Universiteit
Leiden
The Netherlands

Long-term consequences of differences in early growth : epidemiological aspects

Euser, A.M.

Citation
Euser, A. M. (2009, December 8). *Long-term consequences of differences in early growth : epidemiological aspects*. Retrieved from https://hdl.handle.net/1887/14485

Version:	Corrected Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/14485

Note: To cite this publication please use the final published version (if applicable).

9

General discussion

General discussion

The general aim of the studies described in this thesis was of two sorts; in the first place to study the effects of prenatal and early postnatal growth on various adult health outcomes in individuals born preterm or with a low or very low birth weight, and in the second place to address methodological issues closely related to early origins of adult disease studies. In this chapter we will consider the results found in these studies in a more extensive perspective, both theoretically and clinically. At first, we will reflect on the broad scope of definitions, associations, and pathology that lies behind the term 'metabolic syndrome'. Next, we will briefly relate this to the early origins hypothesis and its putative underlying etiological mechanisms. Subsequently, we will consider the sequence of posing research questions, building regression models, and interpreting results in early origins studies. This will be followed by several methodological issues inherently intertwined with the populations studied, after which we will address our main findings in relation to the recent literature about these topics. Finally, clinical relevance and future research perspectives will be discussed.

A metabolic syndrome?

The metabolic syndrome and some of its separate components form important outcome measures in our clinical studies in the HUNT and POPS populations. However, at first glance it becomes evident that this so called metabolic syndrome has no universally accepted definition, and that a confusion of tongues seems to exist. Numerous names and definitions coexist for the syndrome, of which those of the World Health Organization, the American Heart Association, the International Diabetes Federation, and the National Cholesterol Education Program are most widely used.[1-4] While those definitions agree in considering central obesity, impaired glucose tolerance, dyslipidemia, and hypertension as essential components, they differ about corresponding cut-off levels, for these traits are all continuous variables artificially cut into the binary variable physiological versus pathological. Besides, the definitions differ in the algorithm used to cluster components to a syndrome, in how to measure glucose tolerance and obesity, in the appliance or non-appliance of different cut-offs for anthropometric values in different ethnic populations, and in the inclusion of the additional components micro-albuminuria in the WHO definition.[1] The result of this excessive number of definitions is a decreased generalizability of results found, and a thwarted comparison of the prevalence of the metabolic syndrome in different populations, for prevalences in the same population vary impressively depending on the syndrome definition used.[5,6]

The original WHO definition of the metabolic syndrome is unique in the inclusion of microalbuminuria,[1] which is the earliest clinical manifestation of obesity-associated kidney

damage and diabetic nephropathy in humans. The association between the kidney, obesity, and the metabolic syndrome is complex and might be pathologically mediated by both type II diabetes and hypertension.[7] Though not undisputed, microalbuminuria has repetitively been found as a marker of insulin resistance and glucose intolerance that becomes evident before diabetes, and may thus serve as a marker of disease activity.[8] However, even in non-diabetic adults the metabolic syndrome has been shown to be independently associated with an increased risk for chronic kidney disease.[9] So, apart from functioning as a complementary marker of insulin resistance only, the damaged kidney has a dual role with regard to the metabolic syndrome. This might be due to the fact that the kidney is closely associated with hypertension as well. On one hand, the kidney can raise blood pressure by several mechanisms hence provoking hypertension, while on the other hand hypertension aggravates the progression of renal disease.[10] This hypertension found in obesity, another component of the metabolic syndrome, appears to be closely linked to abnormal kidney function caused by simultaneous activation of the renin angiotensin system, of the sympatic nerve system, and by physical compression of the kidneys when visceral obesity is present.[7] However, despite increased pathophysiological understanding, the precise interaction between the kidneys and the metabolic syndrome has not been unraveled yet.

In the pediatric field as well a tangle of definitions for the metabolic syndrome used in parallel exists, with the definition of the International Diabetes Federation being the most recent one.[11] This abundance is not surprising, for in children and adolescents defining 'the metabolic syndrome' is even more complex than in adults. In the first place, several components of the syndrome, e.g. waist circumference and blood pressure, increase with age, and part of them are also influenced by puberty, like fat distribution and insulin sensitivity.[12] Secondly, the end points for which the syndrome might give an increased risk are still far away in time and usually do not occur until in late adulthood. Therefore, direct evidence for the predictive value of the syndrome in childhood for increasing the risk of adult cardiovascular death or even disease is lacking, and instead only surrogate end points are reported.[13] However, the international increase in overweight and obese infants and adolescents[14] has lead to an urge to define the syndrome in this young and dynamic population as well, and numerous definitions coexist.[15] Partly, the problems mentioned above have been resolved by classifying children into age groups with different definitions, and by using age- and sex-specific percentiles or Z-scores in most definitions.[15] However, it should be stressed that anthropometric reference charts generally have a descriptive origin and not a normative one, so when the population as a whole becomes more obese during the years, the same percentile lines represent increased BMI values. This has been clearly shown in the Netherlands between 1980 and 1997.[16] This knowledge should be kept in mind when defining which percentile should serve as cut-off point. Besides, as reference charts tend to result from cross-sectional data collection, the inter-individual variance in the onset of puberty is intertwined in the reference values of individual ages.

