Published in final edited form as:
Am J Hum Biol. 2010 ; 22(3): 330–335. doi:10.1002/ajhb.20995.

Boys Live Dangerously in the Womb

JOHAN G. ERIKSSON[1,2,3,4,5], **EERO KAJANTIE**[2,6], **CLIVE OSMOND**[7], **KENT THORNBURG**[8], and **DAVID J.P. BARKER**[7,8,*]

[1]Department of General Practice and Primary Health Care, University of Helsinki, Helsingin yliopisto, Finland [2]National Institute for Health and Welfare, Department of Chronic Disease Prevention, Helsinki, Finland [3]Vasa Central Hospital, Sandviksgatan 2-4, Vasa, Finland [4]Folkhälsan Research Centre, Helsinki, Helsingfors Universitet, Finland [5]Unit of General Practice, Helsinki University Central Hospital, Finland [6]Hospital for Children and Adolescents, Helsinki University Central Hospital, Helsinki, Finland [7]MRC Epidemiology Resource Centre, University of Southampton, Southampton General Hospital, Southampton, United Kingdom [8]Heart Research Center, Oregon Health and Science University, Portland, Oregon

Abstract

The growth of every human fetus is constrained by the limited capacity of the mother and placenta to deliver nutrients to it. At birth, boys tend to be longer than girls at any placental weight. Boy's placentas may therefore be more efficient than girls, but may have less reserve capacity. In the womb boys grow faster than girls and are therefore at greater risk of becoming undernourished. Fetal undernutrition leads to small size at birth and cardiovascular disorders, including hypertension, in later life. We studied 2003 men and women aged around 62 years who were born in Helsinki, Finland, of whom 644 had hypertension: we examined their body and placental size at birth. In both sexes, hypertension was associated with low birth weight. In men, hypertension was also associated with a long minor diameter of the placental surface. The dangerous growth strategy of boys may be compounded by the costs of compensatory placental enlargement in late gestation. In women, hypertension was associated with a small placental area, which may reduce nutrient delivery to the fetus. In men, hypertension was linked to the mothers' socioeconomic status, an indicator of their diets: in women it was linked to the mothers' heights, an indicator of their protein metabolism. Boys' greater dependence on their mothers' diets may enable them to capitalize on an improving food supply, but it makes them vulnerable to food shortages. The ultimate manifestation of their dangerous strategies may be that men have higher blood pressures and shorter lives than women.

Pregnancies are more likely to have bad outcomes if the baby is a boy (Boklage, 2005; Di Renzo et al., 2007; Ingemarsson, 2003). Boys grow faster than girls from an early stage of gestation, even from before implantation, and this makes them more vulnerable if their nutrition is compromised (Pedersen, 1980; Tanner, 1989). More newborn boys than girls have retarded growth and placental abnormalities and more of them die during the perinatal period (Di Renzo et al., 2007; Ingemarsson, 2003). In the famine in Holland during the Second World War, the number of boys born fell in relation to the number of girls (Ravelli et al., 1999).

*Correspondence to: David J. P. Barker, Heart Research Center, Oregon Health and Science University, Portland, OR 97239,USA. djpbarker@gmail.com.

The nutrition of a fetus depends on various aspects of the mother's nutrition, including her diet, her nutritional stores, and her metabolism, which is the product of her lifetime's nutrition (Jackson, 2000). Fetal nutrition also depends on the placenta's ability to transport nutrients from mother to fetus (Harding, 2001). This ability is reflected in its size. Small babies generally have small placentas. We have previously examined the differences in fetal and placental size at birth among boys and girls born in Helsinki, Finland (Forsen et al., 1999). We found that the small differences in average body measurements concealed large differences in body proportions. Boys tended to be longer than girls at any placental weight. This suggests that boy's placentas are more efficient but may have less reserve capacity, which increases their vulnerability to undernutrition. Boys tend to have larger head circumferences at birth but are thinner than girls. This suggests that they may tradeoff visceral development to protect brain growth. The growth of every human fetus is constrained by the limited capacity of the mother and placenta to deliver nutrients to it (Ounsted et al., 1986). The male fetus, by growing more rapidly and investing in brain growth rather than placental growth, is adopting a more dangerous strategy that puts it at greater risk of becoming undernourished.

