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Could cortisol explain the association
between birth weight and cardiovascular
disease in later life?:
a meta-analysis

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Abstract

Objectives:

Studies about the association between birth weight and circulating cortisol level have been published from 1998 onwards. However, their findings were inconsistent. To quantitatively assess the overall association between birth weight and circulating cortisol level, we aimed to perform a meta-analysis of the published literature.

Methods:

A literature search was conducted in PubMed, and selected papers were systematically reviewed. A pooled regression coefficient was calculated for the entire group as well as for males and females separately.

Results:

Data from 11 study populations were pooled (N=2,301). These populations differed with respect to geographical area, age, sex distribution, inclusion criteria, and gestational age. We found a statistically significant inverse association between birth weight and circulating cortisol level: a 1 kg lower birth weight was associated with a 25.3 (95% CI: 5.9 to 44.8) nmol/l higher cortisol level. Separate results were reported for males and females in 6 study populations. The association in males was 20.6 (95% CI: 4.2 to 37.0) nmol/l per kg and in females it was 30.9 (95% CI: 7.4 to 54.4) nmol/l per kg.

Conclusions:

Differences between study populations hampered the comparability of the included studies. Although the majority of studies were underpowered, by using a meta-analytic approach we found an inverse association between birth weight and circulating cortisol level. Thus, our findings suggest that there is some evidence for a possible role of the hypothalamus-pituitary-adrenal axis in the epidemiological association between birth weight and cardiovascular disease. However, the strength of the overall association between birth weight and circulating cortisol level was weak.

Introduction

There is evidence from epidemiological studies that cardiovascular disease – including its risk factors, such as hypertension and type 2 diabetes – is associated with low birth weight (1-3). The link between cardiovascular disease and low birth weight might be explained by a phenomenon called perinatal programming, i.e. persistent structural, hormonal, and/or metabolic adaptations of an individual in response to specific insults acting at critical periods in development. Alternatively, it might be explained by genes which predispose to intrauterine growth retardation as well as to cardiovascular disease and type 2 diabetes (4).

Pathologically increased activity of the hypothalamus-pituitary-adrenal (HPA) axis – as in Cushing's syndrome – is associated with cardiovascular disease, raised blood pressure, and impaired glucose tolerance. More subtle activation of the HPA axis is associated with a similar but milder phenotype (5-8). Through its effects on several cardiovascular, hormonal, and metabolic targets, and its possible susceptibility to the effects of perinatal programming (9), in the early 1990s the idea was launched that the HPA axis may explain part of the epidemiologic association between birth weight and later cardiovascular disease (10). Evidence for possible programming of the HPA axis in humans was first suggested in 1996 by Clark et al, who found a U-shaped relation between birth weight and glucocorticoid metabolite excretion in 24-h urine samples (11).

In 1998, Phillips et al were the first to report an inverse association between birth weight and circulating cortisol level in a population of elderly men (12). Thereafter, a number of other studies on this topic were published. As these had different study populations, methods, and results, we systematically reviewed the available literature. We conducted a meta-analysis in order to investigate whether there is really an inverse association between birth weight and circulating cortisol level.

Methods

A literature search was conducted for papers published between January 1995 and June 2004 in PubMed. Papers about cortisol in blood in relation to birth weight were searched using combinations of the text words “birth weight”, “birthweight”, “cortisol”, and “hydrocortisone” in title or abstract. We restricted the search to studies in humans and written in English. Papers were identified by title and selected by abstract reviewing. Papers were selected if the abstract indicated that basal cortisol in blood (plasma or serum) had been measured in relation to birth weight in persons aged >1 years. Reference lists of selected papers were searched for further relevant studies. For completeness, a literature search in EMBASE was also performed.

The first 2 authors independently reviewed the selected papers. Of the included papers, the following characteristics were recorded: year of publication and sample size, and sex distribution, age, gestational age, birth weight, and cortisol level of the participants, and the type of cortisol assay.

Table 1. Characteristics of included studies by year of publication.

