Maternal and Child Undernutrition 2

Maternal and child undernutrition: consequences for adult health and human capital

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In this paper we review the associations between maternal and child undernutrition with human capital and risk of adult diseases in low-income and middle-income countries. We analysed data from five long-standing prospective cohort studies from Brazil, Guatemala, India, the Philippines, and South Africa and noted that indices of maternal and child undernutrition (maternal height, birthweight, intrauterine growth restriction, and weight, height, and body-mass index at 2 years according to the new WHO growth standards) were related to adult outcomes (height, schooling, income or assets, offspring birthweight, body-mass index, glucose concentrations, blood pressure). We undertook systematic reviews of studies from low-income and middle-income countries for these outcomes and for indicators related to blood lipids, cardiovascular disease, lung and immune function, cancers, osteoporosis, and mental illness. Undernutrition was strongly associated, both in the review of published work and in new analyses, with shorter adult height, less schooling, reduced economic productivity, and—for women—lower offspring birthweight. Associations with adult disease indicators were not so clear-cut. Increased size at birth and in childhood were positively associated with adult body-mass index and to a lesser extent with blood pressure values, but not with blood glucose concentrations. In our new analyses and in published work, lower birthweight and undernutrition in childhood were risk factors for high glucose concentrations, blood pressure, and harmful lipid profiles once adult body-mass index and height were adjusted for, suggesting that rapid postnatal weight gain—especially after infancy—is linked to these conditions. The review of published works indicates that there is insufficient information about long-term changes in immune function, blood lipids, or osteoporosis indicators. Birthweight is positively associated with lung function and with the incidence of some cancers, and undernutrition could be associated with mental illness. We noted that height-for-age at 2 years was the best predictor of human capital and that undernutrition is associated with lower human capital. We conclude that damage suffered in early life leads to permanent impairment, and might also affect future generations. Its prevention will probably bring about important health, educational, and economic benefits. Chronic diseases are especially common in undernourished children who experience rapid weight gain after infancy.

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This is the second in a Series of five papers about maternal and child undernutrition

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Introduction

This is the second article in the *Lancet* Series on maternal and child undernutrition. The previous article emphasised the magnitude of the problem and its short-term consequences in low-income and middle-income countries.[1] In this paper we address the potential long-term implications of undernutrition.

We start with an assessment of the long-term effects of undernutrition on adult human capital, including height, school achievement, economic productivity, and birthweight of the offspring. We then discuss the relevance to low-income and middle-income countries of the hypothesis on developmental origins of health and disease[2]—namely, that early growth patterns might have long-term effects on risk of development of chronic diseases.[3] Although these issues are still debated,[4,5] published work from high-income countries suggests that intrauterine growth restriction, especially when followed by excessive weight gain in childhood, is associated with increased risk of several chronic diseases. Studies of the developmental origins of adult disease in low-income and middle-income countries are particularly important because adults were born when rates of undernutrition were high and have had to adapt to rapidly changing postnatal diets and environments.

As researchers involved in large cohort studies entailing the long-term follow-up of children born in low-income and middle-income countries, we present a systematic review of published work on the long-term effects of malnutrition, and new analyses of data from

Key messages

- Poor fetal growth or stunting in the first 2 years of life leads to irreversible damage, including shorter adult height, lower attained schooling, reduced adult income, and decreased offspring birthweight
- Children who are undernourished in the first 2 years of life and who put on weight rapidly later in childhood and in adolescence are at high risk of chronic diseases related to nutrition
- There is no evidence that rapid weight or length gain in the first 2 years of life increases the risk of chronic disease, even in children with poor fetal growth
- The prevention of maternal and child undernutrition is a long-term investment that will benefit the present generation and their children

For more on **the Brazil cohort** see http://www.epidemio-ufpel.org.br/_projetos_de_pesquisas/coorte1982/index_english.php

For more on **the Philippines cohort** see http://www.cpc.unc.edu/projects/cebu/

For more on **the South Africa cohort** see http://www.wits.ac.za/birthto20/

cohorts followed up from birth into late adolescence or adult age in Brazil, Guatemala, India, the Philippines, and South Africa.

New data analyses

The new analyses presented here are based on the cohorts in Brazil,[6] Guatemala,[7,8] India,[9,10] the Philippines,[11] and South Africa[12] (table 1). Panel 1 shows the exposures that were assessed. Outcomes were measured in late adolescence in South Africa and in adulthood in the other sites (table 1), and will be referred to as adult outcomes (panel 1).

Potential confounding variables included the participant's age when the outcome variables were measured, years of schooling completed by the mother (in India, by the father), and a measure of early childhood socioeconomic status. In India, occupation of the father was classified in an ordinal six-point scale, whereas in the other sites wealth quintiles were calculated through principal component analysis of household assets.

Unless otherwise stated, we present only confounder-adjusted estimates. For glucose concentrations and blood pressure, further analyses incorporated control for adult height and body-mass index, which are potential mediating factors in the association between undernutrition and adult outcomes. Such adjustment is commonly used in published work and might help understand the role of later growth. All analyses were stratified by sex.

In every analysis, we included only participants with full information in the exposure, outcome, confounding, and stratification variables. With the exception of the dichotomous variable for intrauterine growth restriction, all other exposures were initially coded in four categories and tested for linearity with analysis of variance. Because there was no consistent evidence of non-linearity, we used multiple linear regression analyses.

Results from the five studies were combined with a meta-analytic procedure that included examination of heterogeneity with use of the *Q* test;[17] if results were significant, we used a random-effects model.[18]

Search strategy and selection criteria

14 adult outcomes were selected: height; achieved schooling and educational performance; income and assets; birthweight in the offspring; body-mass index, body composition, and obesity; blood lipids; insulin resistance and type 2 diabetes; blood pressure; cardiovascular disease; lung function; immune function; cancers; bone mass, fracture risk, and osteoporosis; and mental illness. Exposure variables were measured during pregnancy (maternal height and weight before pregnancy, weight gain, micronutrient status and diet), at birth (weight, length, ponderal index, intrauterine growth restriction), and at 2 years of age (stunting, wasting, underweight). Searches of published work were undertaken in the Medline, Embase, CINAHL, EconLit, Psychinfo, and PsychArticles databases, with all possible combinations of exposures and outcomes, which identified more than 15 000 original articles and 700 reviews. The search was narrowed down to articles from low-income and middle-income countries in which outcomes were measured in adulthood or late adolescence. We identified 28 relevant articles originating from populations in low-income and middle-income countries. We excluded studies with low statistical power or poor methodological quality. Information from high-income countries was summarised by selecting high-quality review articles, and was complemented by original research articles if necessary. We complemented the search by contacting investigators involved in long-term cohort studies in low-income and middle-income countries to identify relevant original or review articles and book chapters, and by searching our own personal files.

	Design	Year of cohort recruitment	Age at recruitment	Initial sample	Age at last visit (years)	Number examined in last visit	Attrition rate	Infant mortality (per 1000)	Comments
Brazil (Pelotas)	Prospective cohort	1982	Birth	5914	21–23	4297	23%*	36	All children born in the city's maternity hospitals (>99% of all births) during 1982 were enrolled. All social classes included
Guatemala (four villages)	Community trial	1969–77	Birth–7 years	2392	26–41	1571	23%†	75	Intervention trial with two communities receiving high-energy and protein supplement and two control villages. All children younger than 7 years in 1969 and all born during 1969–77 were enrolled and followed up until 7 years of age or until the study ended in 1977. Furthermore, data were obtained for mothers during pregnancy and breast-feeding periods
India (New Delhi)	Prospective cohort	1969–72	Before pregnancy	8181	26–32	1583	68%‡	47	All married women living in a defined area of the city were recruited and followed up. Pregnancies were identified, and neonates were enrolled and followed up. Primarily middle-class sample
Philippines (Cebu)	Prospective cohort	1983–84	Gestation	3080	21·4	2032	34%	51§	Pregnant women living in 33 neighbourhoods selected by random; first data collection at 30 weeks' gestation. All social classes included
South Africa (Soweto)	Prospective cohort	1990	Gestation	3273	15	2100	22%	27	Pregnant women with a gestational age of 26–32 weeks living in a defined urban geographical area. Predominantly poor, black sample

*Participants known to have died were regarded as having been traced; those who moved out of the study area were regarded as lost to follow-up. †Excludes participants who were no longer living in Guatemala and regards those known to have died as having been traced. ‡Includes participants known to have died and those migrated from the study area. §Infant mortality rate when survey was initiated, based on 1983 Demographic and Health Survey.

Table 1: **Basic characteristics of the five cohort studies included in the new analyses**

Findings

We have organised our results according to the 14 outcomes studied. For every outcome, we considered maternal size and nutrition, newborn infant size, infant and child size, and growth. For eight outcomes, new information is provided from our cohorts. Table 2 shows descriptive statistics for exposure and outcome variables by study site. Brazil tended to show the lowest prevalence of undernutrition, and Guatemala the highest. Birthweight was lowest and intrauterine growth restriction highest in India. When adult outcomes are compared, it should be noted that South African participants are still in their late teens.

