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ORIGINAL ARTICLE

Impact of size at birth and prematurity on adult anthropometry in 4744 middle-aged Danes – The Inter99 study

K. Pilgaard[1]*, K. Færch[1], P. Poulsen[1,2], C. Larsen[1], E.A. Andersson[1], C. Pisinger[4], U. Toft[4], M. Aadahl[4], O. Pedersen[3,5,7], T. Hansen[3,6], K. Borch-Johnsen[1], A. Vaag[1] and T. Jørgensen[4,5]

[1]*Steno Diabetes Center, Gentofte, Denmark*
[2]*Novo Nordisk, Bagsværd, Denmark*
[3]*Hagedorn Research Institute, Gentofte, Denmark*
[4]*Research Center for Prevention and Health, Glostrup Hospital, Glostrup, Denmark*
[5]*Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark*
[6]*Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark*
[7]*Faculty of Health Sciences, University of Aarhus, Aarhus, Denmark*

Low birth weight is related to increased risk of developing cardiovascular disease and type 2 diabetes in adult life. Since obesity is closely associated with type 2 diabetes and cardiovascular disease, the relationship between size at birth and adult anthropometry is of interest as a mediator of the relationship between birth weight and metabolic diseases. The aim of this study was, therefore, to examine the effect of size at birth and prematurity on measures of adult anthropometry taking adult socio-economic status and lifestyle variables into account. Midwife records with information on mother's age and parity as well as weight, length and maturity at birth were traced in 4744 Danes born between 1939 and 1970. Measures of adult anthropometry (weight, height, body mass index (BMI), waist circumference, hip circumference and waist/hip ratio) had previously been recorded together with information on socio-economic factors, lifestyle and parental diabetes status. Mother's age, parity and diabetes status were associated with offspring birth weight. Size at birth was positively associated with adult height and weight, but only weakly associated with BMI and not associated with waist/hip ratio when adjusted for socio-economic and lifestyle factors. Infants born preterm were less growth restricted at birth and grew to be taller and heavier compared with term infants born small for gestational age. Altogether, this study does not find evidence that obesity or a central fat distribution is mediating the relationship between low birth weight and risk of cardiovascular disease or type 2 diabetes in later life.

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Key words: birth weight, BMI, preterm, waist circumference

Introduction

Extensive research has substantiated a link between low birth weight and risk of hypertension,[1] ischemic heart disease[2] and type 2 diabetes[3] in later life. Overweight and especially abdominal obesity are also strongly related to these disorders,[4,5] and it is therefore of interest to explore a possible mediating effect of adult body size in the relationship between size at birth and risk of adult metabolic diseases.

Low birth weight is an indicator of sub-optimal conditions *in utero*. According to the fetal origin hypothesis, adverse events occurring *in utero* at critical periods may change the physiology and structure of multiple organs.[6,7] Experimental studies have reported changes in the hypothalamic–pituitary–adrenal axis as well as in skeletal muscle and adipose tissue morphology and distribution related to low birth weight.[8–10] Moreover, an epidemiological study in men and women born around the Dutch hunger winter of 1944–1945 reported that 50-year-old offspring of women exposed to famine during the first trimester of pregnancy had higher body mass index (BMI) and waist circumference as compared with a control cohort of offspring of unexposed women.[11] However, large-scale studies have reported a positive association between birth weight and BMI among young Swedish military conscripts[12] and middle-aged men born in Finland,[13] questioning the relationship between intrauterine growth restriction and obesity in adult life.

When assessing the influence of birth weight on size in adulthood, confounding variables such as socio-economic status, parental diabetes status and lifestyle factors should be accounted for. Low birth weight is more frequent in offspring of women with lower socio-economic status, and the prevalence of obesity decreases with increasing socio-economic status.[14] Maternal type 2 diabetes is related to fetal hyperinsulinemia and macrosomia, while paternal diabetes is associated with a reduction in fetal growth presumably mediated through gene variants affecting the beta-cell function

*Address for correspondence: K. Pilgaard, Steno Diabetes Center, Kasper Niels Steensens Vej 1, Gentofte 2820, Denmark.
(Email kapg@steno.dk)

already in fetal life. Furthermore, prevention and treatment studies have provided a well-established relationship between lifestyle factors and obesity.[15]

Information on size at birth has been based on self-reports in a number of studies[16–20] aimed at describing the impact of birth size on the risk of obesity, type 2 diabetes or cardiovascular disease. Limits of agreement between self-reported and registered-based birth weights have been in the range of ±1 kg, which may not be clinically or scientifically acceptable when attempting to determine later health consequences.[16]

This study represents an extension to the population-based intervention study on ischemic heart disease and type 2 diabetes, the Inter99 study, comprising 6784 Danes[21] born during 1939–1970. Original midwife records including detailed birth related information have been traced for 4744 of these subjects in order to study the relationship between size at birth and size in adulthood taking prematurity, parental diabetes status, socio-economic factors and lifestyle variables into account.

