Early Life Factors and Blood Pressure at Age 31 Years in the 1966 Northern Finland Birth Cohort

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Abstract—Data on the birth weight–blood pressure relationship are inconsistent. Although an inverse association has been suggested in several large studies, interpretation is complicated by publication and other biases. Few data are available on the relationship between other early growth measures and blood pressure. We examined the shape and size of association between determinants of fetal growth, size at birth, growth in infancy, and adult systolic and diastolic blood pressure at 31 years in the prospective northern Finnish 1966 birth cohort of 5960 participants. Birth weight, birth length, gestational age, ponderal index, and birth weight relative to gestational age showed a significant inverse association with blood pressure at age 31. Rapid growth in infancy ("change-up") was positively associated with blood pressure. Adjusted regression coefficients for birth weight indicated systolic/diastolic blood pressure lower by −1.7 (95% confidence interval [CI], −2.5, −1.0)/−0.7 (95% CI, −1.4, −0.02) mm Hg for 1 kg higher birth weight. The significant inverse association between birth weight and systolic blood pressure persisted without adjustment for adult body mass index for males. Among females, gestational age showed a stronger association with blood pressure than birth weight: gestational age higher by 7 weeks (equivalent to an average of 1 kg higher birth weight) among singletons associated with −2.9 (95% CI, −4.7, −1.1) mm Hg lower systolic blood pressure. Our results support the concept that birth weight, other birth measures, and infant growth are important determinants of blood pressure and hence cardiovascular disease risk in later life. **(*Hypertension*. 2004;44:838-846.)**

Key Words: cardiovascular disease ■ blood pressure ■ pregnancy ■ birth weight ■ growth ■ cohort study

Barker et al[1,2] first reported an inverse linear association between birth weight and systolic blood pressure (SBP), independent of current body weight. Although similar associations have been reported in children[3–9] and adults,[6,10–16] weak, nonlinear, or nonsignificant correlations have also been published,[17–22] and interpretation is complicated by publication and other biases.[22,23]

Most longitudinal studies on adults have been based on historic cohorts or on "follow-back" designs.[2,10,13,24] These have a number of potential limitations including retrospective data collection and an incomplete consideration of confounding factors operating throughout the life course. Prospective studies from birth or early childhood, with few exceptions,[1] have followed up to relatively young ages[4,6,7,9,17,25–27]; to date, no study has reported prospective data from early pregnancy through to early thirties.

We report the association of adult SBP and diastolic BP (DBP) with determinants of fetal growth,[28] size at birth, and growth in infancy and examine whether these associations were modified by factors such as current body size or socioeconomic status (SES) in extensive prospective data from the fetal period until 31 years from the Northern Finland 1966 Birth Cohort (NFBC 1966). The theoretical framework encompassed the life course model whereby biological and environmental factors since pregnancy are hypothesized to contribute to individual disease risk, with attention focused on possible pathways through which their effects might be mediated.[29] Our a priori hypothesis was that birth measures, in particular birth weight, are linearly and inversely associated with, and change-up infant growth realignment positively associated with, adult SBP/DBP, independent of maternal and other neonatal characteristics, lifestyle factors, and SES.

Methods

Births with expected deliveries in 1966 in Northern Finland (96.3% of all 1966 births) were eligible (n=12 058 live births). Women were recruited through maternity health centers (n=157)[30]; ≈80% visited the centers for the first time by the 16th gestational week. Follow-up in 1998 consisted of questionnaires to all offspring (n=11 637 alive) and clinical examinations for those living in the original target or

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Helsinki area (n=8463 eligible). The analyses are based on 5960 (70.4% of eligible; 2858 males and 3102 females) genetically homogenous whites with signed informed consent. The University of Oulu ethics committee approved the study.

Baseline data (Table 1) were collected by questionnaire during the 24th to 28th gestational week. The course of pregnancy was prospectively recorded in maternity records and transferred by midwives onto study forms, as were data on birth (99% in hospitals) and the newborn at time of delivery.[30,31] Growth data were collected at 1 year from child welfare centers (attendance 100%) and at 14 years by questionnaires (97% response).

BP Measurement at Age 31 Years

SBP and DBP were measured twice (averages used) with a mercury sphygmomanometer in a sitting position from the right arm after 15 minutes of rest by trained nurses using a standardized procedure and ongoing quality control.[32]

Early Growth Variables and Other Determinants

Birth weight (±5 g) and birth length (±1 cm) were measured immediately after birth.[30] Gestational age was defined by the mother's last menstrual period. Intrauterine growth pattern was assessed by: (1) percentiles computed for all singleton boys and girls (birth weight relative to gestational age [BW-GA]), where birth weight was defined as appropriate for gestational age if weight was between the 11th and 89th percentiles, large if it was 90th percentile or above, and small if it was 10th percentile or below[19]; and (2) ponderal index (birth weight/length^3) as a measure of thinness/nutrition status. For postnatal growth, participants were defined as "changers," up or down, or "nonchangers" on the basis of comparison of sex-adjusted and gestational age–adjusted SD scores (SDSs; calculated for entire cohort alive at birth/1 year) for weight at birth and 1 year. The change in weight SDS of >0.67 SD[33] (equivalent to 1 "centile band" on standard growth charts) was used to differentiate nonchangers from changers. In regression analyses, change in weight SDS was used as a continuous variable.