Height

Attained height is affected by genetic and environmental factors throughout the growth period. Linear growth failure is largely confined to the intrauterine period and the first few years of life, and is caused by inadequate diets and frequent infections.[19]

Short stature of the mother and poor maternal nutrition stores are associated with increased risk of intrauterine growth retardation.[1,20] Several studies from low-income and middle-income countries report that adult height is positively associated with birthweight[9,21–24] and length.[9,21,23] A 1 cm increase in birthlength is associated with a 0·7–1 cm increase in adult height.[9,21–24]

Early growth failure will lead to reduced adult stature unless there is compensatory growth (so-called catch-up growth) in childhood, which is partly dependent on the extent of maturational delay that lengthens the period of growth. Because maturational delays in low-income and middle-income countries are usually shorter than 2 years,[25] only a small part of the growth failure is compensated for. In Guatemala,[26] there was little evidence of catch-up growth after 3 years of age but in Senegal, where maturational delays were substantial, adults heights were only about 2 cm shorter than the reference despite severe stunting in childhood.[27] In both countries, differences in height between stunted and non-stunted children younger than 5 years remained largely unchanged into adulthood. People who remain in the setting in which they developed childhood undernutrition tend to become short adults.[9,24,25] Improvements in living conditions such as those brought on through adoption can trigger catch-up growth but do so more effectively in very young children.[25,28]

Data from Guatemala suggest that the contributions of the intrauterine and early postnatal period to reduced adult stature are about equal.[29] Because nutrition interventions during pregnancy and early life reduce stunting,[26,30] these interventions might be expected to lead to increased adult stature.[31]

Analyses of height data from our five cohorts are shown in webtables 1a and b and webfigures 1a–f, and are summarised in table 3.

Crude and adjusted results were much the same (webtables 1a and b). Every 1 cm of maternal height was associated with an increase of about 0·5 cm in adult offspring; the only outliers were male adolescents from South Africa, who had not yet attained adult height, which possibly attenuated the association (coefficient 0·16 cm). Highly consistent cross-site effects were noted for birthweight (3·3 cm per kg), intrauterine growth restriction (2·2 cm shorter), weight-for-age at 2 years (2·7 cm per Z score), and height-for-age at 2 years (3·2 cm per Z score). When effect sizes are compared, it is noteworthy that the standard deviation for birthweight is roughly 500 g (table 2), so that a difference of 1 kg is quite large. The association with body-mass-index-for-age at 2 years was much weaker (0·2 cm per Z score) and—for reasons that are unclear—varied substantially among countries, with Guatemala showing a negative coefficient.

See Online for webtable 1 and webfigure 1

***Panel 1:* Exposure variables and adult outcomes that were assessed**

Exposure variables

- Maternal height (cm): measured by the study teams during pregnancy or soon after delivery. No data were available for India
- Birthweight (kg): measured by the research teams except in South Africa where they were obtained from reliable birth records.[13] In Cebu (the Philippines), data for birthweight include interviewer-measured data (60%) and hospital records
- Intrauterine growth restriction: gestational age was calculated from the date of the last menstrual period except in Cebu, in which the Ballard scores[14] were used for all infants with low birthweight or whose mothers had pregnancy complications. Intrauterine growth restriction was defined as a birthweight for gestational age below the tenth percentile of the sex-specific Williams reference curves[15]
- Height-for-age or length-for-age (Z scores): children were measured by the research teams at around 2 years of age, and their height (in South Africa) or recumbent length (other sites) were converted into Z scores with the WHO Growth Standards.[16] Stunting was defined as being less than the Z score cutoff of –2
- Weight-for-age and body-mass-index-for-age (Z scores): defined as above. Underweight and wasting were defined by the Z score cutoff of –2

Adult and adolescent outcomes

- Height (cm): measured by the study teams
- Achieved schooling/education (years): number of years completed with approval
- Income or assets: personal income was measured in local currency in Brazil and Guatemala and expressed in US dollars. Individuals with no income—mostly young adults living with their families or housewives (36% in Brazil and 13% in Guatemala)—were excluded from the analyses. Data from the Philippines and Soweto (South Africa) were not included because few adolescents had independent incomes. In India, household assets were recorded
- Offspring birthweight (g): In Brazil and India, data were obtained from birth records or if unavailable by maternal recall; measured by the research team in Guatemala; and by maternal recall in the Philippines
- Body-mass index (kg/m²): measured by the study teams
- Blood glucose concentration (mmol/L): fasting glucose concentrations were measured in Guatemala and the Philippines. In Brazil, only non-fasting concentrations were available. In India, fasting concentrations and 120-min results from glucose tolerance tests were obtained. This information is not yet available for South Africa. To correct for the skewed distribution in some sites, we used a natural logarithmic transformation
- Systolic blood pressure (mm Hg): measured by the research team in all sites. In Brazil, South Africa, and India, we used the average of two values taken on the same day. In the Philippines and Guatemala, three measures were averaged

	Brazil (Pelotas)		Guatemala (4 villages)		India (New Delhi)		Philippines (Cebu)		South Africa (Soweto)	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Exposure variables										
Maternal height (cm)	156·5 (6·2)	156·4 (5·9)	149·1 (5·3)	149·0 (5·2)	N/A	N/A	150·6 (5·0)	150·5 (5·0)	158·7 (11·2)	158·5 (6·6)
Birthweight (kg)	3·25(0·57)	3·13(0·55)	3·10(0·51)	3·00(0·50)	2·89(0·44)	2·79(0·38)	3·03(0·43)	2·98(0·41)	3·13(0·51)	3·04 (0·50)
Birthweight (<2500 g)	8·0% (7·0–9·0)	10·1% (9·0–11·2)	8·8% (6·4–11·2)	10·6% (7·8–13·4)	16·6% (14·0–19·2)	19·9% (16·7–23·3)	10·8% (7·4–10·9)	9·2% (8·8–12·8)	9·1% (7·5–10·7)	11·4% (9·6–13·2)
IUGR (%)	15·3% (13·9–16·7)	14·4% (13·0–15·8)	34·0% (29·4–38·6)	27·9% (23·2–32·6)	39·8% (36·2–43·4)	40·0% (35·7–44·3)	22·3% (20·2–24·3)	20·1% (18·0–22·2)	15·1% (13·1–17·1)	12·7% (10·9–14·5)
Weight-for-age* (*Z* scores)	0·05(1·13)	0·14(1·03)	–1·73(0·98)	–1·73 (1·01)	–1·48 (1·07)	–1·41(1·08)	–1·68(0·96)	–1·68(0·99)	–0·54(1·32)	–0·34 (1·19)
Weight-for-age* (<–2 *Z* scores)	3·6% (2·9–4·3)	2·6% (2·0–3·2)	35·6% (31·4–39·8)	37·9% (33·3–42·5)	32·3% (29·1–35·5)	27·0% (23·4–30·6)	35·3% (32·4–38·2)	36·6% (33·5–39·8)	12·2% (9·5–14·9)	8·0% (5·9–10·2)
Height-for-age* (*Z* scores)	–0·78(1·28)	–0·61(1·20)	–3·26(1·10)	–3·15 (1·01)	–1·97 (1·18)	–1·90(1·12)	–2·59 (1·12)	–2·50 (1·10)	–1·43 (1·31)	–1·16 (1·19)
Height-for-age* (<–2 *Z* scores)	16·3% (14·9–17·7)	11·6% (10·3–12·9)	87·4% (84·4–90·4)	86·3% (83·0–89·6)	49·4% (46·0–52·8)	43·4% (39·4–47·4)	69·0% (66·2–68·9)	65·6% (62·5–68·9)	29·9% (26·1–33·7)	22·9% (19·5–26·3)
Outcomes (adolescents and adults)										
Height (cm)	173·7 (6·9)	160·7 (6·2)	162·8 (6·1)	150·7 (5·6)	169·7 (6·3)	154·9 (5·7)	163·1 (5·9)	151·2 (5·5)	166·3 (8·1)	158·7 (6·2)
Attained schooling (years)	9·0 (3·2)	9·8 (3·1)	5·4 (3·5)	4·5 (3·2)	13·1 (3·4)	13·9 (3·1)	9·9 (3·4)	11·2 (2·8)	9·6 (3·7)	10·1 (0·9)
Monthly income (log US$)†	5·1 (0·7)	4·8 (0·7)	5·3 (0·9)	3·7 (1·8)	17·2%‡	18·7%‡	N/A	N/A	N/A	N/A
Offspring birthweight (kg)	3·16(0·63)	3·09(0·56)	2·94(0·45)	2·93(0·45)	2·82(0·50)	2·85(0·55)	N/A	2·95 (0·52)	N/A	N/A
BMI (kg/m²)	23·8 (4·1)	23·5 (4·6)	24·7 (3·6)	26·9 (4·8)	24·9 (4·3)	24·6 (5·1)	21·0 (3·1)	20·2 (3·1)	19·7 (3·4)	22·1 (4·4)
BMI (≥25 kg/m²)	30·6% (28·7–32·5)	27·0% (25·1–28·9)	41·1% (37·2–45·0)	62·3% (58·7–65·9)	47·0% (43·7–50·3)	45·4% (41·6–49·3)	7·5% (5·9–9·1)	9·7% (8·0–11·5)	12·8% (10·4–15·2)	29·5% (26·4–32·6)
BMI (≥30 kg/m²)	7·5% (6·4–8·6)	9·1% (7·9–10·3)	8·9% (6·7–11·1)	23·9% (20·7–27·1)	9·5% (7·6–11·4)	13·1% (10·5–15·8)	1·1% (0·4–1·7)	2·0% (1·2–2·9)	3·6% (2·3–4·9)	9·1% (7·1–11·1)
Plasma glucose (mmol/L)§	5·54(0·83)	5·27(0·79)	5·17(0·73)	5·27(1·59)	5·37 (1·21)	5·29(1·18)	5·66(0·52)	5·52 (0·51)	N/A	N/A
Systolic blood pressure (mm Hg)	123·5 (14·4)	111·3 (13·0)	116·8 (11·4)	108·5 (13·0)	118·3 (11·3)	106·7 (11·0)	111·8 (10·8)	99·3 (9·9)	113·4 (25·3)	108·8 (19·7)
Number of participants¶	445–3035	843–2873	348–921	356–878	719–876	513–626	912–1079	762–953	558–1184	577–1251