Method

Study design

The Inter99 study is a Danish population-based, non-pharmacological intervention study aimed at reducing the incidence of ischemic heart disease and type 2 diabetes. The study design has previously been described in detail.[21] The study population comprised 61,301 individuals living in the former Copenhagen County. An age- and sex-stratified random sample of 13,016 individuals were invited, of whom 6784 (52%) participated. Participants were born in 1939–1940, 1944–1945, 1949–1950, 1954–1955, 1959–1960, 1964–1965 and 1969–1970 and living in the Region of Copenhagen, Denmark. The study was performed at the Research Centre for Prevention and Health, Glostrup University Hospital, Glostrup. All participants gave written informed consent before taking part in the Inter99 study. The protocol was in accordance with the Helsinki Declaration, approved by the local ethics committee (KA 98 155) and registered with ClinicalTrials.gov (NCT00289237).

Midwife records

Of the 6784 participants included in the Inter99 study 6235 were born in Denmark and 6191 had a known and valid postal address in the year 2007. Information on the mother's birth date and maiden and marital names was gathered from each participant. Midwife records were identified through the Danish State Archives in 95% of the 4982 participants providing written consent ($n = 4755$). In addition, eight participants provided a copy of their original birth records. Nineteen midwife records were excluded due to either missing information on both birth weight and birth length or due to difficulties in reading the handwriting of the midwife. Altogether, valid birth data on 4744 Danish born citizens were obtained. We performed a comparison between Inter99 participants with traced *v.* not traced midwife records to investigate a possible selection bias.

From the majority of midwife records, information on the mother's age, parity and marital status was provided along with information on the infant regarding the date and time of birth, gender, birth weight and length. Deliveries were considered at term when gestation attained 36 completed weeks and did not exceed 41 completed weeks. Multiple pregnancies ($n = 85$) were excluded from analysis due to the different intrauterine circumstances characterizing multiple pregnancies compared with singletons.[22] Among the 446 cases of singleton preterm births, birth weight and BMI were available in 444 cases, an estimate of gestational age, listed in weeks, was noted in 363 midwife records. The expected day of delivery was based on the first day of the last menstrual period. A number of comparison studies have reported that the presently routine dating, based on an early second-trimester ultrasound examination, is superior to dating based on the last menstrual period in predicting the actual date of delivery, although the real difference is small.[23] Preterm birth was a clinical assessment by the midwife based on the due date together with clinical signs of prematurity.

Health examination and questionnaire

All participants underwent a physical health examination. Height was measured to the nearest centimeter and weight to the nearest 0.1 kg with the participants wearing indoor clothes and no shoes. Waist circumference was measured halfway between the lowest point of the costal margin and highest point of the iliac crest, and hip circumference was measured at the level of the greater femoral trochanter; both were measured to the nearest 0.5 cm with an unstretched tape meter without pressure to the body surface.

Participants completed a self-administered questionnaire on health, socio-economic factors and lifestyle. Maternal and paternal diabetes status (yes, no, unknown) was provided by the participants as part of the questionnaire. A four-class variable of socio-economic status was developed from information on education and work affiliation. Lifestyle comprised assessment of physical activity, diet and alcohol consumption. An estimate of total physical activity was assessed by summing up self-reported time of commuting physical activity and leisure time physical activity. Total physical activity was grouped into four categories: 0–2; 2–4; 4–7; 7–12 h/week.[24] An index of the overall quality of dietary intake was obtained from a validated diet quality score developed using a 48-item food frequency questionnaire.[25] Smoking status was grouped into four categories: daily smoking, occasional smoking, previous smoking and never smoking. Finally, risk of ischemic heart disease was assessed in each individual based on a multifactorial algorithm, the Copenhagen Risk Score.[26]

Size at birth

Birth weight was measured on a stationary scale (birth clinics) or with a steelyard (home delivery) and birth length was

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measured to the nearest 0.5 cm. Ponderal index was calculated as birth weight/birth length^3 (kg/m^3). Low birth weight is commonly defined as the 10th percentile of birth weight for gestational age. Likewise, high birth weight has been set at the 90th percentile of birth weight for gestational age. In a 2003 consensus statement, low birth weight was defined as -2 standard deviations of the mean birth weight for gestational age.[27] We used both definitions of low birth weight in the current study. Participants were divided into six birth weight categories (<2500; 2500–2999; 3000–3499; 3500–3999; 4000–4500; >4500 g) to illustrate trends across the birth weight spectrum. Impact of prematurity *per se* on adult anthropometry was investigated in comparison with a group of term singletons matched for birth weight referred to as small for gestational age (SGA). The SGA participants were selected in a forward manner beginning with the lowest birth weight until the average birth weight was identical to the mean birth weight of the preterm participants. The group of SGA participants had a mean birth weight of 2556 ± 152 g equivalent to 2.08 standard deviations below the mean of the complete study population born at term. Within the group of participants born preterm, the impact of gestational age on adult anthropometry was assessed after adjustment for birth weight S.D. scores (*Z*-scores) for gestational age.

