Long-term consequences of differences in early growth : epidemiological aspects
Euser, A.M.

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Intrauterine growth restriction: no unifying risk factor for the metabolic syndrome in young adults

A.M. Euser
F.W. Dekker
S.I. Hallan

Abstract

Background

The validity and appropriateness of the metabolic syndrome as a cardiovascular risk factor is increasingly debated, partly due to the lack of a unifying underlying pathophysiological mechanism. Intra-uterine growth retardation (IUGR, low birth-weight by gender and gestational length) has been associated with several cardio-vascular problems and could be an important underlying risk factor for the metabolic syndrome.

Methods

The association between IUGR (from the Norwegian Medical Birth Registry) and the metabolic syndrome in 7435 men and women aged 20-30 years from the population-based HUNT-2 study was studied with logistic regression using fractional polynomial models.

Results

In men, there were significant associations with several of the separate components of the metabolic syndrome: central obesity (exponential, $P<0.001$), raised triglycerides (negative linear, $P=0.018$), reduced HDL-cholesterol (U-shaped, $P=0.086$), raised blood pressure (negative linear, $P=0.036$), and impaired glucose-tolerance (negative linear, $P=0.036$). In women, there were significant associations with central obesity (positive linear, $P<0.001$) and raised blood pressure (negative linear, $P=0.003$) but not with the other components. When combining these components into the metabolic syndrome, an exponential association was found in men ($P=0.017$), i.e. increased risk in subjects with high birth weight only. In women, there was no association at all ($P=0.959$).

Conclusions

Low birth weight was not associated with the metabolic syndrome at young adult age. Several associations between birth weight and the separate components of the syndrome were found, however, these associations were partly in different directions.

Introduction

The clustering of central obesity, impaired glucose tolerance or overt diabetes mellitus type 2, dyslipidemia, and hypertension is often referred to as the metabolic syndrome.[1] The syndrome has a high prevalence worldwide, and it has been used widely in research and clinical practice as a cardiovascular risk factor.[2] However, the validity and appropriateness of the metabolic syndrome concept is increasingly debated.[3-6] Authorities have recently advised against it's further use as much fundamental and clinical important information is missing.[6] Making the diagnosis does not improve clinical utility or pathophysiological understanding: it is not clear that the syndrome confers a cardiovascular risk that is different from the sum of its components, nor is a unifying underlying mechanism established.[7]

Intrauterine growth retardation (IUGR) leading to low birth weight has been suggested as an important risk factor for the development of the metabolic syndrome in analogy with associations established with adult cardiovascular disease.[8] For that reason, even 'the small baby syndrome' was proposed as a new name for the metabolic syndrome.[9] Later studies have often only studied separate components of the metabolic syndrome,[10-12] and the findings of the few studies considering the entire metabolic syndrome itself are not unequivocal: associations with both low,[13,14] and high birth weight[15] were found in some studies, while other studies showed no statistically significant association at all.[16-18] It is therefore unclear whether IUGR can be regarded as a common underlying risk factor for the metabolic syndrome. Most of these studies were relatively underpowered, and inappropriate statistical adjustment for current weight or BMI was applied in several studies.[9,13,14,17,18]

Hence, we studied the effect of birth weight on the metabolic syndrome and its individual components in young adults to avoid contamination of our study population with patients with frank diabetes or hypertension. The second Nord-Trondelag Health study (HUNT 2) is a large population based study with birth weights available from the Norwegian Medical Birth Registry. We studied IUGR as a possible unifying underlying risk factor for the metabolic syndrome in the light of an increasing skepticism of defining its individual cardiovascular components as a specific syndrome.

Subjects and methods

Study population
The HUNT 2 study is a general health study conducted 1995-1997 in Nord-Trøndelag County, located in the middle of Norway with a population of 127,000 residents. All residents of this stable and homogeneous Caucasian population aged 20 years and older were invited for an

extensive questionnaire, a brief clinical examination, and a single venous blood specimen without specific instructions. Objectives, methods, and cohort retrieval of the HUNT 2 study are described in detail elsewhere.[19]

At birth, each neonate in Norway is assigned a unique identification number for life. By using this identifier, individual linkage could be performed between the data collected in the HUNT 2 study and perinatal data from the national Medical Birth Registry of Norway which exists since 1967. Therefore, all subjects aged 20-30 years living in Nord-Trøndelag county were eligible for the current study. Subjects with congenital malformations or women who were pregnant at the time of assessment were excluded because of possible influence on body composition and metabolism.