The reason that 'The Metabolic Syndrome' as such does not exist, neither in adults nor in children, is partly inherent to it being a syndrome, as the definition of a syndrome is rather vague. The word 'syndrome' in Greek means 'the confluence', and this confluence is the only basis of a syndrome, which is usually defined as: "a symptom complex of unknown etiology, which is characteristic of a particular abnormality" (MeSH term), or: 'a pattern of multiple anomalies thought to be pathologically related'.[17] However, while the etiology per definition is still unknown in the initial decision of calling a constellation of symptoms a syndrome, it is implicitly expected that this unifying pathological relation will be found in subsequent research. Nevertheless, a satisfying unifying pathological base for the metabolic syndrome has not yet been found, despite intensive research, while the concept of the metabolic syndrome has been used for decades.[18] Various hypotheses have been postulated, of which the insulin resistance hypothesis with glucose intolerance as central key player to explain the pathology of the other features of the syndrome is the most profoundly worked out and generally accepted one.[19] However, it is possible to have the metabolic syndrome without being insulin resistant, and the association of insulin resistance with some of the other components of the syndrome is rather weak, while other more closely related features are excluded from the definition.[20] Other complementary and alternative hypotheses with a more prominent role for central obesity,[3] inflammation,[21] or neurobiology[22] have been proposed, but have not led to a satisfying single underlying etiology, which is, together with the ill-defined dichotomous criteria, grist to the mill of the opponents of the existence of a metabolic syndrome.[20,23]

In addition to the physiologist's point of view from which a unitary causation is lacking, the metabolic syndrome is also criticized from an epidemiologist's point of view. Regardless if the expected common etiology has already been unraveled or not, the practical usefulness of working with a syndrome construct is the improved prediction of disease or complications compared with the sum of its separate components. And this, in turn, can be used in policy making and daily clinical practice. Originally, the metabolic syndrome has been defined because it should predispose to diabetes and cardiovascular disease (CVD).[1] Indeed, the metabolic syndrome is associated with an increased risk of type two diabetes.[24,25] However, as impaired fasting glucose, impaired glucose tolerance, or even overt diabetes form all components of the different definitions, this finding does not really strike like a bolt from the blue. The metabolic syndrome predicts future cardiovascular events in men and women as well.[6,26] But again, objections can be raised; in the first place, the various definitions of the metabolic syndrome do not seem to predict better than existing risk scores for Cardio Vascular Disease (CVD) like the Framingham risk score.[27,28] And more important, they do not predict better than the sum of the separate components.[5,29,30] As the syndrome is composed of components which do all form well established, undisputed risk factors for CVD, a more than additive risk in case of clustering of components ought to form the mere advantage of taking them together in one definition. Taken all this criticism together, the usefulness

of the concept "metabolic syndrome" for the clinician seems to be little, as establishing the diagnosis improves neither pathophysiological understanding nor clinical utility.

While indications for a common underlying etiology of the metabolic syndrome are often searched for in basic research as in animal models, or statistical models like factor analyses, another form of circumstantial evidence can be found in the classical logic form of modus tollens, i.e. "denying the consequent". In science this form became well known when it was used by Karl Popper, who postulates that falsifiability is a prerequisite for a scientific theory. And though no rockbottom of knowledge exists, the best theory is that with the highest empirical content combined with the highest degree of corroboration.[31] With our study on the metabolic syndrome in the HUNT we tested the hypothesis that the metabolic syndrome is a true syndrome with one common underlying etiology. If this first premise is true, the second premise is that all components of the metabolic syndrome should show the same kind of association with this underlying cause. Part of the underlying etiology of the metabolic syndrome - including that of the insulin resistance component – is likely to be formed by early life experiences, for small but recurring effects have been found for several of the separate components e.g. hypertension and glucose intolerance.[32,33] In that case all separate components of the metabolic syndrome should have the same kind of association with an early life parameter, e.g. birth weight. However, we found several statistically significant but inconsistent associations of birth weight with the separate components of the so called metabolic syndrome. Though alternative explanations are imaginable, this result does not corroborate the metabolic syndrome as a true syndrome with one single underlying etiology.

Early origins

Underneath this level of epidemiological associations, several mechanisms have been proposed with regard to the explanation of the replicated associations between early growth and various adult metabolic diseases. Typically, the major contrast is formed by the 'thrifty phenotype' hypothesis which was first postulated by Barker et al. on one hand, and the 'thrifty genotype' hypothesis on the other hand. In the first theory, the fetus is thought to adapt to intrauterine shortage of nutrients by a reduced capacity for insulin production by the pancreas, and insulin resistance, which results in reduced somatic growth *in utero*, and subsequent an increased adult disease sensitivity when growing up in a nutrient rich postnatal environment.[34] In the second theory, reduced insulin-mediated fetal growth and adult insulin resistance, type II diabetes, and disease susceptibility are all regarded as phenotypes corresponding to the same insulin-resistance genotype.[35] Adjacent to these two opposites, other hypotheses have been generated, like the "catch-up growth" hypothesis in which early postnatal catch-up growth is thought to be the pathogeneous link between fetal and adult life by causing over-activation of

the IGF system which in turn will result in secondary insulin resistance.[36] Further, in the "fetal salvage" hypothesis the importance of insulin resistance is stressed while in contrast to the fetal insulin hypothesis beta cell hypoplasia is not thought to play a role in the development of adult disease in this theory.[37] Finally, also increased fetal exposure to cortisol mediated by decreased maternal enzyme activity is suggested to connect low birth weight and adult disease, especially hypertension.[38]

Recently, there is increasing evidence that epigenetic mechanisms, which concern the regulation of gene activity without affecting the genetic DNA code itself, might underlie the associations between early life parameters and adult disease. Epigenetic mechanisms tend to be gene specific and cell specific, and though it is unclear when they exert their effects on human developmental plasticity and subsequent disease susceptibility, this window might well extend from before conception until early postnatal life.[39] Though much has still to be unravelled about epigenetic mechanisms and their role in the early origins of adult disease, they might well form a union between in former partly contradicting hypotheses.

