Wells et al.,

Emerging biological pathways in the double burden of malnutrition

Supplementary Appendices

Appendix 1: Forms of malnutrition throughout the life course and their public health significance

	Definition	Public health significance
Under-nutrition		
Low birth weight (LBW) (1, 2)	Birth weight < 2500 g. Comprises babies born preterm and/or with fetal growth restriction. Very low birth weight < 1500 g.	**a) Statistics:** Globally 20 million (15-20 % of all births). **b) Health impact:** Associated with postnatal mortality and morbidity as well as impaired cognitive development and non-communicable diseases (NCDs) later in life.
Preterm birth (1-5)	Births prior to 37 complete weeks after the first day of the last menstrual period before the pregnancy. Moderate to late preterm (32 to < 37 weeks). Very preterm (28 to < 32 weeks). Extremely preterm (< 28 weeks).	**a)** Globally ~ 15 million infants. **b)** Associated with high risk of neonatal mortality, poor cognitive development and pulmonary sequelae.
Small-for-gestational age (SGA) (1, 2, 4)	Birthweight < 10th centile for a gender-specific completed gestational age. Further divided into term-SGA and preterm-SGA.	**a)** ~ 32.4 million infants (27 % of livebirths) in low- and middle income countries. **b)** Associated with postnatal mortality and morbidity.
Wasting (acute malnutrition) in children, 0-5 years (6, 7)	Weight-for-height more than 2 standard deviation scores (SDS) below the age- and sex-specific median of the 2006 World Health Organization (WHO) child growth standards. Moderate wasting (≥ -3 and < -2 SDS). Severe wasting (< -3 SDS).	**a)** Globally ~ 52 million (7.7 %) children < 5 years are wasted, including 17 million severely wasted. **b)** Associated with impaired immune function, child morbidity and mortality. Recurrent episodes or long-term of wasting may impair linear growth.
Stunting (chronic malnutrition) in children, 0-5 and 5-19 years (7, 8)	Height-for-age more than 2 SDS below the sex-specific median of the 2006 (0-5 years) and 2007 (5-19 years) WHO child growth standards. Moderate stunting (≥ -3 and < -2 SDS). Severe stunting (< -3 SDS).	**a)** Globally ~ 155 million (23 %) children < 5 years are stunted. **b)** Largely irreversible long-term health impacts including cognitive impairment, reduced physical growth potential and birth weight of offspring, increased risk of diet-related NCDs and reduced economic productivity. Stunting in childhood is associated with adult short stature, though some height recovery may occur during later childhood/adolescence.
Underweight in children, 0-5 years (7, 9)	Weight-for-age more than 2 SDS below the sex-specific median of the 2006 WHO child growth standards (0-5 years).	**a)** Globally ~ 94.5 million (14 %) children < 5 years are underweight. **b)** Associated with risk of infectious diseases postnatal mortality. May reflect wasting and/or stunting, and thus a difficult measure to interpret.
Thinness (also referred to as "moderate and severe underweight") in children, 5-19 years (10, 11)	Body Mass Index (BMI)-for-age more than 2 SDS below the sex-specific median of the 2007 WHO child growth standards (0-5 years). Mild thinness (≥ -2 and < -1 SDS).	**a)** Global age-standardised prevalence of 12.4 % in boys and 8.4 % in girls. **b)** Associated with risk of infectious diseases and for girls of childbearing age with mortality, delivery complications, preterm birth, and intrauterine growth retardation.
Anaemia in children (12, 13)	Haemoglobin concentrations < 110 g/l (Children 0–4 years) and < 120 g/l (Children 6–14 years) in populations living at sea level.	**a)** Globally ~ 273 million (43 %) children <5 years. **b)** Associated with impaired cognitive and motor development as well as increased morbidity and mortality.
Underweight in adults (14-16)	BMI < 18.5 kg/m^2. Mild underweight (≥17.0 and < 18.5 kg/m^2). Moderate underweight (≥ 16.0 and <17 kg/m^2). Severe underweight (< 16 kg/m^2). European Society of Clinical Nutrition and Metabolism (ESPEN) proposed cut-offs of <15 and <17 kg/m^2 in females and male respectively to identify low fat-free mass index (FFMI), calculated as fat-free mass/height^2 in kg/m^2.	**a)** Global age-standardised prevalence of 8.8 % in men and 9.7 % in women. **b)** Increased risk of morbidity and mortality, including frailty in old age.