Measurements

At birth, weight was measured in grams, and information on gestational age, congenital malformations, and pregnancy complications was registered by midwifes and obstetricians. Birth weight was expressed as a standard deviation score (SDS) to correct for gestational age and sex using Scandinavian reference values.[20] Out-of-possible-range entries (gestational age <25 or >45 weeks, and/or birth weight <-5 SDS or >5 SDS) were considered as missing values.

In the HUNT 2 study information about diabetes and the use of antihypertensive drugs was obtained by questionnaire. Waist circumference was measured at the level of the umbilicus with a steel tape to the nearest 1.0 cm. Blood pressure was measured three times, and the means of the second and third measurement were taken. Time since last meal was recorded. Fresh serum samples were analyzed within three days.

Definitions

The metabolic syndrome was defined according to the International Diabetes Federation (IDF) criteria: central obesity (waist circumference >94 cm (males) and >80 cm (females)) and at least two of the following four criteria: raised fasting triglyceride level (>1.7 mmol/l), reduced HDL cholesterol (<1.03 mmol/l (males) and <1.29 mmol/l (females)), raised blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg, and/or use of antihypertensive drug treatment), and raised fasting plasma glucose (≥ 5.6 mmol/l or previously diagnosed diabetes mellitus type 2).[21] We also used the American Heart Association / the revised US National Cholesterol Education Program Adult Treatment Panel (AHA / revised NCEP) criteria which differ from the IDF criteria only in defining an elevated waist circumference as ≥102 cm in Caucasian males and ≥88 cm in Caucasian females and at least any three out of the five criteria are required for the diagnosis.[1]

Serum glucose and triglycerides require a fasting state, which was not requested in the large-scale HUNT 2 study and therefore we adjusted them for time since the last meal. To that end, we used time specific percentiles for subjects with normal birth weight corresponding to the cutoff level used in the metabolic syndrome definition. For glucose we used the 95th percentile as this equals 5.6 mmol/l in the truly fasting group. For triglycerides we use the 87.5th percentile as this equals 1.7 mmol/l. This is analogous to adjustments suggested by others.[22,23] Glucose and triglyceride values did not need adjustment in 33% and 12% of subjects, respectively.

Statistical analysis

Data were given by three categories of birth weight SDS using cut-off levels of -1.3 SDS and 1.3 SDS, compatible with the 10th and 90th sex and gestational age specific percentiles respectively. Birth weight < 10th percentile was considered Small for Gestational Age (SGA), birth weight between the 10th and 90th percentiles Appropriate for Gestational Age (AGA), and > 90th percentile Large for Gestational Age (LGA). The effect of birth weight SDS on the adult metabolic syndrome and its separate components was assessed by logistic regression analysis adjusting for the possible confounders age and being born after a pregnancy complicated by preeclampsia. To deal with non-linearity we used fractional polynomial functions in addition to the traditional approach of dividing continuous variables into categories.[24] To check our adjustments for serum glucose and triglycerides in non-fasting subjects, we also performed subgroup analyses in those subjects who could be classified as either having the metabolic syndrome or not having the metabolic syndrome without being dependent on the adjusted serum glucose and / or triglyceride values.

Results

In total, 8596 subjects, i.e. 48% of all subjects born 1967-1977 in Nord-Trøndelag county, participated in the HUNT 2 study. There were no significant differences in birth weight or other perinatal characteristics between our study population and the non-participating young adults of Nord-Trøndelag county (data not shown), 513 subjects had missing data for gestational age and /or birth weight, and 131 had impossible values for these parameters. 318 pregnant women were excluded. Of the remaining 7634 subjects 136 had missing data on one or more components of the metabolic syndrome, so that data of 7498 subjects (3554 males and 3944 females) were analyzed. Birth weight ranged from 1020 to 5630 g, comprising 745 SGA, 5967 AGA, and 745 LGA subjects. Mean birth weight in these groups was 2733 (326), 3506 (415), and 4341 (401), respectively.