Reference number	First author	Publication year of study	Geographical area	Birth weight groups	Sex	N/males	Age (yrs)	Gestational age (weeks)	Birth weight (kg)	Cortisol (nmol/l)
12	Phillips	1998	Hertfordshire, UK	-	M	370/370	59 to 70	NR	NR	344.0±112.0
21	Dahlgren	1998	Côteborg, Sweden	SGA ^a	M/F	53/41	2 to 14	38.9±2.0	NR*	444.0±138
				AGA ^a	M/F	131/93	3 to 15	39.5±1.9	NR*	481.6±NR†
23	Houang	1999	Paris, France	IUGR ^b	M/F	40/20	1.1 to 13.5	38.5±1.8	2.48±0.51	316.3±147.0
				Normal ^b	M/F	26/13	0.9 to 13.6	39.5±1.0	3.20±0.18	262.6±150.0
17	Phillips	2000	Hertfordshire, UK	-	F	306/0	60 to 71	NR	3.40±0.52	350.0±127.6
17	Phillips	2000	Preston, UK	-	M/F	199/92	45 to 54	NR	3.20±0.71	412.5±182.0
17	Phillips	2000	Adelaide, Australia	-	M/F	165/87	20	NR	3.48±0.64	383.5±192.7
16	Levitt	2000	Cape Town, South Africa	UFA ^c	M/F	36/20	20	39.3±0.8†	2.35±0.22†	484.9±166.3
				AFA ^c	M/F	32/15	20	39.3±0.9†	3.05±0.21†	418.6±160.6
18	Szathmári	2001	Budapest, Hungary	LBW ^d	M/F	70/37	20	33.1	1.81±0.38	260.6±65.0
				Normal ^d	M/F	30/16	20	39.5	3.28±0.37	210.7±65.0
15	Kajantie	2002	Helsinki, Finland	-	M/F	421/157	65.1 to 75.8	39.9±1.3	3.41±0.42	384.2±137.0
19	Tenhola	2002	Kuopio, Finland	SGA ^e	M/F	55/20	12	39.0±1.4	2.45±0.32	292.5±217.4¶
				AGA ^e	M/F	55/20	12	39.7±1.5	3.46±0.48	272.1±217.4¶
20	Walker	2002	Edinburgh, UK	AGA ^f	M/F	19/9	22 to 25	32.0±0.8	1.67±0.22	210±165.6§
				IUGR ^f	M/F	15/4	22 to 25	35.2±1.3	1.70±0.21	158±121.2§
				Normal ^f	M/F	27/11	22 to 25	40.1±1.7	3.13±0.44	191±227.6§
22	Herrick	2003	Lanarkshire, UK	-	M/F	251/119	28 to 32	38.9±1.3	3.05±0.40	390.0±145.9

Gestational age, birth weight, and cortisol are shown as mean±SD.

NR: not reported.

* Difference in g between groups estimated from difference in SDS.

† Cortisol data came from a subset of 68 subjects of a larger study population (N=137), whereas data on birth weight and gestational age came from the entire population.

‡ SD could not be calculated because of an impossible value in the paper. We made the assumption that the SD of the AGA group was similar to the SD of the SGA group, which was calculated from the interquartile range.

¶ SD estimated from P value.

§ Value estimated from graph.

Definitions of birth weight groups as reported in the papers:

^a SGA: short or light for gestational age; <-2 SD in height at 2 years of age.

AGA: appropriate-for-gestational-age; short healthy children (N=75) and healthy children with heights within the normal range (±2 SD) (N=56).

^b IUGR: intrauterine growth retardation; birth length for gestational age ≥2 SD below the population mean.

Normal: without intrauterine growth retardation.

^c UFA: underweight for gestational age; birth weight ≤10th percentile.

AFA: appropriate weight for gestational age; birth weight between 25th and 75th percentiles.

^d LBW: low birth weight; gestational age ≤36 weeks and birth weight <2,500 g.

Normal: gestational age ≥38 weeks and birth weight ≥2,500 g.

^e SGA: small-for-gestational-age; birth weight and/or length and/or ponderal index for gestational age >2 SDS below the population mean.

AGA: appropriate-for-gestational-age; birth weight and/or length and/or ponderal index for gestational age ≥-2 and ≤2 SDS of the population mean.

^f AGA: appropriate-for-gestational-age; birth weight <2,000 g and >10th percentile.

IUGR: intrauterine growth retardation; birth weight <2,000 g and <10th percentile.

