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Premature birth was not associated with increased body fatness in four-year-old boys and girls

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Short title: Body composition of prematurely born children

ABSTRACT

Aim: Premature birth is a worldwide problem and increases the risk of chronic disease later in life. Prematurely born infants may have a high percentage of body fat at term equivalent age, but it is unclear if this characteristic is maintained in childhood. Therefore, we compared the size and body composition of four-year-old prematurely born children to such values of full-term controls.

Methods: Between 2013 and 2015 we assessed weight, height, fat mass and fat-free mass, using air displacement plethysmography in 188 reasonably healthy prematurely born four-year-olds (98 boys).

Results: At four years of age, prematurely born children (gestational weeks at birth: 23.3-36.9) tended to be lighter and shorter and to contain less fat mass and fat-free mass than did full-term controls. The gestational age at birth of the prematurely born children correlated positively and significantly ($p < 0.05$) with height, weight, body mass index, fat mass (kg, %), fat mass index and fat-free mass (kg) in girls but not in boys.

Conclusion: Prematurity was not associated with increased body fatness in our four-year-olds. Our findings are relevant in relation to previously published results showing that premature birth is associated with chronic disease later in life.

Key notes

- Premature birth increases the risk of chronic disease later in life and prematurely born infants may have high body fatness, but it is unclear if this is maintained into childhood.
- Prematurity did not increase body fatness in four-year-olds and gestational age at birth correlated with size and fatness in girls.
- These findings are of interest because prematurity is associated with chronic disease later in life.

Key words

Air displacement plethysmography, body composition, premature birth, four-year-old children

Abbreviations

BMI, Body mass index; r, Correlation coefficient.

INTRODUCTION

Prematurity is a worldwide problem occurring in approximately 10% of all births (1). It is not only an important cause of death in young children (1), but it can also be linked to increased blood pressure (2-4) and impaired insulin sensitivity (4-7) later in life. This suggests that in adulthood, prematurely born individuals have an increased risk of disorders commonly known as chronic disease, including hypertension, type 2 diabetes mellitus and heart disease. Mechanisms suggested to be responsible for this link between prematurity and chronic disease include nutrition, oxidative stress, epigenetic changes, endocrine and renal changes (3) as well as an unfavorable intrauterine environment and the growth pattern during infancy and childhood (4,6,7) indicating that prematurity influences the risk for chronic disease in a complex way.

Studies demonstrate that prematurely born infants have a high percentage of body fat at term-equivalent age (8-12). These observations have caused concern that such infants may have an increased risk for obesity later in life, a condition associated with chronic disease. Therefore, authors have studied whether prematurely born individuals have high body fatness and consequently an increased risk for obesity later in life. However, the results of such studies show considerable variation. Stigson et al. (13) reported that prematurely born four-year-olds have a higher percentage of body fat than controls born at term. Gianni et al. (9) made similar observations with respect to five-year-old boys, although the difference between the term and preterm groups was not significant. However, Huke et al. (14) did not find any association between prematurity and increased fat mass in five- to seven-year-old children. Fewtrell et al. (15) made similar observations in children aged 8-12 years.

The variability in these results may have several explanations, for example, different gestational ages at birth or variations in the validity of the body composition method used. In this

paper, we report the body composition of prematurely born four-year-old boys and girls. These children were born after 23.3 to 36.9 gestational weeks and were studied by means of air displacement plethysmography, which is an accurate body composition method (16).

MATERIALS AND METHODS

Subjects

Prematurely born four-year-old children were recruited through pediatric clinics in southeastern Sweden. Inclusion criteria were reasonably healthy children without malformations or serious handicaps. We recruited 188 such children, 90 girls and 98 boys. There were two sets of triplets, one of which comprised all males and one all females. Furthermore, the following twins participated in the study: 11 sets of male twins; nine sets of female twins; five sets of twins in which one was a girl and one was a boy; and one twin boy and two twin girls participating alone. The remaining children (67 boys and 62 girls) were singletons. Information about birth weight, birth length and gestational age at birth was obtained from hospital records.

