diastolic pressure than did the term-born controls. In a subgroup of 238, 24-hour mean systolic pressure for VLBW subjects was 1.8 mmHg (-0.4 to 4.0) higher, whereas 24-hour diastolic pressure was similar (difference 0.8 mmHg, -0.8 to 2.4), as compared with values in those born at term (Table 14). Adjusting for covariates strengthened the differences, and the difference in 24-hour systolic mean pressure became statistically significant.

Based on American Heart Association criteria for hypertension (Pickering et al. 2005), (medication for hypertension or blood pressure > 140/90 mmHg), 10 VLBW and 3 term-born subjects had daytime hypertension (OR 4.0, 95% CI 1.1 to 14.8). A normal (< 135/85 mmHg) daytime pressure combined with an office blood pressure of > 140/90 defined white-coat hypertension (Pickering 2003); nine in each group.

The 3.9-mmHg higher systolic pressure in our VLBW subjects agrees with most of the confidence intervals reported earlier. The studies' findings agree with an estimate of 3 to 4 mmHg higher blood pressure in VLBW/VLGA adults. In our study, this finding was stronger among women, which is in agreement with findings from a study of 195 VLBW adults (Hack et al. 2005) and a study within the Northern Finland Birth Cohort (Järvelin et al. 2004). Other data, however, show clear evidence of higher blood pressure in all VLBW adults, including men: Office and ambulatory pressures were higher in 156 VLBW adults (Doyle et al. 2003); 14,000 male conscripts who were born preterm had higher blood pressure than did their term born peers, with risk for increasing hypertension with decreasing GA (Johansson et al. 2005). Unfortunately, we studied ambulatory blood pressure only in a subgroup of 238 subjects. This number of subjects agreed with our study plan, based on the smaller between-subject variance in ambulatory than in office pressure (Doyle et al. 2003). A larger subgroup would have more reliably shown any possible sex-difference in the VLBW effect.

Ambulatory blood pressure provides information on cardiovascular risk that is additive to the information from office blood pressure (Clement et al. 2003). Our VLBW subjects had 1.8 mmHg (-0.4 to 4.0) higher 24-hour systolic pressure, i.e. not significantly different from a null hypothesis of no difference, although differences adjusted for covariates were statistically significant. The Doyle group's results (2003), however, showed ambulatory blood pressure in adults to be higher in men and women born at VLBW. In any case, it seems likely that the differences between VLBW and term-born subjects are stronger for office blood pressures, supposing a role for reaction to measurement stress. The similar prevalence of white-coat hypertension in our groups left this idea unsupported, but a reaction to a

standardized psychosocial stress test in a further substudy of our cohort supported it by showing higher diastolic blood pressures in VLBW subjects than in term-born subjects after but not before the test (Pyhälä et al. 2009).

Arterial health (III)

VLBW birth was not associated with a lower FMD (Table 14). In fact, FMD in VLBW subjects was 1.1 percent units higher than in the term born subjects (P = 0.06). Among the VLBW participants, cIMT was 437 μm (SD 54), which was 11 μm (95% CI, -5 to 26) thicker than among the term borns. After considering the smaller lumen size among VLBW subjects by calculating an intima-media lumen ratio, their intima media was thicker, and the difference became statistically significant. Means (SDs) were 8.9% (1.6) versus 8.4% (1.0) (P = 0.03).

The fact that cIMT difference was nonsignificant contradicted our hypothesis and went against the recent cIMT findings among young adults born preterm (Lazdam et al. 2010). However, our intima-media lumen ratio finding could indicate cardiovascular risk; see discussion below including other aspects of body and vessel size.

In a study of infants born at BW < 1850 g who were evaluated during puberty, Singhal et al. (2001a) showed FMD findings that were similar to ours: no endothelial dysfunction in the preterm group. Other studies, ones smaller than ours, replicated this in preterm children and adults (Table 9). The larger power of our study is important and, and together with others, it suggests no endothelial dysfunction as existing among young adults born at VLBW.

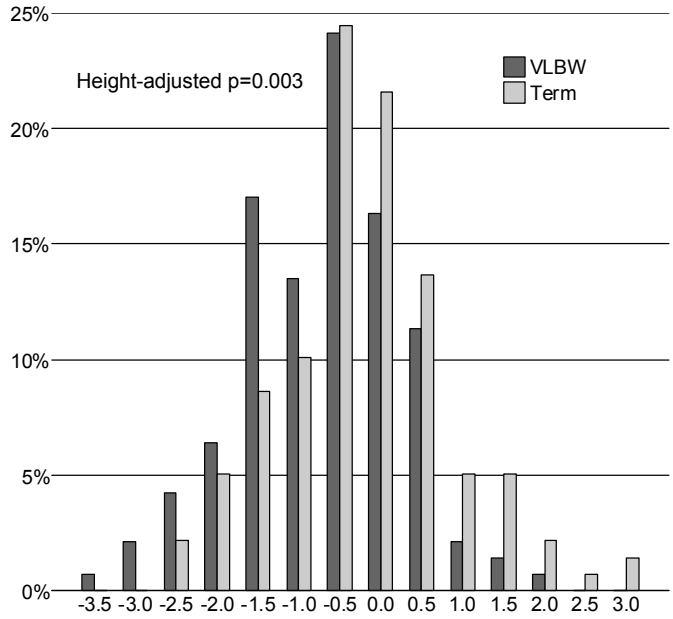
How reliable is our negative FMD finding? I personally performed all but one of the ultrasonography scans. Although I had some prior experience, this was my first scientific work as an ultrasonographer. Although the repeatability of the method was good, there always remain possibilities for measurement error. However, because FMD estimates in VLBW subjects were higher, measurement error in random directions was very inlikely to influence our conclusions about FMD. A higher cIMT, however, among the VLBW subjects could be hidden by the variation caused by any measurement error.

Bone mineral density and vertebral compression deformities (IV)

Mean Z scores for BMD in the lumbar spine (Figure 8) and in the femoral neck were lower for the VLBW subjects, with differences of -0.51 and -0.56 units (Table 14). VLBW subjects also had a lower whole-body BMD Z score, although this difference from the term-born was smaller, -0.33 units (95% CI, -0.56 to -0.11). Lumbar spine BMAD, a BMD- derived index that accounts for bone size, was also lower in VLBW subjects. Ten VLBW and seven term-born subjects had multiple

compression deformities in DXA-derived lateral images of the thoraco-lumbar spine (P = 0.49). We detected a lumbar spine Z score ≤ -1.0 in 44% of the VLBW and in 26% of the term-born subjects, yielding an odds ratio of 2.3 (95% CI, 1.4 to 3.8).

Figure 8. Bone mineral density Z score in the lumbar spine.



Category labels are the upper limits of the categories. From *Hovi et al. PLoS Medicine 2009; 6(8):e1000135*. doi:10.1371/journal.pmed.1000135.g002. © 2009 Hovi et al. Distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Our findings of lower BMD and BMAD in the VLBW group, together with other findings on subjects with a similar degree of prematurity (Table 10), indicate a higher risk for osteoporotic fracture and osteoporosis in later life. Although quite high in each of our groups, the incidence of vertebral compressions is in line with that in healthy young Danish men (Wulff et al. 2004).

Bone mineral density measurement by DXA is the method of choice; BMD t-scores define osteopenia and osteoporosis (Kanis et al. 1994). However, CT techniques revealing bone structure would give even better clues to osteoporotic fracture risk, and only decades of further follow-up will nail down the true fracture risk.

The role of body size regarding the VLBW effect on outcomes (I—IV)

Subjects born at VLBW, in comparison to those born at term, were 5 to 6 cm shorter and had around 10% lower lean body mass. In addition, their BMI was lower, the difference being statistically significant among men but not among women (I, Table 15). As to results with size adjustments, note that we entered different measures of size in models for different outcomes depending on the specific study questions. The estimated group difference for 2-hour glucose – with and without that lean mass adjustment – was similar. (See full model in Table 14.)

Office systolic pressure in the VLBW subjects was higher both with and without size adjustment (current height and BMI): without adjustment, the difference was 3.9 mmHg; with size adjustment it was 5.4 mmHg. As compared with the term-born subjects, the VLBW subjects had, in a basal model, 1.8 mmHg (-0.4 to 4.0) higher 24-hour mean systolic pressure. After adjustment for BMI, this difference increased to 2.4 mmHg (0.2 to 4.6), and after further adjustment for height, it increased further, to 3.2 mmHg (0.8 to 5.5) (II).

When estimating the VLBW effect in predicting cIMT, new analysis after submission of the article for Study III showed that adding current body size had minimal influence (Table 14). BMI adjustment left the higher intima-media lumen ratio in VLBW subjects unchanged. Size adjustment in a model predicting FMD made the positive VLBW effect increase (Table 14).

Entering height into models reduced the difference between VLBW and term subjects in BMD of the lumbar spine from 0.51 SD units (Table 14) to 0.37 SD units. For the femoral neck, the change was smaller, from 0.56 to 0.48 SD units.

VLBW adults were shorter and had a lower lean mass, as in other studies (Weiler et al. 2002; Hack et al. 2003; Wang et al. 2007). Their BMI was more clearly lower among men, which agrees with Hack's findings. A striking difference from their adults born at VLBW is that ours had clearly lower BMIs: 21.7 vs. 22.9 kg/m^2 among men and 21.9 vs. 24.7 kg/m^2 among women (Tables 4 ja 15).

One of the potential roles for size variables in our regression models was to make the estimates of VLBW effects more precise. Although variation in size could explain a proportion of variation in outcomes, precision in our study failed to increase. For example, including height and BMI in models predicting office and 24-hour blood pressure left the width of confidence intervals for the VLBW effect estimates unchanged.

For glucose measurement following a glucose load, the reasons for size-adjustment were obvious; since we gave 75 g glucose to everyone, we adjusted for the lower lean body mass in VLBW subjects when modelling the 2-hour glucose. The absence of any effect from that adjustment implies that the lower amount of

glucose-utilizing tissue among the VLBW adults did not cause their higher 2-hour glucose.

An additional reason for size adjustment was that, regarding blood pressure, shorter people have lower average levels; it may be the case that harmful levels for these individuals are lower as well. One specific level, the limit for hypertension for instance, would thus be lower for the short than for the tall, although reports linking any level of blood pressure to cardiovascular outcome do not include body height in their analysis (Franklin et al. 2001; Clement et al. 2003; Hansen et al. 2006)., Short stature per se, however, with a low SES explaining only part of the results, predicts higher cardiovascular mortality (Kannam et al. 1994; Njolstad et al. 1996; McCarron et al. 2002). What, therefore, are the combined cardiovascular consequences of shorter height and increased blood pressure, both linked to VLBW birth? In our study, entering height into the model made the excess of systolic pressure among our VLBW subjects increase from 3.9 to 5.4 mmHg. The 5- to 6-cm shorter height among VLBW adults could thus add further risk-information to the information from the 3.9-mmHg higher blood pressure, and the height-adjusted pressure difference, 5.4 mmHg, could represent the combined risk difference between VLBW and term-born adults.

Table 15. Anthropometry and body composition of the participants. *

Variable	VLBW	Term	Difference (95% CI)
Men			
Height, cm	174.6 (7.8)	180.5 (6.4)	-5.9 (-8.3 to -3.5)
BMI, kg/m^2	21.7 (1.17)	23.1 (1.14)	-5.9% (-10.4 to -1.1)
Percent body fat	18.1 (6.3)	18.1 (5.4)	0.0 (-2.1 to 2.2)
Lean mass, kg	53.2 (1.17)	60.9 (1.13)	-12.7% (-17.1 to -8.0)
Women			
Height, cm	162.0 (7.7)	167.2 (6.8)	-5.3 (-7.3 to -3.2)
BMI, kg/m^2	21.9 (1.18)	22.4 (1.17)	-2.4% (-6.7 to 2.1)
Percent body fat	29.4 (6.1)	29.9 (5.5)	-0.5 (-2.3 to 1.2)
Lean mass, kg	38.6 (1.16)	42.6 (1.14)	-9.5% (-13.1 to -5.7)

*Values are means and SDs for height and percent body fat. For body mass index (BMI) and for lean mass, the values are geometric means and SDs.

For ambulatory blood pressure, the difference became statistically significant only after size adjustment. We, however, believe that the increase in cardiovascular disease risk implied in this finding only adds to the risk for hypertension and stroke already indicated by the clearly higher office systolic pressure.

Although larger body size is related to larger size of vascular structures such as cIMT (Tilling et al. 2006) size adjustment had no effect on our cIMT and FMD results. However, the cIMT-lumen ratio is another means to account for size. This

ratio was higher among the VLBW subjects. The current literature on cIMT and its relation to later cardiovascular events ignores vascular calibre (Nichols et al. 1999; O'Leary et al. 1999). Speculatively, because the intima-media lumen ratio reveals the proportion of occlusion in the carotid artery, this ratio may be related to occlusive end points. Thus, the higher intima-media lumen ratio in VLBW young adults may indicate risk for later infarctions, although currently no data support this.

Small people have small bones. Smaller bodies need lower areal BMD, and, according to recent recommendations for study of growth-retarded adolescents (Gordon et al. 2008), we entered current height into models predicting BMD Z scores. The resulting reduction in VLBW effect was 27% in the lumbar spine and 14% in the femoral neck. The recommendation to account for smaller size is reasonable, as BMD Z score levels indicating higher risk for fractures may be lower for the short and thin. At least this is reasonable regarding low-energy fractures that involve body weight, such as falling. However, for adults, the diagnostic criteria for osteopenia and osteoporosis do not recognize body size (Kanis et al. 1994). A low BMI in itself is related to an increased fracture risk (De Laet et al. 2005). Therefore, for risk assessment regarding high-energy fractures, choosing BMD Z score without size adjustment seems reasonable. This, however, might exaggerate the risk for low-energy fractures.

Obviously, size adjustments can lead to bias if not interpretated with caution. Size at birth and size at present can both be part of the same causal pathway leading to an outcome that directly relates to size, such as blood pressure. This setting artificially leads to an inverse association, a "reversal paradox," between birth weight and adult blood pressure in the absence of a true association (Tu et al. 2005). In their report, Tu and colleagues demonstrated this problem with simulated data. Real data, however, on 378,707 mostly term-born young Swedish men, showed that an inverse association between birth weight and adult blood pressure exists also in each narrow stratum of adult size (among very narrow strata either by weight, by height, or by BMI) (Lawlor et al. 2007). Thus, in that Swedish population, the birth weight-blood pressure association was actual, and not produced by the mathematical relationships of explanatory variables. In our study, relatively small in the world of epidemiology, the size of our groups would have made a stratified analysis uninformative. Our considerations as to the significance of height-adjusted differences represent our efforts to avoid the "reversal paradox" and the misinterpretation of our results.

4.3 Effects of family background and fetal period (I—IV)

Why do adult disease risk factors accumulate in young adults born at VLBW? For the young adults themselves, or their doctors, this might not seem the most important question; despite the underlying reasons, these individuals have a need for

disease prevention. However, to gain better understanding for solving research questions and tailoring prevention, we extended our secondary aims into this area.

Parents' disease history

We asked the young adults, in a structured questionnaire, about their parents' disease history. About a quarter of the participants reported parental diabetes or hypertension (Table 16). Adjusting for parental diabetes left the estimates for a VLBW-term difference in glucose and insulin concentrations unchanged. A maternal history of current hypertension associated with a 3.7 mmHg (0.0 to 7.5) higher 24-hour systolic pressure, whereas paternal hypertension showed no such association. However, the VLBW effect on blood pressures, after adjustment for parental hypertension, remained similar.