Statistics

The comparison between participants with traced *v.* not-traced midwife records was analyzed by unpaired two-tailed *t*-tests. Linear regression models were used to study the effects of maternal age and parity as well as parental diabetes status on birth weight. The impact of size at birth on adult anthropometry was assessed by linear regression analysis and the effect sizes are provided in changes per 1 S.D. increase in birth weight (523 g), birth length (2.26 cm) or ponderal index (2.35 kg/m^3). We adjusted for confounding variables in four different steps. Model 1 was adjusted for age and sex ($n = 4652$). Model 2 was further adjusted for prematurity, maternal parity and parental diabetes status ($n = 4652$). Model 3 was additionally adjusted for socio-economic status and 'living with partner' ($n = 4314$). Model 4 was further adjusted for lifestyle factors (physical activity, diet, alcohol consumption and smoking; $n = 3973$). The analyses of the relationships between size at birth and waist circumference, hip circumference and waist/hip ratio were additionally adjusted for adult BMI. Tests for linearity between size at birth and size at adulthood were performed in both men and women by adding the explanatory variable of interest as a squared term and as a cubed term. Despite a relatively large number of statistical comparisons being performed, we did not use correction for multiple testing, because the majority of the tests were predefined.

In the questionnaire, a number of participants were unaware of parental diabetes status ($n = 794$) or did not answer the question ($n = 507$). Missing or 'unknown' information on parental diabetes was treated as 'no diabetes'.

In models 3 and 4, we allowed for a gradual decrease in participants due to incomplete information on socio-economic status and lifestyle variables. In comparison, supplementary analyses of the association between birth weight and adult anthropometry were performed both in the large subgroup of complete cases and following simple imputation of missing values within socio-economic factors and lifestyle variables (supplementary material).

SAS version 9.1 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

Results

In the six birth weight categories, the range of mean age was 45.4–47.7 and of mean BMI 25.5 kg/m^2 to 27.3 kg/m^2 (Table 1). There was a larger proportion of girls in the lower birth weight categories, and conversely, there were more boys in the upper birth weight categories. This was also reflected by a lower mean birth weight of girls compared with boys (3430 ± 433 g *v.* 3554 ± 461 g; $P < 0.001$).

Midwife records were traced in 70% of the 6784 participants of the original Inter99 study. Participants with traceable midwife records were slightly leaner, more physically active, less likely to smoke on a daily basis and more likely to have an education compared with participants without traceable midwife records (Table 2). While there were no differences with respect to blood pressure, participants with traceable midwife records had a lower prevalence of type 2 diabetes and lower risk of ischemic heart disease assessed by the Copenhagen Risk Score.[26]

Both birth weight and birth length were positively associated with weight and height and BMI in adulthood (Table 3). An increase in birth weight of 1 kg was associated with a 0.47 kg/m^2 higher BMI in adulthood ($P = 0.003$) in the fully adjusted model. The odds ratio of being overweight in adulthood, reflected by a BMI above 25 kg/m^2, was 1.77 (95% CI: 1.15; 2.74) in participants born at term with a birth weight $\geqslant$90th percentile compared with participants with a birth weight $\leqslant$ 10th percentile in the fully adjusted model. Birth weight and length were both related to the adult waist and hip circumference but neither one was associated with the waist/hip ratio. Ponderal index, indicating thinness at birth, was related to adult weight after correction for age and sex. However, the association was no longer statistically significant after adjusting for parental diabetes, socio-economic factors and lifestyle variables. Furthermore, the ponderal index was inversely related to the waist circumference and hip circumference but not to the waist/hip ratio.

Neither complete case analyses nor analyses with simple imputation of missing socio-economic and lifestyle variables changed the reported associations between size at birth and measures of adult anthropometry (Supplementary material, Table 1).

Table 4 provides a schematic overview of mean birth weight according to gestational age and commonly used