Early life variables considered as potential confounders/modifiers of the early growth–adult BP association are shown in Table 1. Family SES at recruitment based on father's occupation (mother's if single) was classified I (high) to IV (low), and for farmers by farm size.[30] At 31, participant's own SES was based on occupation and employment data. Smoking at 31 was defined as ≥1 cigarette per day; alcohol consumption (continuous [grams per day] and categorized[34]) was estimated from current consumption by frequency, type, and amount[35] (validated against 7-day food diaries[36]); weight and height were measured and body mass index (BMI; weight/height^2) calculated.

Statistical Analyses and Missing Data

Unadjusted means of SBP/DBP at 31 years by early growth and other explanatory variables were compared by ANOVA. Linear and polynomial regression models were used to explore the shape of the association between early growth variables and BP. The effects of confounders/mediators of the birth size/early growth–BP association were examined by multiple regression; impact of adding each variable sequentially was evaluated before fitting the full models. Possible interactions between early growth measures and sex, BMI, and SES (for growth changers/nonchangers also with birth weight, BW-GA, ponderal index) were explored.[37] Participants with missing data were excluded from multivariate analyses. Our total study population (n=5960 attendees) and those with complete data in multivariate analyses (n=4793; 80% of attendees) were compared with the remaining cohort alive at 31 years. There were no substantive differences in gestational age or birth length, but there were fewer low birth weight children (<2500 g; 3% versus 3.8% in both comparisons) and more farmers' children among the attendees (21% versus 16%) and among those with complete data (20% versus 18%) than the remainder alive. Analyses were conducted for (1) the full cohort (twins included); (2) singletons; (3) males (all, singletons); and (4) females (all, singletons).

Results

Early Growth and Maternal Variables and BP at 31 Years

Table 1 shows unadjusted mean SBP/DBP by early growth and maternal variables. Where there was significant (nominal P value <0.05) heterogeneity, SBP was highest among those with the lowest birth weight, birth length, and those born small for gestational age (males), as well as lowest gestational age and those with change-up growth (females).

A similar pattern was found for DBP, although associations were weaker. Twins had higher SBP/DBP than singletons. SBP was highest for children of farmers and for those with mothers in the highest prepregnancy weight tertile.

Participant Adolescent/Adult SES and Health Behavior and BP at 31 Years

Farmers (4% of the population) had the highest SBP but not DBP (data not shown in the tables). Males and females in the highest BMI tertile had the highest SBP and DBP ($P<0.001$) as had males drinking the most alcohol (≥58 g per day; $P<0.05$; 3% of males). Smoking (46% males, 36% females) was associated with lower SBP/DBP ($P<0.05$). Height, weight, and SES at age 14 showed similar associations with BP as the 31-year measurements. Because of high correlations between anthropometry and SES at birth, 14, and 31 years (Pearson's correlation coefficient for BMI at 14 and 31 years 0.56; Spearman's correlation coefficient for SES at birth and 14 years 0.68; $P<0.001$ for both), 14-year data were not included in the final models.

Shape and Size of Association Between Early Growth and BP at 31 Years

Results of regression analyses of SBP/DBP for early growth measures among all participants/singletons are shown in the figure and Table 2. For all participants, a significant inverse sex-adjusted linear association was found between birth weight and SBP (regression coefficient −1.2 [95% confidence interval {CI}, −1.9, −0.5] mm Hg for 1 kg higher birth weight). Adjustment for birth/maternal variables slightly strengthened the inverse association (−1.6 [−2.4, −0.8]), which remained essentially unchanged with the addition of adult variables. For DBP, coefficients ranged from −0.4 (−1.0, 0.2) in the sex-adjusted model to −0.7 (−1.4, −0.02) mm Hg for 1 kg higher birth weight in the fully adjusted model (Table 2). Excluding twins reduced the steepness of the regression slopes (Figure). Of the birth/maternal factors, gestational age and prepregnancy BMI had the largest effect on the regression coefficients (data not shown).

In sex-specific analyses, an unadjusted inverse linear association was found between birth weight and SBP in all and singleton males and all females (Table 2). Adjustment for birth/maternal variables strengthened the association for males, which remained virtually unchanged after further adjustments (−2.2 [−3.3, −1.2]). In females, associations with birth weight after adjustment were statistically significant only when BMI was included. Regression coefficients were all inverse but nonsignificant for the birth weight–DBP association.

