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Preterm birth, early growth and adult metabolic health

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6 Preterm birth and insulin resistance in adulthood:

higher fat mass after poor intrauterine weight gain has larger effects on insulin resistance than does higher fat mass after normal intrauterine weight gain

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Abstract

Objectives:

An increased risk of type 2 diabetes is associated with low birth weight after term gestation, including amplification of this risk by weight gain during infancy and adult body composition. Premature birth is also associated with insulin resistance, but studies conducted so far have not provided follow-up into adulthood. We studied the effects of lower birth weight (as SD score, SDS) and infancy weight gain on insulin resistance in 19-year-olds born before 32 weeks of gestation, and the interaction between lower birth weight SDS and infancy weight gain, as well as between lower birth weight and adult body composition, on insulin resistance.

Methods:

This was a prospective follow-up study in 346 subjects from the Project On Preterm and Small-for-gestational-age infants cohort, in whom fasting glucose, insulin, and C-peptide levels were measured at 19 years. Insulin resistance was calculated with homeostatic modelling (homeostatic model assessment for insulin resistance index, HOMA-IR).

Results:

Birth weight SDS was unrelated to the outcomes. Rapid infancy weight gain until 3 months post-term was weakly associated with higher insulin level (P=0.05). Adult fatness was positively associated with insulin and C-peptide levels and HOMA-IR (all P <0.001). On these parameters, there was a statistical interaction between birth weight SDS and adult fat mass (P=0.002 to 0.03).

Conclusions:

In subjects born very preterm, rapid infancy weight gain until 3 months predicted higher insulin levels at 19 years, but the association was weak. Adult obesity strongly predicted higher insulin and C-peptide levels as well as HOMA-IR. The effect of adult fat mass on these parameters was dependent on its interaction with birth weight SDS.

Introduction

Effects of intrauterine and postnatal growth on the risk, in the general population, of developing type 2 diabetes are well described. Low birth weight after term gestation is associated with insulin resistance, glucose intolerance, and type 2 diabetes in later life (1;2). The effect of low birth weight on increased type 2 diabetes risk is stronger in subjects who catch up in weight during infancy, and in those who become overweight during childhood and in adult life (3-5). Also, low weight in infancy has been associated with type 2 diabetes (1;6).

Less is known about the effects of intrauterine and postnatal growth on insulin resistance in the growing population of survivors of preterm birth. Recently, it was found that 7-year-old children born prematurely were more insulin-resistant than age-matched normal controls (7). The effect of prematurity was irrespective of intrauterine growth, although another study in 6-year-old preterm offspring found higher basal insulin and C-peptide levels in subjects with birth weights below the 10th percentile (8). However, both studies were performed in small populations. Very preterm (i.e., <32 weeks of gestation) infants differ from term children in postnatal growth pattern, which is characterized by an initial slowing of growth followed by late catch-up growth (9;10). To date, 1 study has focused on insulin resistance in relation to postnatal weight gain after preterm birth (11). The investigators found that insulin split products were higher in subjects aged 13 to 16 years with rapid weight gain in the first 2 weeks postnatally. As these 3 studies were conducted in paediatric populations, it remains uncertain whether the observed associations in childhood persist into adult life. For the same reason, it is unknown whether there is interaction between low birth weight and adult body composition on insulin resistance after very preterm birth.

We provide here a prospective long-term follow-up into adulthood of a well-described cohort of men and women born very preterm, in whom insulin resistance was assessed at the age of 19 years. Within this study population, we tested the effects of lower birth weight for gestational age and rapid infancy weight gain on insulin resistance at the age of 19 years. We also tested whether there was interaction between lower birth weight and rapid infancy weight gain, and between lower birth weight and adult body composition, on insulin resistance.