Our adjusted results give no support to the simplest explanation for our findings: If higher blood pressure or higher fasting insulin existed as a result of confounding by inherited characteristics, then with disease-history adjustment, such effects should be attenuated, at least partially. They were not attenuated – either in our study or in other studies (Doyle et al. 2003; Hack et al. 2005; Keijzer-Veen et al. 2005; Dalziel et al. 2007; Keijzer-Veen et al. 2010). After more years of follow-up however, as the parents' disease incidence increase with increasing age, their disease data will gradually become a more reliable source reflecting the parental inheritable characteristics. A new evaluation of our current data with future parental data will therefore shed more light on the potential confounding role of inheritability.

Data on parental education level

Parents of the VLBW subjects, as compared to those of the term born were, on average, less well educated (Tables 13 and 16). However, adjustment for this lower parental education barely changed the estimates of VLBW effects upon glucose and insulin concentration, blood pressure, the intima-media lumen ratio or lumbar spine or femoral neck BMD Z score (Tables 14 and 17).

Lower parental education in VLBW subjects indicates a lower childhood SES. A low SES as compared to the population mean among parents of VLBW subjects is even more profound in the USA (Hack et al. 2002) and is also found in high-income countries other than the USA (Indredavik Evensen et al. 2009). A portion of the effects on blood pressure that seem to be due to VLBW/VLGA birth may be due to the individual's lower SES. Regarding impaired glucose regulation, a low SES did not confound most of those findings (Irving et al. 2000; Lawlor et al. 2006; Thomas et al. 2007; Kaijser et al. 2009). Our consistent results with and without SES support the previous findings suggesting only a small or neglible role for SES in causing risk for hypertension or diabetes in VLBW adults.

Parental education may influence participation decisions in long-term follow-up studies (Wolke et al. 1995). One limitation is that we were unable to report data on the socioeconomic status of nonparticipants. Data on parents' education were retrospective and came from the young adult subjects themselves. However, systematically biased group-difference estimates are unlikely.

Other indicators of SES commonly used include occupational status and income. While each of these indicators may contribute with independent information, we considered our group sizes insufficient for comparisons of a multitude of intercorrelated SES indicators. Because a large proportion of participants were still completing their education, instead of the subject's own education, we utilized that of the parents.

Table 16. Perinatal and current characteristics among participants.

Variable	VLBW (%)	Term (%)	P-value	Article
Parental diabetes	9.2	7.1	0.46	I
Maternal hypertension	22.0	13.3	0.08*	II
Paternal hypertension	12.7	8.4	0.27*	II
Maternal preeclampsia	21.1	7.6	<0.001*	I
Maternal hypertension in pregnancy	3.5	15.1	0.001	IV
Maternal smoking during pregnancy	18.5	16.3	0.62*	III
Antenatal glucocorticoids	4.2			II
Culture-positive sepsis	7.6			IV
Retinal disease of prematurity	5.1			II
Current parental education				
Elementary	5.5	3.6		
Intermediate	47.9	42.6	0.11	I
University	35.0	48.5		
Unknown	11.7	5.3		
Current smoking	21.5	33.7	0.01*	III
Leisure-time exercise intensity				
Walking	29.4	11.8		
Walking or light running	27.0	26.0		
Light running	25.8	28.4	<0.001	I
Brisk running	13.5	32.5		
Unknown	4.3	1.2		

*new analyses

Table 17. Data analysis for detection of possible mediators or confounders of the VLBW-term difference.

Variable	Estimates barely changed after additional adjustments	Estimates barely changed after additional exclusions
Glucose regulation; fasting insulin and 2-hour plasma glucose	Percent body fat, trunk-to-leg fat ratio, waist-to-hip ratio, BMI, lean body mass, height. Preeclampsia*	Multiple births, cerebral palsy, BPD or inhaled glucocorticoids, birth-weight percentile < 10% or > 90%, preeclampsia*
24-hour blood pressure		Longest period between measurements > 1 h
Intima-media lumen ratio	Current smoking, history of a parental CVD event, parental education, current medication, recent infection	
Carotid intima-media thickness	Height, lumen diameter, current medication, recent infection	Current smokers
Flow mediated dilatation	Current medication, recent infection	Current smokers
Bone health: Lumbar spine and femoral neck bone mineral density Z scores	Exercise frequency or duration, calcium and vitamin D intake, parental education	BPD or inhaled or systemic glucocorticoids, inhaled bronchodilators
		Multiple births, SGA, chorion amnionitis

BPD, bronchopulmonary dysplasia; CVD, cardiovascular disease

* We presented our preeclampsia data in our reply to a letter from Manzoni et al. (2007).

Maternal pregnancy disorders (I–IV, additional data)

Among VLBW subjects, in comparison to those born at term, exposure to maternal pre-eclampsia was more common and to gestational hypertension less common; of the term born, 7.6% were exposed to preeclampsia and an additional 15.1% to gestational hypertension (Tables 13 and 16). Exposure to gestational hypertension was unrelated to glucose or insulin concentrations. Exposure to preeclampsia was unrelated to mean concentrations of fasting insulin and 2-hour glucose and mean values of 24-hour systolic pressure. Adjusting for exposure to preeclampsia resulted in subtle changes only in VLBW effects on the blood pressures (I, II). VLBW effects on fasting insulin and 2-hour glucose remained unchanged as well (Manzoni et al. 2007). Effects of mother's smoking during pregnancy did not affect BMD Z scores (IV).

Maternal hypertensive disorders, in particular pre-eclampsia, are frequently sufficiently severe to lead to induction of preterm delivery. Thus, the frequent maternal preeclampsia we found among the VLBW subjects was the expected. That our proportion of VLBW group mothers with preeclampsia was higher, and our proportion with gestational hypertension was lower than those proportions in other preterm/VLBW/VLGA studies (Table 3), may in part be due to diagnostic differences.

Among the mothers of our term-born subjects, preeclampsia and gestational hypertension were more common than among the mothers in the 1966 Northern Finland Birth Cohort, in which incidences of preeclampsia and gestational hypertension were 3.3% and 3.1% (Pouta et al. 2004). Data in that cohort were based on the Hospital Discharge Register; how many cases remained undiagnosed remains unknown. We performed a chart review for all participants and thus assume that the number of undiagnosed cases in our data was smaller.

Although pregnancy disorders were not confounders in many reports on effects of VLBW/VLGA birth, many studies lack sufficient relevant information to make such as judgement (Table 3). Our data suggest that pregnancy disorders provide no easy explanation for our main findings. Data on exposure to tobacco during fetal life becomes important, because it causes retardation of growth and associates with other types of unhealthy parental behaviour (Lieberman et al. 1994; Oken et al. 2005).

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Table 18. Associations of early weight growth with disease risk factors among young adults born with VLBW.

Variable	Birth weight SDS	Birth to term	Other
Glucose regulation			
Fasting insulin	NS	Birth to term: **+31%/SD-unit** (13 to 80), only among SGA	
2-hour plasma glucose	NS		
24-hour blood pressure			
Systolic	NS	Birth to term: **-1.9 mmHg /SD-unit** (- 3.7 to 0.0) (similar for diastolic)	Height SDS from birth to current **NS**
Arterial health			
Carotid artery intima-media thickness,	-7 µm/SD-unit (-14 to 0)	H28 to H32: **-18 µm/100g/4 wks** (-34 to -1) (BMI adjustment attenuated this) Postnatal 6 weeks: **NS**	Periods from H40 to H92 assessed. H68 to H72: **-6 µm/100g/4 wks** (-12 to -0) Infancy until adulthood: **NS**
Brachial artery flow-mediated dilatation,	NS	H28 to 40 in 4-week periods: **NS** Postnatal 6 weeks assessed. Postnatal 2 weeks: **2.2 %-units/100g/4 wks** (0.4 to 4)	Periods assessed: H40 to H92. H56 to H60**: -0.5 %-units/100g/4 wks** (-1.0 to -0.1) H68 to H72: **0.5 %-units/100g/4 wks** (+0.0 to 1.1) Infancy until adulthood: **NS**
Lumbar spine or femoral neck BMD Z-scores	NS	NS	

H, postmenstrual weeks; NS, nonsignificant; SDS, standard deviation score.

Numbers are sex- and age-adjusted regression coefficients (95% confidence intervals), each coefficient originating from a separate model.

Intrauterine growth

Approximately one-third of the subjects born at a VLBW were SGA (Figure 6). They compared with VLBW subjects who were not SGA, had similar fasting insulin, 2-hour glucose, blood pressure, cIMT, FMD, and BMD Z scores. Linear effects of BW SDS – the relative size at birth – on the main outcomes were nonsignificant as well, except that cIMT was higher in those whose BW SDS was smaller (Table 18).

The difficulties involved in interpreting SGA-AGA comparisons among weight-limited groups of preterm infants are obvious. However, the lack of any significant difference in the outcomes between our VLBW AGA and VLBW SGA subjects, and the fact that both groups had higher blood pressure and higher fasting insulin and 2-hour glucose than did the term-born, indicates that both these subgroups are at risk for cardiovascular disease. Our results parallel other results: among VLBW subjects or among subjects grouped by another weight limit, SGA had typically no effect on blood pressure or on glucose regulation (Irving et al. 2000; Doyle et al. 2003; Hack et al. 2005). In short, as risk factors accumulate for those who were born SGA at term, they also accumulate for those who were born at VLBW; among the VLBW, being AGA or SGA plays no major role.

4.4 Effects of postnatal morbidity and growth (I—IV, additional analysis)

Sepsis and BPD

The proportion of VLBW subjects with a specific diagnosis in infancy was small (Table 16). Those with or without retinopathy of prematurity (ROP) had similar 24-hour systolic pressure (II). Neither sepsis nor duration of ventilation or of oxygen therapy was associated with 2-hour glucose or fasting insulin (unpublished results) or with 24-hour systolic pressure. Nor did any predict a lower BMD Z score in the lumbar spine (IV).

Postnatal morbidity had no influence on outcomes. However, our statistical power to detect such influences was low. A larger study would be more informative regarding individual complications and diseases. Alternatively, as the clinically most significant diseases in infancy cause failure to thrive, assessing associations of weight gain in infancy provides information on many diseases simultaneously.

Postnatal growth

For the 100 VLBW subjects with relevant data, mean weight SDS decreased from -1.3 (SD, 1.5) at birth to -2.6 (1.2) at term. Table 18 shows that within the

VLBW group, a higher velocity of weight gain from birth to term associated both with a lower blood pressure and with a smaller cIMT. Faster growth from birth to term was associated with a higher concentration of fasting insulin, but only among the SGA participants. Weight gain velocities from birth to term were not associated with BMD Z scores (I, II, IV).

For a subgroup with data on cIMT and FMD (III), we were able to report how these outcomes associated with a series of weight gain velocities and height SDS gain velocities during 6 postnatal weeks and during 28 to 92 postmenstrual weeks (Table 18).

1. A more rapid weight gain velocity during the 2 first weeks of life associated with a higher FMD.
2. At around 60 postmenstrual weeks, both more rapid weight gain and more rapid height SDS gain were associated with a lower FMD.
3. At around 70 postmenstrual weeks, a more rapid weight gain was associated both with a thinner cIMT and with a higher FMD.

The participants born at VLBW caught up markedly in weight. As compared with those born at term, men still were, however, 12% lower in weight (95% CI, 6.8 to 16.9) and women 8.5% lower (3.8 to 12.9). Change in weight or in height SDS after infancy was unrelated to cIMT or FMD in young adulthood (III).

Early weight gain before term was slow, but similar to that in other follow-up studies initiated in the early 80's (Table 11). Alan Lucas' group investigated the associations of early growth in children with BW < 1850 g whose mean FMD was higher than that in controls: FMD was lower among those who grew rapidly during the 2 first postnatal weeks than among the rest of their low birth weight children (Singhal et al. 2004). Therefore we analyzed the associations of weight gain during that same period. Our participants who grew rapidly had an FMD that was higher. The opposite associations of weight gain in the two studies may reflect different factors composing weight gain velocities in the two study cohorts with differing BW and GA distributions. The differing results are evidence for caution in interpreting results based on infant growth during short periods.

In parallel with our FMD finding, we found other benefits for rapid early growth: Our VLBW participants who grew rapidly with a larger increase in weight between birth and term had a lower blood pressure and a thinner cIMT. No other preterm studies analyzing cIMT in this regard are available, but in two studies, growth from birth to term was unrelated to later blood pressure (Singhal et al. 2001b; Hack et al. 2005) (Table 12). The weight SDS of our infants was very low at term, which may have contributed to the effects of growth variation.

The opposite associations between more rapid weight gain at around 60 and around 70 postmenstrual weeks and arterial health are difficult to explain. Again, they should be interpreted with caution. Experimental nutrition studies covering that period could possibly clarify this issue.

In the rat, bilateral uterine artery ligation in late gestation, roughly corresponding to the couple of months that VLBW infants spend in the NICU, causes a decrease in glucose tolerance, in insulin-stimulated glucose disposal, and in insulin sensitivity (Simmons et al. 2001). Human fetuses exposed to the Dutch famine during any trimester showed lower glucose tolerance (Ravelli et al. 1998; de Rooij et al. 2006). In our study, in line with findings from two other preterm cohorts (Fewtrell et al. 2000; Regan et al. 2006), slow weight gain from birth to term among infants born at VLBW had no influence on insulin resistance in adulthood. As a result, human data from the Dutch famine and from preterm infants challenge the theory of one specific vulnerable period during late gestation for programming of type 2 diabetes in humans.

4.5 Effects of lifestyle – possibilities for prevention (I,IV)

Leisure time conditioning exercise

In a questionnaire, VLBW subjects reported shorter duration of leisure-time conditioning exercise: 53.9% vs. 29.9% usually exercised less than one hour per occasion ($P< 0.001$). Furthermore, 29.4% of the VLBW and 11.8% of the term born subjects reported their leisure-time exercise intensity was comparable to walking ($P< 0.001$). In fasting insulin analysis, the only exercise variable with an influence on the VLBW effect was leisure-time exercise intensity. However, only less than one-tenth of the VLBW effect on fasting insulin faded away with the entering of exercise intensity in the model. When we entered exercise intensity in models predicting office blood pressures, VLBW effects remained the same. Exercise intensity entered in a model predicting lumbar spine BMD Z score attenuated the VLBW effect from -0.37 to -0.26 SD units and made a smaller change in that score in the femoral neck. However, the VLBW effects still were statistically significant (Table 14).

A more detailed presentation of leisure-time conditioning exercise in our VLBW adults involved dichotomizing the data and calculating three odds ratios (Kajantie et al. 2010). Odds ratios for less than once a week frequency, for typical intensity of walking, and for a typical session duration of less than 30 minutes were 1.61 (95% CI, 1.05 to 2.46), 2.75 (1.63 to 4.65), and 3.11 (1.44 to 6.75). These parallel the findings from earlier studies (Rogers et al. 2005; Hack et al. 2007; Saigal et al. 2007). A meta-analysis of 14,000 adolescents and adults, 240 of whom were born at BW < 1750 g, reported an reverse U-shaped relationship between birth weight and

leisure-time physical activity (Andersen et al. 2009). Although in our study exercise failed to play a major mediating role between VLBW birth and cardiovascular risk factors, and although exercise only partially (30%) explained the lower BMD among the VLBW group, it is reasonable to claim that this group would benefit from exercise promotion. Especially because our questionnaire probably provided only a surrogate of bone-strengthening exercise, more valid measurement methods of types of exercise might reveal a larger role for it.

Adiposity

As already mentioned, in comparison to the term born, VLBW subjects had a BMI that was 1.4 kg/m^2 (95% CI, 0.3 to 2.4) lower among men and 0.5 kg/m^2 (95% CI, -0.5 to 1.5) lower among women (I). We determined body composition by DXA in 286 young adults (I), and percent body fat in VLBW and term subjects was similar (Table 15).