TABLE 1. Unadjusted Mean SBP and DBP for Males (n=2858) and Females (n=3102) at 31 Years and Distributions (n, %) of the Study Population by Early Growth and Maternal Variable Categories

	Male			Female		
Variables and Categories	n (%)	SBP Mean (SD)	DBP Mean (SD)	n (%)*	SBP Mean (SD)	DBP Mean (SD)
Early growth variables						
Birth weight, g						
<2500	82 (3)	132.7 (15.0)	82.0 (12.7)	101 (3)	122.9 (15.3)	75.7 (11.4)
2500–2999	300 (11)	131.2 (13.3)	80.6 (11.4)	370 (12)	119.7 (12.0)	74.4 (10.0)
3000–3499	863 (30)	130.7 (12.7)	80.3 (12.0)	1175 (38)	119.9 (12.1)	74.6 (10.8)
3500–3999	1034 (36)	130.2 (12.7)	80.3 (11.2)	1082 (35)	119.6 (12.3)	74.7 (10.9)
4000–4499	453 (16)	128.8 (12.0)	80.0 (10.4)	314 (10)	119.5 (11.6)	74.5 (11.0)
≥4500	126 (4)	130.8 (12.4)	80.4 (10.6)	60 (2)	120.1 (12.1)	75.7 (11.4)
P†		0.048	0.815		0.202	0.819
Length at birth, tertiles‡						
1 (lowest)	685 (24)	131.2 (13.6)	80.6 (11.9)	1136 (37)	120.3 (12.4)	74.8 (10.5)
2	1152 (41)	130.6 (12.6)	80.2 (11.5)	1333 (43)	119.8 (12.5)	74.7 (11.2)
3 (highest)	997 (35)	129.5 (12.1)	80.3 (10.9)	604 (20)	119.0 (11.6)	73.9 (10.3)
P†		0.022	0.788		0.104	0.219
Gestational age (weeks)						
<37	132 (5)	131.3 (13.8)	80.3 (13.1)	141 (5)	122.6 (14.1)	75.7 (10.4)
37–41	2114 (76)	130.3 (12.5)	80.3 (11.3)	2242 (75)	119.9 (12.3)	74.7 (10.9)
≥42	523 (19)	130.1 (13.4)	80.1 (11.3)	605 (20)	119.2 (12.1)	74.1 (10.7)
P†		0.593	0.960		0.015	0.252
BW-GA						
≤10% (small)	274 (10)	132.6 (14.0)	82.1 (11.2)	299 (10)	119.3 (12.4)	74.8 (10.2)
11–90% (appropriate)	2224 (80)	130.0 (12.6)	80.1 (11.5)	2393 (80)	119.9 (12.4)	74.6 (10.9)
≥90% (large)	271 (10)	129.9 (11.9)	79.9 (10.3)	296 (10)	120.8 (11.7)	74.9 (10.6)
P†		0.005	0.018		0.352	0.898
Ponderal index, tertiles‡						
1 (lowest)	947 (33)	130.8 (12.4)	81.0 (11.4)	1024 (33)	119.7 (12.4)	74.5 (10.7)
2	949 (34)	130.4 (12.6)	79.9 (11.6)	1023 (33)	120.4 (12.1)	74.6 (10.8)
3 (highest)	938 (33)	129.8 (13.1)	80.0 (11.1)	1026 (34)	119.7 (12.3)	74.7 (10.9)
P†		0.196	0.080		0.796	0.954
Multiple birth						
No	2789 (98)	130.2 (12.6)	80.3 (11.4)	3041 (98)	119.8 (12.2)	74.5 (10.8)
Yes (twin)	69 (2)	134.9 (14.6)	82.3 (11.1)	61 (2)	123.1 (12.7)	77.7 (8.94)
P†		0.003	0.156		0.039	0.024
Change in weight SDS (0–1 year)§						
Change-down	616 (26)	130.0 (11.8)	80.2 (10.8)	685 (26)	118.7 (11.8)	74.1 (10.9)
No change	1229 (51)	130.1 (12.9)	80.2 (11.5)	1368 (52)	120.2 (12.5)	74.7 (10.9)
Change-up	554 (23)	130.9 (12.8)	80.7 (10.9)	593 (22)	120.7 (12.6)	75.5 (10.8)
P†		0.359	0.658		0.009	0.062
Maternal variables						
SES at recruitment during pregnancy						
I (high)	205 (7)	129.0 (12.4)	79.4 (11.2)	201 (7)	117.6 (11.2)	74.1 (10.8)
II	483 (17)	129.4 (12.6)	80.1 (10.8)	496 (16)	119.6 (12.4)	75.3 (11.0)
III	946 (34)	129.7 (12.4)	80.7 (11.3)	1034 (34)	119.4 (12.3)	74.7 (10.7)
IV (low)	603 (21)	130.5 (13.1)	79.7 (11.1)	680 (22)	120.3 (12.2)	74.6 (11.2)
Farmers, area ≥8 hectares	268 (9)	131.3 (12.3)	80.1 (12.1)	305 (9)	120.5 (12.1)	73.9 (10.4)
Farmers, area <8 hectares	333 (12)	133.2 (13.3)	81.7 (12.1)	364 (12)	121.2 (12.5)	74.5 (10.2)
P†		0.000	0.106		0.013	0.578

