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DEVELOPMENTAL DETERMINANTS OF BLOOD PRESSURE IN ADULTS

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■ **Abstract** Over the past 20 years a large and varied body of research has attempted to make the case for the developmental origins of elevated adult blood pressure (BP). Experimental animal research has identified plausible biological mechanisms through which fetal nutritional insufficiency may affect adult BP. The majority of human epidemiologic studies demonstrate an inverse association of birth weight (the most commonly used marker of fetal nutrition) with adult BP and higher risk of hypertension among individuals with lower weight at birth. The most adverse BP outcomes occur among individuals who were small at birth but relatively large as adults, a finding that suggests a role for postnatal growth. We critically review the literature on proposed mechanisms and epidemiologic evidence for developmental origins of adult BP and hypertension, considering associations with birth weight, maternal nutrition during pregnancy, child growth patterns, and infant feeding.

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INTRODUCTION

Hypertension represents a major public health challenge worldwide owing to its high prevalence, worsening trends, and importance as a risk factor for cardiovascular disease mortality. Based on the most recent U.S. National Health and Nutrition Examination Survey (1999–2000), age-adjusted prevalence of hypertension among adults was 28.4%, and this represents a 30% increase since the prior (1988–1994) survey (34). A selection of age-adjusted prevalence rates from other countries is presented in Table 1 (61). These data provide impressive evidence of the magnitude of this worldwide problem.

Although a great deal is known about modifiable risk factors for hypertension, including obesity, smoking, alcohol consumption, diet, and physical activity, these factors do not fully explain differences in its occurrence. A newer and still controversial area of research draws our attention to the developmental origins of elevated blood pressure (BP) and other noncommunicable diseases. The main tenet of the developmental origins of adult health and disease (DOHaD) hypothesis is that nutritional insufficiency in early life programs disease risk through persistent effects on structure and metabolic function of organ systems. Early life responses to nutritional insufficiency may enhance survival in the short run, but may be maladaptive in later life when the organism no longer is faced with insufficiency (40).

BP is the most studied outcome in tests of the DOHaD hypothesis, largely because of its ease of measurement and known association with cardiovascular disease mortality. A vast literature on this topic has developed over the past two decades. Extensive reviews and meta-analyses of the animal and epidemiologic literature have been published. In addition, the *Annual Review of Nutrition* recently published a review (106) of the effects of maternal nutrition in pregnancy on long-term health outcomes in offspring. Here, we provide a broad overview of the developmental origins of BP and cite recent reviews for readers to consult for further details. We begin by discussing mechanisms through which nutritional

TABLE 1 Age-adjusted prevalence of hypertension in selection populations, based on national survey data (except for India)

	Year	Age range	% Male	% Female
United States	1999–2000	18+	38.3	28.7
Germany	1997–1999	18–79	55.4	56.6
Mexico	1992–1993	20–69	38.6	30.1
China	2000–2001	35–74	28.8	26.6
India*	2002	35+	47.5	48.4
South Africa	1998	15–65	22.9	23.4

*Based on survey of urban adults in Mumbai; n = 88,653.

Data from (61).

factors in early life may influence BP, with an emphasis on kidney development and the role of glucocorticoids. We then review the epidemiologic literature, examining how BP relates to birth weight, maternal nutrition during pregnancy, child growth patterns, and infant feeding. Limitations of human studies are discussed and linked with suggestions for future research.

BLOOD PRESSURE REGULATION: WHAT IS "PROGRAMMABLE" AND WHAT ARE THE MECHANISMS?

BP is regulated through complex physiological mechanisms, involving the kidneys, factors that affect endothelial function and arterial compliance, the sympathetic nervous system, the hypothalamic pituitary adrenal (HPA) axis, and the renin-angiotensin system. Prenatal influences on these systems have been explored as potential mechanisms through which fetal nutritional insufficiency affects long-term BP. The biological plausibility of the DOHaD hypothesis is generally well established by experimental research in animals. Nutritional insufficiency is thought to be the primary programming stimulus (45), although other stressors also play a role. Strong evidence from animal studies shows that fetal growth restriction secondary to maternal dietary restriction (11, 68, 127, 136), manipulation of uterine blood supply (3), or administration of corticosteroids during pregnancy (26, 27) elevates offspring BP. Animal models typically induce fetal nutritional insufficiency by restricting maternal intake of food or specific nutrients. Administration of glucocorticoids during pregnancy mimics the effects of dietary restriction on fetal growth, and this method has been used often in animal models of fetal programming.

Potential Mechanisms

FETAL EXPOSURE TO EXCESS GLUCOCORTICOIDS Glucocorticoid exposure is an attractive explanation for fetal programming of BP because it is a common underlying factor for many structural and physiological changes related to BP regulation. Extensive reviews on the HPA axis and glucocorticoids have been published (e.g., 13, 35, 65, 91, 114). Briefly, fetal exposure to glucocorticoids is normally limited until late in gestation because of low fetal endogenous production, and protection from maternal cortisol through the action of 11ß-hydroxysteroid dehydrogenase type 2 (11ßHSD-2), which converts active cortisol to its inactive form in the placenta. When maternal cortisol levels are elevated or placental expression of 11ßHSD-2 is low (either of which can follow maternal nutritional insufficiency), the fetus can be exposed to excess cortisol. High fetal exposure can reset the fetal HPA axis, resulting in chronic elevation of cortisol levels and altered response to stimuli, with consequences for development of hypertension (13, 104). Cortisol also affects organ growth and differentiation, and can produce permanent deficits

such as reduced nephron number (see below). High cortisol may also affect the mother's ability to properly nourish offspring during lactation (131).

ALTERATIONS IN KIDNEY STRUCTURE AND FUNCTION The hypothesis linking fewer nephrons at birth with increased hypertension risk in adulthood followed the observation that BP is elevated when renal mass is surgically reduced (15, 81, 82). The role of nephrogenesis in fetal programming of adult BP has been reviewed extensively (67, 85). Animal models show that maternal dietary protein restriction or glucocorticoid administration during pregnancy impairs nephrogenesis and results in offspring with smaller kidneys with fewer nephrons (136, 137). Structural deficits have also been observed in the kidneys of growth-retarded human infants (53, 118).