Normal: birth weight >2,000 g.

Statistical analysis

If possible, regression coefficients and their standard errors were directly extracted from the papers. In several papers only the mean circulating cortisol level with standard error or SD was displayed for subgroups of birth weight. In this situation, the regression coefficient was estimated by:

$$b = \frac{\sum n_i (X_i - \bar{X})(Y_i - \bar{Y})}{\sum n_i (X_i - \bar{X})^2},$$

with \bar{Y}_i the mean circulating cortisol level in category i , \bar{X}_i the mean birth weight, and n_i the number of subjects in category i , and with $\bar{X} = \sum n_i \bar{X}_i / \sum n_i$ the estimated overall mean birth weight and $\bar{Y} = \sum n_i \bar{Y}_i / \sum n_i$ the estimated overall mean circulating cortisol level.

The standard error of b was then estimated by:

$$se(b) = \frac{\sqrt{\sum n_i^2 (\bar{X}_i - \bar{X})^2 se_i^2}}{\sum n_i (\bar{X}_i - \bar{X})^2},$$

with se_i the standard error of Y in category i .

Regression coefficients of individual studies were pooled using techniques for meta-analysis (13). To take account of possible heterogeneity between studies, a meta-analysis with random study effect was performed.

Results

Description of the included studies

The primary PubMed search yielded 183 papers. The restriction to studies in humans and written in English limited the search result to 144 titles. Of these, 24 were selected from the abstract. Nine of these were included after having read the full content (12;14-21). One study was conducted in 3 populations of different ages in cohorts from Hertfordshire (UK), Preston (UK), and Adelaide (Australia) (17); one of these populations (the Hertfordshire cohort) was the females of a cohort of which the males had been analyzed earlier with respect to circulating cortisol level (12). One study (14) had included the men and women from the same cohort as had been previously studied by Phillips et al (12;17), and was therefore excluded. In addition, another 2 papers (22;23) were included after having examined the reference lists of the already included papers. The search in EMBASE did not identify any additional relevant papers. Thus, our analysis was based upon 10 papers with the data of 2,301 subjects from 11 study populations.

Table 1 shows the characteristics of the included studies. Sample sizes of the individual study populations ranged from 61 to 421. The majority of studies were performed in Europe.

Although all study populations were mixed, separate results for males and females were reported for 6 study populations (12;15;17;18;20). Inclusion criteria differed substantially between studies. Two studies had included individuals born prematurely (18;20). Studies used different definitions for low birth weight. Mean gestational age ranged from 32.0 to 40.1 weeks, and mean birth weight from 1.67 to 3.48 kg. Mean circulating cortisol level ranged from 158.0 to 481.6 nmol/l. In most studies, cortisol was analyzed in a single venous blood sample drawn between 7:30 and 10:00 h after an overnight fast. In 1 study, an alternative procedure was performed: children were kept in hospital for at least a 24-h period during which they received a normal diet (21). Within the 24 hours, 8 samples were drawn. The mean circulating cortisol level of the samples drawn at 6.00 and 10.00 h was used in the meta-analysis. Cortisol was analyzed by radioimmunoassay in 7 studies (12;17;18;20-23), other immunoassays in 2 studies (15; 19), and by an “ACS auto analyzer” in 1 study (16).

In 5 study populations, a statistically significant inverse association between birth weight and circulating cortisol level was found in males and/or females, or in the population as a whole (12;16-18). To express the relation between birth weight and circulating cortisol level, either linear regression analysis (12;17) or comparison of mean circulating cortisol level between subgroups of birth weight were used by the studies (15;16;18-23). To estimate the regression coefficient from the paper by Tenhola et al (19), data on the mean birth weight of the small-for-gestational-age (SGA) and appropriate-for-gestational-age (AGA) groups were extracted from a previous study by the same research group (24). The standard error of the cortisol values was estimated from the P value of the t test for the difference between the SGA and AGA group. In the paper by Dahlgren et al (21), birth weight was displayed as SD score (SDS) only. To estimate the difference between the SGA and AGA groups in gram, the intrauterine growth curve of the Swedish reference population was used (25). Reported (12;17) and estimated (15;16;18-23) regression coefficients with 95% and 99% CIs of the individual study populations are summarized in Table 2.