We also used size and body composition data collected in 253 four-year-old controls born full-term (137 boys). At birth these children weighed 3.73 ± 0.50 kg (boys) and 3.57 ± 0.46 kg (girls) and they were 52 ± 2 cm (boys) and 51 ± 2 cm (girls) long. At four years of age 12 boys and five girls were overweight while two boys and one girl were obese. Additional descriptions of these children have been published previously (17-19).

Body composition assessment

The session started with an assessment of height to the nearest cm using a stadiometer. Then, body weight, volume and composition were assessed by means of the Pediatric Option of Bod Pod (Body Composition System, COSMED, Concord, CA, USA) using software 5.2.0 as

previously described (16) and based on the Lohman body composition model (20). The volume of the child was always measured in triplicate according to the manufacturer's instructions. Fat mass index, body mass index (BMI) and fat-free mass index were calculated as fat mass (kg), body weight (kg) and fat-free mass (kg), respectively, each divided by length/height (m^2).

Statistics

Values given are means and standard deviations. Groups were compared using analysis of covariance, with age (days) at measurement as a covariate, followed by Tukey's test for post hoc analyses. Linear regression analysis was used to calculate regression coefficients (slopes) and correlation coefficients (r). Multiple regression analysis was used to calculate partial r . Significance was accepted when $p < 0.05$. Statistical analysis was performed using Statistica software 10 (StatSoft Inc., Tulsa, OK, USA).

Ethics

The study was approved by the ethics committee in Linköping (2012/235-31, 2013/298-32). Informed consent was always obtained from one parent and, in most cases, from both parents.

RESULTS

The prematurely born boys and girls are described in Table 1. Gestational age at birth (days) correlated significantly ($p < 0.000001$) with birthweight (g) in boys ($r^2 = 0.667$) and in girls ($r^2 = 0.747$) and with length at birth (cm) in boys ($r^2 = 0.713$) and in girls ($r^2 = 0.712$).

Prematurely born children were divided into late preterm (born after 224 days of gestation) and early preterm (born before 224 days of gestation). Table 2 shows the results obtained when these two groups were compared to each other and to controls born full-term. In

general, prematurely born four-year-olds tended to be lighter and shorter and to contain less fat mass and fat-free mass than did full-term controls. Values for early preterm children were, in most cases, slightly lower than those for late preterm children. However, in boys, early preterm values for fat-free mass and fat-free mass index were not lower than late preterm values for those variables.

Table 3 shows the results obtained when size and body composition variables assessed at four years of age were regressed on gestational age at birth in prematurely born children. In girls, most of the size and body composition variables investigated correlated positively and significantly with gestational age at birth. However, all these relationships were relatively weak, with r^2 -values indicating that only 5 to 12% of the variations in height, weight, BMI, fat mass, fat mass index and fat-free mass were explained by variations in gestational age at birth. As also shown in Table 3, none of the investigated correlations were significant in boys. No significant correlation between fat-free mass index and gestational age at birth was found in boys or girls.

DISCUSSION

The z scores at birth of our prematurely born children tended to be quite low. A possible explanation is that reference data by Niklasson and Albertsson-Wikland (22) were used. This reference is based on Swedish children but includes only singleton infants born to healthy mothers. Our group included triplets and twins, and we did not exclude children whose mothers suffered from hypertension or infections at the time of delivery. These conditions are often associated with premature birth (23), and hypertension during pregnancy is associated with intrauterine growth impairment (24). We consider that not excluding children of mothers with

such conditions has made our group of children more representative of contemporary prematurely born four-year-olds.

Fewtrell et al. (15) pointed out that prematurely born children are known to remain lighter and shorter throughout childhood and adolescence. Our results are consistent with this statement but inconsistent with the results of Stigson et al. (13), who found increased body fatness in prematurely born four-year-olds. These authors used dual-energy X-ray absorptiometry to assess body composition, while we used air displacement plethysmography. Both of these methods are accurate at the group level (16,25). However, Bland and Altman (26) evaluations versus a four-component reference method demonstrated that dual-energy X-ray absorptiometry may be less accurate (25) than air displacement plethysmography (16) at the individual level. Therefore, we believe that there is a risk that dual-energy X-ray absorptiometry may produce misleading results, and this risk increases in a small study. Stigson et al. (13) studied 26 children while our study included 188 children.