Methods

Population

The Project On Preterm and Small-for-gestational-age infants (POPS) study is a nationwide multicenter prospective follow-up study, which comprises 94% of all liveborn very preterm (<32 weeks of gestation) and/or very-low-birth-weight (<1,500 g) infants born in The Netherlands in 1983, and has documented birth, growth, and a number of other characteristics from birth

onwards (12;13). At follow-up visits at age 3 months and 1 year post-term, weight was recorded. At age 19 years, all 637 alive subjects born with a gestational age <32 weeks who were free from congenital skeletal deformations, Down's syndrome, chromosomal abnormalities, multiple congenital deformations or inborn errors of metabolism, and who were not born to mothers with gestational diabetes, were approached by mail to participate in the POPS-19 study. Subjects with diabetes mellitus, or on thyroid hormone or systemic corticosteroids, as well as pregnant women, were excluded. The approval of the medical ethical committees of all participating centres was obtained for the POPS-19 study.

Study protocol

Subjects who gave written informed consent to participate were seen after an overnight fast between 8.30 and 10.00 h between April 2002 and May 2003 at one of the outpatient clinics of the 10 participating centres. Assessors were blinded with respect to the perinatal characteristics of the subjects.

Table 1. Perinatal characteristics of participants and non-responders.

Characteristic	Participants	Non-responders	P
N	346	242	
General			
Males (%)	47.4	66.1	<0.001
Whites (%)	88.3	80.1	0.006
Socio-economic status (1-6)	3.5±1.6	2.8±1.5	<0.001 [a]
Obstetric			
Maternal age (yrs)	26.9±5.7	26.4±5.3	0.23
Parity >0 (%)	46.7	50.6	0.35
Part of multiple pregnancy (%)	24.3	21.5	0.43
Hypertension during pregnancy (%)	16.5	15.3	0.70
Smoking during pregnancy (%)	30.0	31.8	0.67
Drugs and alcohol intoxication (%) [b]	50.9	51.2	0.93
Prolonged rupture of membranes (%)	24.0	24.4	0.91
Neonatal			
Gestational age (weeks)	29.8±1.5	29.8±1.5	0.55
Birth weight			
- g	1,332±333	1,354±278	0.39
- SDS	-0.09±1.02	-0.08±0.90	0.98
Weight at 3 mo			
- g	5,169±871	5,234±896	0.40
- SDS	-0.92±1.32	-0.94±1.42	0.88
Weight at 1 yr			
- g	8,909±119	9,084±140	0.14
- SDS	-1.00±1.15	-0.95±1.38	0.61

Values represent mean±SD or percent. Continuous variables were compared with the unpaired t test.
Dichotomous variables were compared by the χ^2 test.
[a] Mann-Whitney U test.
[b] Smoking, drinking alcohol, or using soft drugs, hard drugs or methadone during pregnancy

Venous blood was obtained after 30 minutes in a supine position. Thereafter, anthropometry was performed, for which assessors had received extensive training prior to the study, and re-training during the entire study period at 2-month intervals. Subjects were measured barefoot while wearing underclothing only. Weight was measured to the nearest 0.1 kg on a balance scale, and height to the nearest 0.1 cm with a fixed stadiometer. Waist and hip circumferences were measured at 0.1-cm accuracy using standard methods (14). Four skinfold thickness measurements were taken in duplicate with a calibrated skinfold calliper on the left side of the body: at triceps, biceps, subscapular, and iliacal regions. From these measurements, fat mass and the corresponding fat-free mass were calculated using the equations of Durnin and Rahaman (15). A more detailed description of skinfold thickness measurements obtained in the POPS-19 study has been published elsewhere (16).

Laboratory analysis

Blood samples were stored at -80 °C and thawed only once immediately before analysis. Glucose was measured in a fully automated computerized laboratory system with an Hitachi 747 (Hitachi, Tokyo, Japan) chemistry analyser, and insulin and C-peptide were measured with highly sensitive radioimmunoassays (Linco, St Charles, MO, USA; detection levels 0.1 mU/l

Table 2. Characteristics of participants at age 19 years by sex.