Data are mean (SD) or prevalence (95% CI). IUGR=intrauterine growth restriction. BMI=body-mass index. N/A=not available. *At roughly 2 years of age. †Geometric mean and SD. ‡Percentage in the highest quintile of income based on assets score for the Delhi cohort. §Geometric mean and SD of fasting glucose, except for Brazil where a non-fasting sample was obtained. ¶Smallest and largest number of participants with available data for the variables under study. For the Delhi cohort, these sample sizes refer to participants for whom complete information is available about occupation of father when the participant was a child, and adult age and BMI. First offspring birthweight is excluded from these values; the sample sizes for this variable are 231 for men and 295 for women.

Table 2: **Exposure and outcome variables, by study site and sex**

Pooled results for all exposures are shown in the webfigures, and those for height-for-age in figure 1. Figure 2 shows the corresponding categorical analyses. There is remarkable similarity across studies, and between males and females. 1 *Z* score of length-for-age or height-for-age at 2 years equals 3·1 cm for boys and 3·2 cm for girls. Because the adult height difference associated with a difference of 1 *Z* score at 2 years is also 3·2 cm, our results suggest that differences observed in the first 2 years will on average remain until adulthood. This finding is consistent with studies on the secular trend in increasing height recorded in all societies as child undernutrition is reduced.[32]

Achieved schooling and educational performance

Undernutrition can affect cognitive development by causing direct structural damage to the brain and by impairing infant motor development[33] and exploratory behaviour.[34] Long-term effects can arise through structural and functional adaptation; the persistence of early deficits, partly because of the absence of opportunities for

	Males		Females		Both sexes	
	Pooled estimate (range)	p*	Pooled estimate (range)	p*	Pooled estimate	p*
Height (cm)						
Maternal height† (cm)	0·47 (0·16 to 0·59)	<0·0001	0·51 (0·46 to 0·54)	<0·0001	0·50	<0·0001
Birthweight (kg)	3·25 (2·72 to 4·19)	<0·0001	3·25 (3·06 to 3·64)	<0·0001	3·25	<0·0001
IUGR (yes/no)	–2·17 (–3·32 to –1·44)	<0·0001	–2·32 (–2·60 to –1·78)	<0·0001	–2·24	<0·0001
WAZ at 2 years (*Z* score)	2·75 (1·83 to 2·86)	<0·0001	2·63 (1·73 to 2·81)	<0·0001	2·69	<0·0001
HAZ at 2 years (*Z* score)	3·26 (3·13 to 3·31)	<0·0001	3·22 (2·92 to 3·50)	<0·0001	3·24	<0·0001

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Schooling (years)						
BAZ at 2 years (Z score)	0·20 (−1·39 to 0·51)	0·03	0·17 (−0·39 to 0·40)	0·08	0·18	0·06
Maternal height† (cm)	0·02 (0·00 to 0·07)	0·04	0·02 (0·01 to 0·06)	<0·0001	0·02	<0·0001
Birthweight (kg)	0·39 (0·16 to 0·48)	<0·0001	0·25 (−0·06 to 0·68)	<0·0001	0·30	<0·0001
IUGR (yes/no)	−0·18 (−0·39 to 0·16)	0·10	−0·25 (−0·52 to 0·28)	0·003	−0·23	0·001
WAZ at 2 years (Z score)	0·51 (0·21 to 0·59)	<0·0001	0·52 (−0·02 to 0·57)	<0·0001	0·52	<0·0001
HAZ at 2 years (Z score)	0·48 (0·32 to 0·51)	<0·0001	0·53 (0·03 to 0·56)	<0·0001	0·50	<0·0001
BAZ at 2 years (Z score)	0·09 (−0·57 to 0·37)	0·51	0·16 (−0·03 to 0·33)	<0·0001	0·16	0·02
Birthweight of the first offspring‡ (g)						
Maternal height† (cm)			7·0 (2·5 to 11·9)	0·02		
Birthweight (kg)			208·0 (190 to 294)	<0·0001		
IUGR (yes/no)			−126·7(−174 to −44)	0·002		
WAZ at 2 years (Z score)			74·7 (31 to 94)	<0·0001		
HAZ at 2 years (Z score)			78·5 (43 to 98)	<0·0001		
BAZ at 2 years (Z score)			14·5 (−2 to 39)	0·37		
Body-mass index (kg/m²)						
Maternal height† (cm)	0·01 (−0·01 to 0·05)	0·15	0·01 (0·00 to 0·02)	0·39	0·01	0·09
Birthweight (kg)	0·71 (0·01 to 1·02)	<0·0001	1·13 (0·91 to 2·21)	<0·0001	0·87	<0·0001
IUGR (yes/no)	−0·50 (−0·82 to 0·03)	<0·0001	−0·76 (−1·42 to −0·38)	<0·0001	-0·60	<0·0001
WAZ at 2 years (Z score)	0·90 (0·39 to 1·26)	<0·0001	0·95 (0·66 to 1·35)	<0·0001	0·92	<0·0001
HAZ at 2 years (Z score)	0·42 (0·06 to 0·63)	<0·0001	0·38 (0·13 to 0·84)	<0·0001	0·40	<0·0001
BAZ at 2 years (Z score)	0·74 (0·33 to 1·13)	<0·0001	0·93 (0·68 to 1·14)	<0·0001	0·81	<0·0001
Glucose concentration‡ (log/mmol/L)						
Maternal height† (cm)	0·067 (0·033 to 0·182)	0·11	−0·011 (−0·113 to 0·082)	0·81	0·031	0·31
Adjusted maternal height§ (cm)	0·034 (−0·019 to 0·184)	0·45	0·005 (−0·109 to 0·104)	0·92	0·020	0·56
Birthweight (kg)	−0·001 (−0·018 to 0·004)	0·84	−0·009 (−0·012 to −0·005)	0·08	−0·004	0·18
Adjusted birthweight§ (kg)	−0·005 (−0·028 to−0·002)	0·28	−0·013 (−0·024 to −0·010)	0·01	−0·009	0·01
IUGR (yes/no)	−0·006 (−0·016 to −0·003)	0·30	−0·005 (−0·028 to 0·006)	0·36	−0·005	0·17
Adjusted IUGR§ (yes/no)	−0·004 (−0·020 to 0·000)	0·43	−0·003 (−0·020 to 0·014)	0·65	−0·004	0·38
WAZ at 2 years (Z score)	0·001 (−0·007 to 0·014)	0·65	−0·002 (−0·011 to 0·000)	0·38	0·000	0·79
Adjusted WAZ at 2 years§ (Z score)	−0·005(−0·010 to 0·006)	0·05	−0·005 (−0·019 to−0·002)	0·05	−0·005	0·005
HAZ at 2 years (Z score)	0·003 (−0·004 to 0·015)	0·15	−0·002 (−0·010 to 0·005)	0·26	0·000	0·76
Adjusted HAZ at 2 years§ (Z score)	−0·002 (−0·008 to 0·010)	0·50	−0·004 (−0·016 to −0·002)	0·13	−0·003	0·13
BAZ at 2 years (Z score)	−0·001 (−0·003 to 0·005)	0·69	0·000 (−0·013 to 0·003)	0·92	−0·001	0·72
Adjusted BAZ at 2 years§ (Z score)	−0·003 (−0·006 to 0·005)	0·16	−0·004 (−0·018 to −0·001)	0·09	−0·004	0·03
Systolic blood pressure (mm Hg)						
Maternal height† (cm)	0·10 (0·04 to 0·19)	0·03	0·06 (0·02 to 0·24)	0·10	0·08	0·07
Adjusted maternal height§ (cm)	−0·01 (−0·10 to 0·04)	0·85	−0·04 (−0·09 to 0·10)	0·38	−0·02	0·45
Birthweight (kg)	−0·54 (−0·86 to 1·24)	0·18	0·11 (−0·51 to 3·16)	0·79	−0·22	0·43
Adjusted birthweight§ (kg)	−2·04 (−3·81 to −0·28)	<0·0001	−1·46 (−1·82 to 0·03)	<0·0001	−1·76	<0·0001
IUGR (yes/no)	−0·26 (−1·76 to 3·28)	0·58	−0·03 (−1·40 to 1·17)	0·95	−0·16	0·65
Adjusted IUGR§ (yes/no)	0·68 (−0·57 to 6·77)	0·13	0·93 (−0·87 to 1·78)	0·05	0·79	0·02
WAZ at 2 years (Z score)	0·98 (0·55 to 1·86)	<0·0001	0·68 (−0·07 to 1·70)	<0·0001	0·83	<0·0001
Adjusted WAZ at 2 years§ (Z score)	−0·72 (−1·10 to −0·30)	0·001	−0·45 (−0·92 to 0·72)	0·039	−0·59	<0·0001
HAZ at 2 years (Z score)	0·96 (0·62 to 2·93)	<0·0001	0·61 (−0·17 to 2·09)	0·001	0·79	<0·0001
Adjusted HAZ at 2 years§ (Z score)	−0·08 (−0·96 to 0·53)	0·68	−0·02 (−1·67 to 2·67)	0·92	−0·05	0·71
BAZ at 2 years (Z score)	0·27 (−1·02 to 0·98)	0·16	0·30 (−0·02 to 0·65)	0·13	0·29	0·04
Adjusted BAZ at 2 years§ (Z score)	−0·76 (−1·26 to −0·22)	<0·0001	−0·48 (−1·19 to 0·11)	0·01	−0·63	<0·0001