Nephrogenesis may be impaired by alterations in the activity of the renin-angiotensin system [reviewed by Rasch and colleagues (105)], possibly through lower renal expression of the angiotensin II type 2 receptor (93). Although protein restriction has been the main animal model, there is also evidence that maternal vitamin A (16) and iron deficiency (77) result in reduced nephron number. When nephron number is reduced, the glomerular filtration rate is increased, resulting in further nephron loss, an increase in BP to sustain hemodynamic function, and a progressive worsening of kidney damage that leads to elevated BP. Altered gene expression in nephron-deficient kidneys (12, 84) may also affect the capacity of nephrons to retain salt and water.

THE VASCULAR SYSTEM In growth-restricted fetuses, elastin in the walls of the aorta and large arteries is deficient, and this defect could eventually lead to arterial stiffness and elevated BP (89, 90). Inconsistent results from humans reflect differences in methods used to measure arterial stiffness, site of measurement, and degree of control for confounding. There is evidence of lower arterial compliance (often measured by pulse wave velocity) in adults who were small at birth (88). Other studies found no relationship of birth weight to pulse wave velocity [e.g., among adults in India (63), Wales (95), and the Netherlands (101)]. A study in Ireland (96) found opposite effects in men and women, whereas a Dutch study (126) found a positive association of birth weight with carotid arterial compliance, but a weaker relationship with brachial and femoral arterial compliance that attenuated when adjusted for height.

Brawley and colleagues (14) reviewed mechanisms through which maternal dietary restriction affects peripheral arterial function, and suggested reduced sensitivity to nitric oxide and reduced endothelium-dependent relaxation as fetal responses with long-term implications for elevated BP. IJzerman and colleagues (58) found a significant association of low birth weight with impaired microvascular function, leading to their suggestion that impaired capillary recruitment is a potential mechanism for fetal programming of BP.

EPIGENETIC MECHANISMS Researchers have suggested alterations in telomere length as a potential mechanism through which hypertension is programmed (7,

25). Briefly, telomeres are noncoding nucleotide sequences found at the ends of chromosomes. During each cycle of DNA replication, a few nucleotides at the ends of chromosomes are invariably lost, thus the telomeres act as a buffer to protect the coding portions of the chromosomes. Telomere attrition eventually prohibits further cell division and results in cellular senescence. As telomeres erode over time, they can be relengthened by the action of the enzyme telomerase, thus preventing the telomeres from becoming too short for cell division.

The potential role for telomere length as a mechanism to explain the developmental origins of adult disease is derived from the following points: Telomere length is largely determined before birth, through genetics and environmental factors (99); short telomeres are associated with elevated pulse pressure and hypertension in adults (5, 25, 115); telomerase activity is high in many fetal tissues, in association with rapid growth in this period (7); and telomerase activity can be regulated by estrogen and possibly other steroid hormones active in utero (5, 6, 25). If telomerase activity were somehow reduced, then the tissues affected, which could include the kidneys, heart, or vasculature, would suffer from abnormally reduced telomeres, which could in turn lead to earlier deterioration of these tissues in adulthood and the resulting hypertension. There is little evidence yet to support this hypothesis, but in recent experiments, fetal growth retardation followed by rapid catch-up growth resulted in elevated telomere attrition in rodent kidneys (5, 25).

Other epigenetic mechanisms have also been proposed. There is evidence that fetal DNA methylation (an important regulator of gene transcription) in utero can be altered through restricting the supply of nutrients to the fetus (83). Folic acid intake has also been suggested as an important factor in fetal DNA methylation (92). For example, feeding pregnant agouti (Avy/a) mice a methyl-supplemented diet (that included folate) altered the offspring's expression of the *agouti* (*Avy*) gene (135), which is associated with obesity and hyperinsulinemia. It has also been recently demonstrated in rats that uteroplacental insufficiency alters gene methylation in the fetal rat kidney (39, 103).

It is also possible, but not well investigated, that clonal selection among rapidly dividing cells during development could select cell lines that are adapted to an abnormal intrauterine environment but that cause chronic disease later in life (132). Metabolic differentiation of cells could have similar effects (132).

OTHER PROPOSED MECHANISMS Fowden & Forhead (35) reviewed endocrine mechanisms of intrauterine programming, with a focus on insulin, thyroid hormones, growth hormone and insulin-like growth factors (IGFs), and glucocorticoids. IGFs are of interest because they are highly responsive to maternal nutritional insufficiency (41), play an important role in prenatal growth, and are related to adult cardiovascular function [see review by Holt (51)]. IGF-I may affect BP through its role in growth of vascular smooth muscle cells and control of regional blood flow by nitric oxide–mediated vasodilation [reviewed by Green (43)].

Hattersley & Tooke (48) proposed that genetically determined insulin resistance underlies both restricted fetal growth and adult insulin resistance and

cardiovascular disease. This hypothesis is supported by a study showing that allele differences in an insulin gene are associated with size at birth (29). Complicating the fetal insulin hypothesis, however, is the possibility of intergenerational programming effects that could be a nongenetic mechanism of inheritance of low birth weight and elevated adult BP. These potential effects are summarized by Drake & Walker (28).

THE ROLE OF BODY COMPOSITION Adult body mass index (BMI) is often considered as a potential confounder of the relationship of birth size to later BP. If variation in body composition is the result of fetal programming, indicators of body composition should be considered as potential mediators rather than confounders. Rogers (109), Oken & Gillman (98), and Martorell et al. (87) recently reviewed evidence for fetal origins of obesity. Most studies report a positive association of birth weight to BMI later in life, although a J-shaped association has also been observed (24). The attenuation of this relationship with adjustment for maternal BMI suggests a role for genetic or behavioral factors that contribute to both enhanced fetal growth and postnatal development of obesity. There is stronger, though not entirely consistent, evidence for fetal programming of fat patterning, with lower birth weight associated with central adiposity after adjustment for BMI. Early postnatal catch-up growth following intrauterine growth restriction may also relate to increased central fat (100).