An immediate consequence of fetal undernutrition is reduced growth and low birthweight (Harding, 2001); a long-term consequence is vulnerability to cardiovascular disorders, including hypertension, later in life (Barker, 1995). Men and women whose birth weights were towards the lower end of the normal range are at increased risk of cardiovascular disease (Barker et al., 1989, 2005; Frankel et al., 1996; Leon et al., 1998; Rich-Edwards et al., 1997). This is thought to reflect fetal programming, the process by which early malnutrition leads to lifelong changes in the body's organs and systems and thereby initiates disease in later life (Barker, 1995; Bateson et al., 2004). Hypertension can be programmed experimentally by manipulating the diets of pregnant animals (Barker et al., 2006). One mechanism underlying the fetal origins of hypertension is a lifelong reduction in the number of nephrons. During development the kidney has low priority because the placenta performs most of its functions, and renal development may be traded off to protect more important organs, including the brain. The higher blood pressure of men than women could indicate that boys more readily trade off their kidneys than girls do.

Not only are boys more vulnerable to undernutrition than girls, but their different path of intrauterine growth could make them respond to different aspects of maternal nutrition and have different placental growth. We here present findings showing that two markers of maternal nutrition, together with the size of the placenta, program hypertension differently in the two sexes.

METHODS

The study sample was selected from men and women who were born during 1934 to 1944 in the Helsinki University Central Hospital and who visited infant welfare clinics in the city. Details of the birth records, child welfare clinic records, and school health records have been previously described (Barker et al., 2005). Their birth records included birthweight, the mother's height, and data on the father's occupation, grouped into middle and lower class, on the basis of an original classification from Statistics Finland. The records also included the weight of the placenta, together with the maximal width of the surface and a lesser width bisecting it at right angles. The mean values of the maximal and lesser diameters were 19.4 (SD 2.2) and 16.9 cm (SD 2.2), respectively. Their lengths were highly correlated with each other ($r = 0.6$) and with birthweight ($r = 0.5$). We used these so-called diameters to estimate the surface area of the placenta. Assuming an elliptical surface, we estimated the area of the placenta as maximal × lesser diameter × $\pi/4$.

We identified 8,760 men and women, born as singletons, who were living in Finland in 1971, when a unique identification number was allocated to each member of the Finnish population. We used random number tables to select a sample of people within the cohort who were still alive and living in Finland. To achieve a sample size in excess of 2,000 people, we selected 2,902 subjects and invited them to a clinic. Nine hundred twenty-eight men and 1,075 women visited the clinic, which was held at the National Public Health Institute in Helsinki. Their average age was 62 years (range 57–70 years). The procedures used at the clinic have been previously described (Barker et al., 2005). Written informed consent was obtained from each subject before any procedures were carried out. The Ethics Committee at the National Public Health Institute, Finland approved the study.

Six hundred forty-four of the subjects, 310 men and 334 women, had been diagnosed as having hypertension giving a prevalence of 32% (Eriksson et al., 2007). We calculated odds ratios for hypertension and assessed their associations with maternal and placental measurements using multiple logistic regressions. Odds ratios for hypertension increased with age and waist circumference and we adjusted for these as in our previous analyses (Eriksson et al., 2007). Measurements of birth, placental, and maternal size were analyzed as continuous variables although presented in Table 1 as groups. Tests for interaction used the product of the variables being studied.

RESULTS

Table 1 shows the mean birthweights and placental measurements in men and women, together with the correlation between birthweight and placental measurements. Mean birthweight and placental weight were higher in boys. When, however, placental measurements were expressed as a ratio to birthweight the values for each of the three placental measurements were lower in boys.

Table 2 shows that hypertension was associated with low birth weight in both men and women. It was not related to the duration of the pregnancy and its association with low birthweight must therefore reflect slow fetal growth. Placental size was differently related to hypertension in the two sexes. Despite the strong correlation between birthweight and placental weight (Table 1), hypertension in men was only weakly related to low placental weight (Table 2) and was unrelated to placental surface area (Fig. 1). Among women, the association between hypertension and placental size matched the association with low birthweight, so that women with low placental weight and area were at increased risk. Short length of both the maximal and lesser diameters predicted later hypertension in women (P = 0.001 and 0.005).

