Maternal Nutrition, Low Nephron Number, and Hypertension in Later Life: Pathways of Nutritional Programming[1,2]

Susan P. Bagby*

OHSU Heart Research Center and Division of Nephrology and Hypertension, Department of Medicine and Research Service, Oregon Health and Science University and Portland Veterans Administration Medical Center, Portland, OR 97239

Abstract

A large body of epidemiologic literature supports an inverse relation between birth weight and both systolic blood pressure and prevalence of hypertension, but mechanisms through which lower birth weight increases risk for hypertension are not established. This article advances the view that 1) permanently reduced nephron number is essential but not alone sufficient to mediate nutritionally induced hypertension; and 2) fetally programmed propensity for increased appetite and accelerated postnatal growth, thus generating inappropriately increased body mass, is a necessary "second hit" to actualize hypertension vulnerability. Based on decades of nephrologic research, this increased ratio of body mass (excretory load) to nephron number (excretory capacity) induces intrarenal compensations (tubular and glomerular hypertrophy with single-nephron hyperfiltration and intrarenal renin-angiotensin II activation), which maintain normal glomerular filtration rate at the expense of systemic and glomerular hypertension and at the risk of progressive renal disease. The vigor of the intrarenal compensatory responses is markedly greater in the immature than in the mature kidney, potentially explaining the greater risk of nephron deficits being present early in life as compared with the minimal risk in adult kidney donors. Effective interventions have not yet been defined. Suboptimal maternal nutrition, pervasive in both developed and developing countries, offers a window of opportunity to enhance the cardiovascular and renal health of future generations.   J. Nutr. 137: 1066–1072, 2007.

Professor David J. P. Barker demonstrated that birth weight across the normal range, a surrogate for fetal nutrition, was inversely proportional to the risk of cardiovascular disease, including hypertension (1,2). The "Barker Hypothesis" proposed that adverse events in utero induce compensatory responses in the fetus that, reflecting the plasticity of this developmental period, persist permanently and thus define an altered phenotype at birth (3). The process has been termed "programming" and may be expressed in alterations in organ structure or function and in setpoints of homeostatic systems. Programming limits the range of postnatal adaptability, thus creating disease *vulnerability*: a postnatal environment substantially altered from the

prenatal setting may present challenges that the programmed organism cannot meet without significant biological costs (4). Disease expression can be viewed as an interaction between the nutritionally programmed birth phenotype and the postnatal environment. Key postnatal factors now known to increase disease risk include nutrient availability (5,6) and disease-specific patterns of infant and childhood growth (7). Since its original formulation, the evidence for developmental origins of modern diseases has expanded to incorporate not only the individual elements of the metabolic syndrome but also renal insufficiency/failure (8), asthma (9), osteoporosis (10), mental illness (11), and cancer (12). This article focuses on the effects of fetal undernutrition to permanently reduce nephron number, the mechanisms by which this may create vulnerability to hypertension, and the evidence for postnatal factors that further enhance disease risk. We advance the thesis that reduced nephron number is an essential, but not sufficient, condition for nutritionally induced hypertension and that additional nutritionally programmed pathways must interact postnatally to actualize disease expression.

Evidence that asymmetric growth restriction reflects clinically significant nutritional programming

Although birth weight has proved to be a surprisingly robust surrogate for the fetal growth environment, the more specific indicator of significant fetal nutrient deficiency is the particular form of intrauterine growth impairment termed "asymmetric

growth restriction." This defined birth phenotype is believed to reflect a stereotypical fetal response to stress (e.g., hypoxia); it involves redistribution of blood flow away from most intra-abdominal organs (kidney, liver, pancreas) and away from skeletal muscle in favor of organs more immediately crucial to fetal well-being (heart, brain, adrenal gland). As a result, body weight is reduced to a greater degree than length, yielding thin infants; liver, kidney, and pancreas are reduced in size to a relatively greater degree than heart, brain, and adrenals (13). The asymmetric growth-restricted phenotype is obstetrically diagnosed only if birth weight (adjusted for gestational age) is below the 10th percentile. However, as more is learned, we may find that the growth-restricted phenotype occurs throughout the lower half of the normal birth-weight range and may provide a more precise marker of nutritional programming than birth weight.
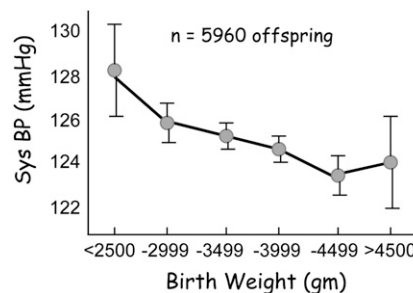
Evidence that the fetal environment modifies risk of hypertension