Table 1. *Baseline characteristics of birth weight categories*

	Category of birth weight					
	<2500 g	2500–2999 g	3000–3499 g	3500–3999 g	4000–4500 g	>4500 g
Infant						
n (men/women)	57/111	264/437	704/938	756/750	302/244	68/28
Birth weight (g)						
Boys	2110 ± 313	2767 ± 141	3278 ± 140	3678 ± 143	4149 ± 138	4685 ± 200
Girls	2124 ± 310	2767 ± 135	3214 ± 142	3670 ± 140	4128 ± 134	4654 ± 188
Birth length (cm)						
Boys	46.3 ± 3.1	49.5 ± 1.3	51.4 ± 1.4	52.8 ± 1.4	54.1 ± 1.5	55.3 ± 1.8
Girls	46.3 ± 2.8	49.4 ± 1.2	51.1 ± 1.3	52.4 ± 1.3	53.7 ± 1.5	54.5 ± 1.7
Ponderal index (kg/m^3)						
Boys	21.5 ± 3.1	22.8 ± 1.7	23.9 ± 1.9	25.0 ± 1.9	26.3 ± 2.2	27.8 ± 2.8
Girls	21.5 ± 2.5	23.0 ± 1.7	24.2 ± 1.8	25.6 ± 1.9	26.7 ± 2.1	28.9 ± 2.9
Birth order	0.9 ± 1.2	0.9 ± 1.2	1.0 ± 1.3	1.3 ± 1.4	1.6 ± 1.4	2.0 ± 1.8
Maternal age at delivery	26.6 ± 5.8	26.4 ± 5.8	26.5 ± 5.6	27.6 ± 5.7	28.6 ± 5.5	29.6 ± 5.2
Maternal history of diabetes (%)	7.2	5.3	6.6	8.0	9.7	15.6
Paternal history of diabetes (%)	12.2	7.9	9.6	8.3	8.2	7.6
Adult						
Age	45.4 ± 7.9	45.5 ± 7.7	45.9 ± 7.8	46.8 ± 8.0	47.4 ± 7.8	47.7 ± 7.1
Weight (kg)						
Boys	81.4 ± 11.7	82.7 ± 13.5	84.3 ± 13.5	86.2 ± 12.8	89.7 ± 15.7	91.3 ± 13.9
Girls	68.2 ± 13.1	68.9 ± 13.4	69.8 ± 13.9	72.2 ± 15.3	74.2 ± 15.8	77.3 ± 19.7
Height (cm)						
Boys	176.8 ± 6.5	177.0 ± 6.6	178.2 ± 6.6	179.5 ± 6.6	181.7 ± 6.7	183.1 ± 7.1
Girls	162.8 ± 6.9	164.5 ± 6.2	165.5 ± 6.0	167.3 ± 6.1	168.2 ± 5.8	167.9 ± 4.9
Body mass index (kg/m^2)						
Boys	26.0 ± 3.6	26.4 ± 3.9	26.5 ± 3.9	26.7 ± 3.6	27.2 ± 4.7	27.2 ± 3.8
Girls	25.8 ± 5.2	25.5 ± 4.8	25.5 ± 4.9	25.8 ± 5.0	26.2 ± 5.6	27.3 ± 6.4
Waist circumference (cm)						
Boys	90.2 ± 10.5	91.4 ± 10.3	92.5 ± 11.1	93.1 ± 10.1	95.0 ± 12.0	95.8 ± 10.9
Girls	79.8 ± 11.7	79.5 ± 12.0	79.3 ± 11.8	80.6 ± 12.2	82.0 ± 13.3	81.9 ± 13.8
Hip circumference (cm)						
Boys	99.1 ± 7.5	100.1 ± 8.0	101.0 ± 7.9	101.7 ± 7.3	103.2 ± 8.5	103.4 ± 7.6
Girls	99.2 ± 11.4	99.6 ± 10.1	99.1 ± 10.9	101.2 ± 11.2	102.2 ± 12.2	104.9 ± 17.5
Waist/hip ratio						
Boys	0.91 ± 0.08	0.91 ± 0.06	0.91 ± 0.07	0.91 ± 0.06	0.92 ± 0.07	0.93 ± 0.06
Girls	0.80 ± 0.06	0.80 ± 0.06	0.79 ± 0.06	0.80 ± 0.06	0.80 ± 0.06	0.78 ± 0.06
SES/lifestyle						
High socio-economic status (%)	75.2	76.4	78.2	79.7	79.3	73.6
Living with partner (%)	80.5	80.6	84.7	84.6	83.6	91.5
Physical active (>112.5 min/week) (%)	86.3	87.2	89.6	90.1	86.9	87.1
Diet (healthy) (%)	10.4	12.7	14.8	15.0	12.1	12.9
Alcohol (≤recommendations) (%)	84.8	87.1	84.8	83.1	84.6	83.3
Smoking (occasionally/every day) (%)	44.6	38.3	36.5	37.4	35.6	36.5

Unadjusted means ± S.D. Singleton ($n = 4659$). High socio-economic status was defined as at least 1 year of education together with a present work affiliation. Official alcohol recommendations were below 14 units/week for women and 21 units/week for men.

definitions of low and high birth weight. The prevalence of low birth weight defined as below 2500 g was 0.4% in boys and 0.7% in girls born at term.

Maternal diabetes of unknown origin ($n = 328$) was associated with an increase in birth weight of 119 g (95% CI: 58; 179 g; $P < 0.001$), while paternal diabetes status ($n = 369$) was non-significantly associated with a birth weight reduction of −36 g (95% CI: −89; 16 g; $P = 0.17$) in participants born at term and accounting for the diabetes status of the spouse. While marital status of the mother had no significant impact on birth weight of the offspring, an increase in maternal age of 1 year corresponded to an increase in birth weight of 4.3 g

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Table 2. *Baseline characteristics of Inter99 participants born in Denmark*