Methodological reflections

Originally, only the effect of birth weight as a proxy for prenatal growth and influences on adult health outcomes was presented,[40] which is quite straightforward. However, it is well known that adult metabolic outcomes, e.g. blood pressure, are strongly positively associated with current adult weight.[41,42] Besides, birth weight and subsequent adult weight are also positively associated.[43] With this triad of associations in mind, researchers have subsequently almost invariably adjusted associations between birth weight and adult outcome for current adult weight with different explanations. Some of them just do so without any explanation,[44] most of them consider current weight or BMI as a potential confounder.[45]

Subsequently, a debate arose about whether this adjustment for current weight in early origin studies was justified, for it might well be an intervening variable in the causal pathway. This controversy was fuelled by Huxley et al. who showed in a meta-analysis that there was little or no relationship between birth weight and adult blood pressure without adjustment for current weight. She postulated the extreme statement that "adjustment for current weight might produce a spurious inverse association even if birth weight and current blood pressure are uncorrelated".[46] Theoretically, this situation might indeed occur as described more formally by Hernán et al. who propagate the use of causal diagrams to encode a priori subject matter knowledge before deciding whether a variable is a confounder that should be adjusted for in the analyses.[47]

Finally, Lucas et al. transposed the main point of the discussion from the interpretation of the changing prenatal weight component to the interpretation of the current weight component. The effect of adding current weight into a regression model with early weight and adult outcome is intricate. Lucas et al. suggests that such a model should be interpreted as the effect of change in weight between birth and adulthood (postnatal centile crossing), rather than the effect of restricted fetal growth.[48] Moreover, it might be that especially those individuals with the lowest birth weights and the highest postnatal weight change have the highest changes on adult diseases.[49,50]

A well defined research question should be considered before building and interpreting any model. Given that the relationship between adult weight as such and adult metabolic diseases has already been sufficiently established, three separate research questions remain. The first one is the one it all started with: what is the effect of birth weight on adult disease? We think it theoretically unjustified to adjust for current adult weight in assessing this association, for adult weight is situated in the causal pathway. Birth weight is a proxy measurement of a dynamic process; prenatal growth (which once more might be considered to be a proxy variable as well, but this falls beyond the scope of this discussion). Birth weight itself alters at the very first day of life, as weight changes rapidly in small infants. Therefore, this potential risk indicator for adult disease should exert its effect through other, biological pathways. Adult size - which is as well a measurement of growth, though postnatal - might be one intervening mechanism, as it is related to birth weight. Since small infants tend to be small adults and large adults have an increased risk ofadult metabolic disease, statistical 'adjustment' for adult size will incorrectly inflate the association between birth weight and adult disease.

The second question is: what is the effect of postnatal growth on adult disease? As we first started with determining the effect of birth weight on adult disease, this subsequent question should be refined to: What is the effect of "growing more than expected from a given birth weight" on adult disease? Therefore in this case it is theoretically justified to build a regression model with adjustment for the effect of birth weight in the statistical model, because the effect of birth weight is known, it lies earlier in time, and we are not longer interested in it for this new, second research question. However, one should not look at the coefficient of birth weight in this model, let alone interpret it, for it is meaningless. If one wants to interpret both separate research questions in one model, one should use our proposed unexplained residual model.

Finally, the third question is: does the effect of postnatal growth on adult disease differ between subjects with a low or a high birth weight? In this case a third model should be built with a third variable to test statistical interaction and one should look at all three coefficients for a proper interpretation of the results found. In this case we especially propagate the

unexplained residual model in contrast to the model of Lucas et al., for the former does not assume an underlying quadratic relation between birth weight and adult disease anymore. This question should be investigated, even if with the first question no association has been found, for the effects found in smaller subgroups might be overruled by the main group analysis.

Reliability

Another problem frequently encountered, especially in multi-center studies, is the reliability of measurements. In our studies about reliability we try to provide practical approaches for two problems: reliability indicators and log transformed variables, and the assessment of reliability in a small study within the context of a large clinical study. It should be stressed that especially the latter should not be regarded as an illegitimate statistical "solution" to improve the reliability by inflating it's coefficient, like estimating an intra-class correlation coefficient in a much more heterogeneous population than the study population it will be used in. On the contrary; the point estimate of the reliability coefficient remains exactly the same, but the precision of the estimate improves, or, if one takes the point of view that this precision could also be effectuated by increasing the number of subjects in the reliability study, the efficiency increases. Still, the clinical question about the reliability of skinfold measurements, and consequently the accuracy of its use in the POPS-19 study, remains open. At this point the methodological and clinical studies confluence and the reliability study shows that the reliability of the solitary skinfold measurements was poor. The sum of the four skinfolds however, had a better reliability and therefore this measure was subsequently used in the POPS-19 study to calculate the corresponding fat percentage, to which end it was first log transformed. At last, the decision if in situations like this special reliability indicators for log transformed variables are needed, should always be based solely on the (skewed) distribution of the errors and not of the distribution of the variable itself.

Population related issues

The populations in which the main effect on adult health outcomes is expected to be found consist largely of infants with a low birth weight or born preterm. However, analyses in this population are complicated at different levels, most of methodological origin. The major problem is formed by different definitions applied in the literature to form a cohort; classification by gestational age[51] or by birth weight.[52] This has important consequences for the subsequent postnatal growth characteristics in the cohorts formed. Besides, no consensus has been reached about the optimum reference grow chart,[53] which complicates comparisons

both between different preterm study populations, and comparison with infants with normal birth weight and gestational age range. Finally, as improvements in neonatal care have only recently facilitated the survival of very preterm and very low birth weight infants, systematic literature about the consequences of early growth in adulthood is lacking in this population thus far.