TABLE 1. Continued

Variables and Categories	Male			Female		
	n (%)	SBP Mean (SD)	DBP Mean (SD)	n (%)*	SBP Mean (SD)	DBP Mean (SD)
Maternal age (years) at delivery						
<20	246 (9)	130.3 (12.9)	82.3 (12.0)	291 (9)	119.1 (11.3)	74.3 (11.0)
20–24	2084 (73)	130.2 (12.5)	80.4 (11.2)	2249 (73)	119.7 (12.3)	74.5 (10.8)
≥35	528 (18)	130.9 (13.3)	79.4 (11.7)	562 (18)	120.9 (12.4)	75.2 (10.5)
P†		0.468	0.005		0.068	0.357
Maternal height before pregnancy, tertiles‡						
1 (lowest)	986 (37)	130.4 (13.2)	79.9 (11.4)	1104 (38)	119.4 (11.7)	74.0 (10.7)
2	793 (29)	130.1 (12.6)	80.0 (11.6)	838 (28)	120.6 (13.0)	75.1 (11.3)
3 (highest)	927 (34)	130.8 (12.5)	80.9 (11.1)	1015 (34)	119.8 (12.2)	74.8 (10.6)
P†		0.531	0.108		0.105	0.084
Maternal weight before pregnancy, tertiles‡						
1 (lowest)	918 (34)	129.5 (12.7)	79.8 (11.5)	1071 (36)	118.8 (11.9)	74.1 (10.5)
2	919 (34)	130.2 (12.6)	80.4 (11.8)	933 (32)	119.6 (12.2)	74.6 (11.0)
3 (highest)	860 (32)	131.5 (12.7)	80.9 (10.9)	951 (32)	121.1 (12.8)	75.2 (11.0)
P†		0.003	0.108		0.000	0.057
Maternal smoking after second month of pregnancy						
No	2408 (86)	130.3 (12.5)	80.3 (11.5)	2620 (87)	119.9 (12.1)	74.6 (10.7)
Yes (at least 1 cigarette/day)	392 (14)	130.0 (14.3)	80.3 (11.0)	408 (13)	119.9 (12.9)	74.8 (11.2)
P†		0.074	0.149		0.844	0.893
Parity						
1	907 (32)	129.9 (12.6)	81.3 (11.9)	972 (32)	119.6 (12.2)	74.8 (10.9)
2–3	1132 (40)	130.4 (12.6)	79.9 (10.8)	1221 (39)	119.7 (12.7)	74.4 (11.1)
≥4	813 (28)	130.7 (13.0)	79.9 (11.5)	902 (29)	120.3 (11.7)	74.6 (10.2)
P†		0.377	0.011		0.428	0.713

*Numbers are for SBP, data on DBP missing for 6 women; †for heterogeneity, analysis of variance; ‡tertile cut-offs (calculated from the whole study population): length at birth 50, 51 cm; ponderal index 26.35, 28.27 kg/m^3; maternal height 158, 163 cm; maternal weight before pregnancy 55, 62 kg; §change in weight SDS >0.67 SD to differentiate nonchangers from catch-up/down groups.