As of 2000, over 80 publications have substantiated the inverse relation between systolic blood pressure (BP)[3] and birth weight in humans (14). Godfrey et al. (15), relating direct measures of maternal nutrition in early pregnancy (triceps skin thickness) to offspring systolic BP at age 11 y, demonstrated a significant inverse relation even at this young age. The birthweight-systolic BP relation is enhanced by increasing adult BMI level (16) and by above-average height (17), suggesting an interaction between birth weight and postnatal gain in body mass. Initial concerns about the significance of the inverse BP-birth weight relation centered around inherent limitations of data sets, the small change in average BP across birth weights, and the need to adjust for current body weight to show the birth weight influence (18). However, new developments mute these arguments. First, studies of the 1966 Northern Finland cohort, incorporating a wide variety of annotated maternal information, demonstrated a strong inverse relation of systolic BP and birth weight independently of current body weight (**Fig. 1**) (19), as did those of Primatesta et al. from the Health Survey for England (20). Second, well-controlled animal models in multiple species have shown hypertensive effects in prenatally undernourished offspring [reviewed in Armitage et al. (21)]. Third, clinical trials examining long-term outcomes have clearly documented the cardiovascular impact of small differences in average BP in large populations (22).

Perhaps more directly relevant to long-term human health are the studies that assess the impact of birth weight not on average BP but on the cumulative prevalence of hypertension. The American Nurses Study I (23) assessed a cohort of women on 2 successive occasions: at ages 30–55 and again 15 y later at ages 46–71 y. Results showed not only that prevalence of hypertension was inversely related to birth weight but additionally that the relation was amplified with aging: lower birth weight increased prevalence of hypertension by ~3% at the younger ages but by ~8.5% at the older ages (23). Collectively, these observations compel the conclusion that an impaired fetal growth trajectory conveys vulnerability to, but does not alone ensure, the later development of hypertension.

Evidence that fetal undernutrition permanently reduces nephron number

Brenner and Chertow were the first to suggest that the reduced nephron number associated with low birth weight could increase

[3] Abbreviations used: AGA, appropriate for gestational age; angII, angiotensin II; BP, blood pressure; GFR, glomerular filtration rate; IUGR, intrauterine growth retardation.

Figure 1 Birth weight is inversely proportional to systolic BP in a 1966 northern Finland birth cohort. In 5960 participants born in 1966, Jarvelin et al. examined the shape and size of the association among determinants of fetal growth, size at birth, growth in infancy, and adult systolic and diastolic BP at 31 y (19). Unlike many prior cohorts, numerous maternal variables were available for assessment of impact. A strong inverse relation between systolic blood pressure and birth weight was apparent, with or without adjustment for current weight. Similar findings were reported in 5 European cohorts by Hardy et al. (74) and in 20 cohorts from 6 Nordic countries by Gamborg (75). Adapted with permission from Jarvelin et al. (19).

risk of both hypertension and chronic renal disease/renal failure (24). To understand the effect of fetal nutrient restriction on renal development, a brief review of nephrogenesis is germane. The final mammalian kidney, the metanephros, develops from 8 wk of gestation in humans, but fully two-thirds of the nephrons form during the third trimester (25). No new nephrons form after 36 wk of gestation. The process of branching morphogenesis involves ingrowth of the ureteral bud into the metanephric mesenchyme and subsequent dichotomous branching, each terminal branch giving rise to a single nephron with its linked glomerulus. This process occurs in an outward direction, laying down concentric layers of nephron units with newly forming, immature nephrons in the outermost (nephrogenic) layer. Slowing of this process during a temporally finite window of development reduces number of layers, yielding normally formed but fewer nephrons.

Based on gold standard stereologic techniques for estimating glomerular number, autopsy studies have shown that obstetrically defined intrauterine growth retardation (IUGR) is associated with reduced nephron number in human infants (26,27), confirming earlier estimates. In a range of animal species, experimental maternal undernutrition or placental insufficiency have now been reproducibly associated with reduced nephron number (28–38) and typically with elevated BP (**Table 1**). In both human (27) and experimental IUGR, nephron number is commonly reduced on the order of 25–30% (Table 1), suggesting the possibility that a finite fraction of total nephrons are subject to nutritional modulation.