We fitted models that included percent body fat, trunk-to-leg fat ratio, and waist-to hip ratio, to assess whether among those born at VLBW these markers underlie the higher fasting insulin or higher 2-hour glucose (Table 17). Estimates of VLBW changed slightly if at all.

Mean BMI among the VLBW subjects was similar to or lower than that of controls also in other studies (Table 4). Neither of two small studies that discovered a more central fat distribution in prepubertal subjects with GA < 34 weeks (Edstedt Bonamy et al. 2005) and in VLBW young adults (Indredavik Evensen et al. 2009) reported adjustment for these variables. In our study, one strength was our capability to measure percent body fat with DXA, which showed that the lower BMI was due to a lower amount of body mass in both fat mass and fat-free mass. A limitation of DXA is that it does not differentiate between visceral and nonvisceral fat.

Diet

Data on intakes of vitamin D and calcium were available. Geometric mean intake of vitamin D among the VLBW subjects was 3.0 µg/day, not significantly lower than that among the controls (3.4 µg/day, P = 0.13). Calcium intakes were 761 and 958 mg/day, respectively, P = 0.003. After adjustment for these intakes, VLBW effect on BMD changed minimally (IV).

All methods assessing intakes of vitamin D and calcium have their limits. Effects of ingested vitamin D, a fat-soluble molecule, are long lasting. Our participants kept a 3-day food diary, which may not optimally reflect long-term intakes. However, food diaries are what the other, less laborious methods of vitamin D intake assessment are validated against (Marshall et al. 2003, 2008; Wu et al. 2009). A food diary covering a whole week or more would better reflect true vitamin D

intake, but we believe that this improvement would leave our conclusions unchanged. As compared with our control group's diet, other studies report similar intakes of vitamin D and calcium in healthy young Finnish adults in the Helsinki area: about 3.7 µg/day and about 1000 mg/day, respectively (The National Findiet 2002 Study 2003). Intakes in our control group do meet the current Nordic recommendations for calcium (700-800 mg/day), but not those for vitamin D (5-7.5 µg/day) (Ravitsemussuunnittelutoimikunta 2005; Pedersen 2008). Another study showing lower BMD in VLBW subjects included no data on vitamin D but reported a similar calcium intake in VLBW and in control children (Wang et al. 2007). In sum, we could find no evidence of diet as mediating the effects of VLBW on BMD.

Smoking

Among our term subjects, smoking was more frequent (Table 16). Current smokers had 24-hour systolic pressure similar to that of the others. The borderline positive VLBW effect on FMD was essentially the same after exclusion of nonsmokers. Office systolic pressure, 24-hour systolic pressure, and intima-media lumen ratio were higher in VLBW subjects also when adjusted for current smoking (II,III).

Other studies based on the current project demonstrate, among VLBW as compared with term-born adults, less alcohol or illicit drug use and lower lifetime-to-date number of sex partners and later start of sexual activity (Kajantie et al. 2008; Strang-Karlsson et al. 2008). Although smoking potentially affects vascular tone and blood pressure (Salvaggio et al. 1992), adjusting for it in our study did not reduce the association of VLBW birth with blood pressure, cIMT-lumen ratio or FMD. Smoking frequency among various VLBW populations varies (Pharoah et al. 1998; Dalziel et al. 2007), and it is important to account for it when investigating blood pressure and related outcomes.

5 General discussion

5.1 Summary of findings

The results in VLBW adults, as compared with those born at term, demonstrate an accumulation of major cardiovascular risk factors: higher fasting insulin, higher 2-hour glucose, and higher office blood pressure, and to a lesser extent ambulatory blood pressure. However, not all variables that we measured in VLBW adults indicated higher cardiovascular risk. Our groups' cIMT, FMD, serum triglycerides, and total- and HDL-cholesterol were similar. These findings, or the ambulatory pressure difference's having been significant only after adjustment, do not change our interpretation of an increased overall cardiovascular disease risk among those who were born at VLBW. Furthermore, we discovered, at all bone sites investigated, a lower BMD Z score, indicating later risk for osteoporotic fracture.

Many of our findings are novel. No OGTT data on VLBW adults existed prior to our report (I). Our findings of no differences in FMD, cIMT, or lipids in adults are consistent with others' findings (Table 9). Our ambulatory blood pressure findings in adults, together with those of another study (Doyle et al. 2003), confirm in adults the findings in younger people. Some evidence existed of a lower BMD in VLBW children and adolescents, as compared to BMD in controls, but these studies were small (Table 10). In addition to ours, there are only a few other studies of preterm-born cohorts of appropriate size that report several components of metabolic health in a single group of adults (Table 3).

5.2 Methodological considerations

Publication bias may reduce the reliability of the existing literature. For example, many VLBW follow-up projects may include unpublished blood pressure measurements. Such inexpensive measurements easily become a part of a medical follow-up visit. If, at any level in the process of creating scientific articles, the decision to publish or not to publish existing data depends on the results, publication bias is inevitable. The likely direction of such bias is to exaggerate risk in preterm subjects.

Other ways of missing the truth exist. Ioannidis, in a 2005 article, used mathematical and graphical explanations to show how vaguely the scientific literature coincides with the real world. He explained why, for any individual published positive result, the probability that it is true increases with, among other things, a lower number of study questions asked, a higher a priori probability of these questions, and the work's being in a less competitive area of research. Ioannidis did not rate the average descriptive epidemiological study very high.

In our project, to keep the number of study questions low, we, like many other researchers, based our questions on biological knowledge and on previous research, consistently used VLBW birth as the primary exposure, and we only utilized statistical methods and outcome variables that are well known and predefined. Thus, we believe that the possibility of our findings' being "false positive" chance findings is negligible.

The statistical power of a study reveals how sensitive it is in detecting any existing difference of predetermined size (Electronic Statistics Textbook 2010). Among many of the studies reviewed in this thesis, and many secondary subgroup analyses involving our own work as well, the number of subjects was relatively low. Larger studies and studies concentrating on specific subgoups among VLBW subjects may confirm our findings, including those on growth patterns and neonatal morbidity.

The setting we chose for studying potential later effects of very preterm birth was an existing VLBW cohort. A VLBW cohort study, as compared with a full GA-range cohort study, finds differences more efficiently in relation to number of participants. A full GA-range cohort study, in turn, would give better estimates of the nature of relationships between the outcomes and decreasing GA or BW. A good alternative would have been studying the extreme lower end of GA. This would have been more flexible for selecting alternative exposure variables such as GA as a continuous variable or BW SDS, the relative size at birth. However, as BW is, and especially as it was earlier, more truthworthy than GA, use of a weight limit in a cohort study is justified.

All of the outcome variables were objective measurements and valid, but some of the key co-variates, such as data on exercise and on parental disease and education status, came from a questionnaire. Methods more objective would have included measuring exercise by accelerometer or obtaining parents' education history from the national registers. In this particular group of interest, questionnaire data may be even less valid than otherwise; in one study, adults born preterm, more than others, tended to answer in a manner that made them appear more socially acceptable (Allin et al. 2006). The potential problems with questionnaire-based covariates in our analyses could hide important confounders, adding to the pool of residual

confounding. Overall, however, we consider our methods sufficiently valid to assess the adjusted differences between the VLBW and term-born subjects.

The effect of exposure on selection can lead to biased estimates. In contrast, all kinds of selection affect generalizibity. Our data on those who died, for instance, are sparse. Our findings are directly generalizable only for groups of VLBW subjects surviving in similar circumstances. VLBW infants born recently experience circumstances with modern neonatal intensive care available; they show a new kind of aetiological spectrum, and they receive modern nutritional and other therapy. In fact, recently born VLBW infants in less-developed countries may resemble our subjects more closely.

5.3 Significance

Differences between the VLBW and the term-born subjects were considerable and may indicate later risk for type-2 diabetes, hypertension, cardiovascular disease, and osteoporosis. One challenge in risk prediction is the uncertainty of how permanent are the risk factors we found. Although obviously a number of individuals are going to migrate from one risk level to another, and may be equally likely to migrate up or down, we need not assume that the group differences that we see in young adults will decrease without active preventive work.

In any population, small blood pressure differences have a high impact. According to data from a 9-year follow-up of a population-based study sample aged 41 to 72, a difference of 4 mmHg means a 1.13-fold (95% CI, 1.08 to 1.15) risk increase of death from ischaemic heart disease or stroke (Hansen et al. 2006). HR for cardiovascular mortality associated with a 4-mmHg higher systolic pressure in a Finnish study with 30-year follow-up was 1.09 (1.08 to 1.11) (Strandberg et al. 2002).

Higher concentrations of fasting insulin and 2-hour glucose concentrations elevate cardiovascular mortality (Pyörälä et al. 2000; Decode Study Group 2001). In one meta-analysis, the highest quartile of insulin was associated with a HR of 1.89 (1.24–2.88) for cardiovascular death (Hu et al. 2004). The percentage of VLBW subjects within that quartile in our study was 33%. Assuming this situation persists for VLBW subjects, their overall HR for cardiovascular death becomes 1.06 due to their higher insulin resistance alone. Adding up the VLBW subject's relative risk for cardiovascular death would include these risk-increases due to systolic pressure and fasting insulin and the risk increase due to higher 24-hour blood pressures and also 2-hour-glucose values and an adding additional increase because of lower respiratory function (unpublished results in our cohort). Allowing some overlap of the risks predicted by interrelated factors, VLBW subjects' relative risk for cardiovascular death could be about 1.3-fold. Regarding the relative risk for an

osteoporotic fracture for those born at VLBW, the 0.5-unit lower BMD Z score we found in the femoral neck or lumbar spine, together with data drawn from cohorts aged 50 and above, translate into a 1.4-to 1.7-fold risk for fracture (Cummings et al. 1993; Marshall et al. 1996).

Increased risk for chronic disease in VLBW subjects necessitates targeted preventive health education for these individuals, who comprise about 10 of every 1000 live births. Infant growth with today's nutrition is much more rapid than 25 years ago, and therefore our findings need replication. Methods of prevention require individual evaluation. For those former VLBW infants who rarely exercise or who have a low lean body mass and a low intake of vitamin D, potential interventions are easy to find. In contrast to many other risk factors for cardiovascular disease, preterm birth is detected early. Initiation in infancy allows sufficient time for a prevention programme; nutritional intervention in healthy newborns, for instance, has improved brachial artery FMD in prepuberty (Raitakari et al. 2005).

Targeting cardiovascular disease prevention at adults who were VLBW/VLGA infants may be of economic significance. Obviously, estimating future cardiovascular disease expense among those born at VLBW/VLGA is difficult, but existing data may provide hints as to the order of magnitude of such expense. Based on a series of assumptions, the VLBW/VLGA subjects' risk for cardiovascular death is 1.3. For simplicity, the relative risk for cardiovascular morbidity may be set at 1.3 as well. The initial hospital-care cost of one VLBW/VLGA baby in Finland is 54,000 €, and total 4-year health-care costs are 68,000 €, as compared with 5,000 € spent for each healthy term-born baby (Korvenranta et al. 2010). Prevention of common adult disease as part of the health visits would require some additional expenses now but would lead to reduced expenses later. In 2003, the annual health care cost of cardiovascular disease in Finland per one million inhabitants was 250 million € (Leal et al. 2006). Adding the estimated value of informal care (by friends and relatives) and the production losses due to morbidity and mortality, Leal et al. estimate that the total cost doubles to 500 million €. Should all these annual costs remain stable, hypothetically, per each million Finns in 2050, annual costs of the first four years of VLBW/VLGA treatment would still be at 130 × 68,000 € = 9 million € in the year 2050. The annual cardiovascular disease costs of VLBW/VLGA subjects at all ages, 1.3% of all Finns in 2050, would be 8.5 million € (assuming that risk for cardiovascular disease were 1.3-fold). Reducing that risk back to population level by preventive measures would annually save 2 million € per one million inhabitants and would thus roughly approximate one-quarter of the annual first 4-year VLBW/VLGA treatment costs.

Our main results support the Barker hypothesis or DOHaD theory that proposes a relationship between exposure during the fetal period and infancy and later disease

(Barker 1994, 1995). During the most recent two decades, clinicians and researchers have strived to specify "windows of vulnerability," which can serve as intervention targets (McMillen and Robinson 2005). Translation of animal-physiology knowledge to human use is hard, since trials in human fetuses or infants can use only a very limited set of interventions. What is called natural experiments such as the Dutch Hunger-winter studies (Roseboom et al. 2006) or preterm cohort studies have proved helpful. Rigorously measured data are available on preterm infants during their first postnatal weeks and months regarding their nutrition, growth, and well-being. Fetuses born at term spend that time in the womb. Lower blood pressure and thinner cIMT in those of our VLBW subjects who gained weight faster from birth to term may indicate that exposures during this period may play an important role in development of cardiovascular disease.

6 Conclusions

1. Young adults born at VLBW displayed higher levels of risk factors that predict onset of type 2 diabetes, hypertension, cardiovascular disease, and osteoporosis. This would require avoidance of additional cardiovascular disease risk factors such as obesity/overweight, inactivity, and smoking. Careful follow-up of VLBW subjects at all ages, enhancing targeted prevention, early diagnosis, and timely treatment, may markedly delay morbidity and mortality.
2. Not all risk factors were higher among those born at VLBW. Their serum triglycerides, total- or HDL cholesterol, percent body fat, and arterial endothelial function were normal. Maintaining this beneficial status will help in disease prevention.
3. The higher risk factor levels among VLBW subjects were not attributable to cardiovascular disease within the family, to lower SES, or to lower BMI. Lower leisure-time exercise intensity among VLBW subjects played a role in their risk for osteoporosis, but no such a connection was evident regarding other outcome variables.
4. When our study subjects were born, the regular feeding guidelines for VLBW infants resulted in deficiencies in nutrition during a typical NICU stay and during early infancy. As compared to those born recently, those babies gained weight slowly. Within this context, a more rapid weight gain before term was associated with lower blood pressure and lower cIMT in adulthood and was unrelated to BMD, glucose or insulin. Rapid weight gain during the first two weeks of life was associated with better endothelial function. Our findings regarding growth in early infancy and chronic disease risk factors in young adulthood suggest that, among slowly growing VLBW infants, a small increase in weight gain velocity before term causes no harm.

7 Future prospects for research

1. To study the long-term effects of the great changes in treatment over recent decades, it is necessary to initiate new studies and recruit existing preterm cohorts born more recently.
2. Some risk factor and disease outcomes may vary by aetiological subgroup and sex. Our nonexistent subgroup differences may simply indicate insufficient power. Sex- and aetiology-specific knowledge will only accumulate from studies with an adequate number of subjects. Adequate assessment of any small subgroups may require a combination of existing datasets. Some subgroups, such as men, those who are neurologically affected, and those with low SES, are especially hard to reach; the researchers need to focus special attention on their recruitment.
3. Knowledge of the mechanisms producing our findings is scarce. Modern techniques, including magnetic resonance imaging and adipocyte metabolism studies, will help in evaluating those mechanisms. Preferably, research settings should be longitudinal, be initiated in early pregnancy, and should cover the whole life span.
4. Planning of intervention studies should aim at reduction of risk for cardiovascular disease. A suitable target group would be a subgroup of preterm infants who are initially at high risk. Nutrition and exercise could prove useful areas for lifetime intervention.

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9 References

Alberti K.G.M.M., Zimmet P., and Shaw J. (2005). The metabolic syndrome--a new worldwide definition. *The Lancet* 366(9491): 1059-62.

Alberti K.G.M.M., Eckel R.H., Grundy S.M., Zimmet P.Z., Cleeman J.I., Donato K.A., Fruchart J.-C., James W.P.T., Loria C.M., and Smith S.C., Jr. (2009). Harmonizing the Metabolic Syndrome: A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 120(16): 1640-45.