Vickers and colleagues (128, 129) offer intriguing evidence that maternal undernutrition in pregnancy produces offspring that are less physically active and hyperphagic throughout their postnatal life, particularly in response to a high-calorie diet. This combination of high energy intake and low activity leads to higher levels of body fat and significantly elevated BP.

There is also evidence of prenatal effects on lean body mass. Singhal and colleagues (122) show that higher birth weight is associated with an increase in fat-free mass, but not fat mass, in adolescents. Similarly, a Guatemalan study found lower fat-free mass in individuals with a history of growth retardation (76). Yajnik describes the "thin-fat" Indian baby who, in response to maternal nutritional insufficiency, is born with a deficit of skeletal muscle but not fat. This pattern persists into adulthood, and is associated with insulin resistance and cardiovascular disease (138).

HUMAN EPIDEMIOLOGIC STUDIES

Although plausible mechanisms have been identified in animal studies, human epidemiologic studies are mostly observational and are ill suited to allow causal inferences about the consequences of early life exposures. Given the recent focus on DOHaD, there are currently no adult studies designed specifically to test the hypothesis. Data used to explore developmental origins of adult BP typically derive from prospective cohort studies or data sources established for other purposes (e.g.,

registries), or from studies that measure current BP and related factors and obtain birth information retrospectively. These studies often lack sufficient data on early exposures and are therefore not ideally suited to test fully the DOHaD hypothesis. Furthermore, the literature is dominated by European studies, where more data are available, particularly from large cohorts, but where poor maternal and fetal nutrition is less prevalent.

The majority of studies use birth weight as an indicator of fetal nutritional status. Studies from the 1980s to mid 1990s typically presented correlation coefficients or beta coefficients from models in which BP is regressed on birth weight. Criticism of birth weight as an indicator of fetal nutritional sufficiency led to studies that considered other birth outcomes (gestational age, length, and body proportions at birth) and maternal diet and nutritional status during pregnancy. The observation that an inverse relation of size at birth to later BP is amplified or seen only when adult size is taken into account led to a new emphasis on the role of postnatal growth (8) and a broadening of emphasis to include "developmental" rather than just fetal origins of adult disease. The human literature is now characterized by a greater focus on potential mechanisms, with measurement of factors that influence BP, such as cortisol levels, arterial compliance, or sympathetic nervous system activity.

Relationship of Birth Weight to Adult Blood Pressure

A substantial body of literature documents an association of birth weight with later BP. The first studies were published in the 1980s: In a large national U.K. cohort, Wadsworth et al. (130) found an inverse relation of birth weight to systolic BP at age 36. Gennser and colleagues (37) found a significantly higher risk of having elevated diastolic BP among Swedish army conscripts who had been growth retarded at birth compared with those whose birth weight was appropriate for gestational age (OR 3.63; 95% CI 1.14 to 12.57).

There have been many subsequent studies, and those published through 1996, with quantitative assessment of the relationship of birth weight to later BP, were reviewed by Leon & Koupilova (73) and Law & Shiell (70). Huxley et al. (57) updated the latter review with 1996–2000 publications. In addition, Huxley et al. (54) more formally reviewed studies that reported regression coefficients of systolic BP on birth weight. In all but 3 of 55 reports (for which the total sample size was 382,514), these regressions, adjusted for current body size, produced a negative coefficient on birth weight, with effects in adults ranging from −0.35 to −5.9 mm Hg per kg. However, many of the estimates have wide confidence intervals, and the 95% CI excluded zero in only about half of the studies. In a formal meta-analysis of systolic BP adjusted for sample sizes, the pooled estimate of the effect of birth weight was −1.38 mm Hg per kg in children and adults combined (113). There was substantial heterogeneity, with smaller studies having larger negative regression coefficients. Huxley et al. (54) point out that of 48 studies that did not report a regression coefficient but included a direction of effect, only 25 found it to be inverse, suggesting publication bias.

Table 2 summarizes adult studies published since 2000, identified by a Pub Med search using key words "blood pressure or hypertension" and "birth weight or fetal growth retardation or fetal programming." This was not intended as an exhaustive search for a formal review or meta-analysis, but to provide a sense of the range of study types and new findings.

The recent studies remain consistent with earlier ones in finding a modest inverse relation of birth weight to adult systolic BP, or a significantly increased risk of hypertension with lower birth weight. Given the controversy about adjustment for current body size, many of the studies report unadjusted values, or values both adjusted and unadjusted for size in adulthood. Details of several of the larger studies are presented to illustrate typical methods and results.

The largest studies take advantage of data collected during physical examinations for military conscription and linked with birth records. For example, in a sample of 165,136 Swedish conscripts, Leon et al. (74) reported a 0.6 (95% CI 0.5–0.7) mm Hg decrease in systolic BP per kg increase in birth weight unadjusted, and a 1.47 (1.37–1.57) mm Hg decrease adjusted for adult height and weight. Lundgren et al. (80), in an even larger sample (276,033) of Swedish 17- to 24-year-old conscripts, reported that risk of having systolic BP above the 90th height-standardized percentile increased by 15% (17% when adjusted for birth length, gestational age, adult height, and BMI) for each 1-standard deviation increase in birth weight. A strength shared by these studies is their very large, representative samples of young adult males. Estimates of effect tend to be precise and highly significant, even when coefficients are small. However, as noted by Leon (74), measurement of BP at conscription may be subject to more error than measurement using more standardized protocols, leading to a possible underestimation of effects.

Among 7876 participants in the Vasterbotten Intervention Program in Sweden, Mogren et al. (94) found that low birth weight (LBW; less than 2.5 kg) significantly elevated risk of hypertension (based on standard cut points and measured BP) in adult men and women, ages 29–41 years. Adjustment for current BMI slightly increased the odds ratios and effects were stronger in women than in men: LBW was associated with a seven times higher likelihood of having adult systolic BP > 160, while the odds ratio in men was 2.16.