We examined what particular aspects of placental growth among men with hypertension were mismatched to their slow fetal growth. We found that it was specifically a disproportion between the growth of the lesser diameter and the fetus that predicted the disorder. The risk of hypertension rose progressively as the ratio of the lesser diameter to birthweight increased (Table 2). There was no similar trend with the ratio of the maximal diameter to birthweight or with the ratio of placental weight to birthweight. In Figure 2, the men are grouped according to their mother's social class. A high ratio of the lesser diameter to birthweight only predicted hypertension in men with middle class mothers. Among women low placental weight and area predicted hypertension similarly in those with middle and lower class mothers.

We grouped the men and women according to their mother's heights, and categorized them as having either short or tall mothers using the median height (160 cm). Among men the ratio of the lesser diameter to birthweight predicted hypertension similarly in the two groups

of mothers. Figure 3 shows that among women, however, low placental weight predicted hypertension more strongly in women who had short mothers. Small placental area and a small lesser diameter also predicted hypertension more strongly in women who had short mothers, though neither interaction was statistically significant (*P* for interaction = 0.09 and 0.06). In these women the lesser diameter predicted hypertension while the maximal diameter did not (*P* = 0.05 and 0.18 in a simultaneous regression).

DISCUSSION

We found that hypertension was associated with low birth weight in both men and women, as has been shown before (Barker et al., 1990; Curhan et al., 1996; Eriksson et al., 2007). An interpretation of this association is that hypertension is initiated by impaired implantation, which leads to slow fetal growth and low birthweight. Impaired implantation is known to initiate preeclampsia of pregnancy and the offspring from such pregnancies have low birthweight and raised blood pressure in childhood and in adult life (Kajantie et al., 2009).

Remarkably, the size of the placental surface was routinely measured in Helsinki in the past. In recognition that the surface was more oval than round two diameters were recorded, a maximal one and a lesser one at right angles to it (Barker et al., 2009). We used these two diameters to estimate the area of the placenta. How closely this area reflects the total surface area for maternal-fetal exchange through the gestational period is not known. The size of the expelled term placenta is an incomplete proxy for its growth dynamics across the span of gestation. We found that the boys had larger placentas at birth than girls, whereas their placentas were smaller than those of girls when related to the weight of the baby. This is consistent with other findings suggesting that boys' placentas are more efficient than girls' placentas, but may have less reserve capacity (Forsen et al., 1999).

We have suggested that growth of the placental surface is polarized from the time of implantation, so that growth along the major axis, which results in the maximal diameter, is qualitatively different to growth along the minor axis (Thornburg et al., 2009). We postulated that growth along the major axis aligns with the rostro-caudal growth axis of the embryo, while growth along the minor axis is nutritionally sensitive (Barker et al., 2009). In pregnancies complicated by preeclampsia, both axes of the placental surface are short (Thornburg et al., 2009). However, while there is a strong graded relation between the risk of preeclampsia and the absolute length of the lesser diameter, there is no similar relation with the maximal diameter. This suggests that tissue along the lesser diameter is linked to the development of preeclampsia through a structure or function that is not shared with tissue along the maximal diameter.

We found that the relation between the placental diameters and later hypertension was different in the two sexes. In men, hypertension was associated with a large lesser diameter in relation to birth weight. In women, it was associated with short diameters and a small placental area. One possible explanation is that boys attempted to compensate for impaired placentation by expanding the placental surface along its minor axis whereas girls did not. We suggest that this expansion occurred toward the end of gestation when the impaired capacity of the placenta to transport nutrients began to limit fetal growth.