Meta-analysis

A 1 kg lower birth weight was associated with a 25.3 (95% CI: 5.9 to 44.8) nmol/l higher circulating cortisol level (Figure 1). In comparison, the association was 27.9 (95% CI: 17.0 to 38.6) nmol/l per 1 kg in a fixed effects model. In one of the papers by Phillips et al (17), only regression coefficients adjusted for age and BMI were displayed. Therefore, an analysis was also performed after exclusion of the 3 study populations in their paper. This strongly reduced the strength of the association to 18.5 (95% CI: -12.7 to 49.7) nmol/l per kg. Furthermore, an analysis was performed after exclusion of individuals born prematurely (18;20). The strength of the association between birth weight and circulating cortisol level hardly changed: 24.2 (95% CI: -0.6 to 48.9) nmol/l per kg.

To test whether the association between birth weight and circulating cortisol level was different between genders, we also performed an analysis on the data of the 5 papers (6 study

populations) that displayed data for males and females separately (12;15;17;18;20). A 1 kg lower birth weight was associated with a 20.6 (95% CI: 4.2 to 37.0) nmol/l higher circulating cortisol level in males (Figure 2A), and a 30.9 (95% CI: 7.4 to 54.4) nmol/l higher cortisol level in females (Figure 2B).

We also studied the relation between the sample size of each study population, and the strength of the association between birth weight and circulating cortisol level. The strength of the association within study populations was irrespective of the sample size (Figure 3).

Discussion

We performed a systematic review of the available literature about the association between birth weight and circulating cortisol level at later age. Although the majority of studies included in our review did not find an effect of birth weight on circulating cortisol level, we found a statistically significant inverse association in a pooled data analysis.

It should be remarked that differences between study populations hampered the comparability of the included studies. First, the included study populations differed in geographical area. It has been demonstrated that there is a small difference in circulating cortisol level between white and black persons (26), but the majority of studies included in our review were performed in Europe. Only 1 study, which was conducted in South Africa, had included the children of “primigravid women of mixed ancestry” (16). Second, there were large differences in age between the included study populations. As has been demonstrated by others, physiological ageing is associated with a reduced amplitude of circadian cortisol fluctuations and altered negative feedback control, but morning circulating cortisol level does not seem to

Table 2. Regression coefficients with 95% and 99% confidence intervals of included study populations.

First author of study	β	95% CI		99% CI	
		lower limit	upper limit	lower limit	upper limit
Phillips, Hertfordshire	21.9	5.5	38.2	0.3	43.4
Dahlgren	-44.8	-94.3	4.8	-109.9	20.4
Houang	32.7	-68.5	133.8	-100.4	165.8
Phillips, Preston	41.3	4.3	78.3	-7.5	90.0
Phillips, Adelaide	36.3	4.0	68.6	-6.3	78.8
Levitt	76.3	25.3	127.3	9.1	143.5
Szathmári	32.8	14.1	51.5	8.2	57.4
Kajantie	-10.7	-50.1	28.7	-65.5	41.2
Tenhola	20.2	-60.3	100.7	-85.7	126.1
Walker	-1.9	-50.0	46.2	-65.2	61.4
Herrick	1.2	-49.7	52.2	-65.8	68.3

A positive regression coefficient indicates an inverse relation between birth weight and circulating cortisol level.

change much with age (27). Third, there were differences in the sex distribution between the included study populations. As differences in A-ring reduction between genders have been reported (28), data were also analyzed separately for males and females. However, we did not find evidence that the association between birth weight and circulating cortisol level was substantially different between genders. This is in line with the findings from a recent study performing dynamic HPA axis function testing, which found that the strength of the relation between birth weight and plasma cortisol rise after adrenocorticotrophin (ACTH) 1-24 was similar for men and women (29). Fourth, studies used different definitions for low birth weight. Finally, 2 studies had included individuals born prematurely. As there is evidence that circulating cortisol level as well as cortisol production are dependent on gestational age (15;20), we also performed an analysis restricted to individuals born after term gestation. However, exclusion of (only a limited number of) individuals born prematurely hardly changed the association between birth weight and circulating cortisol level. As we believe that the 5 aforementioned differences between study populations could not be ignored, a meta-analysis with random study effect was performed, though the strength of the overall association was nearly the same in a fixed effects model.