In an ongoing prospective Iceland Heart Association study, Gunnarsdottir and colleagues (44) found that increased hypertension risk (defined using cut points of 140 mm Hg for systolic and 90 mm Hg for diastolic BP, or taking medication to lower BP) was associated with lower birth weight in women, but not men. Further analysis of the large Helsinki University Central Hospital 1924–1944 birth cohorts in Finland also show lower odds (9) and a lower cumulative incidence of hypertension (defined as a record of having taken medication to lower BP) with increasing birth weight (10, 30, 31).

The inverse association of birth weight with adult BP in these populations with low mortality, little nutritional insufficiency, and high mean birth weights underscores the need to consider failure to reach growth potential rather than small birth size as a measure of fetal nutritional insufficiency. More studies from

TABLE 2 Summary of papers (published since 2000) relating birth weight to adult blood pressure or hypertension*

Location of study	Reference	Sample and study type	n	Age	Result (regression coefficient units are mm Hg per kg BW, 95% CI in parentheses unless otherwise noted)
United Kingdom	(56)	Offspring of participants in Oxford Nutrition Survey of wartime dietary rations in pregnant women	137	50	No association of BW to BP in 110 adults not taking medication for HTN, adjusted (age, gender, BMI, social class, smoking) or unadjusted
United Kingdom	(47)	1946 birth cohort, MRC NSHD	3,157	43	SBP: −2.3 (0.8, 3.5) (men) SBP: −1.8 (0.1, 3.5) (women) Similar when adjusted for adult BMI
United Kingdom	(46)	1946 birth cohort, MRC NSHD	3,534	36–53	See (40). No amplification of effect with age
United Kingdom	(71)	Brompton Study Cohort	346	22	SBP: −2.7 (−0.4, −5.0) unadjusted DBP: −1.6 (−0.1, −3.2) unadjusted
Scotland	(59)	Follow-up of LBW infants and controls born in Edinburgh hospital	61	24	BW < 2 kg predicted higher mean SBP (122 +/− 12 versus 115 +/− 9 in controls, ($P < 0.05$). No effect of BW on DBP
Netherlands	(126)	Amsterdam Growth and Health Longitudinal Study Cohort	281	36	SBP: −3.3 (−5.75, −0.88) unadjusted DBP: −1.8 (−3.49, −0.21) unadjusted SBP: −3.05 (−5.51, −0.60) adjusted (height and weight) DBP: −1.55 (−3.19, 0.08) adjusted
Sweden	(60)	Twins born 1973–1979 Birth/conscription record link	886 male	17–19	Within-twin pairs: SBP: MZ −1.30 (−4.14, 1.54), DZ 0.14 (−3.49, 3.76). Between pairs −2.68 (−4.95, −0.42) MZ, 0.28 (−2.35, 2.91) DZ, adjusted (age, where examined, GA, current height, weight)

(*Continued*)

TABLE 2 (*Continued*)

Location of study	Reference	Sample and study type	n	Age	Result (regression coefficient units are mm Hg per kg BW, 95% CI in parentheses unless otherwise noted)
Sweden	(74)	Conscripts born 1973–1976 linked to birth registry	165,136	18	SBP: −0.60 (−0.7,−0.5) unadjusted SBP: −1.47 (−1.57,−1.37) adjusted (height and weight)
Finland	(33)	FinnDiane study, Finnish diabetic nephropathy	1,543 type I diabetics	33	SBP: −0.96 (−2.54, 0.63) adjusted (age, sex) unchanged by control for BMI, social class, medication. Among full term SBP: −1.90 (−3.71, −0.09) unadjusted SBP 2.37 (−4.08, −0.65) adjusted (medication use, GFR, glycemic control, urinary albumin excretion rate) effects stronger in females, ns in males No effects on DBP SBP: −6.4 (1.0, 11.9) in the 213 people previously diagnosed as having hypertension
Finland	(139)	Subgroup of cohort from Helsinki University Central Hospital 1924–1944 births	500	70	
Denmark	(112)	Obese and nonobese identified at draft board exam	327 obese, 285 nonobese	19.8, 38.8 47.9	SBP: −2.0 (−3.8, 2.2) unadjusted (estimated per kg: at age 38 from reported values for 1-SD BW) SBP: −2.7 (−5.2, 0) adjusted (BMI, age)
Belgium	(78)	Twins	418 twin pairs	18–36	Women: SBP: −4.27 (unadjusted, $p < 0.001$) SBP: −4.20 (adjusted, $p < 0.01$) GA, BMI, age DPB: −2.18 (unadjusted, $p = 0.02$) DBP: −1.23 (adjusted, ns)

					Men: SBP: 0.46 (unadjusted, ns) SBP: −0.89 (adjusted, ns) DBP: 0.90 (crude, ns) DBP: −0.80 (adjusted, ns)
New Zealand	(133)	Dunnedin Multidisciplinary Health and Development Study cohort	891 with 1+ obs.	26 (repeat measures up to age 26)	SBP: −0.55 (−.32, 1.46) adjusted (age, sex, age*sex) SBP: −1.84 (−2.65, 1.02) adjusted (age, sex, height, weight)
Hong Kong	(18)	Follow-up of 1967 Hong Kong hospital birth cohort	122	30	SBP: −6.0 (−10.6, −1.3) adjusted (sex, BMI, mother's education and health during pregnancy) DBP: −3.2 (−6.8, 0.5)
South Africa	(75)	Case control: UGA versus AGA at birth	73 UGA 64 AGA	20	SBP mean = 126 (13.3 SD) versus 122 (11.7) in underweight versus adequate birthweight for GA DBP mean = 73.2 (8.4) versus 69.5 (8.7)
Guatemala	(124)	Follow-up of nutrition intervention study	385	20–29	Women: BW positively associated with SBP ($P < 0.001$) and DBP ($P < 0.05$): no regression analysis Men: no association of BW with BP
Japan	(125)	Medical students	299	23	No correlation of BW with SBP or DBP
Korea	(19)	Students	22 males	20	Significant inverse correlation of BW with DBP (−0.47)
Sweden	(94)	Vasterbotten Intervention Program	7,876	29–41	Males: SBP > 160 OR for LBW = 2.16 (0.51, 9.19) unadjusted, 2.45 (0.57–10.48) adjusted (BMI) SBP > 140 OR for LBW = 1.22 (0.72, 2.06) unadjusted, 1.31 (0.77, 2.22) adjusted DBP > 95 OR for LBW = 2.46 (1.11, 5.44) unadjusted, 3.05 (1.35, 6.89) adjusted DBP > 90 OR for LBW = 1.36 (0.73, 2.51) unadjusted, 1.52 (0.81, 2.82) adjusted