Characteristic	Men	Women	P
N	164	182	
Height			
- cm	179.4±7.7	166.4±7.3	<0.001
- SDS	-0.54±1.08	-0.60±1.13	0.66
Weight			
- kg	69.1±10.7	60.2±10.7	<0.001
- SDS	-0.47±1.12	-0.50±1.39	0.83
BMI			
- kg/m^2	21.4±2.8	21.7±3.2	0.44
- SDS	-0.17±1.10	-0.19±1.24	0.86
Waist circumference			
- cm	79.8±7.9	76.8±8.7	0.001
- SDS	0.19±1.04	0.70±0.98	<0.001
WHR			
- cm/cm	0.87±0.06	0.82±0.08	<0.001
- SDS	0.70±0.92	0.86±0.97	0.12
Absolute fat mass (kg)	11.1±5.2	18.2±6.6	<0.001
Fat-free mass (kg)	57.9±7.3	42.1±6.6	<0.001
Fat percentage (%)	15.7±5.3	29.5±7.1	<0.001
Glucose (mmol/l)	5.2±0.4	4.8±0.4	<0.001
Insulin (mU/l)	8 (6 to 11)	8 (7 to 11)	0.42
C-peptide (mmol/l)	0.66±0.23	0.69±0.21	0.16
HOMA-IR	1.9 (1.4 to 2.6)	1.8 (1.4 to 2.3)	0.46

Values represent mean±SD or median (interquartile range). Variables were compared with the unpaired t test.

and 0.03 mmol/l, respectively; interassay coefficient of variation 4.7-12.2% and 3.2-9.3% at different levels, respectively). A homeostatic model assessment for insulin resistance index (HOMA-IR) was calculated (17). Insulin and C-peptide levels, and HOMA-IR were considered as parameters of insulin resistance. Insulin level and HOMA-IR correlate strongly with Si assessed by the frequently-sampled intravenous glucose tolerance test in young persons (18;19).

Statistical analysis

Auxological data at birth and on subsequent occasions were converted to SD score (SDS), to correct for (gestational) age and sex, using Swedish references for preterm infants (20), and recently collected Dutch references (14;21;22), respectively.

Results in Tables 1 and 2 are presented as mean±SD, or median (interquartile range) if variables were not normally distributed (insulin and HOMA-IR). These variables were ^{10}log-transformed before statistical comparison.

Table 3. Regression analyses of birth weight SDS and infancy weight gain on the parameters of insulin resistance at age 19 years.

Outcome	Crude[a]			Adjusted[b]			Interaction with birth weight SDS		
	N	ß (95% CI)	P	N	ß (95% CI)	P	N	ß (95% CI)	P
Log Insulin									
- Birth weight SDS	346	-0.006 (-0.025 to 0.012)	0.49	339	-0.002 (-0.024 to 0.020)	0.86	-	-	-
- Weight SDS at 3 mo	321	0.017 (0.001 to 0.033)	0.04	315	0.018 (0 to 0.036)	0.05	321	-0.015 (-0.034 to 0.03)	0.10
- Weight SDS at 1 yr	317	0.016 (-0.002 to 0.035)	0.08	313	0.014 (-0.005 to 0.033)	0.15	317	-0.006 (-0.025 to 0.013)	0.53
C-peptide									
- Birth weight SDS	346	-0.020 (-0.043 to 0.002)	0.08	339	-0.020 (-0.043 to 0.003)	0.08	-	-	-
- Weight SDS at 3 mo	321	-0.010 (-0.030 to 0.011)	0.36	315	-0.006 (-0.029 to 0.017)	0.61	321	0.011 (-0.012 to 0.035)	0.34
- Weight SDS at 1 yr	317	-0.003 (-0.026 to 0.019)	0.78	313	-0.003 (-0.027 to 0.021)	0.81	317	0.004 (-0.018 to 0.027)	0.70
Log HOMA-IR									
- Birth weight SDS	345	-0.005 (-0.025 to 0.015)	0.65	338	0 (-0.23 to 0.23)	1.00	-	-	-
- Weight SDS at 3 mo	320	0.017 (0 to 0.035)	0.05	314	0.017 (-0.003 to 0.036)	0.09	320	-0.011 (-0.031 to 0.009)	0.27
- Weight SDS at 1 yr	316	0.020 (0 to 0.040)	0.05	312	0.017 (-0.004 to 0.037)	0.12	316	-0.003 (-0.023 to 0.017)	0.79

[a] Adjusted only for sex.