Table 1. Characteristics of HUNT 2 participants included by categories of intrauterine growth

	Total (n=7498)	SGA (n=750)	AGA (n=5999)	LGA (n=749)	P-values
Age (years)	24.7 (2.9)	24.6 (2.9)	24.8 (2.9)	24.7 (2.9)	0.42
Male gender (%)	47.4	47.7	46.9	51.4	0.15
High education[a] (%)	27.1	25.2	27.5	25.8	0.83
Height (cm)	173.0 (9.0)	169.9 (8.8)	173.0 (8.9)	176.2 (8.8)	<0.001
Weight (kg)	74.3 (14.2)	71.2 (13.7)	74.2 (14.1)	79.0 (14.5)	<0.001
Body Mass Index (kg/m^2)	24.8 (3.9)	24.5 (4.0)	24.7 (3.9)	25.4 (3.9)	<0.001
Family history of DM or CVD[b] (%)	27.9	29.3	27.6	29.4	0.95
Physical inactivity[c] (%)	13.7	13.4	13.7	13.7	0.88
Current smoking (%)	28.3	31.2	28.0	28.6	0.29
Diabetes (%)	0.6	0.9	0.5	0.3	0.08
Antihypertensive treatment (%)	0.3	0.1	0.4	0.4	0.46
Time since last meal (h)	2.38 (2.30)	2.37 (2.42)	2.40 (2.31)	2.26 (2.11)	0.36
Waist circumference (cm)	80.7 (11.1)	79.6 (11.0)	80.5 (11.1)	82.8 (11.0)	<0.001
s-Triglycerides (mmol/l)	1.4 (0.9)	1.5 (0.9)	1.4 (0.9)	1.4 (0.9)	0.062
s-HDL cholesterol (mmol/l)	1.35 (0.34)	1.33 (0.34)	1.35 (0.34)	1.32 (0.33)	0.427
Systolic blood pressure (mmHg)	126.4 (13.2)	127.8 (13.5)	126.2 (13.1)	126.3 (13.2)	0.029
Diastolic blood pressure (mmHg)	71.3 (8.6)	72.1 (8.7)	71.2 (8.6)	71.1 (8.9)	0.039
s-Glucose (mmol/l)	4.9 (0.9)	5.0 (1.0)	4.9 (0.9)	4.8 (0.8)	0.013

Note: Variables are presented as mean (SD) or percentage. a: more than 15 years; b: DM = diabetes mellitus, CVD = cardiovascular disease, i.e. cerebral stroke or myocardial infarction before age 60; c: less than 1 hour per week of light physical activity. SGA (Small for Gestational Age) have birth weight adjusted for gestational age and sex below 10th percentile, AGA (Appropriate for Gestational Age) are between 10th and 90th percentiles, and LGA (Large for Gestational Age) are above 90th percentile. Differences between the three groups were checked with chi-square test in a 2 x 3 cross-table for binary variables and with one-way ANOVA for continuous variables.

Table 2. Adjusted associations between birth weight SDS and separate components of the metabolic syndrome

	Categories of birth weight (percentiles)							Over-all effect of birth weight	
	< 2.5th	2.5-9th	10-24th	25-74th	75-89th	90-97.5th	> 97.5th	Functional form	P-value
MEN (n=3535)									
Central obesity †	1.22	1.03	0.86	1.00	1.23	1.45	2.06	Exponential	< 0.001
Raised TG level ††	1.74	1.38	1.11	1.00	0.99	1.02	1.08	Neg. linear	0.018
Reduced HDL-cholesterol †	1.24	1.26	1.08	1.00	1.03	1.28	1.29	U-shaped	0.086
Raised blood pressure †	1.38	1.21	1.05	1.00	1.05	1.02	1.28	Neg. linear	0.036
Impaired glucose tolerance ††	1.50	1.31	1.25	1.00	0.92	0.86	1.07	Neg. linear	0.036
WOMEN (n=3922)									
Central obesity †	0.72	1.01	0.97	1.00	1.13	1.07	1.31	Pos. linear	< 0.001
Raised TG level ††	1.21	1.25	1.27	1.00	1.38	1.00	1.55	----	0.828
Reduced HDL-cholesterol †	1.19	1.04	1.15	1.00	0.99	0.98	1.18	---	0.879
Raised blood pressure †	1.60	1.15	1.08	1.00	0.89	1.03	0.76	Neg. linear	0.003
Impaired glucose tolerance ††	1.25	1.25	1.15	1.00	1.13	0.69	0.97	---	0.738