The nephropenia observed in human IUGR and in experimental undernutrition in animals reflects a relatively severe form of growth restriction, is associated with the asymmetric growth-restriction phenotype, and by definition represents the lowest centile of birth weights. Can reduced nephron number also explain hypertension vulnerability at higher (low-normal) birth-weight ranges? In fact, several recent studies demonstrate a close linear relation in the primate kidney between nephron number and birth weight *across the normal birth-weight range* (39). In the baboon, Gubhaju and Black showed that the fetal kidney weight during nephrogenesis was tightly and linearly related to nephron number (40). The autopsy study of Hughson et al., measuring nephron number in normal postnatal human kidneys using gold-standard stereologic methods, demonstrated a linear relation between nephron number and birth weight (39) (**Fig. 2**). This predicts that a normally grown infant of 3 kg birth weight

TABLE 1 Maternal protein restriction reduces nephron number in multiple species

Species	Maternal diet	Exposure in gestation	Nephron number	Basal HTN	Stim'd HTN	Ref.
Rat						
Zeman	Low protein	0.0–1.0	↓ (NA)	—	—	(28)
Merlet-Benichou et al.	Low protein	0.0–1.0	↓ (NA)	—	—	(29)
Woods et al.	Low protein	0.0–1.0	↓ 25%	—	—	(30,71)
Vehaskari et al.	Low protein	0.5–1.0	↓ 28%	Yes	-	(31)
Jones et al.	Low protein	0.0–1.0	↓ 30%	Yes	—	(32)
McMullen et al.	Low protein	0.0–1.0	↓ 25–50%	Yes	—	(33)
Sanders et al.	Placental insuff.	0.8–1.0	↓ 30%	No	Yes*	(34)
Sheep						
Gilbert et al.	50% Low calorie	0.1–0.5	↓ 11%	Yes	—	(35)
Gopalakrishnan et al.	50% Low calorie	0.2–0.5	↓ 30%	No	—	(36)
Pig						
Bauer et al.	Spontaneous	Runting	↓	—	—	(37)
Rabbit						
Bassan et al.	Placental Insuff.	0.7–1.0	↓	—	—	(38)
Human						
Hinchliffe et al.	(IUGR)	—	↓	—	—	(27)
Leroy et al.	(IUGR)	—	↓	—	—	(72)
Manalich et al.	(IUGR)	—	↓	—	—	(73)

* Under stimulation of 2% NaCl drinking water.

[i.e., birth weight appropriate for gestational age (AGA)] will go through life with a lower nephron number than an AGA infant of 4 kg. In striking contrast to the prenatal kidney, postnatal kidney size is tightly linked to indices of body surface area, not to nephron number (39). Thus, the enlarging fetal kidney responds to growth stimuli by increasing nephron number; the postnatal kidney responds to growth-related metabolic demand by enlarging existing nephron units.

These informative observations suggest the possibility of a "physiologic nephropenia" as a function of birth weight in the normally grown AGA infant, i.e., in the absence of the asymmetric growth restriction phenotype. If this does occur, does the asymmetric growth-restricted phenotype predict a greater nephron deficit for a given "normal" birth weight? Lampl et al. (41) have in fact shown by ultrasound that 32-wk fetal kidneys of infants subsequently born thin are smaller than those who were not thin. It will be important to learn whether this reflects altered nephron endowment and whether hypertension vulnerability differs between the AGA-thin and the AGA-normally proportioned infant at a given normal birth weight. Second, if birth

Figure 2 Birth weight predicts glomerular number in human populations. Hughson et al. performed gold-standard stereologic assessment of glomerular number in postnatal kidneys from a U.S. population (39). Glomerular number was positively and linearly related to birth weight, most prominently (*shown above*) in younger subjects where age-dependent glomerular loss is expected to be minimal. Limited observations above a birth weight of 4 kg preclude conclusions at higher birth weights. [Adapted with permission from (39).]
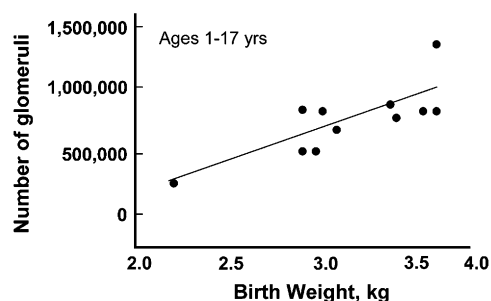
weight reflects nephron number, then birth weight provides the first accessible clue to nephron number in an individual, a crucial piece of information for clinically identifying disease vulnerability.