Our data suggest a possible sex difference regarding the effect of gestational age at birth on size and body composition variables of prematurely born four-year-olds. Thus, we observed significant relationships between gestational age at birth and most such variables in girls, while these relationships were not significant in boys. This may indicate that the last weeks of pregnancy affect the fetal development of boys and girls differently. However, it is also possible that these weeks affect both sexes in a similar way but that boys have a capacity to compensate, after birth, for adverse effects on growth and body composition development occurring during this part of pregnancy.

Our results are in agreement with those by Huke et al. (14) and by Fewtrell et al. (15) and lend no support to the statement that prematurity is associated with an increased percentage of body fat in childhood, which would represent a risk factor for overweight and obesity. Nevertheless, this area deserves further studies. For example, Pringle et al. (27) reported that being born preterm was one factor associated with an increased obesity risk. Furthermore, we want to point out that the relationship between prematurity and chronic disease is complex and therefore it may still be relevant to consider early body composition development in prematurely born children. For example, prematurely born infants may certainly develop overweight and obesity later in childhood, and such children may possibly be more sensitive to a high body fat content than children born full-term. This possibility should be kept in mind because published evidence show that prematurity is associated with chronic disease later in life.

Strengths of this study were that we studied prematurely born children with a known and considerable variation in gestational age at birth using a valid body composition method. Limitations were that the children were recruited from southeastern Sweden only, we did not assess their body composition in infancy, and we did not investigate their energy intake or physical activity.

CONCLUSION

The body fat content of prematurely born Swedish four-year-old boys and girls was not higher than that of full-term controls. The gestational age at birth of these prematurely born children correlated positively with height, weight, BMI fat mass (kg, %), fat mass index and fat-free mass in girls but not in boys. Our findings are relevant in relation to published results showing that premature birth is associated with chronic disease later in life.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Table 1 Description of prematurely born girls and boys in the study. Values are means $\pm$ standard deviations.

At birth	Girls (n=90)	Boys (n=98)
- Gestational age (days)	222 $\pm$ 24 [*]	230 $\pm$ 22 ⁺
- Weight (g)	1710 $\pm$ 640	2053 $\pm$ 656
- Weight z score	-0.93 $\pm$ 1.42	-0.65 $\pm$ 1.36
- Length (cm)	41 $\pm$ 5	44 $\pm$ 5
- Length z score	-1.02 $\pm$ 2.01	-0.54 $\pm$ 1.69
At four years of age		
- Age at measurement (days)	1621 $\pm$ 22	1621 $\pm$ 20
- Weight (kg)	16.6 $\pm$ 2.5	17.7 $\pm$ 2.1
- Height (cm)	105 $\pm$ 5	107 $\pm$ 4
- Body mass index (kg/m ²)	15.1 $\pm$ 1.4 [‡]	15.6 $\pm$ 1.3 [§]
- Fat mass (kg)	4.5 $\pm$ 1.5	4.4 $\pm$ 1.1
- Fat mass (%)	26.5 $\pm$ 6.1	24.7 $\pm$ 4.3
- Fat mass index (kg/m ²)	4.06 $\pm$ 1.19	3.88 $\pm$ 0.88
- Fat-free mass (kg)	12.1 $\pm$ 1.5	13.3 $\pm$ 1.4
- Fat-free mass index (kg/m ²)	11.0 $\pm$ 0.8	11.7 $\pm$ 0.9

^{*}Range: 171-257 days; ⁺ range: 163-258 days; [‡] five girls were overweight and one was obese (21); [§] six boys were overweight and one was obese (21)

Table 2 Size and body composition variables of full-term and preterm girls and boys at four years of age. Prematurely born children were divided into late preterm (born after > 224 days of gestation) and early preterm (born after < 224 days of gestation). Values are means $\pm$ standard deviations*.