Allin M., Rooney M., Cuddy M., Wyatt J., Walshe M., Rifkin L., and Murray R. (2006). Personality in young adults who are born preterm. *Pediatrics* 117(2): 309-16.

American Diabetes Association (2006). Diagnosis and classification of diabetes mellitus. *Diabetes Care* 29(suppl_1): S43-48.

Amiel S.A., Sherwin R.S., Simonson D.C., Lauritano A.A., and Tamborlane W.V. (1986). Impaired insulin action in puberty. *New England Journal of Medicine* 315(4): 215-19.

Ancel P.Y., Saurel-Cubizolles M.J., Di Renzo G.C., Papiernik E., and Breart G. (1999). Very and moderate preterm births: are the risk factors different? *Br J Obstret Gynaecol* 106: 1162 - 70.

Andersen L.G., Angquist L., Gamborg M., Byberg L., Bengtsson C., Canoy D., Eriksson J.G., Eriksson M., Järvelin M.-R., Lissner L., Nilsen T.I., Osler M., Overvad K., Rasmussen F., Salonen M.K., Schack-Nielsen L., Tammelin T.H., Tuomainen T.-P., Sørensen T.I.A., Baker J.L., and NordNet Study G. (2009). Birth weight in relation to leisure time physical activity in adolescence and adulthood: meta-analysis of results from 13 nordic cohorts. *PLoS ONE* 4(12): e8192.

Armitage P., Berry G., and Matthews J.N.S. (2002). Experimental design. Statistical Methods in Medical Research. P Armitage, Blackwell Science**:** 246-55.

Arnold C.C., Kramer M.S., Hobbs C.A., McLean F.H., and Usher R.H. (1991). Very low birth weight: A problematic cohort for epidemiologic studies of very small or immature neonates. *American Journal of Epidemiology* 134(6): 604-13.

Backström M.C., Mäki R., Kuusela A.-L., Sievänen H., Koivisto A.-M., Koskinen M., Ikonen R.S., and Mäki M. (1999). The long-term effect of early mineral, vitamin D, and breast milk intake on bone mineral status in 9- to 11-year-old children born prematurely. *Journal of Pediatric Gastroenterology & Nutrition* 29(5): 575-82.

Barbieri M.A., Portella A.K., Silveira P.P., Bettiol H., Agranonik M., Silva A.A., and Goldani M.Z. (2009). Severe intrauterine growth restriction is associated with higher spontaneous carbohydrate intake in young women. *Pediatric Research* 65(2): 215-20.

Barker D.J.P. (1992). The fetal origins of adult hypertension. *Journal of*

Hypertension - Supplement 10(7): S39-44.

Barker D.J.P. (1994). Mothers, babies, and disease in later life London, BMJ Publishing Group.

Barker D.J.P. (1995). Fetal origins of coronary heart disease. *BMJ (Clinical Research Ed.)* 311(6998): 171-74.

Barker D.J.P., and Osmond C. (1988). Low birth weight and hypertension. *BMJ (Clinical Research Ed.)* 297(6641): 134-5.

Barker D.J.P., Osmond C., Golding J., Kuh D., and Wadsworth M.E. (1989). Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ (Clinical Research Ed.)* 298(6673): 564-67.

Barker D.J.P., Bull A.R., Osmond C., and Simmonds S.J. (1990). Fetal and placental size and risk of hypertension in adult life. *BMJ (Clinical Research Ed.)* 301(6746): 259-62.

Barker D.J.P., Eriksson J., Forsén T., and Osmond C. (2002). Fetal origins of adult disease: strength of effects and biological basis. *International Journal of Epidemiology* 31(6): 1235-39.

Barros F.C., and Victora C.G. (1999). Increased blood pressure in adolescents who were small for gestational age at birth: a cohort study in Brazil. *International Journal of Epidemiology* 28(4): 676-81.

Bazaes R.A., Alegría A., Pittaluga E., Ávila A., Íñiguez G., and Mericq V. (2004). Determinants of insulin sensitivity and secretion in very-low-birth-weight children. *Journal of Clinical Endocrinology & Metabolism* 89(3): 1267-72.

Beck S., Wojdyla D., Say L., Betran A.P., Merialdi M., Requejo J.H., Rubens C., Menon R., and Van Look P.F.A. (2010). The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bulletin of the World Health Organization* 88(1): 31-8.

Belfort M.B., Martin C.R., Smith V.C., Gillman M.W., and McCormick M.C. (2010). Infant weight gain and school-age blood pressure and cognition in former preterm infants. *Pediatrics* 125(6): e1419-26.

Belton N.R., Thistlethwaite D., Wilkinson E.M., Maxwell S., and Elton R.A. (1986). A growth, developmental and nutritional study of low birthweight infants. Health Bulletin 44(4): 239-49.

Bhutta A.T., Cleves M.A., Casey P.H., Cradock M.M., and Anand K.J.S. (2002). Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. *JAMA* 288(6): 728-37.

Bjerager M., Steensberg J., and Greisen G. (1995). Quality of life among young adults born with very low birthweights. *Acta Paediatrica* 84(12): 1339-43.

Blackburn S. (1998). Environmental impact of the NICU on developmental outcomes. *Journal of Pediatric Nursing* 13(5): 279-89.

Bolland M.J., Grey A.B., Gamble G.D., and Reid I.R. (2010). Effect of osteoporosis treatment on mortality: a meta-analysis. *Journal of Clinical Endocrinology & Metabolism* 95(3): 1174-81.

Bradley T.D., and Floras J.S. (2009). Obstructive sleep apnoea and its cardiovascular consequences. *Lancet* 373(9657): 82-93.

Campbell D.M., Hall M.H., Barker D.J., Cross J., Shiell A.W., and Godfrey K.M. (1996). Diet in pregnancy and the offspring's blood pressure 40 years later. *British Journal of*

Obstetrics & Gynaecology 103(3): 273-80.

Carter D.R., Bouxsein M.L., and Marcus R. (1992). New approaches for interpreting projected bone densitometry data. *Journal of Bone and Mineral Research* 7(2): 137-45.

Celermajer D.S., Sorensen K.E., Bull C., Robinson J., and Deanfield J.E. (1994). Endothelium-dependent dilation in the systemic arteries of asymptomatic subjects relates to coronary risk factors and their interaction. *Journal of the American College of Cardiology* 24(6): 1468-74.

Chan S.Y., Mancini G.B.J., Kuramoto L., Schulzer M., Frohlich J., and Ignaszewski A. (2003). The prognostic importance of endothelial dysfunction and carotid atheroma burden in patients with coronary artery disease. *Journal of the American College of Cardiology* 42(6): 1037-43.

Cheung Y.F., Wong K.Y., Lam B.C.C., and Tsoi N.S. (2004). Relation of arterial stiffness with gestational age and birth weight. *Archives of Disease in Childhood* 89(3): 217-21.

Cleary G.M., Higgins S.T., Merton D.A., Cullen J.A., Gottlieb R.P., and Baumgart S. (1996). Developmental changes in renal artery blood flow velocity during the first three weeks of life in preterm neonates. *The Journal of Pediatrics* 129(2): 251-57.

Clement D.L., De Buyzere M.L., De Bacquer D.A., de Leeuw P.W., Duprez D.A., Fagard R.H., Gheeraert P.J., Missault L.H., Braun J.J., Six R.O., Van Der Niepen P., and O'Brien E. (2003). For the Office versus Ambulatory Pressure Study Investigators. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension.[see comment]. *New England Journal of Medicine* 348(24): 2407-15.

Committee on Nutrition. Nutritional Needs of Low-Birth-Weight Infants. (1985). *Pediatrics* 75(5): 976-86.

Cooke R.W. (2004). Health, lifestyle, and quality of life for young adults born very preterm. *Archives of Disease in Childhood* 89(3): 201-6.

Cooper C., Cawley M., Bhalla A., Egger P., Ring F., Morton L., and Barker D. (1995). Childhood growth, physical activity, and peak bone mass in women. *Journal of Bone & Mineral Research* 10(6): 940-7.

Cooper R., Atherton K., and Power C. (2009). Gestational age and risk factors for cardiovascular disease: evidence from the 1958 British birth cohort followed to mid-life. *International Journal of Epidemiology* 38(1): 235-44.

Corretti M.C., Anderson T.J., Benjamin E.J., Celermajer D., Charbonneau F., Creager M.A., Deanfield J., Drexler H., Gerhard-Herman M., Herrington D., Vallance P., Vita J., and Vogel R. (2002). Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: A report of the International Brachial Artery Reactivity Task Force. *Journal of the American College of Cardiology* 39(2): 257-65.

Cummings S.R., Black D.M., Nevitt M.C., Browner W., Cauley J., Ensrud K., Genant H.K., Palermo L., Scott J., and Vogt T.M. (1993). Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. *Lancet* 341(8837): 72-5.

Curll M., Davidson J., and Freer M. (1975). Efficiency of lamb production in relation to the weight of the ewe at mating and during pregnancy. *Australian Journal of Agricultural Research* 26(3): 553-65.

Dalziel S.R., Parag V., Rodgers A., and Harding J.E. (2007). Cardiovascular risk factors at age 30 following pre-term birth. *International Journal of Epidemiology* 36(4): 907-15.

Decode Study Group. The European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. (2001). *Archives of Internal Medicine* 161(3): 397-405.

Doyle L.W., Faber B., Callanan C., and Morley R. (2003). Blood pressure in late adolescence and very low birth weight. *Pediatrics* 111(2): 252-7.

Edstedt Bonamy A.-K., Bendito A., Martin H., Andolf E., Sedin G., and Norman M. (2005). Preterm birth contributes to increased vascular resistance and higher blood pressure in adolescent girls. *Pediatric Research* 58(5): 845-9.

Edstedt Bonamy A.-K., Martin H., Jörneskog G., and Norman M. (2007). Lower skin capillary density, normal endothelial function and higher blood pressure in children born preterm. *Journal of Internal Medicine* 262(6): 635-42.

Edstedt Bonamy A.-K., Andolf E., Martin H., and Norman M. (2008a). Preterm birth and carotid diameter and stiffness in childhood. *Acta Paediatrica* 97(4): 434-37.

Edstedt Bonamy A.-K., Norman M., and Kaijser M. (2008b). Being born too small, too early, or both: does it matter for risk of hypertension in the elderly? *American Journal of Hypertension* 21(10): 1107-10.

Eichenwald E.C., and Stark A.R. (2008). Management and outcomes of very low birth weight. *New England Journal of Medicine* 358(16): 1700-11.

Electronic Statistics Textbook (2010). Tulsa, OK, StatSoft, Inc. Available: http://www.statsoft.com/textbook/.

Emaus N., Berntsen G.K.R., Joakimsen R.M., and Fønnebø V. (2005). Longitudinal changes in forearm bone mineral density in women and men aged 25-44 years: the Tromso study: a population-based study. *American Journal of Epidemiology* 162(7): 633-43.

Eriksson J.G., Forsen T.J., Kajantie E., Osmond C., and Barker D.J.P. (2007). Childhood growth and hypertension in later life. *Hypertension* 49(6): 1415-21.

Escobar G.J., Littenberg B., and Petitti D.B. (1991). Outcome among surviving very low birthweight infants: a meta-analysis. *Archives of Disease in Childhood* 66(2): 204-11.

EURO-PERISTAT Project, with SCPE, EUROCAT, EURONEOSTAT (2008). European Perinatal Health Report 2008. Data from 2004. Retrieved March 31th, 2010, from www.europeristat.com.

European Commission (2007). Programming effects of early nutrition on long-term health. TP5: Food quality and safety. T3.1. 6th EC Framework programme. Retrieved 14th Mar 2011, from ftp://ftp.cordis.europa.eu/pub/food/docs/fp6-tp5-projects.pdf.

Euser A.M., Finken M.J., Keijzer-Veen M.G., Hille E.T., Wit J.M., Dekker F.W., and on behalf of the Dutch POPS-19 Collaborative Study Group (2005). Associations

between prenatal and infancy weight gain and BMI, fat mass, and fat distribution in young adulthood: a prospective cohort study in males and females born very preterm. *American Journal of Clinical Nutrition* 81(2): 480-87.

Fewtrell M.S., Prentice A., Jones S.C., Bishop N.J., Stirling D., Buffenstein R., Lunt M., Cole T.J., and Lucas A. (1999). Bone mineralization and turnover in preterm infants at 8-12 years of age: the effect of early diet. *Journal of Bone & Mineral Research* 14(5): 810-20.

Fewtrell M.S., Doherty C., Cole T.J., Stafford M., Hales C.N., and Lucas A. (2000). Effects of size at birth, gestational age and early growth in preterm infants on glucose and insulin concentrations at 9-12 years. *Diabetologia* 43(6): 714-7.

Fewtrell M.S., Morley R., Abbott R.A., Singhal A., Stephenson T., MacFadyen U.M., Clements H., and Lucas A. (2001). Catch-up growth in small-for-gestational-age term infants: a randomized trial. *American Journal of Clinical Nutrition* 74(4): 516-23.

Fewtrell M.S., Williams J.E., Singhal A., Murgatroyd P.R., Fuller N., and Lucas A. (2009). Early diet and peak bone mass: 20 year follow-up of a randomized trial of early diet in infants born preterm. *Bone* 45(1): 142-9.

Fineli. Finnish Food Composition Database. Release 2. Retrieved from http://www.fineli.fi.

Finken M.J., Keijzer-Veen M.G., Dekker F.W., Frölich M., Hille E.T., Romijn J.A., and Wit J.M. (2006a). Preterm birth and later insulin resistance: effects of birth weight and postnatal growth in a population based longitudinal study from birth into adult life insulin resistance 19 years after preterm birth. *Diabetologia* 49(3): 478-85.

Finken M.J., Inderson A., Van Montfoort N., Keijzer-Veen M.G., van Weert A.W., Carfil N., Frölich M., Hille E.T., Romijn J.A., Dekker F.W., Wit J.M., and Dutch P.-C.S.G. (2006b). Lipid profile and carotid intima-media thickness in a prospective cohort of very preterm subjects at age 19 years: effects of early growth and current body composition. *Pediatric Research* 59(4 Pt 1): 604-9.

Forsdahl A. (1977). Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? *British Journal of Preventive and Social Medicine* 31(2): 91-5.

Forsén T., Eriksson J.G., Tuomilehto J., Teramo K., Osmond C., and Barker D.J. (1997). Mother's weight in pregnancy and coronary heart disease in a cohort of Finnish men: follow up study [see comments]. *BMJ (Clinical Research Ed.)* 315(7112): 837-40.

Fowden A.L., and Hill D.J. (2001). Intra-uterine programming of the endocrine pancreas. *British Medical Bulletin* 60: 123-42.

Franklin S.S., Larson M.G., Khan S.A., Wong N.D., Leip E.P., Kannel W.B., and Levy D. (2001). Does the relation of blood pressure to coronary heart disease risk change with aging? : The Framingham Heart Study. *Circulation* 103(9): 1245-49.

Gairdner D., and Pearson J. (1971). A growth chart for premature and other infants. *Arch Dis Child.* 46(250): 783-7.

Ganpule A., Yajnik C.S., Fall C.H., Rao S., Fisher D.J., Kanade A., Cooper C., Naik S., Joshi N., Lubree H., Deshpande V., and

Joglekar C. (2006). Bone mass in Indian children; relationships to maternal nutritional status and diet during pregnancy; the Pune Maternal Nutrition Study. *Journal of Clinical Endocrinology and Metabolism*.

Geelhoed J.J.M., Fraser A., Tilling K., Benfield L., Davey Smith G., Sattar N., Nelson S.M., and Lawlor D.A. (2010). Preeclampsia and gestational hypertension are associated with childhood blood pressure independently of family adiposity measures: the Avon Longitudinal Study of Parents and Children. *Circulation* 122(12): 1192-9.