[b] Adjusted for sex, race (white or non-white), socio-economic status (≤ or >2), multiple pregnancy (singleton or non-singleton), gestational age (≤ or >30 weeks), parity (0 or >0), and hypertension during pregnancy (yes or no).

Birth weight is a strong predictor of postnatal size. Therefore, the multivariate linear regression model developed by Li et al was used to distinguish between the separate effects of birth weight SDS, and of postnatal size (at the age of 3 months, 1 year, and 19 years) on the parameters of insulin resistance (23). First, the effect of birth weight SDS on the parameters of insulin resistance was studied. Subsequently, residual (observed - expected) postnatal size was entered into the model. Expected postnatal size was based upon birth weight SDS only. Hence, residual postnatal size can be interpreted as growing more (or less) than would be expected from a given birth weight SDS. Thereafter, the interaction term (birth weight SDS x residual, with subtraction of means) was entered. Recently (24), the algebraic concept of this model was explained, showing that it can be rewritten to the model by Lucas et al (25). In the applied model, postnatal size is made statistically unrelated to birth weight SDS.

Analyses with birth weight SDS and infancy weight gain were repeated with adjustment for the possible confounders sex, race (white or non-white), socio-economic status (≤ or >2), multiple pregnancy (singleton or non-singleton), gestational age (≤ or >30 weeks), parity (0 or >0), and hypertension during pregnancy (yes or no). Analyses with adult size and body composition were repeated with adjustment for sex, race, and socio-economic status.

Statistical significance was defined as a P value ≤0.05. Non-linear associations were tested by first producing quarters of birth weight SDS and infancy weight gain. These quarters were compared with respect to the parameters of insulin resistance.

Results

At age 19 years, 637 men and women born before 32 weeks of gestation were still alive and eligible for inclusion: 395 consented to participate, whereas 242 refused or were not traceable. Three of the 395 participants met one of the exclusion criteria (1 woman was pregnant at the time of assessment, and 2 subjects used systemic corticosteroids), 27 failed to give blood, and 19 attended not-fasted. Therefore, 346 individuals were included in the statistical analyses.

Non-response was associated with male sex, non-white race, and lower socio-economic status (Table 1). It was not associated with gestational age or birth weight. Nineteen individuals (6%) had a birth weight <-2 SDS, 73 (23%) had a weight at 3 months <-2 SDS, and 57 (18%) had a weight at 1 year <-2 SDS.

For both sexes, mean values for height and weight were below the population reference means, while the means for waist circumference and waist-to-hip ratio were greater, especially in the women (Table 2). Women had greater absolute and relative fat mass than men. Men had greater fat-free mass and higher glucose levels than women. There was no difference between the sexes for insulin and C-peptide levels and HOMA-IR. Of the women, 121 (67%) used

oral contraceptives at the time of assessment, but there were no significant differences in the parameters of insulin resistance between pill and non-pill users (data not shown).

Birth weight SDS was unrelated to the parameters of insulin resistance (Table 3). Rapid infancy weight gain until 3 months was associated with a higher insulin level and HOMA-IR. After correction for possible confounders, the strength of the relationship with HOMA-IR remained unchanged but statistical significance was lost. Rapid infancy weight gain until 1 year was associated only with higher HOMA-IR, which relationship lost statistical significance after correction for possible confounders. No interaction between birth weight SDS and infancy weight gain on the parameters of insulin resistance was observed. There was no evidence for non-linearity in the associations between early growth and the parameters of insulin resistance (data not shown).

Except for height SDS, all measures of adult size and body composition were strongly associated with insulin and C-peptide levels as well as HOMA-IR (Table 4). Interaction between birth weight SDS and adult absolute and relative fat mass on these parameters was observed. Also, interaction between birth weight SDS and adult height SDS on insulin level and HOMA-IR, and between birth weight SDS and adult waist circumference SDS on HOMA-IR, was found. Figure 1 displays the direction of the interaction of birth weight SDS and adult absolute fat mass on HOMA-IR, showing that higher fat mass after lower birth weight SDS has larger effects on the parameters of insulin resistance than does higher fat mass after higher birth weight SDS.