(*Continued*)

TABLE 2 (*Continued*)

Location of study	Reference	Sample and study type	n	Age	Result (regression coefficient units are mm Hg per kg BW, 95% CI in parentheses unless otherwise noted)
					Females: SBP > 160: OR for LBW = 7.59 (2.74, 21.01) unadjusted, 7.70 (2.76, 21.47) adjusted SBP > 140: OR for LBW = 2.29 (1.26, 4.140) unadjusted, 2.32 (1.27, 4.23) adjusted DBP > 95: OR for LBW = 1.58 (1.48, 5.16) unadjusted, 1.59 (0.48, 5.19) adjusted DBP > 90: OR for LBW = 1.10 (0.47, 2.54) unadjusted, 1.10 (0.47, 2.56) adjusted
Sweden	(80)	Conscript-birth registry link	276,033 males	17–24	High SBP (>90th percentile, height standardized) OR for BW < −2 SD = 1.15 (1.07–1.23) crude, 1.17 (1.08,1.27) adjusted (birth length, GA, adult height, BMI) OR for high SBP if light for GA = 1.33 (1.20, 1.46) adjusted
Sweden	(4)	Subgroup of population-based study of births in 1908, 1914, 1918, 1922, and 1930 Goteborg	438 women	50, 60	BW significantly predicts risk of HTN[a] at age 60 but not at 50 OR for HTN = 0.96 (0.92, 0.99) per 100 g increase in BW unchanged by adjustment for BMI
Sweden	(32)	1913 birth cohort from Gothenburg	478 men	50	SBP: −2.7 (−5.8, 0.4) unadjusted SBP: −3.7 (−6.7, −0.8) adjusted (current weight, GA, place of birth, parity, maternal diabetes, smoking) RR for HTN[b] 0.73 (0.54–0.98) per kg BW unadjusted 0.68 (0.50–0.93) adjusted
Iceland	(44)	Subgroup from Reykjavik study, 1914–1935 birth cohort	4601	50	Referent BW category = 3.75–4.0 kg In women: odds of HTN[c] if BW < 3.45 kg = 1.4 (1.1–1.8)

					No effect in men: OR = 1.0 (0.8–1.3) SBP: −1.2 (p = 0.110 in men, 0.093 in women) adjusted (age) SBP: −1.7 men (p = 0.01) 1.6 women (p = 0.023), adjusted (age, BMI) no association of BW with DBP
Finland	(9)	Helsinki University Hospital 1924–1944 births	13,517	57–77	OR for HTN[b] 0.77 (0.71–0.84) per kg BW, unadjusted
Finland	(10)	Helsinki University Central Hospital births 1934–1944	8,760		Cumulative incidence of HTN[b] related to BW: 20.2% (18.3, 22.1) in BW < 3.0 kg versus 12.3% (10.1, 14.6) in >4.0 kg, unadjusted
Finland	(30)	Helsinki University Central Hospital	7,086	Born 1924–1933	Cumulative incidence of HTN[b] declines with increasing BW in men and women (28.9% in BW ≤ 2.5 kg, 23.8% in BW > 4.0 kg)
Shanghai	(140)	Shanghai Women's Health Study	13,467 women	40–70	Inverse relationship of BW to HTN[d], p for trend = 0.07 BW > 2.5 kg associated with 20%–30% reduction in risk of HTN versus BW < 2.5 kg, unadjusted
Australia	(119)	Community study among Aborigines	767	7–43	SBP: −2.9 (−0.3, −5.5) in adults, adjusted (age, sex, weight) Women: SBP: −4.7 (−0.5, B8.6) Men: SBP: −1.4 (−1.7, B5.0) OR for HTN[e] if LBW = 2.3 (1.3, 3.5)

[a]HTN medication, BP cutpoints SBP > 160, DBP > 95.

[b]HTN medication record.

[c]BP cutpoints SBP > 140, DBP > 90 or medication.

[d]Self report of HTN medication use.

[e]BP cutpoints, SBP > 130, DBP > 85.

*Abbreviations: AGA, adequate weight for gestational age; BMI, body mass index; BP, blood pressure; BW, birthweight; DBP, diastolic blood pressure; GA, gestational age; HTN, hypertension; LBW, low birth weight; MRC NSHD, Medical Research Council National Survey of Health and Development; obs, observation; OR, odds ratio; RR, relative risk; SBP, systolic blood pressure; UGA, underweight for gestational age.

developing and transitional populations with a higher prevalence of poor nutrition are needed to broaden the range of exposures under study. Transitional populations are also more likely to experience changing (in many cases improving) nutritional conditions during childhood and young adulthood. The mismatch of pre- and postnatal environment is precisely the combination of exposures under which we would expect the strongest manifestation of DOHaD (40).

Unfortunately, few studies have been conducted in non-Western populations. Among participants in the Shanghai Women's Health Study (140), LBW was associated with a 20%–30% increase in the risk of hypertension (defined as use of medication) compared with birth weight >2.5 kg. Those who were LBW but were heavier than average as adults were four times more likely to have early-onset (age 20–40) hypertension. Unfortunately, this study relies solely on self-reports, and the sample able to report birth weight represents only about 18% of all study participants, thus raising concerns about recall and selection bias.

In a community of Australian Aborigines, birth weight was inversely associated with systolic BP, and odds of hypertension were elevated with history of LBW, with effects stronger in women than in men (adjusted for current weight) (119). One of the few developing-country studies that do not show an inverse association of birth weight with adult BP is a follow-up of a nutrition intervention study in Guatemala (113). In women whose mothers had received energy or protein supplements during pregnancy, birth weight was *positively* associated with systolic and diastolic BP, but no association was found in men.