Glickstein J.S., Rutkowski M., Schacht R., and Friedman D. (1994). Renal blood flow velocity in neonates with and without umbilical artery catheters. *Journal of Clinical Ultrasound* 22(9): 543-50.

Gluckman P., and Hanson M.A. (2005). Fetal Matrix. Cambridge, Cambridge University Press.

Gluckman P.D., Hanson M.A., Cooper C., and Thornburg K.L. (2008). Effect of in utero and early-life conditions on adult health and disease. *New England Journal of Medicine* 359(1): 61-73.

Goetz R.H., Warren J.V., Gauer O.H., Patterson J.L.J., Doyle J.T., Keen E.N., and McGregor M. (1960). Circulation of the giraffe. *Circulation Research* 8(5): 1049-58.

Gokce N., Keaney J.F., Jr., Hunter L.M., Watkins M.T., Menzoian J.O., and Vita J.A. (2002). Risk stratification for postoperative cardiovascular events via noninvasive assessment of endothelial function: A prospective study. *Circulation* 105(13): 1567-72.

Gordon C.M., Bachrach L.K., Carpenter T.O., Crabtree N., El-Hajj Fuleihan G., Kutilek S., Lorenc R.S., Tosi L.L., Ward K.A., Ward L.M., and Kalkwarf H.J. (2008). Dual energy X-ray absorptiometry interpretation and reporting in children and adolescents: the 2007 ISCD Pediatric Official Positions. *Journal of Clinical Densitometry* 11(1): 43-58.

Grimmer I., Buhrer C., Dudenhausen J., Stroux A., Reiher H., Halle H., and Obladen M. (2002). Preconceptional factors associated with very low birthweight delivery in East and West Berlin: a case control study. *BMC Public Health* 2(1): 10.

Grunau R.E., Whitfield M.F., and Fay T.B. (2004). Psychosocial and academic characteristics of extremely low birth weight (< or =800 g) adolescents who are free of major impairment compared with term-born control subjects. *Pediatrics* 114(6): e725-32.

Grundy S.M., Cleeman J.I., Daniels S.R., Donato K.A., Eckel R.H., Franklin B.A., Gordon D.J., Krauss R.M., Savage P.J., Smith S.C., Jr., Spertus J.A., and Costa F. (2005). Diagnosis and Management of the Metabolic Syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 112(17): 2735-52.

Hack M., Flannery D.J., Schluchter M., Cartar L., Borawski E., and Klein N. (2002). Outcomes in young adulthood for very-low-birth-weight infants.[see comment]. *New England Journal of Medicine* 346(3): 149-57.

Hack M., Schluchter M., Cartar L., Rahman M., Cuttler L., and Borawski E. (2003). Growth of very low birth weight infants to age 20 years. *Pediatrics* 112(1): e30-e38.

Hack M., Schluchter M., Cartar L., and Rahman M. (2005). Blood pressure among very low birth weight (<1.5 kg) young adults. *Pediatric Research* 58(4): 677-84.

Hack M., Cartar L., Schluchter M., Klein N., and Forrest C.B. (2007). Self-perceived health, functioning and well-being of very low birth weight infants at age 20 years. *Journal of Pediatrics* 151(6): 635-41.

Hales C.N., Barker D.J., Clark P.M., Cox L.J., Fall C., Osmond C., and Winter P.D. (1991). Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ (Clinical Research Ed.)* 303(6809): 1019-22.

Hales C.N., and Barker D.J.P. (2001). The thrifty phenotype hypothesis: Type 2 diabetes. *British Medical Bulletin* 60(1): 5-20.

Hamed H.M., Purdie D.W., Ramsden C.S., Carmichael B., Steel S.A., and Howey S. (1993). Influence of birth weight on adult bone mineral density. *Osteoporosis International* 3(1): 1-2.

Hansen T.W., Jeppesen J., Rasmussen S., Ibsen H., and Torp-Pedersen C. (2006). Ambulatory blood pressure monitoring and risk of cardiovascular disease: a population based study. *American Journal of Hypertension* 19(3): 243-50.

Haycock (1998). Development of glomerular filtration and tubular sodium reabsorption in the human fetus and newborn. *British Journal of Urology* 81(S2): 33-38.

Hemingway H., and Marmot M. (1999). Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies. *BMJ (Clinical Research Ed.)* 318(7196): 1460-7.

Hille E.T.M., Dorrepaal C., Perenboom R., Gravenhorst J.B., Brand R., Verloove-Vanhorick S.P., and Dutch P.-C.S.G. (2008). Social lifestyle, risk-taking behavior, and psychopathology in young adults born very preterm or with a very low birthweight. *Journal of Pediatrics* 152(6): 793-800.

Hofman P.L., Regan F., Jackson W.E., Jefferies C., Knight D.B., Robinson E.M., and Cutfield W.S. (2004). Premature birth and later insulin resistance. [Erratum, N Engl J Med. 2004;351:2888]. *New England Journal of Medicine* 351(21): 2179-86.

Hu G., Qiao Q., Tuomilehto J., Eliasson M., Feskens E.J., and Pyorälä K. (2004). Plasma insulin and cardiovascular mortality in non-diabetic European men and women: a meta-analysis of data from eleven prospective studies. *Diabetologia* 47(7): 1245-56.

Hult M., Tornhammar P., Ueda P., Chima C., Edstedt Bonamy A.-K., Ozumba B., and Norman M. (2010). Hypertension, diabetes and overweight: Looming legacies of the Biafran famine. *PLoS ONE* 5(10): e13582.

Huxley R.R. (2006). Fatal flaw in the fetal argument. *British Journal of Nutrition* 95(03): 441-42.

Huxley R.R., Shiell A.W., and Law C.M. (2000). The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. *Journal of Hypertension* 18(7): 815-31.

Huxley R.R., Neil A., and Collins R. (2002). Unravelling the fetal origins hypothesis: is there really an inverse association between birthweight and subsequent blood pressure? *The Lancet* 360(9334): 659-65.

Huxley R.R., Owen C.G., Whincup P.H., Cook D.G., Colman S., and Collins R. (2004). Birth weight and subsequent cholesterol levels: exploration of the "fetal origins" hypothesis. *JAMA* 292(22): 2755-64.

Ichiba H., Shintaku H., Fujimaru M., Hirai C., Okano Y., and Funato M. (2000). Bone mineral density of the lumbar spine in very-low-birth-weight infants: a longitudinal study. *European Journal of Pediatrics* 159(3): 215-8.

Indredavik Evensen K.A., Steinshamn S., Tjønna A.E., Stølen T., Høydal M.A., Wisløff U., Brubakk A.-M., and Vik T. (2009). Effects of preterm birth and fetal growth retardation on cardiovascular risk factors in young adulthood. *Early Human Development* 85(4): 239-45.

Indredavik M.S., Vik T., Heyerdahl S., Kulseng S., Fayers P., and Brubakk A.M. (2004). Psychiatric symptoms and disorders in adolescents with low birth weight. *Archives of Disease in Childhood Fetal & Neonatal Edition* 89(5): F445-50.

Ioannidis J.P.A. (2005). Why Most Published Research Findings Are False. *PLoS Medicine* 2(8): e124.

Irving R.J., Belton N.R., Elton R.A., and Walker B.R. (2000). Adult cardiovascular risk factors in premature babies. *The Lancet* 355(9221): 2135-36.

Johansson S., Iliadou A., Bergvall N., Tuvemo T., Norman M., and Cnattingius S. (2005). Risk of high blood pressure among young men increases with the degree of immaturity at birth. *Circulation* 112(22): 3430-36.

Johansson S., Norman M., Legnevall L., Dalmaz Y., Lagercrantz H., and Vanpee M. (2007). Increased catecholamines and heart rate in children with low birth weight: perinatal contributions to sympathoadrenal overactivity. *Journal of Internal Medicine* 261(5): 480-7.

Johnell O., Kanis J.A., Oden A., Johansson H., De Laet C., Delmas P., Eisman J.A., Fujiwara S., Kroger H., Mellstrom D., Meunier P.J., Melton L.J., 3rd, O'Neill T., Pols H., Reeve J., Silman A., and Tenenhouse A. (2005). Predictive value of BMD for hip and other fractures. *Journal of Bone and Mineral Research* 20(7): 1185-94.

Jones C.A., Bowden L.S., Watling R., Ryan S.W., and Judd B.A. (2001). Hypercalciuria in ex-preterm children, aged 7-8 years. *Pediatric Nephrology* 16(8): 665-71.

Juonala M., Viikari J.S.A., Kähönen M., Taittonen L., Rönnemaa T., Laitinen T., Mäki-Torkko N., Mikkila V., Räsänen L., Åkerblom H.K., Pesonen E., and Raitakari O.T. (2005). Geographic Origin as a Determinant of Carotid Artery Intima-Media Thickness and Brachial Artery Flow-Mediated Dilation: The Cardiovascular Risk in Young Finns Study. *Arteriosclerosis, Thrombosis, and Vascular Biology* 25(2): 392-98.

Järvelin M.-R., Sovio U., King V., Lauren L., Xu B., McCarthy M.I., Hartikainen A.-L., Laitinen J., Zitting P., Rantakallio P., and Elliott P. (2004). Early life factors and blood pressure at age 31 years in the 1966 Northern Finland Birth Cohort. *Hypertension* 44(6): 838-46.

Järvenpää A.-L., and Granström M.L. (1987). Keskosen kehitys, seuranta ja ennuste [The development, social behavior and prognosis of premature infants] (Finnish). *Duodecim* 103(20): 1238-46.

Järvenpää A.-L., Virtanen M., and Pohjavuori M. (1991). The

outcome of extremely low birthweight infants. *Annals of Medicine* 23(6): 699-704.

Kaijser M., Bonamy A.-K.E., Akre O., Cnattingius S., Granath F., Norman M., and Ekbom A. (2008). Perinatal risk factors for ischemic heart disease: Disentangling the roles of birth weight and preterm birth. *Circulation* 117(3): 405-10.

Kaijser M., Edstedt Bonamy A.-K., Akre O., Cnattingius S., Granath F., Norman M., and Ekbom A. (2009). Perinatal risk factors for diabetes in later life. *Diabetes* 58(3): 523-26.

Kajantie E. (2006). Fetal origins of stress-related adult disease. *Annals of the New York Academy of Sciences* 1083: 11-27.

Kajantie E., Hovi P., Räikkonen K., Pesonen A.-K., Heinonen K., Järvenpää A.-L., Eriksson J.G., Strang-Karlsson S., and Andersson S. (2008). Young adults with very low birth weight: Leaving the parental home and sexual relationships-Helsinki Study of Very Low Birth Weight Adults. *Pediatrics* 122(1): e62-72.

Kajantie E., Strang-Karlsson S., Hovi P., Räikkonen K., Pesonen A.-K., Heinonen K., Järvenpää A.-L., Eriksson J.G., and Andersson S. (2010). Adults born at very low birth weight exercise less than their peers born at term. *Journal of Pediatrics* 157(4): 610-6.

Kamel R.M. (2010). The onset of human parturition. *Archives of Gynecology & Obstetrics* 281(6): 975-82.

Kanazawa I., Yamaguchi T., Yamamoto M., Yamauchi M., Kurioka S., Yano S., and Sugimoto T. (2009). Serum osteocalcin level is associated with glucose metabolism and atherosclerosis parameters in type 2 diabetes mellitus. *Journal of Clinical Endocrinology & Metabolism* 94(1): 45-9.

Kanis J.A., Melton L.J., 3rd, Christiansen C., Johnston C.C., and Khaltaev N. (1994). The diagnosis of osteoporosis. *Journal of Bone & Mineral Research* 9(8): 1137-41.

Kannam J.P., Levy D., Larson M., and Wilson P.W. (1994). Short stature and risk for mortality and cardiovascular disease events. The Framingham Heart Study. *Circulation* 90(5): 2241-47.

Kannel W.B., Dawber T.R., Friedman G.D., Glennon W.E., and McNamara P.M. (1964). Risk factors in coronary heart disease. An evaluation of several serum lipids as predictors of coronary heart disease; the Framingham Study. *Annals of Internal Medicine* 61: 888-99.

Kannus P., Niemi S., Parkkari J., Palvanen M., Vuori I., and Jarvinen M. (1999). Hip fractures in Finland between 1970 and 1997 and predictions for the future. *Lancet* 353(9155): 802-5.

Kashyap S. (2007). Enteral intake for very low birth weight infants: What should the composition be? *Seminars in Perinatology* 31(2): 74-82.

Keijzer-Veen M.G., Finken M.J., Nauta J., Dekker F.W., Hille E.T., Frölich M., Wit J.M., van der Heijden A.J., and Dutch P.-C.S.G. (2005). Is blood pressure increased 19 years after intrauterine growth restriction and preterm birth? A prospective follow-up study in The Netherlands. *Pediatrics* 116(3): 725-31.

Keijzer-Veen M.G., Dulger A., Dekker F.W., Nauta J., and van der Heijden B.J. (2010). Very preterm birth is a risk factor for increased systolic blood pressure at a young adult age. *Pediatric Nephrology* 25(3): 509-16.

Kermack W.O., McKendrick A.G., and McKinlay P.L. (1934). Death-Rates in Great Britain and Sweden: Some general regularities and their significance. (Reprint available: doi:10.1093/ije/30.4.678). *Lancet* 31: 698-703.

Kistner A., Celsi G., Vanpee M., and Jacobson S.H. (2000). Increased blood pressure but normal renal function in adult women born preterm. *Pediatric Nephrology* 15(3 - 4): 215-20.

Kistner A., Jacobson L., Jacobson S.H., Svensson E., and Hellstrom A. (2002). Low gestational age associated with abnormal retinal vascularization and increased blood pressure in adult women. *Pediatric Research* 51(6): 675-80.

Kistner A., Celsi G., Vanpee M., and Jacobson S.H. (2005). Increased systolic daily ambulatory blood pressure in adult women born preterm. *Pediatric Nephrology* 20(2): 232-3.

Kitchen W.H., Yu V.Y., Lissenden J.V., and Bajuk B. (1982a). Collaborative study of very-low-birthweight infants: Techniques of perinatal care and mortality. *Lancet* 1(8287): 1454-7.

Kitchen W.H., Ryan M.M., Rickards A., Astbury J., Ford G., Lissenden J.V., Keith C.G., and Keir E.H. (1982b). Changing outcome over 13 years of very low birthweight infants. *Seminars in Perinatology* 6(4): 373-89.

Klein C.J. (2002). Nutrient requirements for preterm infant formulas. *The Journal of Nutrition* 132(6): 1395S-577S.

Kohrt W.M., Bloomfield S.A., Little K.D., Nelson M.E., Yingling V.R., and American College of Sports M. (2004). American College of Sports Medicine Position Stand: physical activity and bone health. *Medicine & Science in Sports & Exercise* 36(11): 1985-96.

Korvenranta E., Linna M., Rautava L., Andersson S., Gissler M., Hallman M., Häkkinen U., Leipälä J., Peltola M., Tammela O., and Lehtonen L. (2010). Hospital costs and quality of life during 4 years after very preterm birth. *Archives of Pediatrics and Adolescent Medicine* 164(7): 657-63.

Koupil I., Leon D.A., and Lithell H.O. (2005). Length of gestation is associated with mortality from cerebrovascular disease. *Journal of Epidemiology & Community Health* 59(6): 473-4.

Kovacs C.S., and Kronenberg H.M. (2006). Skeletal Physiology: Pregancy and lactation. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. MJ Favus. Washington, DC, American Society for Bone and Mineral Research**:** 63-68.

Kramer M.S., and Joseph K.S. (1996). Enigma of fetal infant-origins hypothesis. *Lancet* 348(9037): 1254-55.