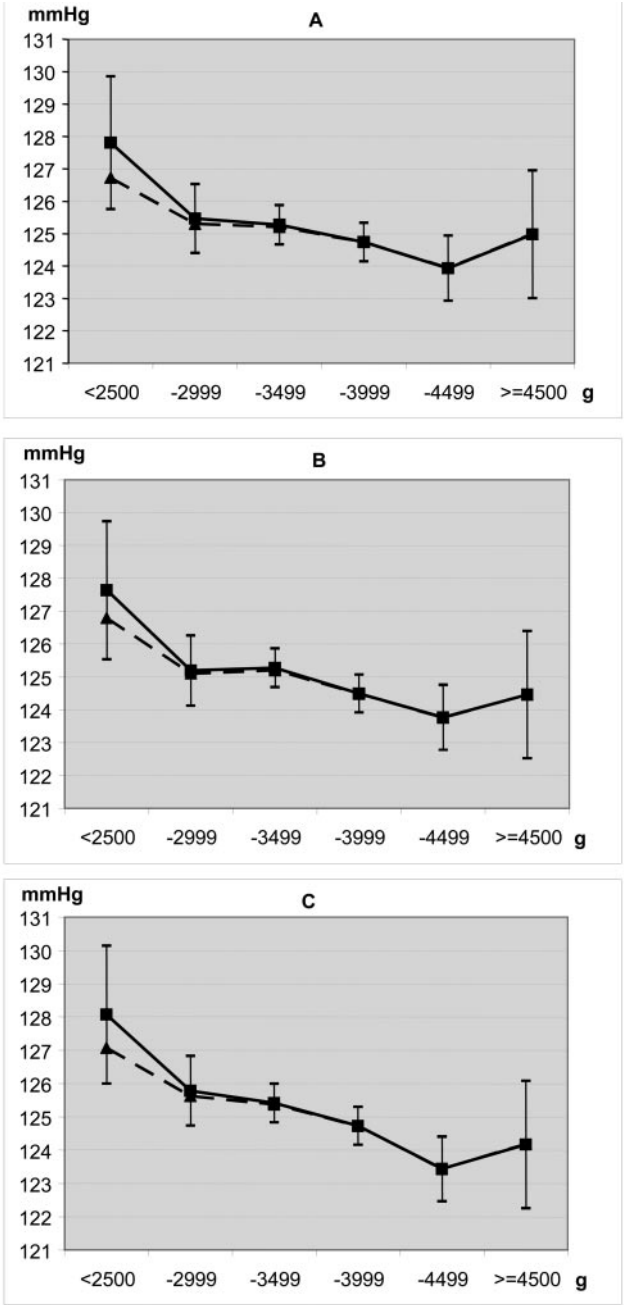
Other birth variables showed a similar pattern with BP, especially SBP. In singleton males and females, fully adjusted coefficients (±BMI) with SBP were all inverse: significant among males but not females for birth length, BW-GA, and (with BMI) ponderal index. Although BW-GA was only weakly associated with SBP in females, the relationship in singleton females between gestational age and SBP was marked and stronger than between birth weight and BP. Seven weeks greater gestation equates to an average of 1 kg higher birth weight; for the gestational age–SBP association in singleton females, 7 weeks greater gestation was associated with approximately −2.9 (−4.7, −1.1, fully adjusted) mm Hg lower SBP, which was independent of birth weight (data not shown), whereas 1 kg higher birth weight corresponds to −1.2 (−2.3, −0.1) mm Hg lower SBP (Table 2).

Change-up growth was significantly, positively associated with SBP in unadjusted and adjusted analyses (≈0.6 [0.2 to 1.0] mm Hg per unit increase in weight SDS), except when BMI (31 years) was included, attenuating the association. There was no consistent pattern for DBP.

There were no statistically significant interactions between birth weight and sex, BMI (31 years), or SES (at birth) for SBP/DBP. Significant interactions were found between gestational age and sex and BMI for SBP ($P<0.05$). Regression coefficients for gestational age and SBP among all participants at lowest/highest tertiles of BMI (cut-offs 22.5, 25.7 kg/m^2) were −6.9 (−10.0, −3.9)/−1.3 (−4.6, 1.9) mm Hg for gestation longer by 10 weeks (similar pattern for males/females). In females, interaction between ponderal index and BMI for SBP was significant ($P=0.009$); the regression estimates at lowest/highest tertiles of BMI (cut-offs 21.8, 24.8 kg/m^2) were −2.7 (−6.0, 0.7)/−0.8 (−3.8, 2.2) per kg/m^3. Change-up growth showed no interactions for SBP with these variables or other birth measures.

Discussion

This study is the first to analyze a comprehensive range of maternal, birth, and childhood measures in relation to adult BP from a large well-characterized general population–based cohort studied since early pregnancy. Our main findings were that (1) the association between birth weight and SBP was inverse-linear, particularly for males, with or without adjustment for current BMI; (2) the association for DBP was inverse but weaker than for SBP; (3) other birth



Association between SBP (mm Hg) at 31 years and birth weight (grams) for whole cohort including twins (solid line) and for singletons (dotted line). The 95% CIs for means are shown for the whole cohort. A, Adjusted for sex. B, Adjusted for sex, gestational age, family SES, parity, maternal height and weight before pregnancy, maternal age, and maternal smoking after second month of pregnancy. C, Adjusted also for SES, smoking, drinking, and BMI at age 31 years.

variables (gestational age, birth length, ponderal index, BW-GA) showed a similar pattern with BP, although less consistent than birth weight; (4) among females, the inverse association between gestational age and BP was stronger than that for birth weight; (5) infant change-up growth associated positively with BP; and (6) association of some early life factors (gestational age, ponderal index) with BP seems to be stronger in leaner adults.

A meta-analysis by Huxley et al[22] of 82 studies with data on birth weight and BP concluded that "birth weight is of little relevance to BP levels in later life." Issues addressed included variable data quality with variation in regression estimates and other measures of association, variable adjustment for confounding,[22] and reporting bias;[22,23] specifically, weaker associations were found in larger studies.[22] Most studies adjusted for current body weight or BMI. It is suggested that this produces artifactual inverse associations between birth weight and BP[22] because birth weight is positively associated with weight in later life, especially in childhood,[38] and current weight is positively associated with BP.[39] Also, current size may be on the causal pathway between early environment and adult disease risk. In our study, inverse associations with birth measures were found in most analyses with and without adjustment for BMI. However, BMI adjustment did remove the significant positive association between change-up growth and SBP.