Compensatory expansion of the placenta has been studied in sheep. Manipulation of placental size by changing the pasture of pregnant ewes is standard practice in sheep farming (McCrabb et al., 1992). If ewes are placed on poor pasture in mid-pregnancy the placenta will enlarge, presumably to extract more nutrients from the mother. If the ewes are returned to good pasture in late pregnancy the enlarged placenta leads to larger lambs than there would otherwise have been. This improves their value to the farmer. We have

previously suggested that compensatory placental enlargement occurs in humans and involves enhanced growth along the minor axis of the surface (Barker et al., 1990Barker et al., 2009). Our new findings suggest that compensatory expansion occurs more readily in boys. This compensatory growth may be beneficial in some circumstances but if the compensation is inadequate, and the fetus continues to be undernourished, the need to share its nutrients with an enlarged placenta may become an added metabolic burden. For boys, in this study, the immediate cost of this burden was low birthweight and the long-term cost was hypertension, perhaps as a result of poor development of low priority organs like the kidney (Barker et al., 2006).

We examined how the effects of two markers of maternal nutrition and metabolism interacted with those of the placental surface in determining later hypertension. There were food shortages in Helsinki before and during the Second World War, and these are likely to have been more severe in lower social class families (Pesonen et al., 2007). We therefore used the mother's socioeconomic status as a marker of her diet around the time of pregnancy. Height reflects nutrition and metabolism in childhood and adolescence, although there are also genetic influences (Tanner, 1989). We therefore used mother's height as a marker of her lifetime nutrition and metabolism.

We found that, among men, the association between a large lesser diameter in relation to birthweight was confined to those whose mothers were middle class. An interpretation of this is that compensatory placental expansion in response to food shortages may only occur in mothers who were better nourished when they conceived. The embryo at the blastocyst stage is sensitive to the mother's nutritional state and in response allocates more or fewer cells to the trophoblast, which becomes the placenta (Kwong et al., 2000). In sheep, placental enlargement can only occur in ewes that were well nourished around the time of conception (McCrabb et al., 1992).

Among women the trends in hypertension with low placental weight and small area did not differ in those with middle class or lower class mothers. The trends, however, were stronger in those whose mothers were short, and in these women it was reduction of the lesser rather than the maximal diameter that was associated with hypertension. An explanation for these findings is that short mothers have lesser protein synthesis during pregnancy and therefore make a lesser amount of amino acids available to the fetus (Duggleby and Jackson, 2001; Jackson, 2000). Around one quarter of the variability in the length of newborn babies is related to maternal protein synthesis, which depends on the size of the mother's visceral mass, which in turn is linked to her height. A small placental area, more specifically a small lesser diameter, would therefore have more severe effects on fetal nutrition if the mother was short.

We suggest that during development in the womb boys are more responsive to the mother's current diet than girls, who respond more to their mother's lifetime nutrition and metabolism. The greater effect of the Dutch famine on boys supports this (Ravelli et al., 1999), as do the greater effects of experimental maternal malnutrition on male animals (Grigore et al., 2008; Ozaki et al., 2001; Woods et al., 2005). Observations in mice show that males are more vulnerable to stress and that core mechanisms underlying this are sex differences in epigenetic placental gene regulation (Mueller and Bale, 2008).

In the womb, boys have a more dangerous growth strategy than girls. They grow more rapidly and invest less in placental growth, which puts them at greater risk of becoming undernourished. After impaired implantation they may more readily attempt to compensate by expansion of the placental surface in late gestation, and may have to sustain an enlarged placenta at the cost of their own nutrition. Although their responsiveness to their mothers'

current diet enables them to capitalize on improving food supply, and promotes their agenda of rapid growth, it makes them vulnerable to food shortages, such as occurred in Helsinki when our study subjects were in the womb. The ultimate manifestation of boys' dangerous strategies may be that men have higher blood pressures and shorter lives than women.

Acknowledgments

Contract grant sponsors: British Heart Foundation, the Academy of Finland, the Päivikki and Sakari Sohlberg Foundation, the Finnish Diabetes Research Foundation, the Finnish Foundation for Cardiovascular Research, the Finnish Foundation for Pediatric Research, the Finnish Medical Society Duodecim, Novo Nordisk Foundation, Sigrid Jusélius Foundation, Juho Vainio Foundation, Yrjö Jahnsson Foundation, Finska Läkaresällskapet, and M. Lowell Edwards Endowment.