Because differences in the association of birth weight with BP have been reported for males and females, Lawlor et al. (72) conducted a meta-regression analysis of 59 observational studies to assess sex differences. Of studies among adults that included males and females and reported linear regression coefficients, 9 presented sex-specific results and 11 presented results for males and females combined. Regression coefficients did not differ by sex: −2.21 (−3.56, −0.86) mm Hg per kg birth weight in males and −2.33 (−3.55, −1.10) in females. Pooled regression coefficients were about one unit larger in studies with males and females combined, which led the authors to suggest that separate results for males and females were more likely to be reported when overall results were weak.

Given the limitations of birth weight, some studies examined the effects of gestational age, birth length, or relative weight (ponderal index or BMI) [see (57) for a review]. For example, a study in 30-year-old Hong Kong adults shows a negative association of birth length and ponderal index with systolic BP and a negative association of length but not weight with diastolic BP (18). Leon et al. (74) compared the separate effects of weight, length, and gestational age on BP in 18-year-old Swedish conscripts. They concluded that the rate of accretion of fetal mass, independent of gestational age, matters most for later BP. Other studies have found associations with both weight and length, but typically considered their separate effects (4).

The clinical relevance of prenatal factors has been questioned based on the small size of birth weight coefficients (generally −1 to −4 mm Hg per kg birth weight). Although such differences may seem small in relation to effects associated with

adult lifestyle risk factors and weight status, even small reductions in a population's mean BP can reduce the number of individuals at risk for hypertension. Although studies typically find weak or no associations of birth weight with diastolic BP, the clinical relevance of effects of systolic BP is greater because high systolic BP, at least in persons older than 50 years, is a much more important cardiovascular disease risk factor than is diastolic BP.

Studies of hypertension risk typically show strong effects of early nutrition and provide perspective on the potential importance of early interventions. For example, young adult males had a 33% increased odds of having high systolic BP if they were born light for gestational age (80). LBW was associated with more than double the risk of systolic BP > 160 mm Hg in 29- to 41-year-old males, and a greater than sevenfold increase in risk among females (94). When estimates are adjusted for adult BMI, coefficients represent the average effect of birth weight on BP at all levels of BMI. However, the most frequent finding is that risk is concentrated in those who were small at birth but large as adults. Judgments about the importance of fetal nutrition should also consider this important combination and potential synergism of risk factors.

In sum, the literature over the past two decades is consistent in showing an inverse association of birth weight with adult systolic BP or an increased risk of hypertension in adults with lower weight at birth.

Maternal Nutrition During Pregnancy and Later Blood Pressure

Fetal growth restriction and metabolic adaptations associated with programming later disease risk are assumed to be the result of fetal *nutritional* insufficiency (45). In most cases, this is secondary to poor maternal nutrition, but may also reflect adequate maternal nutrition along with placental insufficiency or other factors that reduce nutrient availability to the fetus. The ability to study inadequate maternal nutrition is limited by a scarcity of data since, unlike birth weight, maternal nutrition data aside from weight gain are not routinely recorded in clinical records. Animal models provide strong evidence of long-term effects of maternal dietary restriction on offspring BP, but the role of maternal diet and nutritional status during pregnancy has been directly assessed in relatively few human studies.

Several studies used the "natural experiments" of the Dutch Famine and Leningrad Siege, when women were exposed to severe rationing during pregnancy. Offspring exposed to famine in utero did not have significantly elevated BP as adults (110, 111, 123), although their insulin resistance was altered (107). Unfortunately, individual maternal dietary intake data are not available from these studies, so it is difficult to draw conclusions on the effects of maternal dietary restriction. Some studies with individual dietary data show effects of macronutrient imbalance during pregnancy on offspring BP. For example, Sheill et al. (116, 117) found higher BP, and Herrick et al. (50) found higher adult cortisol levels in offspring of mothers who reported high intakes of meat and fish in the second

half of pregnancy. Roseboom et al. (111) found a positive association of maternal dietary protein to carbohydrate ratio with offspring BP, and Campbell et al. (17) found differing effects of carbohydrate, depending on the level of protein intake. In contrast, Huxley & Neil (56) found no relationship of maternal blood levels (more precise indicators of diet) during pregnancy to adult BP in a small sample from the United Kingdom.

Few studies used anthropometric indicators of nutrition status during pregnancy, and most involved youths rather than adults. Maternal prepregnancy BMI and weight gain during pregnancy were unrelated to offspring BP in a study of 17-year-old Israeli military conscripts (69), but other studies in children find elevated offspring BP if the mother had lower skinfold thickness in pregnancy or poor maternal weight gain. For example, in offspring of British women with below-median triceps skinfold thickness, weight gain from 18 to 28 weeks gestation was inversely related to BP at age 11 (22). Godfrey et al. (42) found an inverse relation between maternal skinfold thickness during pregnancy and offspring BP in Jamaican children. In addition, a prospective study of Filipino youths shows that maternal nutritional status during pregnancy is inversely associated with adolescent offspring BP, independent of birth weight (2).

The Role of Postnatal Growth

The relationship of birth size to later BP is often enhanced or present only when current size, typically represented as adult BMI, is taken into account. Studies typically find the highest mean BP or highest risk of hypertension in people who were relatively small at birth but relatively large as adults. This has been interpreted as evidence for an effect of postnatal growth (79); in order to start out small but end up large relative to the population distribution, one must have grown faster in height and/or weight at some time between birth and adulthood. An expanded research focus on postnatal growth has led to a refinement of the fetal origins hypothesis to include postnatal influences (10, 108). Catch-up or more rapid postnatal growth is a hypothesized risk factor for elevated BP in later life, and it has been suggested that coronary heart disease is a disorder of growth (108).