	G i r l s			B o y s		
	Full-term	Late preterm	Early preterm	Full-term	Late preterm	Early preterm
	(n=116)	(n=49)	(n=41)	(n=137)	(n=66)	(n=32)
Weight (kg)	17.9 $\pm$ 2.0 ⁺	17.1 $\pm$ 2.5	16.0 $\pm$ 2.2	18.7 $\pm$ 2.3 [‡]	17.8 $\pm$ 2.2	17.5 $\pm$ 1.8 [§]
Height (cm)	107 $\pm$ 4 ^{+\$}	105 $\pm$ 6	104 $\pm$ 4	109 $\pm$ 4 ⁺	107 $\pm$ 4	106 $\pm$ 3 [§]
Body mass index (kg/m ²)	15.6 $\pm$ 1.2 [‡]	15.4 $\pm$ 1.3	14.8 $\pm$ 1.4	15.8 $\pm$ 1.3	15.6 $\pm$ 1.4	15.6 $\pm$ 1.1
Fat mass (kg)	5.0 $\pm$ 1.1 ⁺	4.8 $\pm$ 1.5	4.1 $\pm$ 1.4 [§]	4.7 $\pm$ 1.0 [‡]	4.5 $\pm$ 1.2	4.2 $\pm$ 0.8
Fat mass (%)	27.7 $\pm$ 4.5 [‡]	27.6 $\pm$ 5.7	25.3 $\pm$ 6.5	25.1 $\pm$ 4.1	25.3 $\pm$ 4.6	23.7 $\pm$ 3.5
Fat mass index (kg/m ²)	4.33 $\pm$ 0.87 [‡]	4.29 $\pm$ 1.16 [‡]	3.78 $\pm$ 1.17	3.98 $\pm$ 0.80	3.96 $\pm$ 0.96	3.71 $\pm$ 0.67
Fat-free mass (kg)	12.9 $\pm$ 1.6 ^{+\$}	12.3 $\pm$ 1.6	11.9 $\pm$ 1.4	14.0 $\pm$ 1.9 [§]	13.3 $\pm$ 1.5	13.4 $\pm$ 1.4

Continued

Table 2, continued

Fat-free mass index (kg/m ²)	11.2 ± 0.9	11.1 ± 0.8	11.0 ± 0.9	11.8 ± 1.0	11.6 ± 0.9	11.9 ± 0.9
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* Groups were compared using analysis of covariance, with age (days) at measurement as a covariate, followed by Tukey's test for post hoc analyses.

⁺ Significantly different from the corresponding value for early preterm children of the same sex (p<0.001)

[‡] Significantly different from the corresponding value for early preterm children of the same sex (p<0.05)

[§] Significantly different from the corresponding value for late preterm children of the same sex (p<0.05)

Table 3 Size and body composition variables, assessed at four years of age, regressed on gestational age at birth in prematurely born boys and girls. The table shows regression coefficients (slope*) and r^2 -values based on partial correlation coefficients (r^+).

Dependent variable	Girls (n=90)		Boys (n=98)	
	Slope	r^2 (p value)	Slope	r^2 (p value)
Height (cm)	0.0502	0.065 (0.016)	0.0261	0.019 (>0.05)
Weight (kg)	0.0331	0.117 (0.001)	0.0060	0.005 (>0.05)
Body mass index (kg/m ²)	0.0155	0.083 (0.006)	-0.0026	0.001 (>0.05)
Fat mass (kg)	0.0177	0.089 (0.004)	0.0060	0.018 (>0.05)
Fat mass (%)	0.0574	0.051 (0.033)	0.0244	0.020 (>0.05)
Fat mass index (kg/m ²)	0.0122	0.064 (0.017)	0.0033	0.010 (>0.05)
Fat-free mass (kg)	0.0155	0.074 (0.010)	-0.0001	0.000 (>0.05)
Fat-free mass index (kg/m ²)	0.0033	0.012 (>0.05)	-0.0059	0.019 (>0.05)

Continued

Table 3, continued

* Calculated as the dependent variable divided by gestational age at birth (days)

⁺ Partial correlation coefficients adjusted for age (days) at measurement.

APPENDIX S1

The body composition study group

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