LITERATURE CITED

Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet. 1989; 2:577–580. [PubMed: 2570282]

Barker DJP. Fetal origins of coronary heart disease. BMJ. 1995; 311:171–174. [PubMed: 7613432]

Barker DJP, Bagby SP, Hanson MA. Mechanisms of disease: in utero programming in the pathogenesis of hypertension. Nature Clin Pract Nephrol. 2006; 2:700–707. [PubMed: 17124527]

Barker DJP, Bull AR, Osmond C, Simmonds SJ. Fetal and placental size and risk of hypertension in adult life. BMJ. 1990; 301:259–262. [PubMed: 2390618]

Barker DJP, Osmond C, Forsén T, Kajantie E, Eriksson JG. Trajectories of growth among children who later have coronary events. N Engl J Med. 2005; 353:1802–1809. [PubMed: 16251536]

Barker DJP, Thornburg K, Osmond C, Kajantie E, Eriksson JG. The surface area of the placenta and hypertension in the offspring in later life. Int J Devel Biol. 2009 (in press).

Bateson P, Barker DJP, Clutton-Brock T, Deb D, D'Udine B, Foley RA, Gluckman P, Godfrey K, Kirkwood T, Mirazoin Lahr M, McNamara J, Metcalfe NB, Monaghan P, Spencer HG, Sultan SE. Developmental plasticity and human health. Nature. 2004; 430:419–421. [PubMed: 15269759]

Boklage CE. The epigenetic environment: secondary sex ratio depends on differential survival in embryogenesis. Human Reprod. 2005; 20:583–587.

Curhan GC, Chertow GM, Willett WC, Spiegelman D, Colditz GA, Manson JE, Speizer FE, Stampfer MJ. Birth weight and adult hypertension and obesity in women. Circulation. 1996; 94:1310–1315. [PubMed: 8822985]

Di Renzo GC, Rosati A, Sarti RD, Cruciani L, Cutuli AM. Does fetal sex affect pregnancy outcome? Gend Med. 2007; 4:19–30. [PubMed: 17584623]

Duggleby SL, Jackson AA. Relationship of maternal protein turnover and lean body mass during pregnancy and birth length. Clin Sci (Lond). 2001; 101:65–72. [PubMed: 11410116]

Eriksson JG, Forsén TJ, Kajantie E, Osmond C, Barker DJP. Childhood growth and hypertension in later life. Hypertension. 2007; 49:1415–1421. [PubMed: 17452506]

Forsén T, Eriksson JG, Tuomilehto J, Osmond C, Barker DJP. Growth in utero and during childhood among women who develop coronary heart disease: longitudinal study. BMJ. 1999; 319:1403–1407. [PubMed: 10574856]

Frankel S, Elwood P, Sweetnam P, Yarnell J, Smith GD. Birthweight, body-mass index in middle age, and incident coronary heart disease. Lancet. 1996; 348:1478–1480. [PubMed: 8942776]

Grigore D, Ojeda NB, Alexander BT. Sex differences in the fetal programming of hypertension. Gend Med. 2008; 5 (Suppl A):S121–S132. [PubMed: 18395678]

Harding JE. The nutritional basis of the fetal origins of adult disease. Int J Epidemiol. 2001; 30:15–23. [PubMed: 11171842]

Ingemarsson I. Gender aspects of preterm birth. BJOG Suppl. 2003; 20:34–38.

Jackson AA. All that glitters. British Nutrition Foundation Annual Lecture. Nutr Bull. 2000; 25:11–24.

Kajantie E, Eriksson JG, Osmond C, Thornburg K, Barker DJP. Preeclampsia is associated with increased risk of stroke in the adult offspring: the Helsinki Birth Cohort Study. Stroke. 2009; 40:1176–1180. [PubMed: 19265049]

Kwong WY, Wild AE, Roberts P, Willis AC, Fleming TP. Maternal undernutrition during the preimplantation period of rat development causes blastocyst abnormalities and programming of postnatal hypertension. Development. 2000; 127:4195–4202. [PubMed: 10976051]

Leon DA, Lithell HO, Vågerö D, Koupilová I, Mohsen R, Berglund L, Lithell UB, McKeigue PM. Reduced fetal growth rate and increased risk of death from ischaemic heart disease: cohort study of 15000 Swedish men and women born 1915–29. BMJ. 1998; 317:241–245. [PubMed: 9677213]

McCrabb GJ, Egan AR, Hosking BJ. Maternal undernutrition during mid-pregnancy in sheep: variable effects on placental growth. J Agric Sci. 1992; 118:127–132.