Discussion

From birth onwards we followed a relatively large cohort of subjects born very preterm. At age 19 years, insulin resistance was assessed using fasting levels of insulin and C-peptide as well as HOMA-IR. We found that rapid infancy weight gain until 3 months predicted higher insulin levels at age 19 years, but the association was weak. Adult fat accumulation strongly predicted higher insulin and C-peptide levels as well as higher HOMA-IR at age 19 years. The effect of adult fat accumulation on these parameters of insulin resistance was dependent on its interaction with birth weight SDS. This was most clearly the case for increased fat mass per se, rather than for more abdominal fat. However, it should be emphasized that the typical centralization of fat distribution occurs with advancing age so that such relationships may become more clear later in adulthood.

It has been suggested that the association between early growth and type 2 diabetes risk is the result of a biological phenomenon which has been called fetal or perinatal programming (26). Throughout the years, several hypotheses based on the concept of programming have been proposed to underlie this association, including the “thrifty phenotype”, “fetal salvage”, “catch-up growth”, and “stem-cell” hypotheses (27-30). There are also indications that the as-

sociation is not the result of programming but of confounding (especially by socio-economic status), selective survival or response (31;32), or genes that affect both the path of early growth and insulin resistance (33). Despite incomplete follow-up, our participants did not significantly

Table 4. Regression analyses of adult size and body composition on the parameters of insulin resistance at age 19 years.

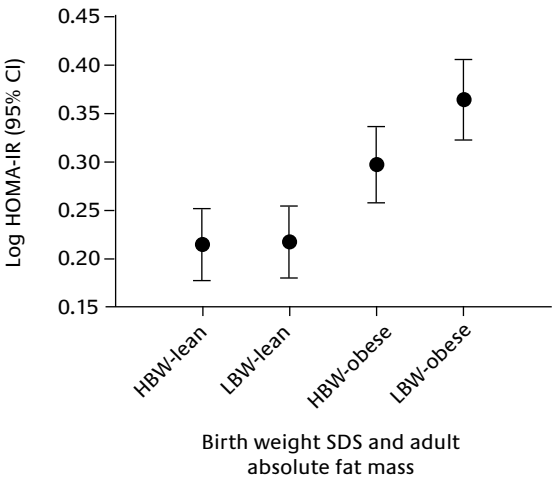
Outcome	Crude[a]			Adjusted[b]			Interaction with birth weight SDS		
	N	ß (95% CI)	P	N	ß (95% CI)	P	N	ß (95% CI)	P
Log Insulin									
- Height SDS	339	0.004 (-0.015 to 0.022)	0.70	333	0.001 (-0.018 to 0.020)	0.93	339	-0.022 (-0.040 to -0.005)	0.01
- BMI SDS	338	0.060 (0.045 to 0.075)	<0.001	332	0.057 (0.042 to 0.072)	<0.001	338	-0.012 (-0.026 to 0.002)	0.09
- Waist circumference SDS	341	0.076 (0.059 to 0.093)	<0.001	335	0.073 (0.056 to 0.091)	<0.001	341	-0.016 (-0.032 to 0)	0.06
- Waist-to-hip ratio SDS	340	0.030 (0.010 to 0.049)	0.003	334	0.045 (0.023 to 0.066)	<0.001	340	-0.007 (-0.026 to 0.012)	0.48
- Absolute fat mass (kg)	335	0.011 (0.008 to 0.014)	<0.001	329	0.011 (0.008 to 0.014)	<0.001	335	-0.005 (-0.009 to -0.002)	0.003
- Fat percentage (%)	337	0.008 (0.005 to 0.011)	<0.001	331	0.009 (0.006 to 0.012)	<0.001	337	-0.004 (-0.007 to 0)	0.03
C-peptide									
- Height SDS	339	0.016 (-0.007 to 0.038)	0.18	333	0.011 (-0.012 to 0.035)	0.34	339	0.001 (-0.020 to 0.022)	0.92
- BMI SDS	338	0.056 (0.037 to 0.075)	<0.001	332	0.055 (0.035 to 0.074)	<0.001	338	-0.017 (-0.035 to 0.001)	0.06
- Waist circumference SDS	341	0.084 (0.063 to 0.106)	<0.001	335	0.083 (0.061 to 0.105)	<0.001	341	-0.012 (-0.032 to 0.008)	0.25
- Waist-to-hip ratio SDS	340	0.045 (0.021 to 0.069)	<0.001	334	0.056 (0.030 to 0.082)	<0.001	340	-0.019 (-0.042 to 0.004)	0.11
- Absolute fat mass (kg)	335	0.016 (0.012 to 0.019)	<0.001	329	0.016 (0.012 to 0.019)	<0.001	335	-0.006 (-0.010 to -0.002)	0.006
- Fat percentage (%)	337	0.013 (0.010 to 0.017)	<0.001	331	0.014 (0.010 to 0.017)	<0.001	337	-0.004 (-0.008 to 0)	0.03
Log HOMA-IR									
- Height SDS	338	0.004 (-0.016 to 0.024)	0.70	332	0.001 (-0.020 to 0.021)	0.93	338	-0.023 (-0.042 to -0.004)	0.02
- BMI SDS	337	0.065 (0.050 to 0.081)	<0.001	331	0.063 (0.047 to 0.079)	<0.001	337	-0.013 (-0.028 to 0.002)	0.09
- Waist circumference SDS	340	0.083 (0.065 to 0.101)	<0.001	334	0.081 (0.062 to 0.099)	<0.001	340	-0.019 (-0.036 to -0.001)	0.04
- Waist-to-hip ratio SDS	339	0.034 (0.013 to 0.055)	0.002	333	0.047 (0.024 to 0.070)	<0.001	339	-0.007 (-0.028 to 0.014)	0.50
- Absolute fat mass (kg)	334	0.012 (0.009 to 0.015)	<0.001	328	0.013 (0.010 to 0.016)	<0.001	334	-0.006 (-0.009 to -0.002)	0.002
- Fat percentage (%)	336	0.009 (0.006 to 0.012)	<0.001	330	0.010 (0.007 to 0.013)	<0.001	336	-0.004 (-0.008 to -0.001)	0.01