The newer focus on postnatal growth is plagued by some of the same problems of interpretation posed by the use of birth weight to represent fetal nutritional sufficiency. First, postnatal growth is the product of complex interactions among genetic and environmental variables. Like birth weight, it is a sensitive but non-specific indicator of nutritional sufficiency. Faster growth typically leads to larger body size, which is positively associated with BP, raising questions about the importance of growth versus its "end product." Growth entails increases in both lean tissue and fat, each of which has different consequences for chronic disease risk. Second, growth in any given interval is not independent of size at the beginning of the interval. Pre- and postnatal growth are part of a continuum, linked by common underlying determinants and because postnatal growth may represent a response to prenatal growth restriction. Thus, evaluation of the separate effects of fetal and postnatal factors is challenging.

Although an effect of growth has sometimes been inferred in the absence of longitudinal growth data, a full understanding of how postnatal growth relates to adult BP requires analysis of serial data from birth to adulthood. Critical questions relate to the timing of effects (e.g., is there a difference in risk associated with more rapid growth in infancy versus childhood?) and to whether rapid linear growth and rapid weight gain are associated with similar risks. See Huxley et al. (57) for a review of studies (published up to 2000) that examine the role of skeletal and nonskeletal growth in predicting systolic BP.

Studies with serial growth data have been conducted primarily in Europe, where childhood school health records can be linked with birth records or where earlier child growth studies were conducted. The different methods used to evaluate the effects of growth are illustrated by the studies described below.

Several analyses that strongly influenced thought about the role of growth are based on a follow-up of cohorts born in the Helsinki University Central Hospital. Eriksson et al. (30) calculated child height, weight, and BMI Z-scores for the large birth cohorts, then plotted mean Z-scores of those with hypertension as adults. Different growth trajectories are demonstrated when Z-scores of those with hypertension deviate from zero. Men from the 1922–1933 birth cohort with hypertension had lower weight at birth, but had caught up in weight by age 7 and had higher weight and BMI Z-scores from age 7 to 15. The Z-scores of those with hypertension increasingly deviated from zero with age, but the differences were small (0.08 SD units at age 15 in males, which is equivalent to about 0.6 kg above the mean in weight), a statistically significant effect because of the large sample. In a similar study of the 1933–1944 cohort, men and women who later developed hypertension were smaller at birth but had BMI and weight Z-scores above zero (0.1–0.15 SD) by age 12. The effects of lower birth weight and higher BMI were found to be additive rather than interactive.

Law and colleagues (71) compared the effects of birth weight, growth in infancy, and growth in early childhood (age 1–5 years) using a method that accounted for their intercorrelation. More rapid early childhood, but not infancy growth, was associated with increased BP in this sample of young adults in the United Kingdom. The highest mean systolic BP was in those who were light at birth but had the most rapid childhood weight gains. However, the effects of growth were substantially attenuated and no longer significant when adult BMI was taken into account. This suggests that more rapid child growth is simply a predictor of greater adult size, a known risk factor for elevated BP. In contrast, Hardy et al. (47) found independent associations of BMI at ages 2, 4, 7, and 15 years with systolic BP at age 43. The associations were negative prior to age 15 in women and up to age 43 in men, but not fully explained by adult BMI in women.

Another approach to the analysis of the relationship of child growth to adult BP was developed by Cole (23) and applied to data from Brazil (52) and Cebu, Philippines (1, 23) to assess the relative importance of growth velocity at different ages. Although these were studies of adolescents rather than adults, they are important in demonstrating the method. When BP is regressed on Z-scores of weight at different ages in the same model, each coefficient is an age-specific measure of

the association between weight and BP. A positive coefficient indicates that faster growth during that interval predicts higher BP. In the Brazil sample, there was a similar effect of weight gain at all ages, whereas in Filipino males, increased risk of elevated BP was associated primarily with mid-childhood to adolescence weight gain. The effects of rapid weight gain on risk of having high BP at age 16 were confined to males who were relatively thin at birth, but had accelerated gain from mid-childhood to adolescence (1).

The question of whether the effects of rapid growth are age-specific has generated considerable controversy. Evidence suggests that small size at birth followed by rapid early postnatal weight gain adversely programs later risk of insulin resistance and hypertension (71, 120). This finding has raised questions about the wisdom of promoting rapid infant growth among those with fetal growth restriction (121). However, not all studies find increased risk associated with infant growth; in fact, a protective effect of more rapid infant growth is suggested by the results from Cebu, Philippines (1). Similarly, in Hong Kong adults, change in ponderal index from 6–18 months of age was inversely associated with BP, that is, becoming relatively fatter in early life reduced systolic BP in adulthood (18).

Few studies directly compare linear growth with growth in weight. Faster height gain is positively associated with BP in some studies (30, 49, 62, 134), but Lundgren and colleagues (80) found that males born small for gestational age have an increased risk of high systolic BP, especially if they are short as adults. More evidence supports a role for accelerated weight gain, which may represent the accumulation of body fat.

In sum, the cumulative evidence suggests that childhood growth trajectories, particularly among those with a history of fetal growth restriction, affect risk of elevated BP in adulthood. It is still not clear whether risks differ depending on the age when more rapid growth occurs or whether the effects of growth are independent of attained size or body composition in adulthood. The inference of growth effects from the observation that risk is highest among those who were small at birth but large as adults does not provide sufficient insight into the nature of the risk that may be related to excess growth. More studies need to span the full growth period, with serial measurements of height, weight, and body composition as well as exposures that influence growth. More rapid growth may itself be programmed: Metabolic adaptations may alter the response to diet and activity of those with a history of nutritional insufficiency in utero (40), facilitating their more rapid growth. A more promising line of research may involve examination of differential growth responses to environmental factors in those with and without a history of fetal nutritional insufficiency.

Other Postnatal Factors

Adult BP may be influenced by early diet. In a recent systematic review (102), data were compiled to examine how BP relates to infant feeding. Exclusive breastfeeding was compared with formula feeding, with adjustment for current age, sex, height, and BMI using data from 26 estimates of systolic BP and 24 estimates

of diastolic BP. On average, breast-feeding was associated with modestly lower average systolic BP (−1.10 mm Hg) compared with formula feeding, with no marked differences by age. The effect was larger in small studies than in large studies, suggesting publication bias. No effects of feeding on diastolic BP were found. Differences in composition of breast milk versus formula, in particular in their fat and sodium content, are thought to be the relevant determinants of long-term effects of infant feeding on BP. This hypothesis is supported by data from a randomized trial to study the effect of a low- or normal-sodium diet (average daily consumption of 0.89 ± 0.26 mol and 2.50 ± 0.95 mol, respectively, over a 25-week intervention period) in Dutch infants (n = 476) (36). At age 15 years (n = 167) systolic and diastolic BP were lower (−3.6 mm Hg and −2.2 mm Hg, respectively) in the low-sodium group.