Mueller BR, Bale TL. Sex-specific programming of offspring emotionality after stress early in pregnancy. J Neurosci. 2008; 28:9055–9065. [PubMed: 18768700]

Ounsted M, Scott A, Ounsted C. Transmission through the female line of a mechanism constraining human fetal growth. Ann Hum Biol. 1986; 13:143–151. [PubMed: 3707043]

Ozaki T, Nishina H, Hanson MA, Poston L. Dietary restriction in pregnant rats causes gender-related hypertension and vascular dysfunction in offspring. J Physiol. 2001; 530:141–152. [PubMed: 11136866]

Pedersen JF. Ultrasound evidence of sexual difference in fetal size in first trimester. BMJ. 1980; 281:1253. [PubMed: 7427655]

Pesonen AK, Räikkönen K, Heinonen K, Kajantie E, Forsén T, Eriksson JG. Depressive symptoms in adults separated from their parents as children: a natural experiment during World War II. Am J Epidemiol. 2007; 166:1126–1133. [PubMed: 17875582]

Ravelli AC, van der Meulen JHP, Osmond C, Barker DJP, Bleker OP. Obesity at the age of 50 y in men and women exposed to famine prenatally. Am J Clin Nutr. 1999; 70:811–816. [PubMed: 10539740]

Rich-Edwards JW, Stampfer MJ, Manson JE, Rosner B, Hankinson SE, Colditz GA, Willett WC, Hennekens CH. Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. BMJ. 1997; 315:396–400. [PubMed: 9277603]

Tanner, JM. Fetus into man. 2. Ware; Castlemead: 1989.

Thornburg K, Barker DJ, Osmond C, Kajantie E, Eriksson JG. In preeclampsia, the placenta grows slowly across its minor axis. Int J Devel Biol. 2009 in press.

Woods LL, Ingelfinger JR, Rasch R. Modest maternal protein restriction fails to program adult hypertension in female rats. Am J Physiol Regul Integr Comp Physiol. 2005; 289:R1131–R1136. [PubMed: 15961538]

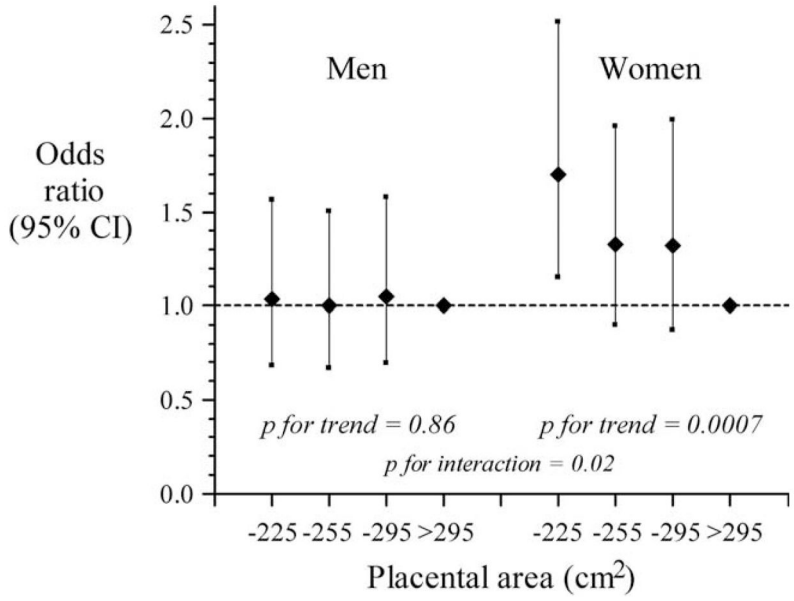

Fig. 1.
Odds ration for hypertension in men and women according to placental surface area.