The adjusted coefficient for SBP, with or without adjustment for BMI, was ≈3× that reported from other large studies of similar size.[22] Possible reasons for the larger regression estimates in our study include its careful design and conduct, high population representation, accuracy of measurements, and the ability to examine/control for potential confounders/mediators including singleton/twin status. Many previous studies relied on recalled data from questionnaires,[14] with some important confounders rarely adjusted for. Our study showed, especially among males and in all participant analyses, that adjustment for maternal characteristics tended to increase the size of the inverse regression coefficients, whereas adult variables had little effect. Few studies have reported estimates adjusted for gestational age or parental SES,[22] despite their association with birth weight[28] and cardiovascular risk factors.[40]

One particular strength of this study was that of contemporary measures, taken immediately after birth. Timing of birth weight measurement, as well as inaccuracy and rounding, may introduce a source of error. Errors in birth weight estimates would, because of "regression dilution" bias,[41] tend to underestimate the true strength of the association with health outcomes. As a result of standardized national maternity and child health care systems operating since the 1940s, staff were trained to record pregnancy and delivery events and take birth measurements,[42] improving accuracy. In our study, as in others, the birth weight–BP association was the most consistent among the early growth measures, possibly because birth weight is the most accurately measured; birth length requires the stretching technique, and gestational age is mostly based on mother's recall of the last menstrual period before pregnancy. In our study, last menstrual period was recorded at the beginning of pregnancy, decreasing the risk of recall bias.

There are some methodological points to consider. Clinical examination at 31 was restricted to those still living in the original study area or in the capital city area, which comprised the largest migrated group. Although this, together with nonresponse (30%), introduces possible bias, neither birth nor early sociodemographic data differed materially between those attending clinical examination or included in

TABLE 2. Unadjusted and Adjusted Linear Regression Coefficients Between SBP and DBP and Birth Weight, Birth Length, Ponderal Index, Gestational Age, BW-GA, and Catch-Up Growth in the 1966 Northern Finland Birth Cohort*

	SBP [mm Hg]			
Early Growth Variable	Adjusted for or Stratified by Sex β (95% CI)	Adjusted for Birth and Maternal Variables β (95% CI)	Adjusted for Birth, Maternal and Adult Variables Except BMI‡ β (95% CI)	Adjusted for Birth, Maternal and Adult Variables‡ β (95% CI)
Birth weight (per kg)				
All participants§	−1.2 (−1.9, −0.5)	−1.6 (−2.4, −0.8)	−1.5 (−2.3, −0.7)	−1.7 (−2.5, −1.0)
All males	−1.3 (−2.2, −0.3)	−2.2 (−3.4, −1.1)	−2.2 (−3.3, −1.1)	−2.2 (−3.3, −1.2)
All females	−1.1 (−2.1, −0.2)	−1.0 (−2.1, 0.1)	−0.9 (−2.0, 0.3)	−1.2 (−2.3, −0.2)
Singleton males	−1.0 (−2.0, −0.03)	−2.0 (−3.2, −0.9)	−2.0 (−3.2, −0.9)	−2.0 (−3.2, −0.9)
Singleton females	−0.9 (−1.9, 0.1)	−0.9 (−2.1, 0.2)	−0.8 (−2.0, 0.4)	−1.2 (−2.3, −0.1)
Birth length (per 10 cm)				
All participants§	−2.8 (−4.5, −1.1)	−3.3 (−5.3, −1.4)	−3.1 (−5.0, −1.1)	−2.6 (−4.5, −0.8)
Singleton males	−1.9 (−4.4, 0.6)	−4.1 (−7.0, −1.3)	−4.1 (−7.0, −1.2)	−3.7 (−6.5, −1.0)
Singleton females	−2.7 (−5.1, −0.2)	−2.1 (−4.9, 0.7)	−1.8 (−1.6, 1.0)	−1.1 (−3.7, 1.6)
Ponderal index (per kg/m^3)				
All participants§	−0.9 (−2.4, 0.5)	−1.0 (−2.5, 0.4)	−1.1 (−2.5, 0.4)	−2.2 (−3.6, −0.9)
Singleton males	−1.5 (−3.7, 0.6)	−1.7 (−3.9, 0.4)	−1.8 (−4.0, 0.4)	−2.1 (−4.2, −0.1)
Singleton females	0.1 (−1.9, 2.0)	−0.1 (−2.1, 1.8)	−0.1 (−2.1, 1.8)	−1.8 (−3.7, 0.1)
Gestational age (per 10 weeks)				
All participants§	−2.8 (−4.7, −0.9)	−2.8 (−4.7, −0.9)	−2.8 (−4.7, −1.0)	−3.2 (−5.0, −1.4)
Singleton males	0.3 (−2.5, 3.2)	0.2 (−2.7, 3.0)	−0.1 (−2.9, 2.8)	−0.5 (−3.2, 2.2)
Singleton females	−4.4 (−7.1, −1.7)	−4.4 (−7.1, −1.7)	−4.1 (−6.7, −1.4)	−4.2 (−6.7, −1.6)
BW-GA (per 10% difference, ×10)				
All participants§	−1.4 (−2.6, −0.2)	−2.3 (−3.6, −1.0)	−2.2 (−3.5, −0.9)	−2.6 (−3.8, −1.4)
Singleton males	−2.4 (−4.2, 0.6)	−3.6 (−5.5, −1.6)	−3.5 (−5.4, −1.6)	−3.5 (−5.3, −1.6)
Singleton females	0.0 (−1.7, 1.7)	−0.8 (−2.7, 1.0)	−0.7 (−2.5, 1.2)	−1.4 (−3.1, 0.4)
Change in weight SDS between 0 and 1 years				
All participants§	0.5 (0.2, 0.9)	0.5 (0.2, 0.9)	0.6 (0.2, 0.9)	0.3 (−0.03, 0.6)
Singleton males	0.6 (0.1, 1.1)	0.6 (0.1, 1.1)	0.6 (0.1, 1.1)	0.2 (−0.3, 0.7)
Singleton females	0.5 (−0.01, 0.9)	0.6 (0.1, 1.0)	0.5 (0.1, 1.0)	0.3 (−0.1, 0.8)