Together with others,[54] we suggest classification of small infants by gestational age, for in this population this is a better predictor of survival than birth weight.[55] Next, in every gestational age category a classification of appropriate for gestational age (AGA) or small for gestational age (SGA) can be made. For an optimal distinction between AGA and SGA, preferably an up-to-date growth chart from the same population should be available. To avoid bias of non-random missing data at lower gestational ages, when the timing of delivery is strongly related to poor growth, a combination of anthropometry of live born infants and intra-uterine ultrasound growth estimates of fetuses of the same gestational age not born yet has been proposed.[53] However, fetal ultrasound has systematic and random inaccuracies, which seem both to be related with birth weight.[56]

Taken in account these limitations encountered early in the follow up of cohorts of low birth weight or preterm subjects, new problems are likely to accumulate in the same cohorts at adult follow up. First, selection bias might be introduced by a high mortality in the perinatal period leading to selective survival. In the POPS cohort, 27% of the infants died within the first year of life,[55] and 28% were deceased before the age of 19 years.[57] The in-hospital mortality was strongly associated with gestational age, and hence with the incidence and severity of the respiratory distress syndrome.[55] It is plausible that metabolic parameters affecting perinatal survival also affect the metabolic profile, including body composition, at age 19. For example, while in small infants born very preterm hypoglycemia and hypotension are important life threatening conditions to overcome, at age 19 right the opposite conditions of insulin resistance and hypertension are considered to be a health disadvantage. At low gestational ages and low birth weights, infants with a protective metabolic profile will have a better survival, while at higher gestational ages and birth weights metabolic profile does not influence survival anymore and infants with all metabolic profiles will have equal changes to survive till age 19. However, while selective mortality might form an explanation for associations found, it should not be considered as a bias in this case, for survival until adult age is a prerequisite for developing disease at adult age, and hence might be considered to be 'in the causal pathway' of low birth weight and adult disease.

A second issue, closely related to the first, might affect both the internal and internal validity of studies in the cohort. This concerns the effect of medical treatment on survival and the changes in neonatal care during the years. One keystone of treatment of infants born very

preterm is antenatal corticosteroid (betamethasone) administration, which significantly reduces neonatal mortality (RR 0.69, 95% CI 0.58 to 0.81).[58] Antenatal corticosteroids exert a major effect by reducing the incidence of Infant Respiratory Distress Syndrome (IRDS), but the effects are likely to be pleiotropic, possibly also affecting metabolic systems [59,60]. In this way its use in certain individuals could have changed the effects of the selective survival of certain metabolic profiles as described above. While the first trial with corticosteroids in humans took place in 1972,[61] the first structured review about this subject was published only in 1990.[62] This means that in 1983 when the POPS cohort was started, the prescription of antenatal corticosteroids was still dependent on the personal views of the gynecologists. However, it does not seem likely that this non-randomized allocation of a treatment has led to confounding, for it was random with regard to other risk factors that may have influenced the outcome studied, i.e. metabolic profile.

Nowadays antenatal corticosteroids are standard treatment in impending preterm delivery and synthetic surfactant has a widespread application after its initial introduction in the early 1980s.[63] Compared with the POPS cohort of 1983, this has led to an increase in survival of very preterm infants, but not in a change in disease free survival, because at present, the sicker infants survive as well.[64] For this reason the generalizability of the results found in studies in the POPS cohort, including those in this thesis, to the current generation of infants born very preterm is unclear. While for the incidence of handicaps or bronchopulmonary disease a distinct trend can be shown, this is harder to predict for the adult metabolic outcomes. While on the one hand the availability of surfactant has decreased the importance of pulmonary function to survive the first days of life and thereby placing more weight on the importance of a suitable metabolic profile of the neonate to survive, on the other hand the effect of antenatal corticosteroids is likely to be more pleiotropic as explained above and act on both pulmonary and metabolic systems. However, it is inherent to the introduction of a new treatment that the long-term effects, both intended and unintended cannot be studied until late future has turned into present.

Finally, selection bias could have been introduced by a low response rate, which was the case in both the POPS-19 and the HUNT 2 studies. In POPS non-response was associated with male sex, non-Dutch origin, low maternal education, and severe handicaps,[57] while in the HUNT study the main reasons for non-participation in the age group studied were having moved out of the county or lack of time.[65] However, in neither of the two studies non-response was associated with birth weight or gestational age. For this reason, as an association with determinant i.e. birth weight and non-response is lacking, non-response can not have introduced bias in this situation, irrespective of the unknown outcome of the missing subjects.

Apart from all these deliberations, an interesting remaining question is whether differences found in the association between early growth and adult metabolic disease in the POPS population compared with the HUNT study might be (partly) explained by the prematurity of the first subjects. It would be tempting to say so, for the mean gestational age forms a major difference between the two populations and unfortunately a control group for the POPS has never been recruited in the past. But, on the other hand, gestational age is not the only difference between the populations, apart from the age of the adult health assessment, the studies are also conducted in two different countries i.e. the Netherlands and Norway. To distort the hypothesized effect of prematurity on the association between early growth and adult disease, factors that differ between the different countries should have an influence on both prematurity and the relation between early growth and adult disease. One of the most important factors that might have these specific multiple effects will be the national level of prosperity that among others will work through in the mean birth weight, quality of neonatal care, and the development and treatment of adult diseases as well. This national level of prosperity, for example expressed as the gross national product, is similar, so it is not likely to overshadow the possible effect of prematurity in this context. However, as the level of overlap between the two populations was too limited for proper comparison – only 28 very preterm subjects in the HUNT, we can not be certain.