	Women			Men		
	Traced ($n = 2558$)	Not traced ($n = 659$)	*P*-value	Traced ($n = 2186$)	Not traced ($n = 832$)	*P*-value
Age (years)	45.8 ± 7.9	45.7 ± 8.3	0.784	46.8 ± 7.7	46.1 ± 8.1	0.025
Height (cm)	166.0 ± 6.2	165.9 ± 6.3	0.633	179.1 ± 6.8	178.6 ± 6.68	0.047
Weight (kg)	70.8 ± 14.3	72.7 ± 16.1	0.005	85.6 ± 13.7	86.9 ± 15.2	0.032
BMI (kg/m^2)	25.7 ± 5.0	26.4 ± 5.5	0.002	26.7 ± 3.9	27.2 ± 4.4	0.001
Waist circumference (cm)	80.1 ± 12.2	81.9 ± 13.3	0.002	93.0 ± 10.8	94.3 ± 11.8	0.005
Hip circumference (cm)	100.5 ± 11.2	101.4 ± 12.3	0.078	101.5 ± 7.8	101.8 ± 8.7	0.378
Systolic BP (mmHg)	125.4 ± 15.9	125.9 ± 17.6	0.480	132.2 ± 15.1	132.5 ± 15.0	0.639
Diastolic BP (mmHg)	79.0 ± 10.3	79.4 ± 11.1	0.417	83.7 ± 10.3	84.3 ± 10.2	0.109
High socio-economic status (%)	77.8	71.6	<0.001	82.1	78.0	0.011
Living with partner (%)	81.1	78.1	0.090	86.7	78.7	<0.001
Physical activity (>112.5 min/week) (%)	90.3	88.2	0.100	88.2	86.2	0.090
Diet (healthy) (%)	19.6	22.0	0.170	12.5	13.3	0.553
Alcohol (⩽recommendations) (%)	84.8	80.1	0.004	79.3	73.1	<0.001
Smoking (occasionally/every day) (%)	36.9	44.5	<0.001	37.6	46.6	<0.001
Type 2 diabetes (%)	3.7	8.0	<0.001	6.5	8.8	0.030
Low risk of IHD (%)	83.0	73.8	<0.001	84.1	78.1	<0.001

BMI, body mass index; BP, blood pressure; IHD, ischemic heart disease.

Comparison between Inter99 participants with traceable *v.* non-traceable midwife records. Risk of ischemic heart disease was estimated according to the Copenhagen Risk Score.

(95% CI: 1.6; 7.1 g; $P < 0.001$). Newborns of nulliparous women were significantly lighter and shorter compared with infants born by uni- or multiparous women. Mean birth weight increased by 62 g (95% CI 51; 72g; $P_{trend} < 0.001$) per pregnancy after adjustment for sex and parental diabetes status.

While 11.3% of girls were born preterm, the corresponding number for boys was 7.3% ($P < 0.001$). Nulliparous women had an increased risk of preterm delivery compared to uni- or multiparous women (<0.001). Maternal age, marital status and parental diabetes status did not affect the risk of preterm delivery. Maternal age and parity were closely associated, but restricting the analysis to nulliparous women and hereby omitting the influence of previous pregnancies did not alter the non-existing relationship between maternal age and risk of preterm delivery (data not shown).

Infants born preterm were shorter at birth and had a higher ponderal index suggestive of less growth restriction and a more proportional growth compared with term infants matched for birth weight (Table 5). In adult life, preterm infants were heavier and taller than term infants with a comparable low birth weight, while no differences in BMI or waist/hip ratio were observed. Among the participants born preterm, birth weight *z*-score was associated with adult height (β: 0.60 (95% CI: 0.06; 1.15; $P = 0.029$)) but not with other measures of anthropometry in adult life. Gestational age showed a minor but significant association with the waist/hip ratio after adjustment for confounders including birth weight *z*-score and BMI: A shortening of gestational age by 1 week increased the waist/hip ratio by 0.004 cm (95% CI: 0.0003; 0.007; $P = 0.03$).

Discussion

In this study, valid birth data was collected on 4744 of the 6784 participants from the Inter99 study. Birth weight and birth length were positively associated with adult weight, height, BMI, waist and hip circumference in middle-aged Danes. Participants born preterm were less growth restricted at birth and grew to be taller and heavier than participants born SGA.

Birth weight was positively related to adult BMI in a linear manner with an odds ratio of being overweight (BMI ⩾ 25 kg/m^2) of 1.77 in participants with a high birth weight (⩾90th percentile) *v.* participants with a low birth weight (⩽10th percentile) after adjusting for confounding variables. Opposed to these findings, previous studies have reported that obesity is predicted by a low birth weight[28] or is maybe related to birth weight in a J- or U-shaped manner.[29,30]. It has been proposed that observations of a U- or J-shaped relationship between size at birth and BMI in adulthood may result from failure to control for socio-economic status, as low socio-economic status is associated both with low birth weight and adult obesity.[31] However, in our study, adjusting for socio-economic status and lifestyle did not alter the relationship between birth weight and BMI in adulthood substantially.