Two recent human studies have supported a link between reduced nephron number and essential hypertension (42,43). However, there is as yet no direct evidence linking reduced nephron number to hypertension in human IUGR.

Evidence that reduced nephron number is not alone sufficient to mediate nutritionally programmed hypertension: a 2-hit hypothesis

Brenner and Chertow first proposed the concept of "nephron dosing": reduction in nephrons with a fixed body mass or transplantation of a small kidney into a large recipient created an imbalance between excretory load and excretory capacity that enhanced risk of both hypertension and renal disease (24). In fetal undernutrition states, the reduction in kidney size (and nephron number) in full-term offspring is typically proportional to the reduction in body weight. At birth, then, there is no imbalance between body size and nephron number. We have thus proposed that in the context of congenitally fewer nephrons, the superimposition of postnatal body mass excess (whether fat or lean) is required to create the imbalance that generates hypertension. Emerging data now support the view that nutritional programming actively induces, concomitantly with fewer nephrons, a propensity to accelerated postnatal growth via enhanced appetite (44).

Altered energy metabolism as a result of nutrient deprivation in utero was first described by Hales and Barker (45) as the "thrifty phenotype," depicting enhanced energy utilization efficiency and insulin resistance as effective fetal strategies for preferentially shunting fuel away from muscle to protect heart and brain. More recently, studies of fetal undernutrition have also shown increased appetite and enhanced deposition of more fat than lean tissue. Vickers et al., in a rat model of severe maternal caloric restriction throughout pregnancy, found increased food intake in offspring well into adulthood, accompanied by central obesity, hypertension, and insulin resistance (44). In our microswine model of maternal protein restriction applied

during late gestation and early suckling, offspring of restricted sows ingested an average of 20% more food (as g/kg per meal) than control offspring (E. DuPriest, P. Kupfer, B. Lin, K. Sekiguchi, and S. B. Bagby, unpublished data). In South African children born small for gestational age, only those with subsequent access to food experienced accelerated growth and increased risk of obesity and diabetes (5). Thus, in our current view, maternal undernutrition sows the seeds of hypertension in offspring by directly generating 2 essential vulnerabilities: *1*) absolutely and permanently low nephron number and *2*) increased appetite, the latter ensuring elevated body mass via percentile-crossing growth acceleration when postnatal food is available. Excretory demand (body mass) thus grows to exceed the fixed lower excretory capacity (nephron number), mandating postnatal renal adaptations to enhance excretion by mechanisms that create additional disease risk (see below).

According to this concept, obesity is not necessary for the development of hypertension in those born small and subsequently experiencing accelerated growth. This is borne out in human studies in the remarkable Finnish cohorts, where annual growth data were serially collected from birth through 11–15 y of age and subsequent adult disease could be identified by medication records. Barker et al. showed that 1404 (of 8760) children who later became hypertensive were born small, exhibited an asymmetric growth phenotype, and developed accelerated increase in BMI between 3 and 11 y, supporting the role of an abnormal postnatal growth pattern in actualizing disease vulnerability (1). In a further analysis, incorporating individuals who developed diabetes and/or hypertension, those individuals whose accelerated growth leveled off after age 7 to achieve average BMI developed only hypertension in adulthood; in contrast, those whose BMI continued to rise between 7 and 15 y of age developed both hypertension and diabetes (2). Thus, obesity is not required but adds independent and well-documented additional mechanisms (46) that promote hypertension.