Acute energy deficiency (AED) (15)	A state of negative energy balance resulting in a steadily declining body weight and energy stores.	**a)** No data available. **b)** Lowers resistance to infection and work capacity.
Short stature in adults (11)	No universal definition currently available, reflecting significant inter-population variability in average height. Potential categorisations include 10th centile, lowest quartile. A universal approach matching that in children could be height-for-age >2 SDS below the sex-specific median of the 2007 (5-19 years) WHO growth standards, equivalent to < 161.9 and < 150.1 cm at 19 years for males and females respectively.	**a)** No data available. **b)** Similar risk as for stunting in childhood.
Sarcopenia in adults (17-19)	Progressive and generalised loss of skeletal muscle tissue, strength and function as a result of ageing. Cut-off points depend on the assessment technique used to measure muscle mass, strength and function. It is suggested to use a value of more than 2 SDS below a sex-specific mean reference value of healthy young adults.	**a)** Globally 5-13 % in persons above 60 years. **b)** Results in physical disability, poor quality of life and mortality.
Anaemia in woman of reproductive age (12, 13)	Haemoglobin concentrations < 120 g/l (Non-pregnant women) and < 110 g/l (Pregnant woman) in populations living at sea level.	**a)** Globally ~ 496 million (29 %) non-pregnant and ~ 32 million (38 %) pregnant women. **b)** Low levels of haemoglobin during pregnancy are associated with risk of miscarriage, stillbirths, preterm delivery and having a LBW child. Associated with maternal morbidity, mortality, fatigue, lethargy and low productivity.
Overweight		
High birth weight (fetal macrosomia) (20)	Birth weight > 4000-4500 g. May be divided into 3 categories: Birth weight ≥ 4000 and <4500 g (Grade 1). Birth weight of ≥ 4,500 and <5000 g (Grade 2). Birth weight ≥5,000 g (Grade 3).	**a)** Prevalence varies between 5-20 %. **b)** Grade 1: Increased risk of labour complications. Grade 2: An additional risk of maternal and newborn morbidity. Grade 3: An additional risk of still birth and neonatal mortality.
Large-for-gestational age (20)	Birth weight ≥ 90th percentile for a given gestational age.	**a)** No data, but definition automatically extends to ~10%. **b)** Depending on gestational age, risks are similar to those of high birth weight.
Overweight and obesity in children, 0-5 years (7, 21)	Weight-for-height more than 2 SDS above the age- and sex-specific median of the 2006 WHO child growth standards.	**a)** Increasing in all regions of the worlds, the estimated global number of overweight children < 5 years is ~ 41 million (6 %). **b)** Overweight from an early age has been found to track throughout childhood, adolescence and into adulthood, where it increases the risk of diet-related NCDs.
Overweight (but not obesity) in children, 5-19 years (10, 11)	BMI-for-age more than 1 SDS to 2 SDS above the sex-specific median of the 2007 WHO child growth standards. A SDS > 1 is equivalent to a BMI of 25.4 and 25.0 kg/m^2 at 19 years for boys and girls, respectively.	**a)** No data available. **b)** Overweight from an early age has been found to track throughout childhood, adolescence and into adulthood, where it increases the risk of diet-related NCDs.
Obesity in children, 5-19 years (10, 11)	BMI-for-age more than 2 SDS above the sex-specific median of the 2007 WHO child growth standards. A SDS > 2 is equivalent to a BMI of 30 kg/m^2 at 19 years for both sexes.	**a)** Global age-standardised prevalence of 7.8 % in boys and 5. 6 % in girls **b)** Same as for overweight. In addition, obesity lowers self-esteem, increases risk of psychosocial problems and lowers educational attainment.
Overweight in adults (14, 22-24)	BMI ≥ 25.0 and < 30 kg/m^2. Ethnic-specific criteria representing increased risk for Asian populations are suggested by a WHO expert consultation: BMI ≥ 23.0 and < 27.5 kg/m^2.	**a)** Global age-standardised prevalence of 36.9 % in men and 38.0 % in women **b)** A risk factor for a wide array of NCDs, including cardiovascular and kidney diseases, type-2-diabetes, some cancers, and musculoskeletal disorders.

Obesity in adults (14, 22, 24)	BMI ≥ 30 kg/m^2. Severe obesity/obese class 2 (≥ 35 and <40 kg/m^2) and morbid obesity/obese class 3 (≥ 40 kg/m^2). Ethnic-specific criteria representing high risk for Asian populations are suggested by a WHO expert consultation: BMI ≥ 27.5.	**a)** Global age-standardised prevalence of 10.8 % in men and 14.9 % in women (obesity). Severe (2.3 % and 5.0 %) and morbid (0.64 % and 1.6 %) obesity. **b)** Same as for overweight. In addition, obesity lowers self-esteem, increases risk of psychosocial problems and lowers educational attainment.
Abdominal obesity in adults. Determined based on waist circumference (25)	Risk of metabolic complications is increased with a waist circumference > 94 cm (men) and > 80 cm (women). Risk of metabolic complications is substantially increased with a waist circumference > 102 cm (men) and > 88 cm (women). Ethnic-specific criteria where the risk of metabolic complications is increased. Europid: >94 (men) and >80 (women); South Asian, Chinese and Japanese: >90 (men) and >80 (women).	**a)** No data available. **b)** Same as for overweight and obesity by BMI.
Abdominal obesity in adults. Determined based on waist–hip ratio (25)	Risk of metabolic complications is substantially increased with a waist–hip ratio > 0.90 (males) and > 0.85 (females).	**a)** No data available. **b)** Same as for overweight and obesity by BMI.
Sarcopenic obesity (26-30)	Loss of muscle mass, while fat mass is preserved or even elevated. Thus, body weight may be maintained. No universal definition, various proposals to categorize a combination of low muscle mass and high adiposity.	**a)** Across 10 high and low-/middle-income countries, national prevalence ranged from 1.3% (India) to 11.0% (Spain). Prevalence varies according to diagnostic criteria used. **b)** Elevated cardio-metabolic risk in association with impaired physical function and frailty
High body fatness (fat percentage) in adults (31)	Cut-off values for obesity by fat percentage: 25 % (men) and 35 % (women), corresponding to a BMI of 30 kg/m^2 in young Caucasians. These may be replaced by cut-offs based on fat mass index, which is a size-adjusted index of adiposity independent of the magnitude of fat-free mass.	**a)** No data available. **b)** Same as for overweight and obesity by BMI.