Kramer M.S., Platt R.W., Wen S.W., Joseph K.S., Allen A., Abrahamowicz M., Blondel B., Breart G., and Fetal/Infant Health Study Group of the Canadian Perinatal Surveillance S. (2001). A new and improved population-based Canadian reference for birth weight for gestational age. *Pediatrics* 108(2): E35.

Kunst A., Draeger B., and Ziegenhorn J. (1984). UV-methods with hexokinase and glucose-6-phosphate dehydrogenase. Methods of Enzymatic Analysis. H Bergmeyer. Weinheim, Germany, Verlag Chemie GmbH. **6:** 163-72.

Kurl S., Heinonen K., Lansimies E., and Launiala K. (1998). Determinants of bone mineral

density in prematurely born children aged 6-7 years. *Acta Paediatrica* 87(6): 650-3.

Kurl S., Heinonen K., and Lansimies E. (2000). Effects of prematurity, intrauterine growth status, and early dexamethasone treatment on postnatal bone mineralisation. *Archives of Disease in Childhood Fetal & Neonatal Edition* 83(2): F109-11.

Kuschel C.A., and Harding J.E. (2009). Multicomponent fortified human milk for promoting growth in preterm infants. *Cochrane Database of Systematic Reviews*(1): CD000343.

Kyrklund-Blomberg N.B., Granath F., and Cnattingius S. (2005). Maternal smoking and causes of very preterm birth. *Acta Obstetricia & Gynecologica Scandinavica* 84(6): 572-77.

De Laet C., Kanis J.A., Oden A., Johanson H., Johnell O., Delmas P., Eisman J.A., Kroger H., Fujiwara S., Garnero P., McCloskey E.V., Mellstrom D., Melton L.J., 3rd, Meunier P.J., Pols H.A.P., Reeve J., Silman A., and Tenenhouse A. (2005). Body mass index as a predictor of fracture risk: a meta-analysis. *Osteoporosis International* 16(11): 1330-8.

Laitinen J., Kiukaanniemi K., Heikkinen J., Koiranen M., Nieminen P., Sovio U., Keinanen-Kiukaanniemi S., and Järvelin M.R. (2005). Body size from birth to adulthood and bone mineral content and density at 31 years of age: results from the northern Finland 1966 birth cohort study. *Osteoporosis International* 16(11): 1417-24.

Lakka H.-M., Laaksonen D.E., Lakka T.A., Niskanen L.K., Kumpusalo E., Tuomilehto J., and Salonen J.T. (2002). The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 288(21): 2709-16.

Lammi N., Blomstedt P.A., Moltchanova E., Eriksson J.G., Tuomilehto J., and Karvonen M. (2009). Perinatal risk factors in young adult-onset type 1 and type 2 diabetes - a population-based case-control study. *Acta Obstetricia et Gynecologica Scandinavica* 88(4): 468-674.

Lauren L., Järvelin M.-R., Elliott P., Sovio U., Spellman A., McCarthy M., Emmett P., Rogers I., Hartikainen A.-L., Pouta A., Hardy R., Wadsworth M., Helmsdal G., Olsen S., Bakoula C., Lekea V., Millwood I., and Group E.-B.S. (2003). Relationship between birthweight and blood lipid concentrations in later life: evidence from the existing literature. *International Journal of Epidemiology* 32(5): 862-76.

Law M.R., and Wald N.J. (2002). Risk factor thresholds: their existence under scrutiny. *BMJ (Clinical Research Ed.)* 324(7353): 1570-6.

Lawlor D.A., Davey Smith G., Clark H., and Leon D.A. (2006). The associations of birthweight, gestational age and childhood BMI with type 2 diabetes: findings from the Aberdeen Children of the 1950s cohort. *Diabetologia* 49(11): 2614-7.

Lawlor D.A., Leon D.A., and Rasmussen F. (2007). Growth trajectory matters: interpreting the associations among birth weight, concurrent body size, and systolic blood pressure in a cohort study of 378,707 Swedish men. *American Journal of Epidemiology* 165(12): 1405-12.

Lazdam M., de la Horra A., Pitcher A., Mannie Z., Diesch J., Trevitt C., Kylintireas I., Contractor H.,

Singhal A., Lucas A., Neubauer S., Kharbanda R., Alp N., Kelly B., and Leeson P. (2010). Elevated blood pressure in offspring born premature to hypertensive pregnancy: Is endothelial dysfunction the underlying vascular mechanism? *Hypertension* 56(1): 159-65.

Leal J., Luengo-Fernandez R., Gray A., Petersen S., and Rayner M. (2006). Economic burden of cardiovascular diseases in the enlarged European Union. *European Heart Journal* 27(13): 1610-9.

Lee K.S., Kim B.I., Khoshnood B., Hsieh H.L., Chen T.J., Herschel M., and Mittendorf R. (1995). Outcome of very low birth weight infants in industrialized countries: 1947-1987. *American Journal of Epidemiology* 141(12): 1188-93.

Leino M., Raitakari O., Porkka K., Taimela S., and Viikari J. (1999). Associations of education with cardiovascular risk factors in young adults: the Cardiovascular Risk in Young Finns Study. *International Journal of Epidemiology* 28(4): 667-75.

Leon D.A., Koupilova I., Lithell H.O., Berglund L., Mohsen R., Vagero D., Lithell U.B., and McKeigue P.M. (1996). Failure to realise growth potential in utero and adult obesity in relation to blood pressure in 50 year old Swedish men.[see comment]. *BMJ (Clinical Research Ed.)* 312(7028): 401-6.

Leon D.A., Johansson M., and Rasmussen F. (2000). Gestational age and growth rate of fetal mass are inversely associated with systolic blood pressure in young adults: an epidemiologic study of 165,136 Swedish men aged 18 years. *American Journal of Epidemiology* 152(7): 597-604.

Lewington S., Clarke R., Qizilbash N., Peto R., Collins R., and Prospective Studies C. (2002). Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies.[Erratum appears in Lancet. 2003 Mar 22;361(9362):1060]. *Lancet* 360(9349): 1903-13.

Ley D., Stale H., and Marsal K. (1997). Aortic vessel wall characteristics and blood pressure in children with intrauterine growth retardation and abnormal foetal aortic blood flow. *Acta Paediatrica* 86(3): 299-305.

Li J.-M., and Shah A.M. (2004). Endothelial cell superoxide generation: regulation and relevance for cardiovascular pathophysiology. *American Journal of Physiology - Regulatory Integrative & Comparative Physiology* 287(5): R1014-30.

Libby P., Egan D., and Skarlatos S. (1997). Roles of infectious agents in atherosclerosis and restenosis: an assessment of the evidence and need for future research. *Circulation* 96(11): 4095-103.

Lieben L., Callewaert F., and Bouillon R. (2009). Bone and metabolism: a complex crosstalk. *Hormone Research* 71 Suppl 1: 134-8.

Lieberman E., Gremy I., Lang J.M., and Cohen A.P. (1994). Low birthweight at term and the timing of fetal exposure to maternal smoking. *American Journal of Public Health* 84(7): 1127-31.

Ligi I., Grandvuillemin I., Andres V., Dignat-George F., and Simeoni U. (2010). Low birth weight infants and the developmental programming of hypertension: A focus on vascular factors. *Seminars in Perinatology* 34(3): 188-92.

Liljedahl M., Martin H., Magnuson A., Montgomery S.M., and Schollin J.

(2008). Endothelial function in children with a history of premature prolonged rupture of membranes and bronchopulmonary dysplasia--a pilot study. *Acta Paediatrica* 97(7): 909-14.

Lindstrom K., Winbladh B., Haglund B., and Hjern A. (2007). Preterm infants as young adults: a Swedish national cohort study.[Erratum appears in Pediatrics. 2007 Oct;120(4):936]. *Pediatrics* 120(1): 70-7.

Lockwood C.J. (2002). Predicting premature delivery--no easy task. *New England Journal of Medicine* 346(4): 282-4.

Lopez A.D., Mathers C.D., Ezzati M., Jamison D.T., and Murray C.J. (2006). Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 367(9524): 1747-57.

Lorenz M.W., von Kegler S., Steinmetz H., Markus H.S., and Sitzer M. (2006). Carotid intima-media thickening indicates a higher vascular risk across a wide age range: Prospective data from the carotid atherosclerosis progression study (CAPS). *Stroke* 37(1): 87-92.

Lucas A., and Morley R. (1994). Does early nutrition in infants born before term programme later blood pressure? *BMJ (Clinical Research Ed.)* 309(6950): 304-8.

Lussana F., Painter R.C., Ocke M.C., Buller H.R., Bossuyt P.M., and Roseboom T.J. (2008). Prenatal exposure to the Dutch famine is associated with a preference for fatty foods and a more atherogenic lipid profile. *American Journal of Clinical Nutrition* 88(6): 1648-52.

Manzoni P., Grazia Baù M., Farina D., Hovi P., Andersson S., and Kajantie E. (2007). Glucose regulation in young adults with very low birth weight. *New England Journal of Medicine* 357(6): 616-17.

Marschner I.C., Simes R.J., and Keech A. (2007). Biases in the identification of risk factor thresholds and J-curves. *American Journal of Epidemiology* 166(7): 824-31.

Marshall D., Johnell O., and Wedel H. (1996). Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ (Clinical Research Ed.)* 312(7041): 1254-9.

Marshall T.A., Eichenberger Gilmore J.M., Broffitt B., Levy S.M., and Stumbo P.J. (2003). Relative validation of a beverage frequency questionnaire in children ages 6 months through 5 years using 3-day food and beverage diaries. *Journal of the American Dietetic Association* 103(6): 714-20; discussion 20.

Marshall T.A., Eichenberger Gilmore J.M., Broffitt B., Stumbo P.J., and Levy S.M. (2008). Relative validity of the Iowa Fluoride Study targeted nutrient semi-quantitative questionnaire and the block kids' food questionnaire for estimating beverage, calcium, and vitamin D intakes by children. *Journal of the American Dietetic Association* 108(3): 465-72.

Martyn C.N., Barker D.J., Jespersen S., Greenwald S., Osmond C., and Berry C. (1995). Growth in utero, adult blood pressure, and arterial compliance. *British Heart Journal* 73(2): 116-21.

Martyn C.N., and Greenwald S.E. (2001). A hypothesis about a mechanism for the programming of blood pressure and vascular disease in early life. *Clinical & Experimental Pharmacology & Physiology* 28(11): 948-51.

Mathews T.J., and MacDorman M.F. (2007). Infant mortality statistics from the 2004 period linked birth/infant death data set. *National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System* 55(14): 1-32.

Matthews D.R., Hosker J.P., Rudenski A.S., Naylor B.A., Treacher D.F., and Turner R.C. (1985). Homeostasis model assessment: insulin resistance and Î²-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28(7): 412-19.

McCarron P., Okasha M., McEwen J., and Smith G.D. (2002). Height in young adulthood and risk of death from cardiorespiratory disease: A prospective study of male former students of Glasgow University, Scotland. *American Journal of Epidemiology* 155(8): 683-87.

McKeigue P.M., Lithell H.O., and Leon D.A. (1998). Glucose tolerance and resistance to insulin-stimulated glucose uptake in men aged 70 years in relation to size at birth. *Diabetologia* 41(10): 1133-8.

McMillan J.A., Feigin R.D., Accardo J.A., and Oski F.A. (2006). Oski's pediatrics principles and practice Electronic material. Philadelphia (PA), Lippincott Williams & Wilkins.

McMillen I.C., and Robinson J.S. (2005). Developmental origins of the metabolic syndrome: Prediction, plasticity, and programming. *Physiological Reviews* 85(2): 571-633.

Ment L.R., Oh W., Ehrenkranz R.A., Phillip A.G., Vohr B., Allan W., Makuch R.W., Taylor K.J., Schneider K.C., Katz K.H., and et al. (1994). Low-dose indomethacin therapy and extension of intraventricular hemorrhage: a multicenter randomized trial. *Journal of Pediatrics* 124(6): 951-5.

Mi J., Law C., Zhang K.-L., Osmond C., Stein C., and Barker D. (2000). Effects of infant birthweight and maternal body mass index in pregnancy on components of the insulin resistance syndrome in China. *Annals of Internal Medicine* 132(4): 253-60.

Mikkola K., Leipälä J., Boldt T., and Fellman V. (2007). Fetal growth restriction in preterm infants and cardiovascular function at five years of age. *Journal of Pediatrics* 151(5): 494-9.

Mitchell P., Liew G., Rochtchina E., Wang J.J., Robaei D., Cheung N., and Wong T.Y. (2008). Evidence of arteriolar narrowing in low-birth-weight children. *Circulation* 118(5): 518-24.

Mogren I., Hogberg U., Stegmayr B., Lindahl B., and Stenlund H. (2001). Fetal exposure, heredity and risk indicators for cardiovascular disease in a Swedish welfare cohort. *International Journal of Epidemiology* 30(4): 853-62.

Morken N.-H., Källen K., Hagberg H., and Jacobsson B. (2005). Preterm birth in Sweden 1973â€“2001: Rate, subgroups, and effect of changing patterns in multiple births, maternal age, and smoking. *Acta Obstetricia & Gynecologica Scandinavica* 84(6): 558-65.

Morley R., Harland P., Law C.M., and Lucas A. (2000). Birthweight and social deprivation: influences on serum lipids and fibrinogen. *Acta Paediatrica* 89(6): 703-7.

Moster D., Lie R.T., and Markestad T. (2008). Long-term medical and social consequences of preterm birth. *New England Journal of Medicine* 359(3): 262-73.

Muglia L.J., and Katz M. (2010). The enigma of spontaneous preterm birth. *New England Journal of Medicine* 362(6): 529-35.

Münck P., Haataja L., Maunu J., Parkkola R., Rikalainen H., Lapinleimu H., Lehtonen L., and PipariStudyGroup (2010). Cognitive outcome at 2 years of age in Finnish infants with very low birth weight born between 2001 and 2006. *Acta Paediatrica* 99(3): 359-66.

Mzayek F., Sherwin R., Fonseca V., Valdez R., Srinivasan S.R., Cruickshank J.K., and Berenson G.S. (2004). Differential association of birth weight with cardiovascular risk variables in African-Americans and Whites: the Bogalusa heart study. *Annals of Epidemiology* 14(4): 258-64.

National Center for Health Statistics (2007). Final natality data. Very low birthweight by race. US, 2003-2005. Retrieved June 16th, 2008, from www.marchofdimes.com/peristats.

National Center for Health Statistics (2008a). Final natality data. US, 2004-2006. Retrieved Apr 10th, 2011, from www.marchofdimes.com/peristats.

National Center for Health Statistics (2008b). Final natality data. US, 2006. Retrieved May 27th, 2010, from www.marchofdimes.com/peristats.

The National Findiet 2002 Study (Finnish) [Finravinto 2002 -tutkimus]. Kansanterveyslaitoksen julkaisuja B3 Helsinki: Kansanterveyslaitos 2003. ISBN 951-740-338-0. Retrieved from www.ktl.fi.

National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy. (2000). *American Journal of Obstetrics and Gynecology* 183(1): S1-S22.

National Institute fo Health and Welfare (2009). Births and newborns 2008. Statistical Summary 22/2009. Official Statistics of Finland, Health 2009. . Retrieved from http://www.stakes.fi/EN/tilastot/statisticsbytopic/reproduction/parturients.htm.

National Institute of Child Health and Development (2003). A strategic plan 2005-2010. Appendix B4. Retrieved Feb 10th, 2011, from http://www.nichd.nih.gov/publications/pubs/ppb_strategicplan2010/upload/PartI.pdf.

National Research and Development Centre for Welfare and Health, Finland (2005). Parturients, Deliveries and Births. Statistical Summary. Retrieved Feb 27th, 2008, from http://www.stakes.fi/NR/rdonlyres/702BDD53-EB53-4060-A8B2-67E925918C88/0/Tt21_05.pdf.