*Analyses include those with all data in the fully adjusted model: whole cohort n=4793; all males n=2338; all females n=2455; singleton males n=2287; singleton females n=2403.

†Adjusted for sex as appropriate, gestational age in analyses for birth weight, birth length, ponderal index, and change in weight SDS score between 0 and 1 years, and in all analyses for family social class, parity, maternal height and weight before pregnancy, maternal age, and smoking after second month of pregnancy.

‡Adjusted for †plus adult factors: social class, smoking, and drinking, with and without BMI.

§All-participant analyses also adjusted for sex.

the final multivariate analyses and the remainder alive. Although our statistical power was high for all participant analyses, it was lower in some strata, especially twins. Although there were only 130 twins in our sample, inclusion of twin data allowed us to show their impact on the birth weight–BP relationship in a general population sample. In contrast to some previous studies,[43] twins had significantly higher adult BP than singletons and made an important contribution to higher adult SBP among low–birth weight children (Figure).

We selected potential confounders/mediators of the birth weight/BP association based on their theoretical importance and were guided by the mechanisms possibly underlying the association. These include biological factors and environmental factors (such as SES, smoking, alcohol), which are known to be associated with fetal growth/outcome or may mediate the association between fetal factors and adult cardiovascular disease (CVD). It can be questioned whether maternal factors (such as height and weight) should be considered traditional confounders because they might indicate common genetic background on the "causal" pathway or perhaps indicate shared nutritional or metabolic environment. In practice, the birth measures were associated with later BP with or without adjustment for these factors, so whatever the mechanism, the associations are not fully "explained" by well-known determinants of birth weight or BP. Although our epidemiological study dating back to the 1960s does not permit broader inferences as to possible mechanisms, it does point to areas for further basic research.

We found evidence of interactions such that the inverse association between gestational age and SBP (and ponderal