Main results in relation to the literature

With regard to prenatal growth and the adult metabolic syndrome, we found that birth weight was inconsistently associated with the separate components of the syndrome in men and women. In general, these findings are in agreement with recent systematic reviews about the association between birth weight and these individual outcomes.[32,66-70] However, contrary to most previous findings[66,71-76] we did not find a significant association between low birth weight SDS and the metabolic syndrome as a composite construct. There are several explanations for this discrepancy. First it might partly be explained by publication bias. Second, inappropriate statistical adjustment for current weight or BMI was applied in several studies[25,75 66] as we explained in chapter 6. Third, in these previous studies often only separate components of the metabolic syndrome were analyzed, while in the conclusions report about 'the metabolic syndrome'.[72-74] All together, this weakens the validity of low birth weight as a unifying risk factor for the metabolic syndrome.

We found that IUGR was associated with low-normal kidney function in young adults from the general population. This is consistent with a recent systematic review of observational studies (including ours) in which an Odds Ratio of 1.8 was found for the effect of low birth weight on low adult glomerular filtration rate. This effect size was relatively consistent for

other renal outcomes reviewed like end stage renal disease or albuminuria.[77] Our results are also in agreement with findings in subjects born very prematurely from the POPS cohort.[78] A pathological basis supporting these clinical findings has been found in autopsy studies in which a low nephron number was observed in low-BW subjects.[79-81]

Regarding the effect of early growth on adult body composition we found in infants born very preterm that prenatal growth was positively associated with weight, height, and BMI at age 19; i.e. mainly with body size. These findings are consistent with studies in term born populations[43,82] and indicate that the positive association between birth weight and adult BMI is already determined in the first two trimesters of pregnancy. We did not confirm the J- or U-shape relation between birth weight and adult BMI found in some other studies.[45,83,84] This suggests that either these associations are established during the third trimester of pregnancy, or that there is another link than BMI between reduced fetal growth and adult disease. Fat-free mass has been proposed,[85] but our data do not support this. More early postnatal weight gain however, was associated with both a higher BMI and a higher percentage body fat at age 19 y. Our results confirm studies in adults,[83,86,87] and it may be concluded from our data that the positive associations found between early catch-up growth and fatness in childhood[88,89] persist into young adulthood. Our study adds that the higher BMI found was partly accounted for by a higher percentage body fat, at least in premature infants, and that the association was independent of birth weight. Finally, we also found that a greater postnatal weight gain was associated with a higher adult waist circumference, both when adjusted and unadjusted for current height (SD scores). This finding agrees with the results of Fall et al[83] and Li et al.[86] In some studies, both low birth weight and early growth have been associated with a more truncal and abdominal fat pattern[83,90,91] but only after adjustment for current BMI. Again, we think it is theoretically incorrect to adjust for current BMI -which includes current fat mass- in analyses with fat mass and fat distribution as outcomes.

Clinical relevance and future perspectives

In contrast with the methodological studies that can be applied directly in future research, the clinical studies in this thesis are mainly of a descriptive nature. With regard to the effect of prematurity a less favorable adult body composition was found, while low birth weight was associated with reduced kidney function and a slightly less favorable metabolic profile at young adult age. Therefore, prevention of prematurity and low birth weight should be stressed. However, when prematurity or low birth weight is already an accomplished fact, the focus should be on systematic screening of these infants and adults for the sake of prevention, life style advices, and early treatment of metabolic diseases. With regard to recommendations about early catch-up growth even more caution is warranted, for at first

place it is not proven that preventing this catch-up growth in low birth weight or (very) preterm infants also prevents adult metabolic disease and, more important, early catch-up growth is considered to be important for neurodevelopmental outcome.[92-94] In general, growth should be considered as a proxy measurement for early life influences, not as the causal agent itself. In this context, the associations we found, though of small size, signify that lifelong effects of early life influences seem to exist in these specific populations as well, and that more research on underlying mechanisms is required.

As mentioned before, the outcomes of the POPS-19 study might not be fully generalizable to the current generation of preterm infants. Therefore, ideally a new research cohort should be formed for a prospective study, with special attention for an appropriate term control group, prenatal ultrasound measurements, and drawing cord blood. However, follow-up in the POPS (and HUNT) should be continued as well, for age 19 is still young to develop a full blown metabolic syndrome, let alone cardiovascular events, and this should be studied at older age. At subsequent follow-up, new focuses could be the acquiring of DNA of sibs and parents for the role of genetics and epigentetics in prematurity, growth, and disease, and the reproduction and offspring of the POPS infants. An imaging technique like a DEXA body scan should also be desirable as part of this follow-up, to study more precisely the adult body composition of subjects born preterm, and in second place for the external validation of skinfold measurements in this population. A related issue that could be studied in this context is the supposed altered body composition of SGA and preterm subjects which seems to continue in adulthood that will exert an effect on the estimation of GFR by using formulas dependent on creatinin and body weight. Finally, when in the same subjects body composition, renal function, and possible intermediate hormones like adiponectin are assessed, this might unravel more of the association between metabolic diseases and kidney disease.