[a] Adjusted only for sex.

[b] Adjusted for sex, race (white or non-white), and socio-economic status (≤ or >2).

differ from non-responders in perinatal characteristics. Non-response was higher among men, non-whites, and those with lower socio-economic status. As expected, we found that subjects with lower socio-economic status had higher parameters of insulin resistance than those with higher socio-economic status, but the difference was not statistically significant. We also found that whites were as equally insulin-resistant as the rather heterogeneous group of non-whites, including 11 subjects of Mediterranean origin, 10 Africans, 15 Asians, and 4 others (data not shown), while it is known that prevalence rates of type 2 diabetes are substantially higher among blacks and Indians. The question arises whether selective response could account for (part of) the observed associations in our study sample. Statistical adjustment for a number of variables, including socio-economic status and race, in regression analyses hardly changed any of the coefficients between early growth and the parameters of insulin resistance. This makes bias introduced by selective response less likely, although it does not exclude the possibility completely. A possible relationship between birth weight SDS and the parameters of insulin resistance would be concealed if the low birth weight SDS subjects with a high risk of insulin resistance selectively declined to participate. Furthermore, the relationship between infancy weight gain and insulin level would be artificial if the slow weight gain subjects with a high risk of insulin resistance selectively refused to participate. This seems not very likely. Moreover, although non-response was associated with demographic factors linked to insulin resistance, in the entire birth cohort (N=1,012) there were no effects of race or socio-economic status on birth weight SDS or infancy weight gain.

Figure 1. Effects of birth weight SDS and adult absolute fat mass on log HOMA-IR at age 19 years.



LBW: lower birth weight SDS.
HBW: higher birth weight SDS.