Table 3. *Influence of size at birth on measures of adult anthropometry*

	By 1 S.D. increase in birth weight	By 1 S.D. increase in birth length	By 1 S.D. increase in ponderal index
Weight (kg)			
Model 1	2.18 (1.77; 2.58)***	2.22 (1.81; 2.62)***	0.55 (0.15; 0.95)**
Model 2	2.47 (1.99; 2.95)***	2.43 (1.96; 2.89)***	0.37 (−0.05; 0.79)
Model 3	2.49 (1.99; 2.98)***	2.42 (1.94; 2.91)***	0.38 (−0.06; 0.82)
Model 4	2.41 (1.91; 2.91)***	2.44 (1.95; 2.93)***	0.25 (−0.19; 0.70)
Height (cm)			
Model 1	1.65 (1.47; 1.82)***	1.88 (1.71; 2.06)***	0.14 (−0.04; 0.33)
Model 2	1.87 (1.66; 2.08)***	2.08 (1.88; 2.29)***	−0.00 (−0.19; 0.19)
Model 3	1.84 (1.63; 2.06)***	2.02 (1.81; 2.23)***	0.04 (−0.16; 0.23)
Model 4	1.87 (1.64; 2.09)***	2.06 (1.84; 2.28)***	−0.00 (−0.20; 0.21)
BMI (kg/m^2)			
Model 1	0.23 (0.10; 0.36)***	0.17 (0.04; 0.30)*	0.14 (0.01; 0.27)*
Model 2	0.27 (0.11; 0.42)***	0.19 (0.03; 0.34)*	0.13 (−0.01; 0.26)
Model 3	0.28 (0.12; 0.44)***	0.20 (0.04; 0.36)*	0.12 (−0.02; 0.26)
Model 4	0.24 (0.09; 0.40)**	0.20 (0.04; 0.35)*	0.09 (−0.05; 0.23)
Waist circumference (cm)			
Model 1	0.33 (0.18; 0.48)***	0.55 (0.40; 0.70)***	−0.21 (−0.36; −0.06)**
Model 2	0.39 (0.20; 0.57)***	0.66 (0.49; 0.84)***	−0.26 (−0.41; −0.10)**
Model 3	0.39 (0.20; 0.58)***	0.65 (0.47; 0.84)***	−0.25 (−0.41; −0.08)**
Model 4	0.41 (0.22; 0.61)***	0.70 (0.51; 0.90)***	−0.27 (−0.43; −0.10)**
Hip circumference (cm)			
Model 1	0.54 (0.40; 0.68)***	0.76 (0.62; 0.90)***	−0.10 (−0.24; 0.04)
Model 2	0.55 (0.38; 0.72)***	0.81 (0.64; 0.98)***	−0.18 (−0.33; −0.03)*
Model 3	0.54 (0.36; 0.72)***	0.77 (0.60; 0.95)***	−0.16 (−0.32; −0.00)*
Model 4	0.54 (0.36; 0.73)***	0.79 (0.61; 0.97)***	−0.18 (−0.34; −0.02)*
Waist : hip ratio			
Model 1	−0.001 (−0.003; 0.000)	−0.001 (−0.003; 0.001)	−0.001 (−0.003; 0.000)
Model 2	−0.001 (−0.003; 0.001)	−0.000 (−0.002; 0.002)	−0.001 (−0.003; 0.001)
Model 3	−0.000 (−0.003; 0.001)	−0.000 (−0.002; 0.002)	−0.001 (−0.003; 0.001)
Model 4	−0.001 (−0.003; 0.001)	0.000 (−0.002; 0.002)	−0.001 (−0.003; 0.001)

BMI, body mass index.

Mean change in variables per 1 S.D. change in birth weight, birth length or ponderal index (95% CI). 1 S.D. in birth weight was 523 g. 1 S.D. in birth length was 2.26 cm. 1 S.D. in ponderal index was 2.35 kg/m^3. Model 1: adjusted for age and sex ($n = 4652$). Model 2 was further adjusted for prematurity, maternal parity and parental diabetes status ($n = 4652$). Model 3 was additionally adjusted for socio-economic status and 'living with partner' ($n = 4314$). Model 4 was further adjusted for lifestyle factors (physical activity, diet, alcohol consumption and smoking; $n = 3973$). The analysis of the relationship between size at birth and waist circumference, hip circumference and waist : hip ratio were additionally adjusted for current BMI.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

An additional part of the diversity in the literature may arise from an age-dependent effect of birth size on size in adult life. In a study of young and elderly monozygotic twins, birth weight was found to be associated with multiple anthropometric measures in young twins, but only with height in elderly twins. This could indicate an environmental effect on body size, which in time dilutes the importance of birth weight on body composition.[32]

It has been suggested that waist circumference may be the best obesity-related predictor of type 2 diabetes.[33] Waist circumference is related to intra-abdominal fat mass,[34] and waist/hip ratio can be used as a measure of the distribution between intra-abdominal and peripheral fat mass. We observed a positive relationship between size at birth and waist circumference, indicating that infants born large are prone to abdominal fat accumulation. However, we also found a positive relationship between birth weight and hip circumference, and no relationship between size at birth and waist/hip ratio after adjustment for BMI. This indicates that individuals born with a high birth weight do not have a higher proportion of intra-abdominal to peripheral fat for a given degree of obesity. A number of smaller studies have reported an inverse relationship between birth weight and waist/hip ratio after adjustment for current BMI,[28,35] and one study reported a positive association between birth weight and waist/hip ratio in a subgroup of male offspring of parents with diabetes.[36] We have previously in a cohort of young healthy men found low birth weight to be associated with central fat accumulation as assessed by Dual energy X-ray

Table 4. *Size at birth stratified by percentile, standard deviations and gestational age*