Evidence that the nephron number:body mass ratio induces renin-angiotensin II activation to maintain glomerular filtration rate

A large body of experimental work has taught us how the individual nephron, the functional unit of the kidney, responds to a chronic relative increase in excretory load (either via increased body mass at a fixed nephron number or reduced nephron number at a given body mass) (47–49) (**Fig. 3**). The existing nephrons undergo enlargement involving most prominently glomeruli and proximal tubules, the latter via increased length as well as internal and external diameter (50). In the glomerulus, capillary number and overall volume increase, the afferent arteriole dilates, and the efferent arteriole constricts, leading to increased glomerular capillary pressure and thereby to increased single-nephron glomerular filtration rate (GFR). Total-body GFR is either increased (in the case of a primary increase in body mass) or restored toward normal (in the case of a primary reduction in nephron number, as in uninephrectomy). Animal studies and human clinical trials with renin-angiotensin system blockade strongly support the view that intrarenal angiotensin II (AngII) mediates single-nephron hyperfiltration, but mechanisms are not fully understood.

A recent hypothesis, compellingly put forward by Thomson and colleagues (51) to explain diabetes-related glomerular hyperfiltration, may prove relevant to the pathophysiology of hypertension in nutritionally programmed disease. This proposes that proximal tubular hypertrophy is the primary event, driving
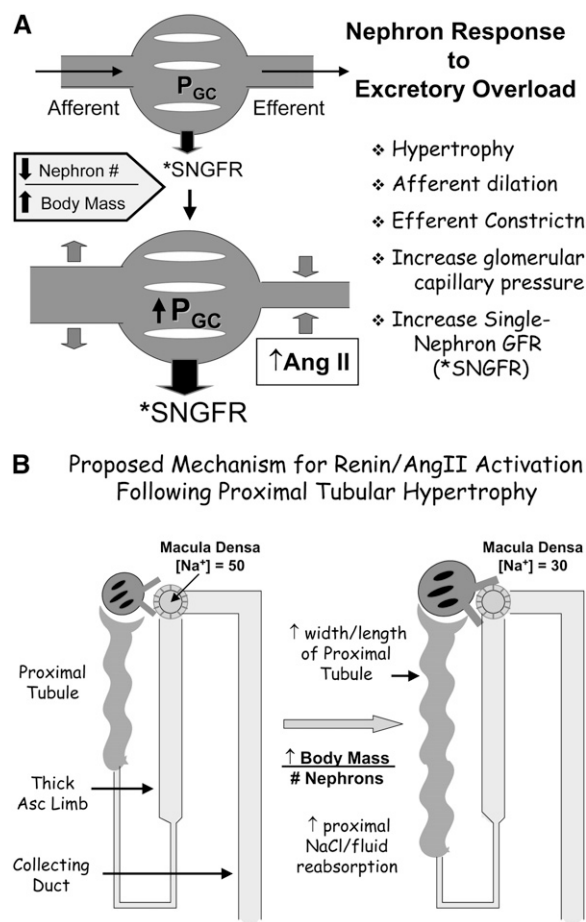
Figure 3 Projected renal responses to a relative decrease in nephron number. A reduction in nephron number (excretory capacity) and/or an increase in body mass (excretory load) induces a stereotypic response in available functioning nephrons. Glomerular hypertrophy (increased volume and capillary number) is associated with hyperfiltration (via afferent dilatation and efferent constriction, which increases capillary pressure) (*Top panel*); tubule enlargement (predominantly the proximal tubule via increased wall thickness and tubule length) is associated with increased Na reabsorption, potentially inducing secondary renin-AngII activation via macula densa signals (*Lower panel*, see text).

a macula-densa-mediated renin-AngII activation, AngII-mediated efferent vasoconstriction, and glomerular hyperfiltration. According to this scenario, as postnatal accelerated growth proceeds in the face of low nephron number, the longer and more Na-avid proximal tubule reabsorbs excess NaCl and delivers less to the macula densa, triggering a signal (low [NaCl]) that is perceived as inadequate GFR. This causes sustained resetting of the macula densa signal to increase GFR until delivery to the sensing site is restored to normal. The macula densa response includes 2 key effectors: increased renin release (inducing efferent vasoconstriction) and reduced ATP (causing afferent vasodilation) (52). Sanders et al. have recently provided indirect support for this mechanism in growth-restricted rat offspring after placental restriction (53). According to these investigators, GFR is restored to normal by macula-densa-mediated single-nephron hyperfiltration, but with important disadvantageous consequences: *1*) enhanced intrarenal AngII contributes to NaCl retention in excess of body fluid needs, promoting hypertension; and *2*) vulnerability to renal injury and progressive loss of existing nephrons via persistently high glomerular capillary pressure, promoting glomerulosclerosis and proteinuria with subsequent tubulointerstitial inflammation (54) (Fig. 3).