WAZ=weight-for-age *Z* score. HAZ=height-for-age *Z* score. BAZ=body-mass-index-for-age *Z* score. IUGR=intrauterine growth restriction. *Data are adjusted coefficients from linear regression analyses, using all exposures as continuous variables, except IUGR, which was included in the model as a dummy variable (0=no; 1=yes). †Information about maternal height not available for India. ‡Glucose and offspring birthweight not available for South Africa. §Additional adjustment for adult BMI and height. ¶Adjusted for individual's age when the outcome variables were measured, years of schooling completed by the mother (in India, by the father), and a measure of early childhood socioeconomic status.

Table 3: **Summary of the pooled adjusted results from the five cohort studies: height, schooling, income/assets, offspring birthweight, body-mass index, blood pressure, and glucose concentration¶**

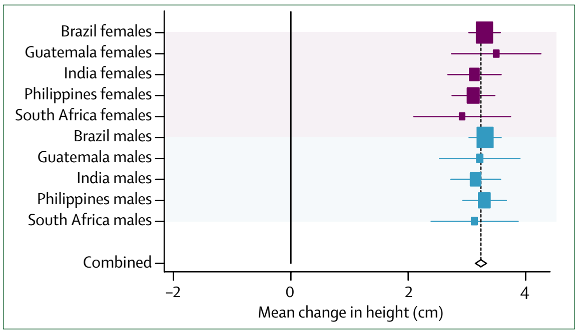

Figure 1: **Forest plot for effect of height-for-age at 2 years on height**
Mean change per unit change in height-for-age *Z* score at 2 years.

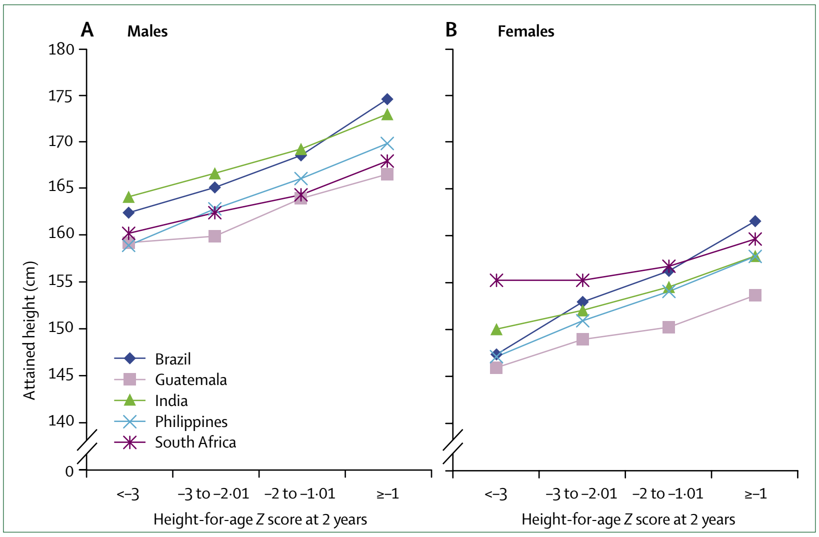

Figure 2: **Attained height according to height-for-age at 2 years in the five cohorts, for males (A) and females (B)**

See **Online** for webtable 2 and webfigure 2

remediation in deprived environments; and by altering the way in which individuals deal with learning.[35]

Birthweight is positively associated with cognitive skills in children, but the effect of environmental factors weakens this association over time.[36] A review of studies from high-income countries—nine investigating adolescent outcomes and six adult outcomes—showed that intrauterine growth restriction had little or no measurable effect on cognitive performance.[37]

Studies from Guatemala[38,39] and Zimbabwe[40] report long-term associations between early child growth and education. In Guatemala, height and head circumference at 2 years (but not birthsize) were inversely associated with educational achievement in adult women.[29] In Cebu, stunting at 2 years was associated with delayed school entry, greater grade repetition and dropout rates, decreased graduation rates from primary and secondary school, and lower school performance.[41] In Guatemala, food supplementation during early childhood improved schooling in women by 1·2 years, and tests scores in men and women.[42] In Zimbabwe, a difference of 3·4 cm in height-for-age at 3 years was associated with almost an additional grade of achieved schooling.[40]

Although there are few follow-up studies from childhood to adult age, substantial evidence suggests an association between stunting and present or later cognitive ability or school performance in children from low-income and middle-income countries. Of 18 cross-sectional studies reviewed, only three did not report significant associations with height-for-age. Excluding studies of children admitted for severe malnutrition, four of five longitudinal studies report that height-for-age predicts school or cognitive test performance in later life. A re-analysis of longitudinal data from the Philippines, Jamaica, Peru, and Indonesia, together with new data from Brazil and South Africa, showed that stunting between 12 and 36 months of age predicted poorer cognitive performance and/or lower school grades attained in middle childhood.[43]

Analyses of attained schooling are shown in webtables 2a and b and webfigures 2a–f, and summarised in table 3. Data from South Africa were not included in the pooled estimates because most 15-year-old children were still at school. Almost all undernutrition indicators were associated with lower educational achievement.

In several analyses (webtables 2a and b), adjustment for confounding reduced the magnitude of the crude effects. After adjustment, the strongest positive predictors of schooling were height-for-age (about 0·50 years of schooling per *Z* score; figure 3) and weight-for-age (0·52 years per *Z* score). For birthweight, every 1 kg (roughly 2 *Z* scores) was associated with an additional 0·30 years of schooling. Intrauterine growth restriction showed an inverse association, whereas associations with child body-mass-index-for-age and maternal height were much weaker. These results are consistent with recent analyses.[43,44]

Income and assets

Poverty is both a cause and an outcome of poor human development, and investments in child nutrition are being promoted as a strategy for economic development.[40,45–47] Better child nutrition improves cognition and schooling, as discussed. It can also affect adult earnings through reduced lean body mass (including shorter height) and decreased productivity in jobs requiring manual labour. In the Guatemala trial, the nutrition intervention led to increased body size and improved work capacity.[31,48]

These indicators of physical and intellectual human capital, in turn, have been associated with increased earnings. Adult height is positively associated with income, even in urban settings and even after adjustment for education.[49] The economic returns to schooling are substantial; for central America, 1 additional year of schooling is associated with 12–14% increased lifetime earnings,[50] and much the same effects were estimated in Brazil.[51] Exposure to famine in early life in China was associated with shorter stature and lower incomes.[52] Exposure to improved nutrition before, but not after, 3 years of age was associated with higher hourly wages in Guatemalan men. For exposure from 0 to 2 years, the increase was US$0·67 per h (95% CI 0·16–1·17), which equates to a 46% increase in average wages.[53]

The only study showing a direct association between growth in infancy and adult income was undertaken in a high-income country, Finland.[54] Data for adult income levels are available for Brazil and Guatemala, and for household assets from India (webtable 3). We made no attempt to do pooled analyses. Individuals from Brazil and Guatemala who had no independent income were excluded, but similar results were obtained when they were included.

Income levels were much the same in Guatemala and Brazil, although the cohort in Brazil was just entering the labour market (table 2). Confounder adjustment led in most cases to reduced effect estimates (webtables 3a and b). Most indicators of undernutrition were associated with lower income in Brazil and fewer assets in India, but in Guatemala few associations were significant. The most consistent results for men were for height-for-age: 1 *Z* score was associated with an 8% increase in income in Brazil (p<0·0001) and Guatemala (p=0·07), as well as with an increase of 0·27 household assets in India (p<0·0001). Associations with weight were less consistent.

Salaries were substantially lower for women than for men (table 2). The only significant associations for women were between height-for-age and income in both Brazil and Guatemala (8% and 25%, respectively), and with number of assets in India. In Brazil and India, there were also positive associations with weight-for-age. Body-mass index was not associated with income or assets in any of the three countries.

Birthweight in the next generation

Maternal bodysize is strongly associated with size of newborn children.[55] As shown above, undernourished girls tend to become short adults, and thus are more likely to have small children. However, evidence from low-income and middle-income countries for the intergenerational effects of undernutrition is scarce.