Nichols W.W., Pepine C.J., and O'Rourke M.F. (1999). Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke. *New England Journal of Medicine* 340(22): 1762-3.

Nijpels G. (1998). Determinants for the progression from impaired glucose tolerance to non-insulin-dependent diabetes mellitus. *European Journal of Clinical Investigation* 28 Suppl 2: 8-13.

Nilsson P.M., Ostergren P.O., Nyberg P., Soderstrom M., and Allebeck P. (1997). Low birth weight is associated with elevated systolic blood pressure in adolescence: a prospective study of a birth cohort of 149378 Swedish boys. *Journal of Hypertension* 15(12 Pt 2): 1627-31.

Njolstad I., Arnesen E., and Lund-Larsen P.G. (1996). Body Height, Cardiovascular Risk Factors, and Risk of Stroke in Middle-aged Men and Women: A 14-Year Follow-up of the Finnmark Study. *Circulation* 94(11): 2877-82.

Norman M., and Martin H. (2003). Preterm birth attenuates association between low birth weight and endothelial dysfunction. *Circulation* 108(8): 996-1001.

Norman M. (2008). Low birth weight and the developing vascular tree: a systematic review. *Acta Pædiatrica* 97(9): 1165-72.

Norman M. (2010). Preterm Birth--An Emerging Risk Factor for Adult Hypertension? *Seminars in Perinatology* 34(3): 183-87.

Northway W.H., Jr., Rosan R.C., and Porter D.Y. (1967). Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. *New England Journal of Medicine* 276(7): 357-68.

Nuyt A.M. (2008). Mechanisms underlying developmental programming of elevated blood pressure and vascular dysfunction: evidence from human studies and experimental animal models. *Clinical Science* 114(1): 1-17.

Nwasokwa O.N., Weiss M., Gladstone C., and Bodenheimer M.M. (1996). Effect of coronary artery size on the prevalence of atherosclerosis. *The American Journal of Cardiology* 78(7): 741-46.

O'Brien E., Mee F., Atkins N., and O'Malley K. (1991). Accuracy of the SpaceLabs 90207, Novacor DIASYS 200, Del Mar Avionics Pressurometer IV and Takeda TM-2420 ambulatory systems according to British and American criteria. *Journal of Hypertension - Supplement* 9(6): S332-3.

O'Donovan D.J., and Fernandes C.J. (2004). Free radicals and diseases in premature infants. *Antioxidants & Redox Signaling* 6(1): 169-76.

O'Leary D.H., Polak J.F., Kronmal R.A., Manolio T.A., Burke G.L., and Wolfson S.K., Jr. (1999). Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *New England Journal of Medicine* 340(1): 14-22.

Oken E., Huh S.Y., Taveras E.M., Rich-Edwards J.W., and Gillman M.W. (2005). Associations of maternal prenatal smoking with child adiposity and blood pressure. *Obesity Research* 13(11): 2021-8.

Oren A., Vos L.E., Bos W.-J.W., Safar M.E., Uiterwaal C.S.P.M., Gorissen W.H.M., Grobbee D.E., and Bots M.L. (2003). Gestational age and birth weight in relation to aortic stiffness in healthy young adults: two separate mechanisms? *American Journal of Hypertension* 16(1): 76-9.

Orozco L.J., Buchleitner A.M., Gimenez-Perez G., Roque I Figuls M., Richter B., and Mauricio D. (2008). Exercise or exercise and diet for preventing type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews*(3): CD003054.

Orsini L.S., Rousculp M.D., Long S.R., and Wang S. (2005). Health care utilization and expenditures in the United States: a study of osteoporosis-related fractures. *Osteoporosis International* 16(4): 359-71.

Osmond C., Barker D.J., Winter P.D., Fall C.H., and Simmonds S.J. (1993). Early growth and death from cardiovascular disease in women. *BMJ (Clinical Research Ed.)* 307(6918): 1519-24.

Ounsted M., and Sleigh G. (1975). The infant's self-regulation of food intake and weight gain. Difference in metabolic balance after growth constraint or acceleration in utero. *Lancet* 1(7922): 1393-7.

Painter R.C., Roseboom T.J., van Montfrans G.A., Bossuyt P.M.M., Krediet R.T., Osmond C., Barker D.J.P., and Bleker O.P. (2005). Microalbuminuria in adults after prenatal exposure to the Dutch famine. *Journal of the American Society of Nephrology* 16(1): 189-94.

Painter R.C., de Rooij S.R., Bossuyt P.M., Phillips D.I., Osmond C., Barker D.J., Bleker O.P., and Roseboom T.J. (2006). Blood pressure response to psychological stressors in adults after prenatal exposure to the Dutch famine. *Journal of Hypertension* 24(9): 1771-8.

Painter R.C., de Rooij S.R., Bossuyt P.M., de Groot E., Stok W.J., Osmond C., Barker D.J., Bleker O.P., and Roseboom T.J. (2007). Maternal nutrition during gestation and carotid arterial compliance in the adult offspring: the Dutch famine birth cohort. *Journal of Hypertension* 25(3): 533-40.

Paravicini T.M., and Touyz R.M. (2006). Redox signaling in hypertension. *Cardiovascular Research* 71(2): 247-58.

Pedersen J.I. (2008). Vitamin D requirement and setting recommendation levels - current Nordic view. *Nutrition Reviews* 66(10 Suppl 2): S165-9.

Pescatello L.S., Franklin B.A., Fagard R., Farquhar W.B., Kelley G.A., Ray C.A., and American College of Sports M. (2004). American College of Sports Medicine position stand. Exercise and hypertension. *Medicine & Science in Sports & Exercise* 36(3): 533-53.

Pesonen E. (2004). Extrinsic and intrinsic factors relating to intimal thickening in children. *Acta Paediatrica Supplement* 93(446): 43-7.

Pharoah P.O., Stevenson C.J., Cooke R.W., and Stevenson R.C. (1994). Clinical and subclinical deficits at 8 years in a geographically defined cohort of low birthweight infants. *Archives of Disease in Childhood* 70(4): 264-70.

Pharoah P.O., Stevenson C.J., and West C.R. (1998). Association of blood pressure in adolescence with birthweight. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 79(2): F114-F18.

Philip A.G.S. (2005). The evolution of neonatology. *Pediatric Research* 58(4): 799-815.

Phillips D.I., and Barker D.J. (1997). Association between low birthweight and high resting pulse in adult life: is the sympathetic nervous system involved in programming the insulin resistance syndrome? *Diabetic Medicine* 14(8): 673-7.

Pickering T.G. (2003). White coat hypertension. Hypertension Primer. JL Izzo and Black HR. Dallas, American Heart Association.

Pickering T.G., Hall J.E., Appel L.J., Falkner B.E., Graves J., Hill M.N., Jones D.W., Kurtz T., Sheps S.G., and Roccella E.J. (2005). Recommendations for blood pressure measurement in humans and experimental animals: Part 1: Blood pressure measurement in humans: A statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High

Blood Pressure Research. *Hypertension* 45(1): 142-61.

Pihkala J., Hakala T., Voutilainen P., and Raivio K. (1989). Uudet suomalaiset sikiön kasvukäyrät [Characteristics of recent fetal growth curves in Finland] (Finnish). *Duodecim* 105(18): 1540-6.

Platt M.J., Cans C., Johnson A., Surman G., Topp M., Torrioli M.G., and Krageloh-Mann I. (2007). Trends in cerebral palsy among infants of very low birthweight (<1500 g) or born prematurely (<32 weeks) in 16 European centres: a database study. *The Lancet* 369(9555): 43-50.

Pohlandt F. (1994a). Bone mineral deficiency as the main factor of dolichocephalic head flattening in very-low-birth-weight infants. *Pediatric Research* 35(6): 701-3.

Pohlandt F. (1994b). Prevention of postnatal bone demineralization in very low-birth-weight infants by individually monitored supplementation with calcium and phosphorus. *Pediatric Research* 35(1): 125-9.

Port S., Demer L., Jennrich R., Walter D., and Garfinkel A. (2000). Systolic blood pressure and mortality. *Lancet* 355(9199): 175-80.

Pouta A., Hartikainen A.-L., Sovio U., Gissler M., Laitinen J., McCarthy M.I., Ruokonen A., Elliott P., and Järvelin M.-R. (2004). Manifestations of metabolic syndrome after hypertensive pregnancy. *Hypertension* 43(4): 825-31.

Public Health Agency of Canada (2008). Canadian Perinatal Health Report 2008. Retrieved from http://www.phac-aspc.gc.ca/publicat/2008/cphr-rspc/index-eng.php.

Pyhälä R., Räikkönen K., Feldt K., Andersson S., Hovi P., Eriksson J.G., Järvenpää A.-L., and Kajantie E. (2009). Blood pressure response to psychosocial stress in young adults with very low birth weight - The Helsinki Study of Very Low Birth Weight Adults. *Pediatrics* 123(2): 731-34.

Pyörälä M., Miettinen H., Laakso M., and Pyörälä K. (2000). Plasma insulin and all-cause, cardiovascular, and noncardiovascular mortality: the 22-year follow-up results of the Helsinki Policemen Study. *Diabetes Care* 23(8): 1097-102.

Raitakari O.T., Ronnemaa T., Jarvisalo M.J., Kaitosaari T., Volanen I., Kallio K., Lagstrom H., Jokinen E., Niinikoski H., Viikari J.S.A., and Simell O. (2005). Endothelial function in healthy 11-year-old children after dietary intervention with onset in infancy: the Special Turku Coronary Risk Factor Intervention Project for children (STRIP). *Circulation* 112(24): 3786-94.

Rakow A., Johansson S., Legnevall L., Sevastik R., Celsi G., Norman M., and Vanpee M. (2008). Renal volume and function in school-age children born preterm or small for gestational age. *Pediatric Nephrology* 23(8): 1309-15.

Ravelli A.C., van der Meulen J.H., Michels R.P., Osmond C., Barker D.J., Hales C.N., and Bleker O.P. (1998). Glucose tolerance in adults after prenatal exposure to famine.[see comment]. *Lancet* 351(9097): 173-7.

Ravitsemussuunnittelutoimikunta (2005). Suomalaiset ravitsemussuositukset - ravinto ja liikunta tasapainoon (Finnish) [Finnish nutrional recommendations]. Valtion

ravitsemusneuvottelukunta c/o Elintarvikevirasto.

Regan F.M., Cutfield W.S., Jefferies C., Robinson E., and Hofman P.L. (2006). The impact of early nutrition in premature infants on later childhood insulin sensitivity and growth. *Pediatrics* 118(5): 1943-49.

Rich-Edwards J.W., Stampfer M.J., Manson J.E., Rosner B., Hankinson S.E., Colditz G.A., Willett W.C., and Hennekens C.H. (1997). Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. *BMJ (Clinical Research Ed.)* 315(7105): 396-400.

Robinson S., Walton R.J., Clark P.M., Barker D.J., Hales C.N., and Osmond C. (1992). The relation of fetal growth to plasma glucose in young men. *Diabetologia* 35(5): 444-6.

Rogers M., Fay T.B., Whitfield M.F., Tomlinson J., and Grunau R.E. (2005). Aerobic Capacity, Strength, Flexibility, and Activity Level in Unimpaired Extremely Low Birth Weight (<=800 g) Survivors at 17 Years of Age Compared With Term-Born Control Subjects. *Pediatrics* 116(1): e58-65.

de Rooij S., Painter R., Roseboom T., Phillips D., Osmond C., Barker D., Tanck M., Michels R., Bossuyt P., and Bleker O. (2006). Glucose tolerance at age 58 and the decline of glucose tolerance in comparison with age 50 in people prenatally exposed to the Dutch famine. *Diabetologia* 49(4): 637-43.

Roseboom T.J., van der Meulen J.H., Ravelli A.C., van Montfrans G.A., Osmond C., Barker D.J., and Bleker O.P. (1999). Blood pressure in adults after prenatal exposure to famine. *Journal of Hypertension* 17(3): 325-30.

Roseboom T.J., van der Meulen J.H., Osmond C., Barker D.J., Ravelli A.C., and Bleker O.P. (2000a). Plasma lipid profiles in adults after prenatal exposure to the Dutch famine. *American Journal of Clinical Nutrition* 72(5): 1101-6.

Roseboom T.J., van der Meulen J.H., Osmond C., Barker D.J., Ravelli A.C., Schroeder-Tanka J.M., van Montfrans G.A., Michels R.P., and Bleker O.P. (2000b). Coronary heart disease after prenatal exposure to the Dutch famine, 1944-45. *Heart* 84(6): 595-8.

Roseboom T.J., de Rooij S., and Painter R. (2006). The Dutch famine and its long-term consequences for adult health. *Early Human Development* 82(8): 485-91.

Rosen C.L., Larkin E.K., Kirchner H.L., Emancipator J.L., Bivins S.F., Surovec S.A., Martin R.J., and Redline S. (2003). Prevalence and risk factors for sleep-disordered breathing in 8- to 11-year-old children: association with race and prematurity. *Journal of Pediatrics* 142(4): 383-9.

Rosmalen J.G.M., Oldehinkel A.J., Ormel J., de Winter A.F., Buitelaar J.K., and Verhulst F.C. (2005). Determinants of salivary cortisol levels in 10-12 year old children; a population-based study of individual differences. *Psychoneuroendocrinology* 30(5): 483-95.

Ross R. (1993). The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 362(6423): 801-9.

Rossi P., Tauzin L., Marchand E., Simeoni U., and Frances Y. (2006). [Arterial blood pressure and arterial stiffness in adolescents are related to gestational age]. *Archives des Maladies du Coeur et des Vaisseaux* 99(7-8): 748-51.

Rotteveel J., van Weissenbruch M.M., Twisk J.W.R., and Delemarre-Van de Waal H.A. (2008a). Abnormal lipid profile and hyperinsulinaemia after a mixed meal: additional cardiovascular risk factors in young adults born preterm. *Diabetologia* 51(7): 1269-75.

Rotteveel J., van Weissenbruch M.M., Twisk J.W.R., and Delemarre-Van de Waal H.A. (2008b). Infant and childhood growth patterns, insulin sensitivity, and blood pressure in prematurely born young adults. *Pediatrics* 122(2): 313-21.

Saigal S., Szatmari P., Rosenbaum P., Campbell D., and King S. (1991). Cognitive abilities and school performance of extremely low birth weight children and matched term control children at age 8 years: a regional study. *Journal of Pediatrics* 118(5): 751-60.

Saigal S., Pinelli J., Hoult L., Kim M.M., and Boyle M. (2003). Psychopathology and social competencies of adolescents who were extremely low birth weight. *Pediatrics* 111(5 Pt 1): 969-75.

Saigal S., Stoskopf B., Streiner D., Paneth N., Pinelli J., and Boyle M. (2006). Growth trajectories of extremely low birth weight infants from birth to young adulthood: a longitudinal, population-based study. *Pediatric Research* 60(6): 751-8.

Saigal S., Stoskopf B., Boyle M., Paneth N., Pinelli J., Streiner D., and Goddeeris J. (2007). Comparison of current health, functional limitations, and health care use of young adults who were born with extremely low birth weight and normal birth weight. *Pediatrics* 119(3): E562-73.

Salvaggio A., Periti M., Quaglia G., Marzorati D., and Tavanelli M. (1992). The independent effect of habitual cigarette and coffee consumption on blood pressure. *European Journal of Epidemiology* 8(6): 776-82.

Schlüssel M.M., de Castro J.A.S., Kac G., da Silva A.A.M., Cardoso V.C., Bettiol H., and Barbieri M.A. (2010). Birth weight and bone mass in young adults from Brazil. *Bone* 46(4): 957-63.