HBW-lean: birth weight SDS ≥0 and absolute fat mass ≤median for sex (N=78).
LBW-lean: birth weight SDS <0 and absolute fat mass ≤median for sex (N=90).
HBW-obese: birth weight SDS ≥0 and absolute fat mass >median for sex (N=85).
LBW-obese: birth weight SDS <0 and absolute fat mass >median for sex (N=81).

Although the majority of full-term small-for-gestational-age (SGA) babies show catch-up growth after birth (34), infancy weight gain of our study population was slow, which is reflected by the low mean weight SDS at 3 months and 1 year. However, in contrast to full-term SGA babies, many very preterm infants suffer from life-threatening conditions after birth which require a shift in energy expenditure, enabling them to survive at the expense of somatic growth; e.g. by respiratory distress necessitating assisted ventilation, or infections.

To date, a number of studies have investigated the effect of infancy weight gain on later type 2 diabetes (3;11;35;36). In middle-aged subjects, low weight at birth and at age 1 year were associated with type 2 diabetes, but the rate of weight gain in the first year of life was unrelated to type 2 diabetes (35). However, in 1-year-old infants born SGA, catch-up growth in weight until age 1 years was associated with higher fasting insulin levels (3). Similarly, in children aged 8 years, rapid weight gain between birth and age 3 years was related to insulin resistance (36). Also in prematurely born subjects aged 13 to 16 years, effects of early postnatal weight gain on later insulin resistance have been reported. Boys and girls with rapid weight gain in the first 2 weeks postnatally had higher concentrations of proinsulin and 32-33 split proinsulin (11). Our findings in young adults born very preterm support these previous observations in paediatric populations.

We found that lower birth weight SDS strongly modified the effect of greater absolute and relative fat mass on insulin and C-peptide levels as well as HOMA-IR in young adulthood, which is consistent with previous studies in full-term 20-year-old subjects (5). We also found an interaction effect between lower birth weight SDS and greater adult height SDS on insulin level and HOMA-IR, but this probably reflects the effect of greater absolute fat mass (which is closely related to height). The interaction between lower birth weight SDS and greater adult relative fat mass (which is independent of height) on the parameters of insulin resistance suggests an effect of adult fat accumulation rather than of height.

Conclusions

In conclusion, our study in a relatively large cohort of men and women born very preterm showed that rapid infancy weight gain until 3 months predicted higher insulin levels at age 19 years, but the association was weak. Adult fat accumulation strongly predicted higher insulin and C-peptide levels as well as higher HOMA-IR at age 19 years. The effect of adult fat accumulation on these parameters of insulin resistance was dependent on its interaction with birth weight SDS.

A previous study in the same cohort showed that rapid infancy weight gain was a strong predictor of adult fat accumulation (16), whereas this study showed only a weak effect of rapid infancy weight gain until 3 months on insulin level (and no effect on C-peptide level and

HOMA-IR) in young adulthood. At present, it is unclear whether interventions aimed at discouraging infancy weight gain would improve adult body composition and reduce the chance of developing type 2 diabetes. However, recent evidence suggests that rapid infancy weight gain of very preterm infants is beneficial for several neurodevelopmental outcomes (37;38), making intervention (i.e., undernutrition) hard to justify.

Recently, it was found that the survivors of very preterm birth are already more insulin-resistant at the age of 7 years (7). In line with these observations, we found that HOMA-IR (which normally approximates to 1 in young non-obese persons, if glucose is measured in mmol/l and insulin in mU/l (17)) was relatively high in our study population. Also, we found that our subjects had already some centralization of fat distribution compared with population references. As there is strong tracking of obesity from childhood to young adulthood (39), we would like to call upon paediatricians and primary healthcare workers to be alert to fat accumulation during childhood in the follow-up of very preterm subjects, especially of those born SGA, and to intervene, even though it has not yet been tested whether weight reduction in very preterm subjects can reverse insulin resistance. The question of whether the survivors of very preterm birth, and especially those born SGA who subsequently become overweight, have a premature onset of type 2 diabetes remains very interesting and should be addressed.

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