Studies also differed in their analytical methods: either linear regression analysis or comparison of mean circulating cortisol level between subgroups of birth weight. If the latter method was used – which was the case for most studies – it was always necessary to estimate the regression coefficient and the standard error. In one of the studies by Phillips et al (17), only

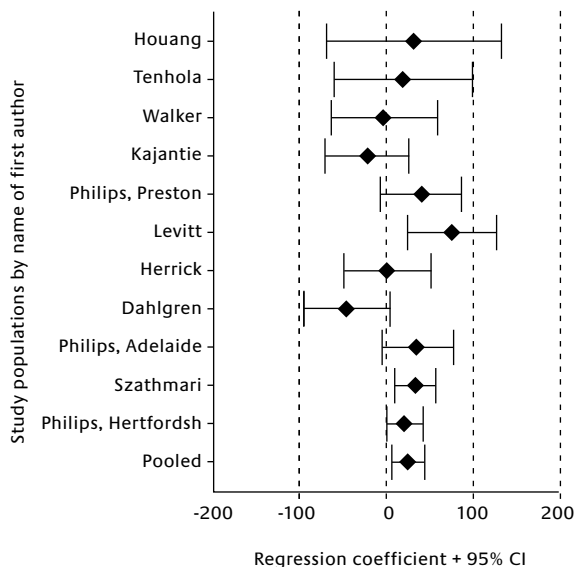


Figure 1. Individual and pooled regression coefficients with 95% confidence intervals.

Increase in circulating cortisol level (nmol/l) for each 1 kg lower birth weight with 95% CI (X axis), displayed for each study population (Y axis, by name of first author, ordered by CI width), and for the pooled data.

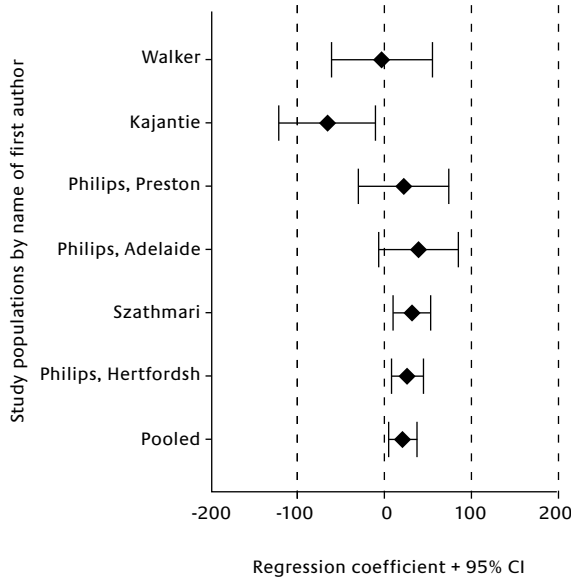


Figure 2. Individual and pooled regression coefficients with 95% confidence intervals – analyses by gender.

Increase in circulating cortisol level (nmol/l) for each 1 kg lower birth weight with 95% CI (X axis), displayed for each study population where data were provided by gender (Y axis, by name of first author), and for the pooled data.