Note: Logistic regression analysis showing the odds ratio for different components of the metabolic syndrome by categories of birth weight SDS. For studying the over-all effect of birth weight as a continuous variable we used fractional polynomial functions. P-values for the overall effect of birth weight and a description of the functional form are given. All analyses were adjusted for age and being born after a pregnancy complicated by preeclampsia. † The different components of the metabolic syndrome were dichotomized according to the International Diabetes Federation definition: central obesity if waist circumference >94 cm in men and >80 cm in women; reduced HDL-cholesterol if <1.03 mmol/l in men and <1.29 mmol/l in women; raised blood pressure if systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg and/or anti-hypertensive medication. †† Cut-off depends on time since last meal, see text and Figure 1.

Table 3. Adjusted associations between birth weight SDS and the metabolic syndrome using different definitions and study groups

	MEN			WOMEN		
	MS y/n	Functional form	P-value	MS y/n	Functional form	P-value
IDF criteria, all included	343/3192	Pos. exponential	0.017	283/3639	---	0.959
IDF criteria, subgroup [†]	247/2878	Pos. exponential	0.004	197/2809	---	0.932
AHA / rNCEP criteria, all included	407/3128	Pos. exponential	0.130	215/3707	---	0.984
AHA / rNCEP criteria, subgroup [†]	131/1015	---	0.475	130/2085	---	0.956

Note: Logistic regression analysis with fractional polynomial functions was used to study the association between birth weight SDS as a continuous variable and the metabolic syndrome. P-values for the overall effect of birth weight and a description of the functional form are given. IDF = International Diabetes Foundation, AHA / r NCEP = American Heart Association / the revised US National Cholesterol Education Program Adult Treatment Panel. MS y/n gives the number of subjects with and without the metabolic syndrome. † Subgroup of subjects who could be classified as either having the metabolic syndrome or not having the metabolic syndrome without being dependent on the adjusted serum glucose and / or triglyceride values.

Characteristics of our study population as young adults, i.e. data from the HUNT 2 examination, are displayed in Table 1. Unadjusted broad categories of birth weight showed that body size was positively associated with birth weight, while other demographic, medical history variables, and the components of the metabolic syndrome were either not different or could indicate a non-linear effect. There were no differences in time since last meal by birth weight group, and no associations with age, sex, waist circumference, HDL cholesterol or blood pressure. Serum glucose and triglycerides were significantly associated with time after meal (test-for-trend 0.006 and <0.001, respectively).

Table 2 shows the gender specific associations between birth weight SDS and the separate components of the metabolic syndrome, adjusted for age and preeclampsia as no other variables were significantly associated. In men, the odds ratio for central obesity seemed to be increased in subjects with very low birth weight SDS (OR 1.22) and in subjects with higher birth weight (OR 1.23, 1.45, and 2.06). Using fractional polynomial functions we found a highly significant over-all association with birth weight (P<0.001), but the functional form was a positive exponential function, i.e. no increased risk with lower birth weights. The expected negative linear effect, i.e. increased risk with lower birth weights, was found for raised triglycerides (P=0.018), raised blood pressure, (P=0.036) and impaired glucose tolerance (P=0.036). For reduced HDL-cholesterol there was a U-shaped association with birth weight (P=0.086). In women, there was a positive linear association between birth weight and central obesity, (P<0.001) and a negative linear association with raised blood pressure (P=0.003). Birth weight was not significantly associated with raised triglycerides, reduced HDL-cholesterol, or impaired glucose tolerance.

The prevalence of the metabolic syndrome according to the IDF criteria was 9.7% in men and 7.2% in women. Table 3 shows a significant association between birth weight and the metabolic syndrome in men (P=0.017) with a positive exponential form, illustrated in Figure 1. This implies no increased risk among those with low birth weight SDS. Repeating the analyses in the subgroup of men not needing adjusted glucose and/or triglycerides cut-offs for the diagnosis of the metabolic syndrome gave very similar results. However, when metabolic syndrome was defined according to the AHA / revised NCEP criteria the association was weaker even in subjects with high birth weight. In women, there was no association between birth weight and the metabolic syndrome irrespective of syndrome definition and study group used (Figure 1).