Reduced nephron number does not always lead to hypertension: why?

Although reduced nephron number may be capable of conferring vulnerability to hypertension, it clearly does not always do so. Contrast, for example, the effects of fewer nephrons from birth with those of loss of nephrons in the mature individual. Congenitally reduced nephron number in humans, e.g., renal agenesis, carries a substantial risk of later hypertension and renal disease (55). Remarkably, however, uninephrectomy in adult renal transplant donors has a very low risk of hypertension or proteinuria, even after decades of follow-up (56). Animal studies support this age-dependent difference (57,58). The differing intensity of the renal adaptation to reduced nephron number may be key. Relative to the adult, the immature mammal has increased renal growth potential for both hypertrophy and hyperplasia (59,60), and an increased basal level of renin-AngII activity (61,62). The compensatory hyperfiltration in response to nephron deficit is substantially more effective in the young as compared with the mature kidney (63). A more vigorous compensatory tubular hypertrophy and/or a greater AngII response in youth may proportionally enhance hypertension and renal disease risk in the long term because it also more effectively preserves GFR in the short term.

A third nutritionally programmed pathway may contribute to hypertension risk

So far, discussion has focused on intrarenal renin-AngII activation as a consequence of excess body weight gain postnatally. However, there is also evidence that primary programming of the renin-AngII system components may be induced by nutrient deficit in utero and manifested by enhanced activity postnatally, contributing to hypertension and renal risk. This could, for example, amplify the intrarenal AngII response when body weight begins to increase. Many studies in experimental animal models report prenatal and/or postnatal abnormalities of renal renin-AngII parameters in offspring following fetal nutrient restriction, e.g., low intrarenal AngII levels at birth (30) and increased renal AngII Type 1 receptors (64–66). Franco et al. have reported in rats that intrauterine nutrient deficits (50% maternal calorie restriction) lead, in 4-mo-old offspring, to enhanced AngII-induced oxygen free radical formation, the latter blocked by inhibitors of NADPH oxidase (67). It is therefore possible that fetal nutritional deficit operates via a third prohypertensive pathway, direct prenatal programming of renin-AngII components, leading to postnatally enhanced AngII production, amplified AngII responses, and/or accelerated AngII-dependent injury via oxidative pathways.

In summary, maternal and/or fetal undernutrition activates multiple compensatory fetal responses that persist postnatally, promoting later development of hypertension and renal disease. The effects of nutritional programming are present at birth and, via structural and functional mechanisms, create disease vulnerability. The latter is manifest by the asymmetric growth-restricted phenotype and is mediated by reduced nephron number, by altered appetite/energy metabolism, and by the potential for intrinsically enhanced renin-AngII activity. If the postnatal environment presents adequate nutrients (or overrides appetite via highly palatable foods), the programmed increase in appetite ensures excess food intake, accelerated growth, excess body mass for nephron number, and intrarenal renin-AngII activation that is appropriate for restoration of GFR but inappropriate for body fluids and BP. The altered energy metabolism, with insulin resistance and propensity for deposition of fat more than lean tissue and central more than peripheral fat distribution, simultaneously favors obesity and the additional prohypertensive mechanisms that this brings.

Maternal undernutrition is a dominant theme in developing countries, particularly as individuals born small in nutrient-scarce rural areas migrate to urban areas, where they experience substantial increases in caloric availability and intake (6). A similar dynamic affects new immigrants acclimating to Westernized countries. That suboptimal maternal nutrition is also important in residents of developed countries was recently shown by Robinson et al. in the UK (68): in a cohort of women of childbearing age whose diet was ranked in quartiles based on a "prudent diet" score and educational level, 55% of the least-educated women fell into the "least prudent" diet quartile. Although this article has not touched on the opposite end of the nutrition spectrum, maternal overnutrition is of equal concern (69,70): via high risk of obesity and diabetes in offspring of obese mothers or mothers on a high fat diet, maternal overnutrition also creates risk of adult hypertension and renal disease. The nutritional sciences community will be critically important for creating mechanisms to identify at-risk individuals, for carrying out research to define molecular mechanisms and effective interventions, and for developing public policies to counteract the abnormalities of maternal nutrition that threaten the health of future generations.

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