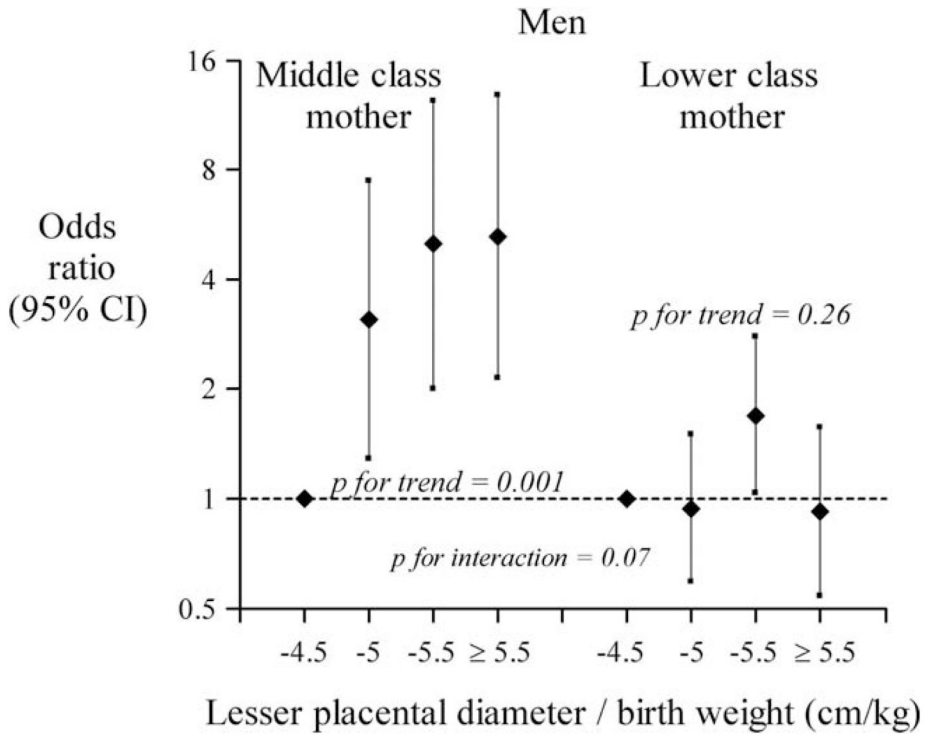

Fig. 2.
Odds ratios for hypertension in men according to the mother's socioeconomic status and the ratio of the lesser placental diameter to birthweight.

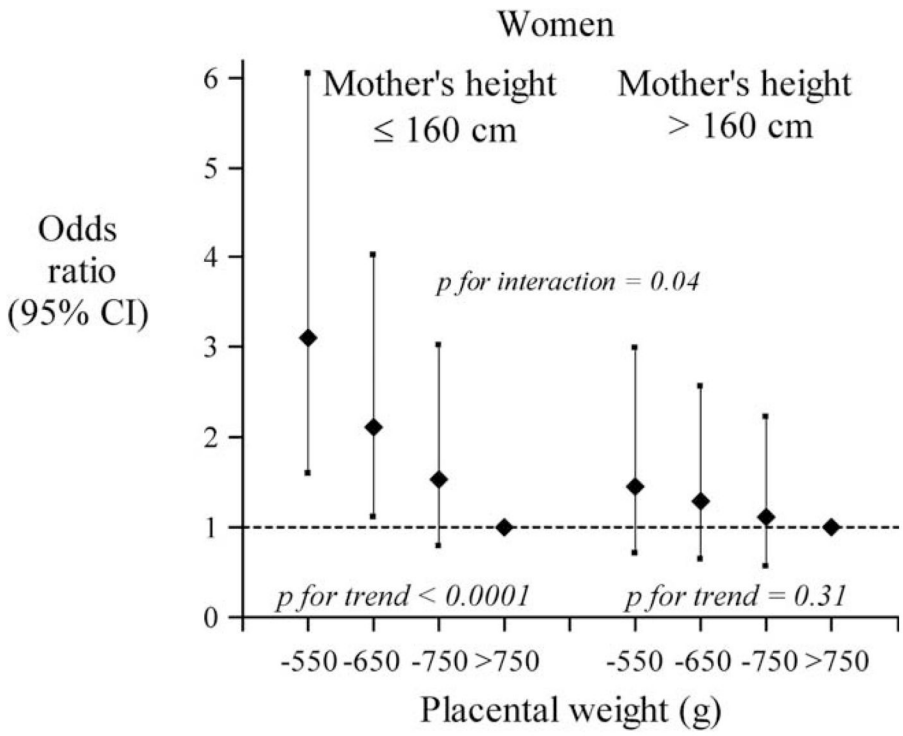

Fig. 3.
Odds ratios for hypertension in women according to mother's height and placental weight.