References

1. WHO Consultation. Definition, diagnosis and classification of diabetes mellitus and its complications. 31-33. 1999. Geneva.
2. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Curr Opin Cardiol 2006 Jan 1921;1-6.
3. International Diabetes Federation: The IDF consensus worldwide definition of the metabolic syndrome. http://www.idf.org/webdata/docs/Metabolic_syndrome_definition.pdf. 2-9-2005.
4. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001 May 16 285;2486-2497.
5. Lawlor DA, Smith GD, Ebrahim S. Does the new International Diabetes Federation definition of the metabolic syndrome predict CHD any more strongly than older definitions? Findings from the British Women's Heart and Health Study. Diabetologia 2006 Jan 1949;41-48.
6. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002 Dec 4 288;2709-2716.
7. Hall JE, Kuo JJ, da Silva AA, de Paula RB, Liu J, Tallam L. Obesity-associated hypertension and kidney disease. Curr Opin Nephrol Hypertens 2003; 12:195-200.
8. Lane JT. Microalbuminuria as a marker of cardiovascular and renal risk in type 2 diabetes mellitus: a temporal perspective. Am J Physiol Renal Physiol 2004; 286:F442-F450.
9. Kurella M, Lo JC, Chertow GM. Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. J Am Soc Nephrol 2005; 16:2134-2140.
10. Ritz E, Adamczak M, Zeier M. Kidney and hypertension-causes. Update 2003. Herz 2003; 28:663-667.
11. Zimmet P, Alberti KG, Kaufman F, Tajima N, Silink M, Arslanian S et al. The metabolic syndrome in children and adolescents - an IDF consensus report. Pediatr Diabetes 2007; 8:299-306.
12. Bloch CA, Clemons P, Sperling MA. Puberty decreases insulin sensitivity. J Pediatr 1987; 110:481-487.
13. Daniels SR. Metabolic syndrome and cardiovascular abnormalities in children. J Am Coll Cardiol 2008; 52:939-940.
14. Ebbeling CB, Pawlak DB, Ludwig DS. Childhood obesity: public-health crisis, common sense cure. Lancet 2002; 360:473-482.
15. Ford ES, Li C. Defining the metabolic syndrome in children and adolescents: will the real definition please stand up? J Pediatr 2008; 152:160-164.
16. Fredriks AM, Van BS, Wit JM, Verloove-Vanhorick SP. Body index measurements in 1996-7 compared with 1980. Arch Dis Child 2000; 82:107-112.
17. Gelehrter TD, Collins FS, Ginsburg D. Clinical Genetics. In: Kelly PJ, editor. Principles of Medical Genetics. 2 ed. Baltimore: Williams and Wilkins; 1998. 273-310.
18. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988 Dec 1937;1595-1607.
19. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005 Apr 16 -22 365;1415-1428.
20. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2005; 28:2289-2304.
21. Haffner SM. The metabolic syndrome: inflammation, diabetes mellitus, and cardiovascular disease. Am J Cardiol 2006; 97:3A-11A.

22. van DG, Buwalda B. Neurobiology of the metabolic syndrome: an allostatic perspective. Eur J Pharmacol 2008; 585:137-146.
23. Gale EA. The myth of the metabolic syndrome. Diabetologia 2005 Sep 1948;1679-1683.
24. Wannamethee SG, Shaper AG, Lennon L, Morris RW. Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. Arch Intern Med 2005; 165:2644-2650.
25. Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA. Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. Am J Epidemiol 2002 Dec 1 156;1070-1077.
26. Hu G, Qiao Q, Tuomilehto J, Balkau B, Borch-Johnsen K, Pyorala K. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. Arch Intern Med 2004; 164:1066-1076.
27. Stern MP, Williams K, Gonzalez-Villalpando C, Hunt KJ, Haffner SM. Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? Diabetes Care 2004; 27:2676-2681.
28. McNeill AM, Rosamond WD, Girman CJ, Golden SH, Schmidt MI, East HE et al. The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. Diabetes Care 2005 Feb 1928;385-390.
29. Fadini GP, Coracina A, Inchiostro S, Tiengo A, Avogaro A, de Kreutzenberg SV. A stepwise approach to assess the impact of clustering cardiometabolic risk factors on carotid intima-media thickness: the metabolic syndrome no-more-than-additive. Eur J Cardiovasc Prev Rehabil 2008; 15:190-196.
30. Sattar N, McConnachie A, Shaper AG, Blauw GJ, Buckley BM, de Craen AJ et al. Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. Lancet 2008; 371:1927-1935.
31. De Vries G. De ontwikkeling van Wetenschap. Een inleiding in de wetenschapsfilosofie. 1 ed. Groningen: Wolters-Noordhoff; 1984.
32. Schluchter MD. Publication bias and heterogeneity in the relationship between systolic blood pressure, birth weight, and catch-up growth--a meta analysis. J Hypertens 2003 Feb 1921;273-279.
33. Harder T, Rodekamp E, Schellong K, Dudenhausen JW, Plagemann A. Birth weight and subsequent risk of type 2 diabetes: A meta-analysis. American Journal of Epidemiology 2007; 165:849-857.
34. Hales CN, Barker DJP. Type-2 (On-Insulin-Dependent) Diabetes-Mellitus - the Thrifty Phenotype Hypothesis. Diabetologia 1992; 35:595-601.
35. Hattersley AT, Tooke JE. The fetal insulin hypothesis: an alternative explanation of the association of low birthweight with diabetes and vascular disease. Lancet 1999; 353:1789-1792.
36. Cianfarani S, Germani D, Branca F. Low birthweight and adult insulin resistance: the "catch-up growth" hypothesis. Arch Dis Child Fetal Neonatal Ed 1999; 81:F71-F73.
37. Hofman PL, Cutfield WS, Robinson EM, Bergman RN, Menon RK, Sperling MA et al. Insulin resistance in short children with intrauterine growth retardation. J Clin Endocrinol Metab 1997; 82:402-406.
38. Edwards CRW, Benediktsson R, Lindsay RS, Seckl JR. Dysfunction of Placental Glucocorticoid Barrier - Link Between Fetal Environment and Adult Hypertension. Lancet 1993; 341:355-357.
39. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med 2008; 359:61-73.
40. Barker DJ, Bull AR, Osmond C, Simmonds SJ. Fetal and placental size and risk of hypertension in adult life. BMJ 1990; 301:259-262.