Figure 1. Absolute risk for developing the metabolic syndrome in (A) men and (B) women at age 20-30 years associated with birth weight SDS. The risk is expressed as a probability with 95% confidence intervals using logistic regression analyses with fractional polynomial functions adjusted for age and preeclampsia in the pregnancy. The reference lines indicate the observed prevalence in men and women.
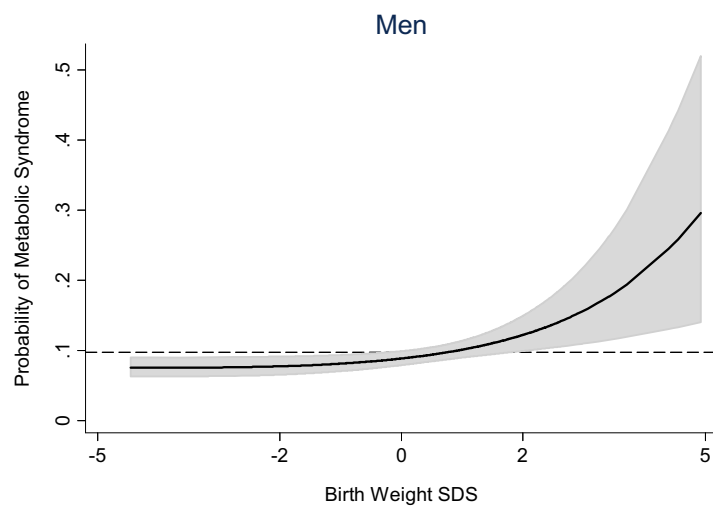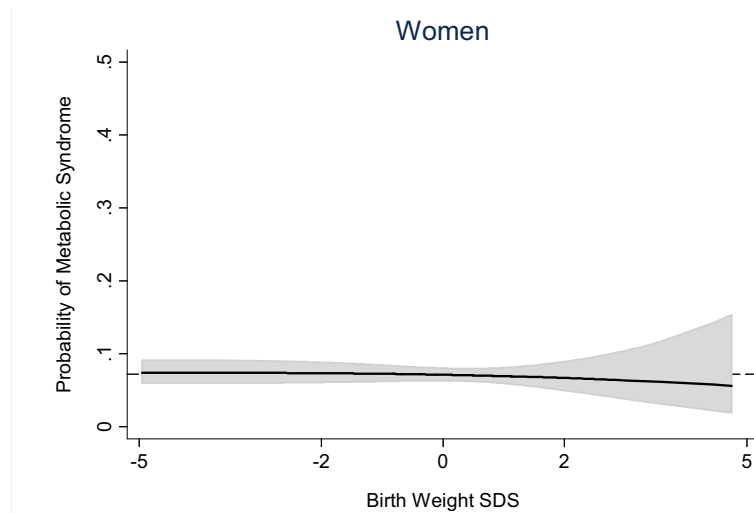
Figure 1A:

Figure 1B:

Discussion

This large-scaled population-based study describes the relationship between birth weight and the metabolic syndrome at young adult age. Birth weight SDS was both negatively, not at all, and positively associated with the separate components of the metabolic syndrome. In both men and women, low birth weight was not significantly associated with the metabolic syndrome itself. This does not support IUGR as a common pathophysiological mechanism for the metabolic syndrome.