TABLE 1

Mean birthweight and placental measurements, and correlation between birthweight and placental measurements among men and women

	Men (n = 928)			Women (n = 1075)			P for difference in means	P for difference in correlations
Measurement	**Mean**	**SD**	**Correlation with birthweight**	**Mean**	**SD**	**Correlation with birthweight**		
Baby								
Weight (g)	3,476	501		3,353	465		<0.001	–
Placenta								
Weight (g)	655	124	0.64	643	120	0.56	0.03	0.04
Maximal diameter (cm)	19.5	2.3	0.44	19.3	2.2	0.44	0.06	0.99
Lesser diameter (cm)	17.0	2.2	0.50	16.8	2.2	0.44	0.13	0.12
Weight to birthweight ratio (%)	18.9	2.9		19.3	3.0		0.006	
Maximal diameter to birthweight ratio (cm/kg)	5.7	0.8		5.8	0.8		<0.001	
Lesser diameter to birthweight ratio (cm/kg)	4.9	0.7		5.1	0.8		<0.001	
Area (cm^2)	262	58	0.51	257	58	0.47	0.06	0.32
Thickness (g/cm^2)	2.57	0.56	−0.03	2.57	0.55	−0.04	0.93	0.70

TABLE 2

Odds ratios for hypertension according to birthweight and placental size in men and women

	Men			Women		
Measurement	**Cases/subjects**	**Odds ratio**	**95% CI**	**Cases/subjects**	**Odds ratio**	**95% CI**
Birthweight (g)						
≤2,500	15/35	2.9	1.3–6.7	15/37	3.6	1.5–8.8
−3,000	43/113	2.6	1.4–4.7	86/211	3.5	1.8–6.7
−3,500	125/363	2.1	1.3–3.4	126/428	2.0	1.1–3.7
−4,000	95/296	1.8	1.1–3.0	91/317	1.9	1.0–3.6
>4,000	32/121	1.0	Baseline	16/80	1.0	Baseline
P for trend		0.003			<0.001	
OR per kg (95% CI)		0.64 (0.48–0.86)			0.52 (0.39–0.70)	
Placental weight (g)						
≤550	82/214	1.6	1.0–2.5	97/261	2.0	1.3–3.2
−650	86/285	1.1	0.7–1.7	115/370	1.6	1.0–2.5
−750	83/241	1.2	0.8–1.9	83/282	1.3	0.8–2.1
>750	58/186	1.0	Baseline	39/160	1.0	Baseline
P for trend		0.06			<0.001	
OR per 100 g (95% CI)		0.89 (0.79–1.01)			0.80 (0.71–0.90)	
Placental surface area (cm^2)						
≤225	75/222	1.0	0.7–1.6	101/290	1.7	1.2–2.5
−255	80/247	1.0	0.7–1.5	91/308	1.3	0.9–2.0
−295	77/227	1.0	0.7–1.6	73/227	1.3	0.9–2.0
>295	75/227	1.0	Baseline	66/245	1.0	Baseline
P for trend		0.86			<0.001	
OR per 50 cm^2 (95% CI)		0.99 (0.87–1.12)			0.81 (0.71–0.91)	
Lesser placental diameter–birth weight ratio (cm/kg)						
≤4.5	72/242	1.0	Baseline	55/215	1.0	Baseline
−5	88/287	1.2	0.8–1.8	97/322	1.2	0.8–1.8
−5.5	86/209	2.0	1.3–3.1	89/259	1.5	1.0–2.3
>5.5	61/185	1.4	0.9–2.2	90/274	1.5	1.0–2.2

	Men			Women		
Measurement	**Cases/subjects**	**Odds ratio**	**95% CI**	**Cases/subjects**	**Odds ratio**	**95% CI**
P for trend		0.01			0.06	
OR per cm/kg (95% CI)		1.31 (1.06–1.61)			1.18 (0.99–1.40)	

OR, odds ratio; CI, confidence interval.