Scott J.R., Bernhisel M.A., and Azziz R. (2003). Danforth's obstetrics & gynecology Electronic material. Philadelphia (PA), Lippincott Williams & Wilkins.

Siewert-Delle A., and Ljungman S. (1998). The impact of birth weight and gestational age on blood pressure in adult life: a population-based study of 49-year-old men.[erratum appears in Am J Hypertens 1999 Jan;12(1 Pt 1):113]. *American Journal of Hypertension* 11(8 Pt 1): 946-53.

Silveira P.P., Portella A.K., Diorio J., Gaudreau H., Levitan R., and Meaney M.J. (2009). Intrauterine growth restriction is associated with increased impulsivity using the Snack Delay Test in 3 years old girls. Pediatric Academic Societes' Annual Meeting E-PAS2009:2500.3, Baltimore.

Simmons R.A., Templeton L.J., and Gertz S.J. (2001). Intrauterine growth retardation leads to the development of type 2 diabetes in the rat. *Diabetes* 50(10): 2279-86.

Simmons R.A. (2009). Developmental origins of adult disease. *Pediatric Clinics of North America* 56(3): 449-66.

Singhal A., Kattenhorn M., Cole T.J., Deanfield J., and Lucas A. (2001a). Preterm birth, vascular function, and risk factors for atherosclerosis. *Lancet* 358(9288): 1159-60.

Singhal A., Cole T.J., and Lucas A. (2001b). Early nutrition in preterm

infants and later blood pressure: two cohorts after randomised trials. *Lancet* 357(9254): 413-19.

Singhal A., Fewtrell M., Cole T.J., and Lucas A. (2003). Low nutrient intake and early growth for later insulin resistance in adolescents born preterm.[see comment]. *Lancet* 361(9363): 1089-97.

Singhal A., Cole T.J., Fewtrell M., Deanfield J., and Lucas A. (2004). Is slower early growth beneficial for long-term cardiovascular health? *Circulation* 109(9): 1108-13.

Singhal A., Cole T.J., Fewtrell M., Kennedy K., Stephenson T., Elias-Jones A., and Lucas A. (2007). Promotion of faster weight gain in infants born small for gestational age: is there an adverse effect on later blood pressure? *Circulation* 115(2): 213-20.

Slemenda C., Miller J., Hui S., Reister T., and Johnston C.J. (1991). Role of physical activity in the development of skeletal mass in children. *J Bone Miner Res.* 6(11): 1227-33.

Smith G.D., Whitley E., Gissler M., and Hemminki E. (2000). Birth dimensions of offspring, premature birth, and the mortality of mothers. *The Lancet* 356(9247): 2066-67.

Smith G.D., Sterne J., Tynelius P., Lawlor D.A., and Rasmussen F. (2005). Birth weight of offspring and subsequent cardiovascular mortality of the parents. *Epidemiology* 16(4): 563-69.

Statistics Finland (2010a). Quality description, deaths (Last modification Apr 15th, 2010). Retrieved Jan 23rd, 2011, from http://www.stat.fi/til/kuol/2009/kuol_2009_2010-04-15_laa_001_en.html#1.Relevanceofstatisticalinformation.

Statistics Finland (2010b). Quality description, population structure 2009 (Last modification Mar 19th, 2010). Retrieved Jan 23rd, 2011, from http://www.stat.fi/til/vaerak/2009/vaerak_2009_2010-03-19_laa_001_en.html#2.Methodologicaldescriptionofsurvey.

Stewart A.L., Reynolds E.O., and Lipscomb A.P. (1981). Outcome for infants of very low birthweight: survey of world literature. *Lancet* 1(8228): 1038-40.

Stevenson C.J., West C.R., and Pharoah P.O. (2001). Dermatoglyphic patterns, very low birth weight, and blood pressure in adolescence. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 84: F18-F22.

Strandberg T.E., Salomaa V.V., Vanhanen H.T., and Pitkälä K. (2001). Blood pressure and mortality during an up to 32-year follow-up. *Journal of Hypertension* 19(1): 35-9.

Strandberg T.E., Salomaa V.V., Vanhanen H.T., Pitkälä K., and Miettinen T.A. (2002). Isolated diastolic hypertension, pulse pressure, and mean arterial pressure as predictors of mortality during a follow-up of up to 32 years. *Journal of Hypertension* 20(3): 399-404.

Strang-Karlsson S., Räikkönen K., Pesonen A.K., Kajantie E., Paavonen E.J., Lahti J., Hovi P., Heinonen K., Järvenpää A.L., Eriksson J.G., and Andersson S. (2008). Very low birth weight and behavioral symptoms of attention deficit hyperactivity disorder in young adulthood: the Helsinki study of very-low-birth-weight adults. *American Journal of Psychiatry* 165(10): 1345-53.

Symonds M.E., and Gardner D.S. (2006). Experimental evidence for early nutritional programming of

later health in animals. *Current Opinion in Clinical Nutrition & Metabolic Care* 9(3): 278-83.

Tenhola S., Martikainen A., Rahiala E., Herrgård E., Halonen P., and Voutilainen R. (2000). Serum lipid concentrations and growth characteristics in 12-year-old children born small for gestational age. *Pediatric Research* 48(5): 623-8.

Thomas C., Hyppönen E., and Power C. (2007). Prenatal exposures and glucose metabolism in adulthood: are effects mediated through birth weight and adiposity? *Diabetes Care* 30(4): 918-24.

Tilling K., Lawlor D.A., Davey Smith G., Chambless L., and Szklo M. (2006). The relation between components of adult height and intimal-medial thickness in middle age: the Atherosclerosis Risk in Communities Study. *American Journal of Epidemiology* 164(2): 136-42.

Toivonen E., Hemmilä I., Marniemi J., Jørgensen P.N., Zeuthen J., and Lövgren T. (1986). Two-site time-resolved immunofluorometric assay of human insulin. *Clinical Chemistry* 32(4): 637-40.

Trotter A., Maier L., Grill H.J., Kohn T., Heckmann M., and Pohlandt F. (1999). Effects of postnatal estradiol and progesterone replacement in extremely preterm infants. *Journal of Clinical Endocrinology & Metabolism* 84(12): 4531-5.

Tu Y.K., West R., Ellison G.T., and Gilthorpe M.S. (2005). Why evidence for the fetal origins of adult disease might be a statistical artifact: the "reversal paradox" for the relation between birth weight and blood pressure in later life.[see comment]. *American Journal of Epidemiology* 161(1): 27-32.

The United Nations Children's Fund and World Health Organization (2004). Low Birthweight: Country, regional and global estimates. Retrieved from

US Congress and Office of Technology Assessment (1987). Neonatal Intensive Care for Low Birthweight Infants: Costs and Effectiveness (Health Technology Case Study 38), OTA-HCS-38. Retrieved from

Uthaya S., Thomas E.L., Hamilton G., Dore C.J., Bell J., and Modi N. (2005). Altered adiposity after extremely preterm birth. *Pediatric Research* 57(2): 211-5.

Wang D., Vandermeulen J., and Atkinson S.A. (2007). Early life factors predict abnormal growth and bone accretion at prepuberty in former premature infants with/without neonatal dexamethasone exposure. *Pediatric Research* 61(1): 111-6.

Ward A.M.V., Moore V.M., Steptoe A., Cockington R.A., Robinson J.S., and Phillips D.I.W. (2004). Size at birth and cardiovascular responses to psychological stressors: evidence for prenatal programming in women. *Journal of Hypertension* 22(12): 2295-301.

Watterberg K.L., and Scott S.M. (1995). Evidence of early adrenal insufficiency in babies who develop bronchopulmonary dysplasia. *Pediatrics* 95(1): 120-5.

Weiler H.A., Yuen C.K., and Seshia M.M. (2002). Growth and bone mineralization of young adults weighing less than 1500 g at birth. *Early Human Development* 67(1-2): 101-12.

Weisglas-Kuperus N., Hille E.T.M., Duivenvoorden H.J., Finken M.J.J., Wit J.M., van Buuren S., van Goudoever J.B., Verloove-Vanhorick S.P., and for the Dutch P.-C.S.G. (2009). Intelligence of

very preterm or very low birthweight infants in young adulthood. *Archives of Disease in Childhood - Fetal and Neonatal Edition* 94(3): F196-F200.

Wendelhag I., Liang Q., Gustavsson T., and Wikstrand J. (1997). A new automated computerized analyzing system simplifies readings and reduces the variability in ultrasound measurement of intima-media thickness. *Stroke* 28(11): 2195-200.

Verloove-Vanhorick S.P., Verwey R.A., Brand R., Gravenhorst J.B., Keirse M.J., and Ruys J.H. (1986). Neonatal mortality risk in relation to gestational age and birthweight. Results of a national survey of preterm and very-low-birthweight infants in the Netherlands. *Lancet* 1(8472): 55-7.

Whincup P.H., Kaye S.J., Owen C.G., Huxley R., Cook D.G., Anazawa S., Barrett-Connor E., Bhargava S.K., Birgisdottir B.E., Carlsson S., de Rooij S.R., Dyck R.F., Eriksson J.G., Falkner B., Fall C., Forsen T., Grill V., Gudnason V., Hulman S., Hypponen E., Jeffreys M., Lawlor D.A., Leon D.A., Minami J., Mishra G., Osmond C., Power C., Rich-Edwards J.W., Roseboom T.J., Sachdev H.S., Syddall H., Thorsdottir I., Vanhala M., Wadsworth M., and Yarbrough D.E. (2008). Birth weight and risk of type 2 diabetes: a systematic review. *JAMA* 300(24): 2886-97.

Willemsen R.H., Leunissen R.W., Stijnen T., and Hokken-Koelega A.C. (2009). Prematurity is not associated with reduced insulin sensitivity in adulthood. *Journal of Clinical Endocrinology and Metabolism* 94: 1695-700.

Vohr B.R., Allan W., Katz K.H., Schneider K.C., and Ment L.R. (2010). Early predictors of hypertension in prematurely born adolescents. *Acta Paediatrica* 99(12): 1812-18.

Wolke D., Söhne B., Ohrt B., and Riegel K. (1995). Follow-up of preterm children: important to document dropouts. *The Lancet* 345(8947): 447-47.

Woods J.R., Jr. (2001). Reactive oxygen species and preterm premature rupture of membranes-a review. *Placenta* 22 Suppl A: S38-44.

Voors A.W., Harsha D.W., Webber L.S., and Berenson G.S. (1982). Relation of blood pressure to stature in healthy young adults. *American Journal of Epidemiology* 115(6): 833-40.

World Health Organization (1999). Definition, Diagnosis, and Classification of Diabetes Mellitus and Its Complications: Report of a WHO consultation.(WHO/NCD/NCS/99.2). Retrieved Apr 10th, 2011, from http://whqlibdoc.who.int/hq/1999/WHO_NCD_NCS_99.2.pdf.

World Health Organization (2005). The World health report : Make every mother and child count. Retrieved Jan 23rd, 2011, from http://www.who.int/entity/whr/2005/en/index.html.

World Health Organization (2006). Promoting optimal fetal development. Report of a technical consultation. Retrieved Feb 10th, 2011 from http://www.who.int/nutrition/publications/fetal_dev_report_EN.pdf.

Wu H., Gozdzik A., Barta J.L., Wagner D., Cole D.E., Vieth R., Parra E.J., and Whiting S.J. (2009). The development and evaluation of a food frequency questionnaire used in assessing vitamin D intake in a sample of healthy young Canadian adults of diverse ancestry. *Nutrition Research* 29(4): 255-61.

Wulff R., Holst A.K., Nielsen T.L., Andersen M., Hagen C., and Brixen K. (2004). Morphometric X-ray absorptiometry: Reference data for vertebral dimensions in a population-based sample of young Danish men. *Acta Radiologica* 45(8): 859-65.

Zamora S.A., Belli D.C., Rizzoli R., Slosman D.O., and Bonjour J.P. (2001). Lower femoral neck bone mineral density in prepubertal former preterm girls. *Bone* 29(5): 424-7.

Zureik M., Bonithon-Kopp C., Lecomte E., Siest G., and Ducimetiere P. (1996). Weights at birth and in early infancy, systolic pressure, and left ventricular structure in subjects aged 8 to 24 years. *Hypertension* 27(3): 339-45.

Appendix

How information sources were searched and evaluated for this review

Among methods for accumulating the relevant literature regarding the cardiovascular and osteoporotic risk factors in preterm/VLBW/VLGA subjects, I performed a search in Medline® and evaluated the results systematically: I first sought all articles on blood pressure, glucose regulation, endothelial function, and bone density. I combined search limits regarding categories of preterm birth and assessment age to create in June 2010 a suitable set of 904 article titles to browse (Table 19). For endothelium and bone mass, the number of studies was sufficiently small for manual browsing ignoring any age limit. I double-checked the performance of the search algorithms; they had to find at least the most important articles of which I was aware in advance. On February 9^{th,}, 2011, a similar Medline search revealed 42 new articles, only a few of which were relevant; these are cited in the text.

By reading all titles, many abstracts, and many articles and by using software to search through full texts of many more articles, I excluded twin studies, studies with undesired assessment ages, or undesired outcomes. I included some studies with hundreds of preterm participants, despite the fact that the effect of preterm birth was outside those authors' main focus.

Age limits in Medline did misclassify some articles. Additionally, the search words I chose could, especially for endothelial function, fail to locate relevant articles, because outcome nomenclature is highly variable.

Table 19. Results of a systematic search. Numbers of articles after combining exposures to outcomes at different ages.

Outcome	Ages, years	Exposure				
		No birth data limit	VLBW	Preterm OR ELBW	(BW OR LBW) AND GA	Three columns combined*
All studies in Medline®	All		4,880	33,950	17,498	48,643
	≥ 2		1,085	7,077	5,869	12,338
	≥ 13		645	4,852	4,708	9,103
Bone density	All	30,556	17	97	66	**146**
	≥ 2		4	28	25	50
	≥ 13		2	9	16	22
Insulin and glucose metabolism	All	310,510	79	593	905	1,368
	≥ 2		15	142	407	**498**
	≥ 13		8	89	314	375
Blood Pressure	All	229,552	82	508	409	844
	≥ 2		12	73	194	**250**
	≥ 13		10	45	158	192
Endothelial function	All	73,778	12	99	96	**177**
	≥ 2		2	18	36	50
	≥ 13		2	12	31	41
The bolded combined						**904**

*note that due to overlap, numbers do not necessarily sum up.

These correspond to the search in July 2010.

Search key for Table 19

Search	**Search syntax in OVID web,** 2010 Wolters Kluwer Health
VLBW	exp Infant, very low birth weight
Preterm OR ELBW	exp Infant, Extremely low birth weight OR exp Infant, premature
(BW OR LBW) AND GA	(exp Infant, low birth weight OR exp Birth weight) AND exp Gestational age
≥ 2 years	Preschool child (2 to 5 years) OR Child (6 to 12 years) OR Adolescent (13 to 18 years) OR Young adult OR All adult (19 plus years)
≥ 13 years	Adolescent (13 to 18 years) OR Young adult OR All adult (19 plus years)
Bone density	Bone density
Glucose and insulin metabolism	(exp Insulin resistance OR exp Blood glucose OR exp Glucose intolerance OR exp Glucose metabolism disorders OR exp Glucose tolerance test OR Insulin/metabolism) NOT *Diabetes, gestational
Blood pressure	exp Blood pressure OR exp Blood pressure determination OR exp Blood pressure monitoring, ambulatory
Endothelial function	exp Vascular Resistance OR exp endothelium, (vascular/physiology, physiopathology OR exp tunica intima) OR exp Carotid arteries/ultra sound OR exp Vasodilation/physiology

* an asterisk in front of a Medical subject heading (MeSH) –word indicates only articles that focus on that