Further evidence of early diet composition effects comes from a follow-up study of mothers and offspring randomly assigned to receive a dried milk supplement. In young adulthood (age 23–27 years), BP was higher among those who consumed more supplement at 3 months of age [+1.07 mm HG systolic BP per quartile of milk consumption (≤682, 710–795, 824–909, ≥937 ml)], independent of birth weight and adult BMI, a finding that suggests an effect of diet composition independent of growth (86).

Summary of Study Limitations and Directions for Future Research

Taken as a whole, animal and human studies provide strong evidence that adult BP has developmental origins. However, the human epidemiologic literature is characterized by weaknesses that have led to continued skepticism about the importance of developmental versus adult lifestyle factors (38, 55). Below, we consider some of these weaknesses and suggest directions for future research to address them.

THE NEED FOR BETTER CHARACTERIZATION OF NUTRITIONAL EXPOSURES Although it is convenient, birth weight is an inadequate marker of fetal nutritional insufficiency. This is underscored by a lack of strong evidence that maternal diet affects birth weight, and by the fact that maternal diet in pregnancy can affect offspring BP independent of size at birth (2, 66). There has been inadequate research on maternal nutrition during pregnancy with careful quantification of maternal dietary intakes and nutritional stores. A promising new approach is the use of a maternal supply–fetal demand model (64) to better characterize fetal nutritional sufficiency. Better characterization of fetal growth patterns, and in particular growth of specific organs through serial fetal ultrasound, may also improve our ability to identify the key programming influences.

INCONSISTENT MEASUREMENT AND DEFINITION OF BP OUTCOMES For practical reasons, most studies use casual or single-occasion rather than ambulatory BP measurements. Few studies compare effects of birth weight on BP using both methods. One such study found similar coefficients estimated using casual versus

ambulatory BP measurement in elderly adults (139), one found stronger effects with casual measurements in young adults (78), and one found stronger effects of ambulatory measurements in adolescent girls (97). In addition, hypertension has not been consistently defined across studies. Records or self-report of using medications to lower BP may bias estimates toward the null since many cases of hypertension are not diagnosed and treated. Studies that use different BP cutpoints to define hypertension make it difficult to compare results across studies. Ideally, studies should use standardized measurement and definition of outcomes.

INADEQUATE CONSIDERATION OF POSTNATAL EXPOSURES, INCLUDING LACK OF LONGITUDINAL DATA ON POSTNATAL GROWTH, AND FACTORS SUCH AS DIET AND PHYSICAL ACTIVITY THAT INFLUENCE GROWTH There is no research testing whether responsiveness to environmental factors is altered by early nutrition. The observation that fetal growth restriction in rats results in lower levels of physical activity (128) and overeating, particularly in response to a high-fat diet (117), provides the biological rationale for asking whether there may be similar effects in humans.

INAPPROPRIATE STATISTICAL MODELING There is controversy about interpretation of results when models adjust for current body size in assessing early life predictors of adult BP (38). Typically, variables such as adult BMI are considered as potential confounders of the relationship. However, growth and adult body size may *mediate* the relationship of early life factors and adult BP and their inclusion in the model may bias estimates. When adult size is included in models, the effects of early size can be interpreted only in the context of adult size. Lucas and colleagues (79) therefore recommend assessing and reporting results from three regression models, illustrated here with birth weight and adult BMI as the exposures. The "early" model includes birth weight alone, the "combined" model includes birth weight and adult BMI, and the "interaction" model includes a birth weight $\times$ adult BMI interaction term. The early origins hypothesis would be supported when there is a negative coefficient on birth weight in the early model, and a negative coefficient of birth weight and the interaction term in the interaction model. The most important aspect of developmental factors may be their ability to potentiate the effects of adverse lifestyle factors in adulthood; thus, future research should focus on explorations of interactions of early and later life risk factors.

LACK OF CLARITY ABOUT THE ROLE OF GROWTH AND INADEQUATE INFORMATION ABOUT THE IMPORTANCE OF TIMING OF EXPOSURES The expansion of the fetal origins hypothesis to include postnatal developmental factors is important but not sufficient. Future research should focus on the identification of precisely what aspect of growth matters. Is it simply a predictor of adult body composition, which, in turn, affects risk of elevated BP? Or does rapid growth pose other challenges, for example, to kidney function compromised by prenatally impaired nephrogenesis? To inform appropriate interventions, we need to determine whether more rapid

growth has different long-term consequences depending on when it occurs and whether there are differential effects of rapid growth of lean versus fat mass.

THE ROLE OF GENETICS The design of most epidemiologic studies does not allow for testing hypotheses about the role of genetics. If common genetic factors relate to both poor fetal growth and elevated BP in adults, we may mistakenly infer a casual affect of fetal retardation. Moreover, maternal BP may be an important confounder of the association between fetal growth retardation and adult hypertension since it is both inversely associated with infant birth weight and the offspring's adult BP (21). Twin studies show that controlling for genetic factors may attenuate, but not fully explain, the observed inverse association of birth weight with adult BP (20, 78).

CONCLUSION

Substantial evidence from animal and human studies supports a role for long-term effects of early nutritional exposures in the development of elevated BP and hypertension. Although developmental factors may not be among the strongest risk factors for hypertension, their importance should be recognized and used to bolster early life prevention efforts, including optimization of maternal nutrition during pregnancy and prevention of excess weight gain. Developmental factors may play a greater role in developing and transitional country settings, where populations of adults among whom low birth weight was common are now exposed to rapid changes in diet and activity that are conducive to the development of cardiovascular diseases. An appreciation of the potential for greater susceptibility of such individuals offers further opportunities for targeted intervention in adulthood.

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