Ramakrishnan and colleagues[56] have shown that for every 100 g increase in maternal birthweight, her child's birthweight increased by 10–20 g, but studies were primarily undertaken in high-income countries. In Guatemala, birthweight rose by 29 g per 100 g increase in maternal birthweight, and birthlength rose by 0·2 cm for every 1 cm increase in mother's birthlength.[56] In India, maternal birthweight is a strong predictor of offspring birthweight, even after adjustment for maternal adult size.[20]

In Guatemala, weight and height were assessed in children younger than 3 years whose mothers participated in the nutrition supplementation trial as children.[57] Children born to women who had received a protein-energy supplement were on average 0·8 cm taller (95% CI 0·16–1·44) than were those whose mothers received a low-energy supplement.

Data for birthweight of firstborn offspring were available for all sites except South Africa (webtable 4, figure 4, and table 3). Undernutrition was associated with lower birthweight in the next generation. Adjustment for confounding led to reductions of about 10–20% in the crude effect sizes. Every 1 kg of birthweight was associated with a 208 g increase in offspring birthweight, roughly to 100 g per *Z* score of maternal birthweight. Maternal intrauterine growth restriction was associated with a pooled reduction of 127 g, and both weight-for-age and height-for-age—but not body-mass-index-for-age—were associated with increases of about 70–80 g per *Z* score (figure 5). There was a small association between maternal height and birthweight of their grandchildren.

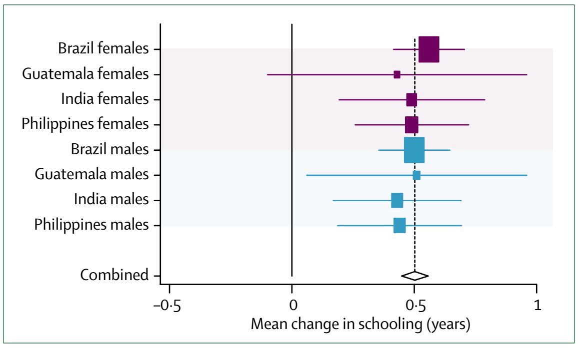

Figure 3: **Forest plot for effect of height-for-age at 2 years on attained schooling**
Mean change per unit change in height-for-age *Z* score at 2 years.

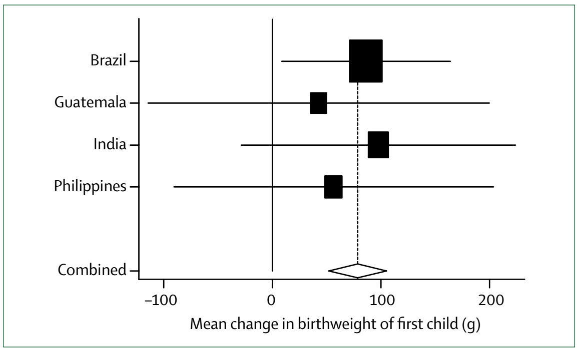

Figure 4: **Forest plot for effect of height-for-age at 2 years on offspring birthweight (females only)**
Mean change per unit change in height-for-age *Z* score at 2 years.

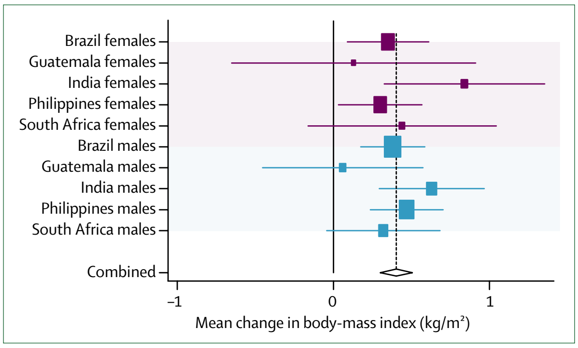

Figure 5: **Forest plot for effect of height-for-age at 2 years on body-mass index**
Mean change per unit change in height-for-age *Z* score at 2 years.

See Online for webtable 3

See Online for webtable 4

See Online for webtable 5 and webfigure 3

Body-mass index, body composition, and obesity

Maternal nutritional status during pregnancy can affect offspring bodysize and composition by production of long-term deficits in fetal lean body mass,[58] altering sensitivity of the hypothalamic-pituitary-adrenal axis[59] which affects appetite and physical activity,[60,61] or through the action of specific components of the maternal diet on gene expression.[62,63]

Four studies from low-income and middle-income countries showed that impaired fetal nutrition results primarily in long-term deficits in lean rather than in fat mass.[64] In New Delhi (India)[9] and Guatemala,[29] birthweight was positively related to adult lean mass in both men and women, but with fat mass or sum of skinfolds[9] only in women. Birthlength was positively related to adult lean mass and sum of skinfolds (Indian men and women), fat mass (Guatemalan men and women), fat-free mass (Guatemalan men), and percentage of body fat (Guatemalan women). In Brazil, birthweight was associated with lean mass in 18-year-old men.[65] In Shanghai adults, waist circumference was higher in those who weighed less than 2·5 kg or more than 3·5 kg than it was in those in the middle of the distribution.[66] This bimodal distribution is consistent with two different pathways—undernutrition and maternal obesity or gestational diabetes affecting the risk of bigger babies,[67,68] which is not part of this review.

There are few data for associations between birthweight and fat distribution. A review of evidence mainly from European studies reports that with adjustment for adult body-mass index, lower birthweight relates to central adiposity represented by the subscapular to triceps skinfold ratio and in some cases, waist to hip ratio.[64] In men and women from New Delhi[9] and in men from Cebu,[21] birthweight and birthlength were inversely related to skinfold ratio. In adults from New Delhi, birthweight was not associated with the waist to hip ratio, but by contrast, birthweight was positively associated with adult waist to hip ratio in women from Guatemala.[9,29]

Recent reviews of how infant size and growth relate to later risk of obesity[69–71] focused on heavy rather than undernourished children, and included very few studies of adults or people from low-income and middle-income countries. In nearly all studies, larger size and growth rates were directly associated with increased risk of obesity in later life. By contrast, linear growth retardation in the first 2 years of life is associated with lower lean body mass in adulthood. In Guatemala, a difference of 1 standard deviation in length at 2 years of age was associated with an effect size of nearly 0·5 standard deviations for adult fat-free mass.[29] In Delhi, body-mass index gain in infancy was more strongly associated with adult lean than fat mass.[9] However, in Brazil weight gain in the first 2 years of life was associated with lean mass in 18-year-old men, whereas later weight gain was more strongly associated with fat mass.[65]

Early childhood stunting was associated with lower adult body-mass index but greater central adiposity in Guatemalan adults after adjustment for overall fatness and confounders.[72] However, previous stunting was not associated with total or central adiposity in adults from New Delhi[9] or in Jamaican 17–18-year-olds.[73]

Webtables 5a and b, figure 5, and webfigures 3a–f show analyses of body-mass index, and table 3 provides a summary. Crude and adjusted results were much the same. There was an inverse association with intrauterine growth restriction and no association with maternal height. Adult body-mass index was strongly and positively associated with birthweight, weight-for-age, and body-mass index at 2 years of age, and less strongly associated with height-for-age (figure 5). Guatemalan men showed a different pattern for most exposures.

Blood lipids

Intrauterine malnutrition and early life growth patterns can result in metabolic and physiological programming, with lifelong effects on the risk of cardiovascular disease. Unhealthy lipid profiles can be a potential mechanism underlying these associations,[74] and animal studies have supported this notion.[75] Changes in liver microstructure can mediate this effect.[76]

Three systematic reviews on newborn size and lipid concentrations are available from high-income countries.[77–79] The most recent study[79] reported a pooled estimate of –1·39 mg/L total cholesterol (95% CI –1·81 to –0·97 mg) per kg of birthweight. Stronger associations were noted in small studies and in infancy. Several studies reported fractions and triglycerides, but most of these associations were null and, as for total cholesterol, inverse associations were most common in small studies.[79] Abdominal circumference, showing liver size, could be a better predictor of adult lipid concentrations than could birthweight,[74] but data for this association are scarce.

Five studies from low-income and middle-income countries are available. In South Africa, intrauterine growth restriction was not associated with lipid concentrations at 20 years of age.[80] In people aged 45 years from Beijing, low birthweight was related to raised triglycerides and reduced HDL cholesterol, after adjustment for sex and adult body-mass index.[81] In Guatemala, birthweight was not associated with serum lipids at 24 years of age; in men, there were inverse trends with total cholesterol and LDL cholesterol, with borderline significance.[82] A Gambian study[83] assessed lipid concentrations in men (mean age 36 years) born in the season of nutritional deprivation (known as the hungry season) and in the harvest seasons, and reported no differences in total, HDL, or LDL cholesterol, or triglycerides. In Brazil, birthweight was not associated with total cholesterol, its fractions, or triglycerides, in 18-year-old men (Horta BL, Universidade Federal de Pelotas, personal communication).