	Boys		Girls	
	Birth weight (g)	Birth length (cm)	Birth weight (g)	Birth length (cm)
Term pregnancy ($n = 1989/2224$)	3554 ± 461	52.4 ± 2.0	3430 ± 433	51.7 ± 1.8
90th percentile	4200	55	4000	54
10th percentile	3000	50	2900	50
+2 S.D. of the mean	4476	56.4	4296	55.3
−2 S.D. of the mean	2632	48.4	2564	48.1
Preterm pregnancy (weeks)				
−1 ($n = 16/20$)	2859 ± 225	49.8 ± 1.6	2938 ± 357	49.6 ± 1.2
−2 ($n = 29/62$)	2836 ± 228	49.4 ± 1.1	2748 ± 197	49.0 ± 1.3
−3 ($n = 41/70$)	2595 ± 310	48.5 ± 1.6	2650 ± 224	48.9 ± 1.5
−4 ($n = 23/33$)	2550 ± 164	48.6 ± 1.5	2410 ± 253	47.5 ± 1.7
−5 + 6 ($n = 17/29$)	2199 ± 269	46.2 ± 1.5	2195 ± 258	46.2 ± 2.0
−7 + 8 ($n = 4/10$)	1875 ± 290	42.8 ± 5.3	1820 ± 291	44.0 ± 2.9
−9 + 10 ($n = 2/2$)	1375 ± 35	40.0 ± 1.4	1825 ± 601	44.5 ± 3.5
−11 + 12 ($n = 1/4$)	1100	38.0	1325 ± 333	39.3 ± 1.9
Unknown GA ($n = 29/54$)	2550 ± 400	48.6 ± 2.0	2583 ± 442	48.3 ± 2.3

Mean ± S.D. Deliveries were considered at term when gestation attained 36 completed weeks and did not exceed 41 completed weeks. GA, gestational age.

Table 5. *Participants born preterm v. participants born at term matched for birth weight*

	Preterm	Term	*P*-value
n (Boys/girls)	444 (161/283)	146 (58/88)	
Birth weight (g)[a]	2556 ± 403	2556 ± 152	0.927
Birth length (cm)[a]	48.1 ± 2.4	48.9 ± 1.4	<0.001
Ponderal index (kg/m^3)[a]	22.8 ± 2.3	22.0 ± 1.9	<0.001
Height (cm)[b]	168.7 ± 8.9	167.8 ± 9.3	0.011
Weight (kg)[b]	73.6 ± 14.5	71.3 ± 14.6	0.045
BMI (kg/m^2)[b]	25.8 ± 4.7	25.2 ± 4.1	0.222
Waist circumference (cm)[b]	83.8 ± 12.4	82.5 ± 12.5	0.184
Hip circumference (cm)[b]	99.4 ± 10.0	98.0 ± 8.3	0.190
Waist : hip ratio[b]	0.84 ± 0.08	0.84 ± 0.09	0.399

BMI, body mass index.
Mean ± S.D. Deliveries were considered at term when gestation attained 36 completed weeks and did not exceed 41 completed weeks.
[a] Adjusted for sex, maternal parity and parental diabetes status.
[b] Adjusted for sex, maternal parity, parental diabetes status, socio-economic factors and lifestyle variables.

Absorptiometry despite similar BMI and waist/hip ratio,[8] substantiating the low sensitivity of these proxy indices of body fat distribution.

We demonstrate that height in adulthood is significantly associated with birth weight and birth length in a positive manner. Adult height is inversely associated with type 2 diabetes,[37] coronary heart disease and mortality.[38,39] It may therefore be speculated that height represents a marker or perhaps even a mediator of the association between size at birth and risk of adult disease. Alternatively, a common genotype may be responsible for reduced birth weight, lower adult height and risk of disease. Recent genome-wide association studies have identified 20 variants with influence on adult height.[40,41] One variant with effects on both height in childhood and height in adulthood is described,[42] but none have to our knowledge identified variants affecting both birth length and adult height, and none of the genetic variants for height have been associated with risk of diabetes. Furthermore, a recent study reported a non-genetic association between birth weight and adult height in young and elderly monozygotic twins.[32] Thus, current data suggest that the associations between low birth weight, short adult height and type 2 diabetes as well as cardiovascular disease may be related to non-genetic mechanisms, consistent with the idea of a developmental origin of adult disease.

The prevalence of preterm birth was in our study slightly higher than that reported by others.[43] Maturity at birth was a midwife assessment based on clinical signs of maturity as well as the expected date of delivery. The due date was calculated from the last menstrual period. This method is biased when menstruation is irregular or ovulation delayed. In comparison, the primary advantage of a modern ultrasound-based estimate of the due date is a reduction in postterm deliveries[44] and not preterm deliveries. In addition, the participants born preterm had a mean birth weight for gestational age within the expected range and a higher ponderal index compared with SGA participants. This indicates that the reported prevalence of preterm delivery is overall correct, although it does not rule out the possibility that some participants born at term with a low birth weight were misclassified as preterm deliveries.

Information on maternal smoking during pregnancy would have added important information to our data. Smoking during pregnancy is a known risk factor of fetal growth restriction[45] and associated with preterm delivery.[46] We observed the highest prevalence of smoking among participants with a birth weight below 2500 g. Owing to the high inheritance of smoking habits,[47,48] we speculate that maternal smoking during pregnancy may also account for some degree of fetal growth restriction in this study.