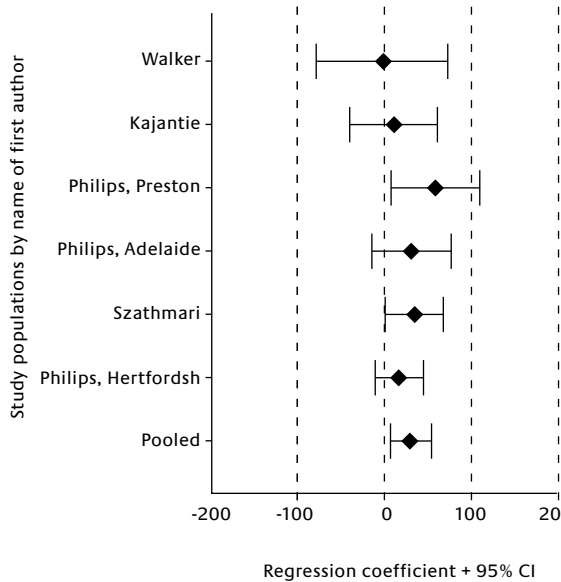


Figure 2B. Females

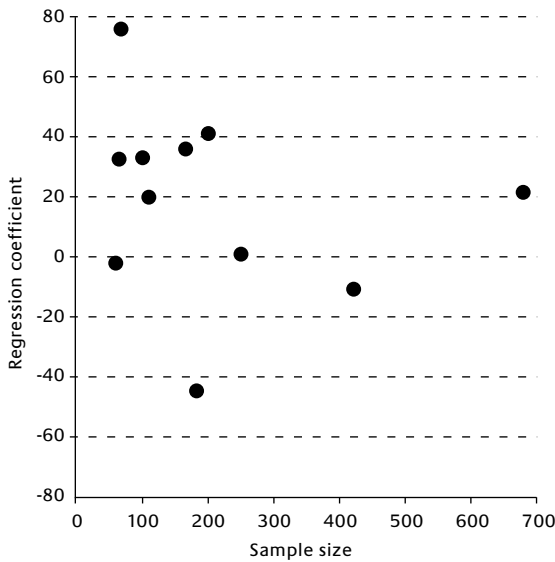


Figure 3. Funnel plot: regression coefficient versus sample size of the 11 included study populations.

The number of individuals within each study population (X axis) is plotted against its regression coefficient (Y axis).

adjusted data were reported (adjusted for age and BMI). As there are constraints in adjusting for current size in “fetal origins” studies (30), we also performed an analysis after exclusion of their data. This strongly reduced the magnitude of the pooled regression coefficient. However, earlier studies in the same subjects from Hertfordshire showed a positive relation between birth weight and current BMI in the males (31), and no relation at all in the females (32). Furthermore, current BMI was inversely associated with circulating cortisol level. Thus, adjustment for current BMI would rather decrease the relation between birth weight and circulating cortisol level than enhance it, implying that we only underestimated the true effect of birth weight on cortisol. Therefore, we did not exclude their data from our meta-analysis.

Our meta-analysis was based upon published data only. There may be a tendency to selectively publish results from large studies that are statistically significant. However, most studies included in our analysis were negative, i.e. they showed no statistically significant relation between birth weight and circulating cortisol level. Moreover, we did not find an association between the sample size of each study population and the strength of the association between birth weight and circulating cortisol level. We therefore believe that there is only minimal influence of possible publication bias on the outcomes of our meta-analysis.

How could the inverse association between birth weight and circulating cortisol level be explained? Circulating cortisol reflects the balance between cortisol production, and reversible interconversion to cortisone by 11 β -hydroxysteroid dehydrogenases (11 β -HSDs) and irreversible breakdown by A-ring reductases. Elevated circulating cortisol level may therefore result from increased cortisol production as well as decreased inactivation. The elderly males from

Hertfordshire with low birth weight had elevated 24-h urinary excretion of cortisol metabolites and enhanced responses of plasma cortisol to ACTH 1-24 (33). Their cortisol and ACTH levels after overnight low-dose dexamethasone suppression did not differ from the other men (33;34). Unexpectedly, their ACTH and cortisol responses to corticotrophin releasing hormone after dexamethasone were blunted rather than enhanced (34). Similar to the men, the females from Hertfordshire with low birth weight had enhanced cortisol responsiveness to synthetic ACTH (29). There is no evidence in humans that low birth weight is associated with alterations in activities of 11 β -HSDs (11). Interestingly, however, in line with earlier findings in rats (35), a recent study in small preterm infants showed that reduced placental 11 β -HSD type 2 activity was associated with less cortisone relative to cortisol in cord blood and lower birth weight (36).

Conclusions

Papers about the association between birth weight and basal cortisol level have been published from 1998 onwards. Sources of heterogeneity hampered the comparability of these studies. Although the majority of studies were underpowered, by using a meta-analytic approach we found an inverse association between birth weight and circulating cortisol level. Thus, our findings suggest that there is some evidence for a possible role of the HPA axis in the epidemiological association between birth weight and cardiovascular disease, at least in persons born after term gestation, but it is emphasized that the strength of the overall association between birth weight and basal cortisol level is weak.

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