The reviews have shown that adjustment for adult nutritional status increased the negative association of birthweight and lipids, suggesting that postnatal growth plays an important part.[84] The Brazilian study noted no association with birthweight, but rapid weight gain between 2 and 4 years was associated with increased concentrations of VLDL cholesterol and triglycerides at age 18 years (Horta BL, personal communication). However, the only randomised trial—from Guatemala—did not accord with this finding; children supplemented in utero or up to 36 months of age had lower triglycerides and higher HDL cholesterol (men only) in adulthood. Improved nutrition at any age before 7 years was not associated with total or LDL cholesterol.[85] Specific components of the young child's diet, such as breastmilk, might have a role.[86]

Insulin resistance and type 2 diabetes

Type 2 diabetes results from a combination of insulin resistance and insulin secretory failure. The so-called thrifty phenotype hypothesis[87] proposed that under-nourished fetuses and infants make changes (reduced lean-tissue growth and insulin sensitivity, up-regulation of the cortisol axis, and impaired pancreatic development) that cause diabetes in later life. There is strong evidence from animals that maternal dietary deprivation leads to diabetes and insulin resistance in offspring.[60,88,89]

Published work shows inconsistent evidence for the effect of maternal size and nutrition on insulin resistance and type 2 diabetes. Poorer glucose tolerance was associated with higher maternal weight in India[90] but lower maternal body-mass index in China.[81] Fasting glucose was unrelated to maternal size or nutritional supplementation in the Guatemala trial,[39,82,85] or to season of birth in The Gambia.[83]

All studies from high-income countries show associations of lower birthweight with later type 2 diabetes and insulin resistance.[22,91] The risk is greatest for people who became obese, and adjustment for adult body-mass index consistently strengthens the association with low birthweight, suggesting an important effect of weight gain in later life. There is an increased risk of diabetes associated with very high birthweight,[22,92] which has been linked to maternal diabetes in pregnancy. Three studies from low-income and middle-income countries (all adjusting for adult weight) showed higher glucose concentrations in people with lower birthweight,[10,80,81] whereas the two studies that did not adjust showed no associations.[82,93] In four studies of diabetes and impaired glucose tolerance, one (Mysore, India) showed a positive association with ponderal index at birth,[90] one (Delhi, India) showed no association with birth size,[10] one (China) showed an association with low birthweight,[66] and one (South Africa, adjusted for adult size) showed a higher prevalence in small for gestational age births.[80] Three studies[81,90,91] (all adjusting for adult size) showed inverse associations between birthweight and insulin resistance, whereas two without adjustment showed no relation.[80,93] Three studies recorded no associations between birth size and insulin secretion.[80,90,94]

Two studies in high-income countries showed an increased risk of diabetes in people who had low weight in infancy.[95] In studies in low-income and middle-income countries, fasting insulin was positively related to 18-month weight in The Gambia, but there was no association between 18-month weight and fasting glucose.[83] In Delhi, India, diabetes and impaired glucose tolerance were associated with low weight at 1 and 2 years of age (adjusted for adult body-mass index).[10] This study showed a strong association of accelerated body-mass index gain in childhood, after infancy, with diabetes and impaired glucose tolerance. In the Guatemala trial, supplementation during infancy was associated with a small reduction in adult fasting glucose concentration.[85]

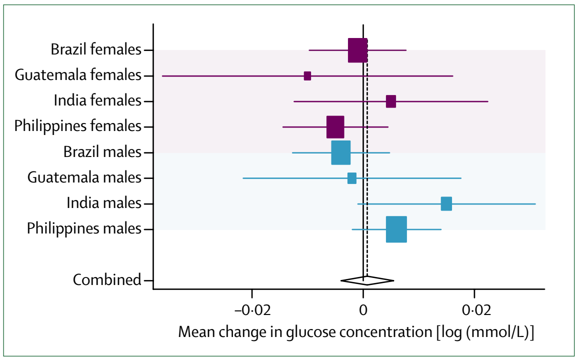

Figure 6: **Forest plot for effect of height-for-age at 2 years on glucose concentration**
Mean change per unit change in height-for-age *Z* score at 2 years.

Concentrations of fasting blood glucose were available in Guatemala and the Philippines; in Brazil, we obtained a random glucose measurement, and measured fasting and 120-min concentrations from a glucose tolerance test in Delhi. Because the random measurements in Brazil were close to fasting levels in the other sites (table 2), the pooled analyses included the four sites.

Results are expressed in natural log scale (webtables 6a and b, figure 6, and table 3). Adjustment for socioeconomic confounders, age, and skin colour (in Brazil and South Africa only) did not produce consistent changes in effect sizes. None of the pooled adjusted estimates was significant but after additional adjustment for adult body-mass index and height, birthweight, weight-for-age, and body-mass-index-for-age at 2 years showed significant inverse associations with blood glucose concentrations (table 3).

See Online for webtable 6

Blood pressure

Animal studies provide strong evidence that blood pressure is raised in offspring of mothers who are exposed to diet restriction during pregnancy. Inadequate nutrition is postulated to reduce the size and number of nephrons, thereby restricting adult renal functional capacity.[96–98] Early nutrition can also affect the renin-angiotensin system,[99,100] exposure to glucocorticoids,[101] and arterial distensibility,[102,103] and it has indirect effects on blood pressure through body composition.

Evidence for an association of maternal diet during pregnancy with raised blood pressure in later life is sparse. An effect of macronutrient imbalance is suggested in European cohorts[104–106] and in one study of adolescents in low-income and middle-income countries,[107] but results differ. Maternal calcium supplementation can reduce offspring blood pressure, as shown in a trial in Argentina.[108] Low maternal fat stores or inadequate pregnancy weight gain is related to elevated offspring blood pressure in Jamaican children[109,110] and Filipino adolescents,[107] but there is little evidence for adults in low-income and middle-income countries.

Many reviews and meta-analyses relate birthweight to adult blood pressure.[4,111–116] Across a wide range of birthweights, most studies report an inverse association of birthweight to systolic blood pressure and hypertension prevalence in later life as well as weaker, less consistent inverse associations with diastolic blood pressure. Effects can amplify with age.[117] Large studies tend to find less significant effects than do small studies.[113] The association of birthweight with later blood pressure strengthens when adjusted for adult body-mass index, suggesting a role for postnatal growth.[4,84,118,119] Individuals at highest risk are those with intrauterine growth restriction but a high body-mass index in adulthood. A study of blood pressure in adults from Shanghai showed a U-shaped relation with birth weight, emphasising the importance of examining non-linear relations.[66]

In Beijing adults,[81] an increase of 1 kg in birthweight was associated with –2·9 mm Hg systolic and –1·7 mm Hg diastolic blood pressure after adjustment for adult body-mass index. Much the same findings were reported for Australian Aboriginals.[120] By contrast, studies from India[93,121] and Guatemala[82] showed no inverse relation of birthweight to adult blood pressure. In India, birthlength was positively associated with adult systolic blood pressure and left ventricular mass,[121] and in the Guatemala trial birthweight was positively associated with systolic and diastolic blood pressure in the daughters, but not sons, of women taking nutrition supplements.[82]

A systematic review of 23 studies recorded a positive association between rapid postnatal growth or weight gain and later blood pressure, but no studies included adults in low-income and middle-income countries.[113] The timing of compensatory growth is important. There is no evidence that rapid infant weight gain increases adult blood pressure. Conversely, adults in Hong Kong with large increases in ponderal index during infancy had lower blood pressure,[122] and male Filipino adolescents with higher weight and height velocity in infancy had decreased risk of high blood pressure.[123]

In our new analyses, data for systolic and diastolic blood pressure were available for all five cohorts. Because both sets of results were almost identical, we present only those for systolic blood pressure. Except for South Africa, adjustment for confounders other than adult body-mass index and height did not produce substantial changes in the effect estimates (webtables 7a and b, figure 7). The adjusted results differed across sites. In the pooled analyses, weight, height, and body-mass-index-for-age at 2 years were positively associated with systolic blood pressure.

See Online for webtable 7

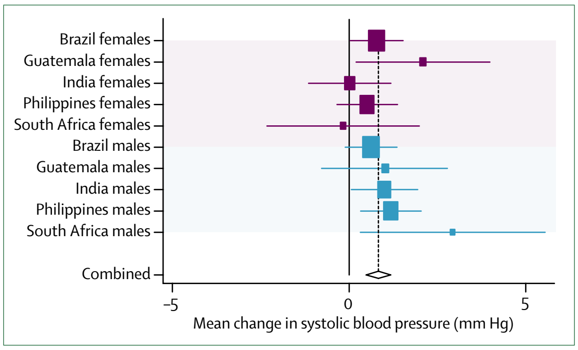

Figure 7: **Forest plot for effect of height-for-age at 2 years on systolic blood pressure**
Mean change per unit change in height-for-age *Z* score at 2 years.

Further adjustment for adult body-mass index and height led to important changes in the coefficients for birthweight (table 3), which became negative in most countries. This pattern was also noted, albeit to a lesser extent, for anthropometric indices measured at 2 years, especially weight-for-age and body-mass-index-for-age.

Cardiovascular disease

The possible biological mechanisms underlying associations between undernutrition and cardiovascular disease are similar to those involved in the aetiology of high blood pressure, lipids, and diabetes.