Detailed information on maternal parity, parental diabetes status, socio-economic status and lifestyle variables was available on the majority of participants. In general, adjusting for maternal parity and parental diabetes status strengthened the reported associations. Surprisingly, additional information on socio-economic status and lifestyle variables did not change the results.

The limitations of birth weight as a measure of fetal growth or nutritional state have been illustrated previously by Miller *et al.*[49] It was shown that infants having the same external body dimensions differ in birth weights by as much as 30–40% due to differences in soft tissue mass. The ponderal index is proposed to be a more comprehensive measure of infant body composition and nutritional status. A low ponderal index at birth, indicating thinness, is related to perinatal morbidity,[50] increased risk of type 2 diabetes[51] and systolic hypertension[52] in adult life. In the light of the close association between weight and length at birth and size in adulthood, it was somewhat surprising that the ponderal index was not strongly associated with adult anthropometry after adjustment for lifestyle factors. This was in contrast to a Swedish study of 165,109 young men in which a positive association between the ponderal index at birth and BMI at young adult age was reported.[53] One likely explanation for the diversity in findings from these two studies is a mean age difference of 28 years between the cohorts, giving rise to a relatively higher impact of environmental factors on body composition in our study of middle-aged men and women compared to the Swedish study of young men. It is noteworthy that we found an inverse relationship between the ponderal index and both the waist and hip circumference. Although the ponderal index was not related to the BMI or waist/hip ratio, these findings indicate that thinness at birth also matters in adult life.

In our comparison of participants born preterm with a matched group of term participants born small for gestational age, we found preterm deliveries to be related to a higher ponderal index, indicating a more proportional growth pattern and less intrauterine growth restriction. Participants born preterm grew to be taller and heavier in adult life compared with the SGA participants, although not reaching the average weight and height of the study population. Within the group of participants born preterm, birth weight *z*-score was exclusively related to adult height, indicating that fetal growth may have a more profound effect on bone growth compared with growth of the soft tissue.

We report a positive association between maternal age and birth weight, although it is of minor magnitude. Maternal parity, however, had a clinically significant impact on birth weight in boys and girls. In accordance with previous studies,[45,54] first born infants were significantly lighter at birth compared with children born by uni- or multiparous women. It has been suggested that the relatively stronger uterine muscles in nulliparous women may cause a physical limitation of the fetal growth compared with those in uni- and multiparous women.[55] Other factors known to affect birth weight, such as smoking, pre-pregnancy weight and weight gain during pregnancy, have also been shown to account for some – but not all – of the size differences between first born and consecutive born infants.[45,55] At this point of time, it is uncertain to what extent the lower birth weight of the first born child may confer an increased disease susceptibility in later life, but our data emphasize the importance of considering maternal parity when exploring effects of birth weights in later life.

We found maternal diabetes developed at an unknown age to be associated with increased birth weight of the offspring while paternal diabetes was insignificantly associated with a reduction in birth weight. Hyppönen *et al.* also found lower birth weight in children of fathers with diabetes but higher birth weight in children born to mothers developing diabetes at some point in adult life.[56] In accordance with the fetal insulin hypothesis, a small number of type 2 diabetes variants has been shown to reduce birth weight in the range of 20–30 g pr allele.[57–59] In 2733 participants from the Inter99 study, we recently showed that individuals carrying more than the average type 2 diabetes risk alleles had a reduction in birth weight of 35 g indicating a modest overall effect of type 2 diabetes risk variants on birth weight.[59] A possible reducing effect of maternal genotype on offspring birth weight is exceeded by the opposing effect of maternal hyperglycemia and subsequent fetal hyperinsulinemia.

We found that the Inter99 participants with traceable midwife records were healthier in terms of anthropometric risk factors, prevalence of diabetes and risk of ischemic heart disease compared with 30% of the Inter99 participants without traceable midwife records. In the original Inter99 study, the response rate was 52.5% and non-responders had more admissions for cardiovascular disease and diabetes than responders.[21] Accordingly, our birth weight data may not be representative of the entire Danish population but preferentially represent the healthier part of the population. Since low birth weight in many studies has been associated with both diabetes and cardiovascular disease, our data may be skewed toward the upper range of the birth weight spectrum.

Using valid information on size at birth we found a significant impact of birth weight and birth length on weight, height, waist and hip circumference in middle-aged Danes. Birth weight was not related to the waist/hip ratio but was positively related to adult BMI, although the magnitude of this relationship was modest. Altogether, we do not find evidence that obesity or central fat distribution, as reflected in the waist/hip measurements, mediates the relationship between low birth weight and risk of cardiovascular disease or type 2 diabetes in later life. In the future, this extension to the Inter99 study will provide a valuable research resource to determine the impact of – and interactions between – fetal phenotypes, genetic constitution and postnatal risk factors on adult health and disease.

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Statement of Interest

K. Borch-Johnsen is the head of the Steno Diabetes Center, a hospital integrated in the Danish National Healthcare Service, but owned by Novo Nordisk. K. Borch-Johnsen holds shares in Novo Nordisk Inc. The other authors declare that they have no duality of interest associated with this manuscript.

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