41. Carnethon MR, Loria CM, Hill JO, Sidney S, Savage PJ, Liu K. Risk factors for the metabolic syndrome: the Coronary Artery Risk Development in Young Adults (CARDIA) study, 1985-2001. Diabetes Care 2004; 27:2707-2715.
42. Lloyd-Jones DM, Liu K, Colangelo LA, Yan LL, Klein L, Loria CM et al. Consistently stable or decreased body mass index in young adulthood and longitudinal changes in metabolic syndrome components: the Coronary Artery Risk Development in Young Adults Study. Circulation 2007; 115:1004-1011.
43. Pietilainen KH, Kaprio J, Rasanen M, Winter T, Rissanen A, Rose RJ. Tracking of body size from birth to late adolescence: contributions of birth length, birth weight, duration of gestation, parents' body size, and twinship. Am J Epidemiol 2001; 154:21-29.
44. Forrester TE, Wilks RJ, Bennett FI, Simeon D, Osmond C, Allen M et al. Fetal growth and cardiovascular risk factors in Jamaican schoolchildren. BMJ 1996; 312:156-160.
45. Curhan GC, Chertow GM, Willett WC, Spiegelman D, Colditz GA, Manson JE et al. Birth weight and adult hypertension and obesity in women. Circulation 1996; 94:1310-1315.
46. Huxley R, Neil A, Collins R. Unravelling the fetal origins hypothesis: is there really an inverse association between birthweight and subsequent blood pressure? Lancet 2002 Aug 31 360;659-665.
47. Hernan MA, Hernandez-Diaz S, Werler MM, Mitchell AA. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. Am J Epidemiol 2002; 155:176-184.
48. Lucas A, Fewtrell MS, Cole TJ. Fetal origins of adult disease-the hypothesis revisited. BMJ 1999; 319:245-249.
49. Law CM, de SM, Osmond C, Fayers PM, Barker DJ, Cruddas AM et al. Initiation of hypertension in utero and its amplification throughout life. BMJ 1993; 306:24-27.
50. Leon DA, Koupilova I, Lithell HO, Berglund L, Mohsen R, Vagero D et al. Failure to realise growth potential in utero and adult obesity in relation to blood pressure in 50 year old Swedish men. BMJ 1996; 312:401-406.
51. International Classification of Diseases (ICD) 10, WHO. 2007.
52. Sherry B, Mei Z, Grummer-Strawn L, Dietz WH. Evaluation of and recommendations for growth references for very low birth weight (< or =1500 grams) infants in the United States. Pediatrics 2003; 111:750-758.
53. Hutcheon JA, Platt RW. The missing data problem in birth weight percentiles and thresholds for „small-for-gestational-age". Am J Epidemiol 2008; 167:786-792.
54. Arnold CC, Kramer MS, Hobbs CA, McLean FH, Usher RH. Very low birth weight: a problematic cohort for epidemiologic studies of very small or immature neonates. Am J Epidemiol 1991; 134:604-613.
55. Verloove P, Verwey RA, Brand R, Keirse MJ. Importance of gestational age. Lancet 1986; 1:1494.
56. Dudley NJ. A systematic review of the ultrasound estimation of fetal weight. Ultrasound Obstet Gynecol 2005; 25:80-89.
57. Hille ET, Elbertse L, Gravenhorst JB, Brand R, Verloove-Vanhorick SP. Nonresponse bias in a follow-up study of 19-year-old adolescents born as preterm infants. Pediatrics 2005; 116:e662-e666.
58. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2006; 3:CD004454.
59. Verhaeghe J, van BR, van HE, Coopmans W. Exogenous corticosteroids and in utero oxygenation modulate indices of fetal insulin secretion. J Clin Endocrinol Metab 2005; 90:3449-3453.
60. Moise AA, Wearden ME, Kozinetz CA, Gest AL, Welty SE, Hansen TN. Antenatal steroids are associated with less need for blood pressure support in extremely premature infants. Pediatrics 1995; 95:845-850.

61. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 1972; 50:515-525.
62. Crowley P, Chalmers I, Keirse MJ. The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials. Br J Obstet Gynaecol 1990; 97:11-25.
63. Halliday HL. Surfactants: past, present and future. J Perinatol 2008; 28 Suppl 1:S47-S56.
64. Stoelhorst GM, Rijken M, Martens SE, Brand R, den Ouden AL, Wit JM et al. Changes in neonatology: comparison of two cohorts of very preterm infants (gestational age <32 weeks): the Project On Preterm and Small for Gestational Age Infants 1983 and the Leiden Follow-Up Project on Prematurity 1996-1997. Pediatrics 2005; 115:396-405.
65. Holmen J, Midthjell K, Krüger Ø., Langhammer A., Holmen T.L., Bratberg G.H. et al. The Nord-Trøndelag Health Study 1995-97 (HUNT 2): Objectives, contents, methods and participation. Norsk Epidemiologi 2003 2006; 13:19-32.
66. Yarbrough DE, Barrett-Connor E, Kritz-Silverstein D, Wingard DL. Birth weight, adult weight, and girth as predictors of the metabolic syndrome in postmenopausal women: the Rancho Bernardo Study. Diabetes Care 1998 Oct 1998;1652-1658.
67. Byberg L, McKeigue PM, Zethelius B, Lithell HO. Birth weight and the insulin resistance syndrome: association of low birth weight with truncal obesity and raised plasminogen activator inhibitor-1 but not with abdominal obesity or plasma lipid disturbances. Diabetologia 2000 Jan 1943;54-60.
68. Lauren L, Jarvelin MR, Elliott P, Sovio U, Spellman A, McCarthy M et al. Relationship between birthweight and blood lipid concentrations in later life: evidence from the existing literature. Int J Epidemiol 2003 Oct 1932;862-876.
69. Lawlor DA, Hubinette A, Tynelius P, Leon DA, Smith GD, Rasmussen F. Associations of gestational age and intrauterine growth with systolic blood pressure in a family-based study of 386,485 men in 331,089 families. Circulation 2007; 115:562-568.
70. Newsome CA, Shiell AW, Fall CH, Phillips DI, Shier R, Law CM. Is birth weight related to later glucose and insulin metabolism?--A systematic review. Diabet Med 2003 May 1920;339-348.
71. Barker DJ, Hales CN, Fall CH, Osmond C, Phipps K, Clark PM. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. Diabetologia 1993 Jan 1936;62-67.
72. Eriksson JG, Forsen T, Tuomilehto J, Jaddoe VWV, Osmond C, Barker DJP. Effects of size at birth and childhood growth on the insulin resistance syndrome in elderly individuals. Diabetologia 2002; 45:342-348.
73. Mi J, Law C, Zhang KL, Osmond C, Stein C, Barker D. Effects of infant birthweight and maternal body mass index in pregnancy on components of the insulin resistance syndrome in China. Ann Intern Med 2000 Feb 15 132;253-260.
74. Parker L, Lamont DW, Unwin N, Pearce MS, Bennett SM, Dickinson HO et al. A lifecourse study of risk for hyperinsulinaemia, dyslipidaemia and obesity (the central metabolic syndrome) at age 49-51 years. Diabet Med 2003 May 1920;406-415.
75. Laaksonen DE, Lakka HM, Lynch J, Lakka TA, Niskanen L, Rauramaa R et al. Cardiorespiratory fitness and vigorous leisure-time physical activity modify the association of small size at birth with the metabolic syndrome. Diabetes Care 2003 Jul 1926;2156-2164.
76. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics 2005 Mar 115;e290-e296.
77. White SL, Perkovic V, Cass A, Chang CL, Poulter NR, Spector T et al. Is Low Birth Weight an Antecedent of CKD in Later Life? A Systematic Review of Observational Studies. Am J Kidney Dis 2009.

78. Keijzer-Veen MG, Schrevel M, Finken MJ, Dekker FW, Nauta J, Hille ET et al. Microalbuminuria and lower glomerular filtration rate at young adult age in subjects born very premature and after intrauterine growth retardation. J Am Soc Nephrol 2005; 16:2762-2768.
79. Hoy WE, Hughson MD, Bertram JF, Douglas-Denton R, Amann K. Nephron Number, Hypertension, Renal Disease, and Renal Failure. Journal of the American Society of Nephrology 2005; 16:2557-2564.
80. Hinchliffe SA, Lynch MR, Sargent PH, Howard CV, Van Velzen D. The effect of intrauterine growth retardation on the development of renal nephrons. Br J Obstet Gynaecol 1992; 99:296-301.
81. Manalich R, Reyes L, Herrera M, Melendi C, Fundora I. Relationship between weight at birth and the number and size of renal glomeruli in humans: a histomorphometric study. Kidney Int 2000; 58:770-773.
82. Sorensen HT, Sabroe S, Rothman KJ, Gillman M, Fischer P, Sorensen TI. Relation between weight and length at birth and body mass index in young adulthood: cohort study. BMJ 1997; 315:1137.
83. Fall CH, Osmond C, Barker DJ, Clark PM, Hales CN, Stirling Y et al. Fetal and infant growth and cardiovascular risk factors in women. BMJ 1995 Feb 18 310;428-432.
84. Parsons TJ, Power C, Manor O. Fetal and early life growth and body mass index from birth to early adulthood in 1958 British cohort: longitudinal study. BMJ 2001; 323:1331-1335.
85. Singhal A, Wells J, Cole TJ, Fewtrell M, Lucas A. Programming of lean body mass: a link between birth weight, obesity, and cardiovascular disease? Am J Clin Nutr 2003; 77:726-730.
86. Li H, Stein AD, Barnhart HX, Ramakrishnan U, Martorell R. Associations between prenatal and postnatal growth and adult body size and composition. Am J Clin Nutr 2003; 77:1498-1505.
87. Eriksson J, Forsen T, Osmond C, Barker D. Obesity from cradle to grave. Int J Obes Relat Metab Disord 2003; 27:722-727.
88. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. BMJ 2000; 320:967-971.
89. Stettler N, Kumanyika SK, Katz SH, Zemel BS, Stallings VA. Rapid weight gain during infancy and obesity in young adulthood in a cohort of African Americans. Am J Clin Nutr 2003; 77:1374-1378.
90. Barker M, Robinson S, Osmond C, Barker DJ. Birth weight and body fat distribution in adolescent girls. Arch Dis Child 1997; 77:381-383.
91. Law CM, Barker DJ, Osmond C, Fall CH, Simmonds SJ. Early growth and abdominal fatness in adult life. J Epidemiol Community Health 1992; 46:184-186.
92. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics 2006; 117:1253-1261.
93. Hack M, Breslau N, Weissman B, Aram D, Klein N, Borawski E. Effect of very low birth weight and subnormal head size on cognitive abilities at school age. N Engl J Med 1991; 325:231-237.
94. Casey PH, Whiteside-Mansell L, Barrett K, Bradley RH, Gargus R. Impact of prenatal and/or postnatal growth problems in low birth weight preterm infants on school-age outcomes: an 8-year longitudinal evaluation. Pediatrics 2006; 118:1078-1086.