Several studies in high-income countries have shown that birthweight is inversely associated with the risk of coronary heart disease[124] and stroke.[125–127] The hazard ratio for coronary heart disease in the Helsinki cohort study was 3·63 in men who weighed less than 2·5 kg at birth compared with those weighing more than 4·0 kg. Lower birthweight has also been associated with increased carotid intima media thickness, reduced arterial compliance, and impaired endothelial function, which are all considered to be precursors of cardiovascular disease.[127] Evidence from low-income and middle-income countries is limited to one study from India;[121,128] prevalence of coronary heart disease was inversely related to birthweight after adjustment for adult body-mass index (14% in men and women older than 45 years weighing <5 lbs [2·27 kg] compared with 4% for those weighing >7 lbs [3·18 kg] at birth). Arterial compliance was unrelated to birthweight.

A systematic review concluded that lower infant weight is associated with an increased risk of coronary heart disease in men.[95] Shorter childhood height, but accelerated childhood weight gain, are associated with increased risk of cardiovascular disease.[125,126] Several studies show an increased risk of cardiovascular disease in shorter men and women; however, no studies were identified from low-income and middle-income countries.

Lung function

Lung architecture develops in utero and during the first 2–3 years of life.[129] Early impairment of nutrition or oxygen availability can permanently damage lung structure and function.[130] Forced expiratory volume in 1 second (FEV_1) and forced vital capacity show pulmonary development and have been used as outcomes in several studies of early determinants.

A meta-analysis of eight studies (six from Europe), showed positive associations between birthweight and FEV_1 after adjustment for age, smoking, and height.[131] The two non-European studies included a retrospective cohort of men and women aged 38–59 years from India, in whom mean FEV_1 and forced vital capacity were positively associated with birthweight irrespective of smoking; however, this study did not adjust for socioeconomic status.[132] In the Pelotas cohort in Brazil, both indicators were lowest in 18-year-olds with low birthweight, especially those with intrauterine growth restriction, but the effect disappeared after adjustment for socioeconomic and gestational confounding factors.[133]

Immune function

Studies from The Gambia note that individuals born in the hungry season show immune system changes—suggesting lower thymic output and reduced cellular and humoral responses—that might lead to long-term programming effects.[134,135]

In Pakistani adults[136] and Filipino adolescents,[137] antibody response to selected vaccines was lower in people who were small at birth than in those with a birthweight of 2500 g or more. A Gambian study showed that young adults born in the annual hungry season were substantially more likely to die from infections than were those born the rest of the year.[138,139] This finding was not confirmed in other settings with similar seasonal variability and high adult mortality because of infectious diseases,[140,141] nor in the Dutch famine study in 1944.[142] Further studies are needed to establish the clinical significance of these findings for adults.

Cancers

Unlike other outcomes considered here, cancers are associated with larger size in early life, possibly reflecting increased exposure to growth factors before or after birth, or both.[143–146] Most of the published work relates to breast cancer.

In high-income countries, studies have shown consistent positive association between birthweight and premenopausal breast cancer.[143–146] The risk typically increases by 20–40% from lowest to highest birthweight categories. Much the same associations were reported for prostate, haemopoietic, and colorectal cancers. Data from low-income and middle-income countries are scarce. A small study in China showed no association between birthweight and breast cancer,[147] although in Poland, women of higher birthweight were at increased risk.[148]

Although data are scarce, no associations have been reported between weight in infancy and cancers.[95] Single studies have suggested that higher energy intake in childhood is associated with increased cancer risk, and famine exposure is protective.[149] However, there is no convincing evidence that higher bodyweight in childhood predicts cancer in later life; in fact some trials have suggested that the opposite notion could be true.[143–145] There are no data from low-income and middle-income countries to date. Studies from high-income countries have shown that taller adults have an increased risk of several cancers; however, the Chinese study showed no association for breast cancer.[147]

Bone mass, fracture risk, and osteoporosis

Bone mass is a composite measure of skeletal size and mineral density. It peaks in young adulthood and subsequently decreases, resulting in a heightened risk of osteoporosis and bone fractures in old age. Bone mass in elderly people results from the rate of mineral loss and the mass accumulated during skeletal growth, which in turn depends on dietary calcium and vitamin D status.

Maternal calcium intake and vitamin D status in pregnancy are positively related to bone mass in children.[150] No studies have examined adult outcomes.

Short birthlength is associated with an increased risk of bone fractures in adults.[150] Positive correlations between birthweight or weight in infancy and adult bone-mineral content or density suggest that fetal and infant growth make important contributions to adult bone mass.[150] Correlations are stronger for bone-mineral content than for density, and are reduced after adjustment for adult height, indicating that early weight predicts adult bone mass through its effect on skeletal size. A study from Finland showed higher risk of hip fracture in adults who grew rapidly from birth to 7 years and slowly from 7 to 15 years.[150]

Mental illness

Specific forms of mental illness are thought to be affected by adverse intrauterine experience, including maternal undernutrition. Alterations in brain development, occurring sometime in midgestation, can precipitate evolving malfunction that manifests in early adulthood. The neurodevelopmental hypothesis is supported by significant changes in the size and structure of features of the brain in some adults diagnosed with schizophrenia. Other effects of prenatal undernutrition, such as changes in arousal and sleep waves, are consistent with schizophrenia.[151] The strong link between poverty and mental health[152] can be partly explained by nutritional factors.

Studies investigating the Dutch Famine report more than a two-fold increase in risk for schizophrenia associated with malnutrition in midgestation.[153] A very severe famine in China in 1958–61 indicated a similar level of risk of schizophrenia in a low-income or middle-income setting.[154] Studies of the Chinese example suggest that an increased risk of mental illness is robustly associated with prenatal exposure to famine.[155] Bennet and Gunn state that “nutritional inadequacy, in one form

	Maternal size and nutrition	Size of newborn baby	Infant and child size and growth
Height			
Published work	Insufficient evidence	Strong, positive	Strong, positive
New analysis	Consistent association with maternal height	Positive association with birthweight and negative association with IUGR	Strong associations with height for age and weight-for-age; no association with BMI-for-age
Achieved schooling and educational performance			
Published work	Insufficient evidence	Weak, positive	Strong, positive
New analysis	Weak positive association with maternal height	Strong positive association with birthweight; negative association with IUGR	Strong positive association with height and weight-for-age; weak association with BMI-for-age
Income and wealth			
Published work	Insufficient evidence	Indirect evidence, mediated through schooling and adult size	Indirect evidence, mediated through schooling and adult size
New analysis	No association with maternal height	Positive association with birthweight; negative association with IUGR in two of three countries.	Positive association with height and weight-for-age; no association with BMI-for-age
Bodysize of offspring			
Published work	Insufficient evidence	Strong, positive	Strong, positive
New analysis	Weak direct association between maternal height and birthweight of their grandchildren	Strong positive association of maternal and offspring birthweight; inverse association between maternal IUGR and offspring birthweight	Positive associations between weight and height-for-age—but not BMI-for-age—with birthweight of the offspring
BMI, body composition, and obesity			
Published work	Insufficient evidence	Strong, positive with lean body mass; no clear association with fat mass	Positive association between large infant size and both lean and fat mass
New analysis	No association with maternal height	Strong positive association with birthweight and negative association with IUGR	Strong positive association with BMI-for-age and weight-for-age; weak positive association with height-for-age
Insulin resistance and type 2 diabetes			
Published work	Inconsistent	Weak, inverse (low birthweight associated with higher risk)*	Strong evidence that rapid weight gain increases risk of diabetes
New analysis	No association with maternal height	No association with birthweight except when adult BMI was adjusted for, when an inverse association became apparent	No association with height-for-age. Negative associations with weight and BMI-for-age after adjustment for adult BMI and height
Blood pressure			
Published work	Weak, inconsistent	Moderate, negative	Strong positive, synergistic with small newborn size
New analysis	No association	No consistent association with birthweight except when adult BMI was adjusted for, when an inverse association became apparent	Positive association with weight and height-for-age, and to a lesser extent with BMI-for-age. Associations tended to become negative after adjustment for adult BMI and height
Cardiovascular disease			
Published work	Insufficient evidence	Little evidence of a negative association after adjustment for adult size†	Evidence for an association between small size—especially when followed by rapid weight gain—and cardiovascular disease, but no studies from low-income and middle-income countries
Lung function			
Published work	Insufficient evidence	Strong, positive	Insufficient evidence
Immune function			
Published work	Inconsistent	Inconsistent	Insufficient evidence
Blood lipids			
Published work	Insufficient evidence	Evidence of no association	Inconsistent
Cancers			
Published work	Insufficient evidence	Studies from high-income countries show evidence of a positive association for some cancers, confirmed in one of only two studies identified from low-income and middle-income countries	Inconsistent
Bone mass, fracture risk, and osteoporosis			
Published work	Insufficient evidence	Insufficient evidence‡	Insufficient evidence
Mental illness			
Published work	Little evidence between intrauterine exposure to famine and schizophrenia	Little evidence of inverse association between birthweight, depression, and suicide	Insufficient evidence

BMI=body-mass index. IUGR=intrauterine growth restriction. *In most studies from high-income countries, inverse associations are reported. †Not true for studies from high-income settings, where inverse associations are noted (no adjustment for adult size). ‡Studies from high-income countries show consistent associations between birthweight and adult bone mass.

Table 4: **Summary of the evidence, particularly from low-income and middle-income settings, on the associations between maternal and child undernutrition and adult exposures**

or another is one of the largest single non-genetic contributors to mental retardation and aberrant neural development".[151]

Several cohort studies have reported associations between low birthweight and depression in men, but not in women,[36] also between infant size and depression in both men and women, after adjustment for socioeconomic status, and with suicide in men.[95] We identified no studies from low-income and middle-income countries.