Our results might have been affected by limitations in study design or data collection. In the HUNT 2 study, subjects were not asked specifically to attend fasted. We therefore used different cut-offs for increased glucose and triglyceride depending on time after last meal, but some random misclassification can not be excluded. The effect of random misclassification is dilution of the observed effects, implying that we might have underestimated the true effect. However, repeating analyses in a smaller subgroup not relying on glucose or triglyceride values for diagnosing or excluding metabolic syndrome gave similar results. The participation rate in HUNT 2 for this age group was quite low (49%). However, there were no statistically significant differences in either birth weight or gestational age between participants and non-respondents. While non-response might have been related to the presence of metabolic syndrome, it is unlikely that this would result in bias, as bias requires selective non-response of a subgroup with both a certain birth weight category and a certain metabolic status. For example only a high non-response in those subjects with both a low birth weight and presence of the metabolic syndrome. This situation seems very unlikely. Another limitation is the absence of information about the possible confounders catch-up growth and breastfeading. Finally, in non-linear relationship settings, low number of data points in the very low or very high range pose a special problem which is difficult to assess. We therefore cannot totally exclude lack of power as a possible cause of non-significant associations in our study, but our study did after all include 750 SGA subjects.

The large study population in combination with few missing data on birth weight forms a major strength of our study. Furthermore, both birth weight and gestational age were registered at birth, which avoids recall bias. We expressed birth weight in SDS, which adjusts for the possible interference of sex and gestational age. Besides, information on potential important confounders was taken into account. Though studying the effect of early origins in relatively young adults has the clear advantage that disturbing life-style effects have accumulated less frequently, it might have been too young to detect some possible associations as the prevalence of the metabolic syndrome increases with increasing age. Therefore, the current research question should also be examined in an older population in future.

Birth weight was inconsistently associated with the separate components of the metabolic syndrome in our study. The effect of high birth weight SDS on elevated waist circumference has also been described previously.[13] A negative association was found between birth weight and triglycerides in men, and even though it has been found in earlier studies, it was not in the majority of (small) studies on this topic.[25] However, most of these studies did not do separate analyses of men and women, and in those who did so a negative effect in men was found in five of six studies. We found a U-formed association between birth weight and HDL cholesterol in men. Most other studies have found no association,[25] which could be caused by the use of linear regression analysis and the joint evaluation of men and women. Like other studies, we found only a small effect of low birth weight on elevated blood pressure.[26,27] We found a negative association between low birth weight and glucose levels in males only, while a previous review found that most studies reported a negative association in both men and women.[28]

Contrary to most previous findings, we did not find a significant association between low birth weight SDS and the metabolic syndrome. This discrepancy could partly be explained by publication bias, a phenomenon that has also been described for studies on fetal origins of blood pressure.[27] Furthermore, a substantial part of the inverse associations found and published by others might also be explained by adjustments for current body size, mostly BMI. It is well known that BMI is positively related with risk factors for cardiovascular disease, and there is also a positive relation to birth weight.[29] High BMI should therefore be considered as an intermediate rather than a confounder, and thus, we think it is theoretically unjustified to adjust for indicators of adult body composition.[30,31]

A medical syndrome is usually defined as an aggregate of symptoms and signs conferring an increased risk unified by a common underlying pathophysiological process. The latter is important for a better understanding of the disease, both regarding prediction, diagnosis, and treatment. The metabolic syndrome was initially thought to be caused by insulin resistance, but more recent studies have shown that only 48% of insulin resistant subjects also have the metabolic syndrome.[32] As current knowledge is based on association studies only, it may well be that there is a more basic defect resulting in insulin resistance and other cardiovascular risk factors. IUGR could be such a basic unifying defect, as low birth weight has nowadays repeatedly been associated with adult cardiovascular disease[8] and its separate risk factors, both in this study as well as in other studies.[13,26,27] The early studies supported low birth weight as a risk factor for the metabolic syndrome,[9,13,14] but our data weigh against this hypothesis. Obviously, this does not exclude that a common pathological base for the metabolic syndrome might still be found in future, e.g. catch-up growth has been suggested to be such a risk factor.[33] However, like with low birth weight and the metabolic syndrome, the majority of the current studies supporting this hypothesis studied one or more separate components of the

syndrome only.[33] Furthermore, longitudinal data from population-based cohorts have recently shown that metabolic syndrome was only weakly associated with cardiovascular risk, and that the joint syndrome was not better than the sum of its components.[34] In this context, finding opposite effects of low birth weight on different components of the metabolic syndrome but no effect on the syndrome itself does not provide additional support for metabolic syndrome concept.

In conclusion, several significant but inconsistent associations were found between birth weight and the separate components of the metabolic syndrome. However, no significant association was found between low birth weight and the metabolic syndrome itself.

Acknowledgements

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