TABLE 2. Continued

DBP [mm Hg]			
Adjusted for or Stratified by Sex β (95% CI)	Adjusted for Birth and Maternal Variables β (95% CI)	Adjusted for Birth, Maternal and Adult Variables Except BMI‡ β (95% CI)	Adjusted for Birth, Maternal and Adult Variables‡ β (95% CI)
−0.4 (−1.0, 0.2)	−0.6 (−1.3, 0.2)	−0.5 (−1.2, 0.2)	−0.7 (−1.4, −0.02)
−0.2 (−1.1, 0.6)	−0.6 (−1.6, 0.5)	−0.6 (−1.6, 0.4)	−0.6 (−1.6, 0.4)
−0.6 (−1.5, 0.2)	−0.6 (−1.6, 0.4)	−0.5 (−1.5, 0.4)	−0.9 (−1.8, 0.1)
−0.1 (−1.0, 0.8)	−0.4 (−1.5, 0.7)	−0.4 (−1.5, 0.6)	−0.4 (−1.4, 0.6)
−0.5 (−1.3, 0.4)	−0.5 (−1.5, 0.5)	−0.4 (−1.4, 0.6)	−0.7 (−1.7, 0.2)
−0.3 (−1.8, 1.2)	−0.4 (−2.2, 1.3)	−0.4 (−2.1, 1.4)	0.03 (−1.6, 1.7)
0.4 (−1.9, 2.7)	−0.2 (−2.8, 2.4)	−0.4 (−3.0, 2.2)	0.01 (−2.5, 2.5)
−0.4 (−2.6, 1.8)	−0.1 (−2.6, 2.3)	0.1 (−2.4, 2.5)	0.7 (−1.6, 3.0)
−1.4 (−2.6, −0.1)	−1.3 (−2.6, −0.1)	−1.3 (−2.6, −0.04)	−2.4 (−3.6, −1.1)
−1.4 (−3.3, 0.6)	−1.3 (−3.3, 0.7)	−1.2 (−3.2, 0.8)	−1.6 (−3.5, 0.3)
−1.0 (−2.7, 0.7)	−1.1 (−2.8, 0.6)	−1.1 (−2.8, 0.7)	−2.5 (−4.2, −0.9)
−1.1 (−2.8, 0.5)	−1.4 (−3.1, 0.3)	−1.3 (−3.0, 0.4)	−1.7 (−3.3, −0.1)
−0.2 (−2.7, 2.4)	−0.5 (−3.0, 2.1)	−0.4 (−2.9, 2.2)	−1.0 (−3.4, 1.5)
−1.8 (−4.1, 0.6)	−1.8 (−4.1, 0.6)	−1.6 (−3.9, 0.8)	−1.6 (−3.8, 0.6)
−0.4 (−1.5, 0.7)	−0.8 (−1.9, 0.4)	−0.7 (−1.9, 0.5)	−1.1 (−2.2, 0.02)
−0.4 (−2.1, 1.2)	−0.9 (−2.7, 0.8)	−1.0 (−2.7, 0.8)	−0.9 (−2.6, 0.7)
0.2 (−1.3, 1.7)	−0.2 (−1.8, 1.4)	−0.1 (−1.7, 1.5)	−0.7 (−2.3, 0.8)
0.3 (−0.01, 0.6)	0.3 (−0.03, 0.6)	0.3 (−0.01, 0.6)	0.0 (−0.2, 0.3)
0.3 (−0.2, 0.7)	0.2 (−0.3, 0.6)	0.2 (−0.3, 0.6)	−0.2 (−0.7, 0.2)
0.3 (−0.2, 0.7)	0.3 (−0.2, 0.7)	0.3 (−0.1, 0.7)	0.1 (−0.3, 0.5)

index and SBP for females) was larger among those in the lowest third of adult BMI than in the highest, suggesting etiologic factors for CVD could differ by body size. Animal and human studies suggest that nutritional and hormonal mechanisms may help explain associations between reduced fetal growth and later CVD risk factors.[27,44] Low ponderal index is a marker of poorer fetal nutrition, as is partly shorter gestation.[28] In rodents, β-cell size and total pancreatic β-cell weight in progeny have been reported to be lower when dams were on a low-protein, nonoptimal diet.[44] This may result in impaired insulin-mediated growth in the fetus and insulin resistance in adult life,[45] with associated high BP but not necessarily obesity. Stern et al[46] suggested that in humans, the nongenetic environmental component may be more important for disease development in lower–birth weight individuals than in those with higher birth weights. Because high–birth weight individuals tend to have higher adult weight than those with average birth weight,[15,38] there may be a genetic component[46] in the etiology of CVD risk with higher BMI, whereas poor fetal growth and nutrition may be relatively more important among thinner adults. However, it is not possible to rule out a genetic component that could also associate with poorer fetal growth and nutrient intake, and later risk of higher BP.

Some studies[4,8,11,12] exploring growth measures other than birth weight have shown varying associations with BP, more often inverse with SBP than with DBP as in our study. Our results indicate that not only markers of intrauterine growth

restriction and its determinants but other factors related to the intrauterine environment such as determinants of preterm birth[31] and later growth patterns may be important in development of CVD risk. Positive growth realignment, change-up, includes children whose in utero growth does not follow their genetic growth potential because of restricted nutrient supply.[47–49] Our study did not fully support this because we did not observe any interaction of change-up growth in infancy with indicators of fetal growth (ie, the association between change-up growth and later BP was no more marked for participants with lower birth weight, ponderal index, or BW-GA). However, our results strengthen the argument that associations between a wide range of early growth measures and BP are etiologically important and that the mechanisms in disease development might differ for males and females, despite recent suggestions that sex differences in the association between birth weight and BP were a chance finding.[50]

Perspectives

Our study, the largest to date with extensive pre/perinatal and early life data until 31 years, adds support to the concept that the fetal environment is an important determinant of future BP patterns and CVD risk. Investigations are needed to understand whether fetal programming of endocrine and metabolic pathways occurs in humans, as it does in laboratory animals. Such studies need to include genetic markers associated with prenatal growth and chronic disease risk and whether programming is modified or affected by infant and childhood growth patterns. This would offer insights into the effects of prenatal neuroendocrine and metabolic factors on the fetus and open avenues to explore possible interventions.

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