Discussion

Table 4 summarises the review of published data and our new analyses, restricted to anthropometric indicators of undernutrition (panel 2). We provide strong evidence that adequate nutrition in utero and in the first 2 years of life is essential for formation of human capital. Undernourished children are more likely to become short adults, to have lower educational achievement, and to give birth to smaller infants. Undernutrition is also associated with lower economic status in adulthood. At present our cohorts are too young to assess the association between undernutrition and life expectancy, but in view of the direct association between longevity and schooling,[159] such an association will probably become apparent in the long term. Because of the major importance of nutrition for human capital, the amount of research on this issue is remarkably small. Areas in which further research is particularly needed are listed in panel 3.

The effect of undernutrition spans at least three generations, as suggested by the small but significant association between grandmother's height and birthweight of children born to women from the five cohorts. Because of their fairly small magnitude, intergenerational effects do not preclude achievement of progress by acting only on the present generation.

The results of outcomes related to chronic disease were not so straightforward (table 4). Adult body-mass index seems to be strongly affected by the childhood indices related to weight, and to a lesser extent by height-for-age. Because body-mass index includes fat and lean mass, its associations with early weight and height might have different biological implications. Glucose concentrations were not associated with any of the exposures, but it should be noted that participants in the five cohorts are fairly young and that a post-glucose-load concentration was available in only one cohort. In high-income countries, the association of lower birthweight with raised glucose concentration is seen mainly with post-glucose-load values. Systolic and diastolic blood pressure were positively associated with childhood weight and height, and to a lesser extent to body-mass-index-for-age, but these associations were small and their clinical relevance is questionable. Taken together, our results show weaker associations between size at birth or in infancy with outcomes related to chronic disease than do those arising from cohorts in developed countries. In addition to the young age of our cohorts, other factors might have a role, including the fact that the causes of low birthweight are different and there is less catch-up growth compared with developed settings, and that some of our cohorts were not undergoing the nutrition transition.

We analysed five long running prospective cohorts in low-income and middle-income countries in a similar way. The consistency of most results is remarkable, considering that study sites are located in South and Central America, sub-Saharan Africa, and south and east Asia. Because analyses were defined a priori, our results are not affected by publication bias.

There were substantial increases in the coefficients after adjustment for adult body-mass index and height. In earlier analyses related to the Barker hypothesis, adjustment for present size was a standard procedure, but this practice has been challenged.[84] Our reviews of studies from low-income and middle-income countries on lipid profiles, diabetes, blood pressure, and cardiovascular disease showed that the negative effects of undernutrition often only become apparent—or at least were strengthened—after such adjustment. If an early weight and present weight or body-mass index are included in the same regression equation, the coefficient associated with the early weight measure will become negative whenever weight gain is positively associated with the outcome. For example, a negative association with birthweight that becomes apparent only when adult body-mass index is included in the statistical model does not suggest that low birthweight itself is a risk factor; in fact, postnatal excessive weight gain might have a large role.[70,84,95,119]

For the outcomes for which no new data are presented, there is insufficient evidence linking undernutrition to long-term changes in immune function or blood lipids, or in indicators related to osteoporosis. Birthweight is positively associated with lung function, and there is some

Panel 2: What this paper does not cover

This paper addresses maternal and child undernutrition through the use of anthropometric indicators. There are other dimensions of undernutrition that are equally important. These include micronutrient deficiencies—eg, iodine, iron, vitamin A, and calcium—which might lead to long-term consequences. An earlier *Lancet* Series addressed the long-term consequences of iodine and zinc deficiency on intellectual development,[156] and these deficiencies were incorporated in the estimates of burden of diseases included in the first paper in this Series.[1]

Breastfeeding can also have long-term health consequences. A recent series of systematic reviews addressed its association with body-mass index, blood pressure, diabetes and related indicators, blood lipids, and schooling.[86]

Two important studies on the effects of short exposures to malnutrition during famines in Europe—the Dutch famine[157,158] and Leningrad siege studies—were cited only when evidence from low-income and middle-income countries was very scarce. Although these investigations provide unique information about crucial periods when undernutrition is likely to have lasting effects, they were deemed not to be representative of the situation in such countries when undernutrition acts throughout longer time periods including pregnancy, infancy, and childhood.

Panel 3: Areas for future research

- Association between rapid weight and length gain at different age intervals in infancy and childhood with human capital and outcomes related to chronic disease, to define the age after which rapid growth should be avoided
- Long-term effects of weight gain in late childhood stratified in previously stunted and non-stunted children, and for children with and without intrauterine growth restriction
- Long-term effects of micronutrient deficiencies in childhood
- Association between undernutrition and long-term changes in immune function, blood lipids, osteoporosis, and mental illness
- Improved quantification of the economic effect of undernutrition on adult productivity
- Interactions between genes and environmental factors in long-term outcomes

evidence that undernutrition might contribute to mental illness. By contrast with these findings (ie, showing detrimental effects of undernutrition), studies suggest a positive association between birthweight and the incidence of some cancers.

A recent symposium[160] addressed the contrasting perspectives of auxology and biomedicine—“poor growth is poor health”—and evolutionary biology and anthropology—“poor growth is adaptive”. The evidence for the biomedical stance is overwhelming and recognised by the symposium participants, but the two approaches are not incompatible. In response to poor nutrient availability at the cellular level, vital functions are preserved, linear growth is stopped, and muscle and fat can be metabolised for continued function. Thus poor growth can be a survival strategy. However, the evidence that growth failure has a huge cost is overwhelming: compared with people who grow well, there is increased susceptibility to infections and greater mortality[1] and losses in human capital in survivors. A population of stunted people will indeed have lower nutritional requirements than will a population with unrestricted growth, which might be seen as an adaptation; however, such a population will be less likely to be competitive in the modern world because of reduced human capital.

Rapid weight gain is especially relevant in low-income and middle-income countries that are undergoing rapid transition and facing an epidemic of overweight and obesity. The long-term effects of early undernutrition might be compounded by the adoption of diets and lifestyles of developed countries.[134] A baby of low birthweight, who is stunted and underweight in infancy and gains weight rapidly in childhood and adult life, can represent a worst-case scenario for cardiovascular and metabolic disease.[10,134,161,162] However, rapid weight gain in infancy is associated with lower morbidity and mortality in low-income and middle-income settings,[1,163] and as shown above, bodysize at 2 years of age is clearly associated with enhanced human capital. Although these are sufficient reasons for strong efforts in the prevention of undernutrition, attention should also be given to preventing excessive weight gain after infancy.

To design evidence-based policies, the potential hazards of rapid weight gain in different age ranges should be established. There is growing evidence that a high birthweight[64] and weight gain in infancy lead primarily to accumulation of lean body mass, whereas gaining weight later in childhood is more likely to result in accumulation of fat mass.[9,22,65,164] A recent meta-analysis centred on studies from high-income countries concluded that “there is insufficient evidence to recommend prevention of adult disease through strategies to alter infant growth.”[95] Therefore, present evidence does not accord with limiting weight gain in the first year of life, and suggests that rapid weight gain becomes hazardous only later in childhood. Further research is needed to establish the exact age when rapid weight gain does more harm than good.

The first article in this Series proposed stunting as a better overall indicator of undernutrition than underweight.[1] In countries undergoing the nutrition transition, monitoring length-for-age and weight-for-length in young children has been argued to be more appropriate than monitoring weight-for-age,[165] because weight gain can reflect children becoming taller, fatter, or both. Our findings support this argument. Height-for-age at 2 years was more closely related to outcomes for human capital than birthweight, weight-for-age, or body-mass-index-for-age. Body-mass-index-for-age was not an important predictor of human capital, although it is highly predictive of adult body-mass index. Countries undergoing the nutrition transition should consider the advantages of assessing height-for-age and body-mass-index-for-age, in view of their different predictive values.

Because of the observational nature of our analyses, the possibility of residual confounding cannot be ruled out. However, that adjustment for confounders, including socioeconomic indicators, made little difference to estimates of effect size is reassuring. In the one trial included in our analysis, exposure to a nutritious supplement during pregnancy and early childhood, compared with exposure to low-energy supplement, led to greater adult height, schooling (women only), improved scores on tests of intelligence and reading, greater income, and better growth of the next generation.[31,38,48,57,166,167]

Our results strongly suggest that undernutrition leads to long-term impairment. This evidence, combined with the well-known short-term effects of undernutrition, is sufficient for giving the prevention of undernutrition high priority in national health, education, and economic agendas in low-income and middle-income countries.[45,168] At the same time as investments are made against undernutrition, middle-income countries undergoing the nutrition transition should also address the negative consequences of rapid weight gain, especially in later childhood.

Contributors

CGV convened the working group, and conceptualised and coordinated the preparation of the paper. PCH led the analyses. Primary responsibility for specific topics were as follows: height and economic productivity (RM); education and mental health (LR); intergenerational effects, lipids, and immunity (CGV); body composition and blood pressure (LA); and diabetes, cardiovascular disease, cancer, and bone health (CF and HSS). All authors provided original data and contributed to the final paper.

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Conflict of interest statement

We declare that we have no conflict of interest.

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