References to Appendix 1

1. WHO. Low birth weight policy brief. 2014. Report No.: WHO/NMH/NHD/14.5.
2. Katz J, Lee AC, Kozuki N, Lawn JE, Cousens S, Blencowe H, et al. Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis. The Lancet. 2013;382(9890):417-25.
3. Kramer MS, Papageorghiou A, Culhane J, Bhutta Z, Goldenberg RL, Gravett M, et al. Challenges in defining and classifying the preterm birth syndrome. Am J Obstet Gynecol. 2012;206(2):108-12.
4. Lee AC, Katz J, Blencowe H, Cousens S, Kozuki N, Vogel JP, et al. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. The Lancet Global Health. 2013;1(1):e26-e36.
5. March of Dimes, PMNCH, Save the Children, WHO. Born too soon: the global action report on preterm birth. Geneva: World health organization; 2012.
6. WHO. Wasting policy brief. 2014. Report No.: WHO/NMH/NHD/14.8.
7. Global Health Observatory data repository: Joint child malnutrition estimates [Internet]. 2017 [cited 18-02-2018]. Available from: http://apps.who.int/gho/data/node.main.ngest?lang=en.
8. WHO. Stunting policy brief. 2014. Report No.: WHO/NMH/NHD/14.3.
9. WHO. NLIS Country Profile Indicators Interpretation Guide. Geneva, Switzerland: World Health Organization; 2010.
10. Abarca-Gómez L, Abdeen ZA, Hamid ZA, Abu-Rmeileh NM, Acosta-Cazares B, Acuin C, et al. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. The Lancet. 2017;390(10113):2627-42.
11. de Onis M. Development of a WHO growth reference for school-aged children and adolescents. Bulletin of World Health Organization. 2007;85(09):660-7.

12. Stevens GA, Finucane MM, De-Regil LM, Paciorek CJ, Flaxman SR, Branca F, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995-2011: a systematic analysis of population-representative data. Lancet Glob Health. 2013;1(1):e16-25.
13. Stoltzfus RJ DM. Guidelines for the use of iron supplements to prevent and treat iron deficiency anaemia. Washington, DC; 1998.
14. (NCD-RisC) NRFC. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet. 2016;387(10026):1377-96.
15. Shetty PS, James WPT. Body mass index - A measure of chronic energy deficiency in adults. Rome, Italy: Food and Agriculture Organization of the United Nations; 1994.
16. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, Muscaritoli M, Nyulasi I, Ockenga J, Schneider SM, de van der Schueren MA, Singer P. Diagnostic criteria for malnutrition - An ESPEN Consensus Statement. Clin Nutr. 2015 Jun;34(3):335-40.
17. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412-23.
18. Morley JE, Anker SD, von Haehling S. Prevalence, incidence, and clinical impact of sarcopenia: facts, numbers, and epidemiology-update 2014. J Cachexia Sarcopenia Muscle. 2014;5(4):253-9.
19. Shafiee G, Keshtkar A, Soltani A, Ahadi Z, Larijani B, Heshmat R. Prevalence of sarcopenia in the world: a systematic review and meta- analysis of general population studies. J Diabetes Metab Disord. 2017;16:21.
20. American College of O, Gynecologists' Committee on Practice B-O. Practice Bulletin No. 173: Fetal Macrosomia. Obstet Gynecol. 2016;128(5):e195-e209.
21. WHO. Childhood overweight policy brief. 2014. Report No.: WHO/NMH/NHD/14.6.
22. NHLBI. NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Obesity in Adults. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. Bethesda (MD): National Heart, Lung, and Blood Institute; 1998. Report No.: 98-4083.
23. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384(9945):766-81.
24. WHO. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. The Lancet. 2004;363(9403):157-63.
25. WHO. Waist circumference and waist–hip ratio: report of a WHO expert consultation, Geneva, 8–11 December 2008. Geneva; 2011.
26. Stenholm S, Harris TB, Rantanen T, Visser M, Kritchevsky SB, Ferrucci L. Sarcopenic obesity: definition, cause and consequences. Curr Opin Clin Nutr Metab Care. 2008 Nov;11(6):693-700.
27. Bosy-Westphal A, Müller MJ. Identification of skeletal muscle mass depletion across age and BMI groups in health and disease--there is need for a unified definition. Int J Obes (Lond). 2015 Mar;39(3):379-86.
28. Prado CM, Siervo M, Mire E, Heymsfield SB, Stephan BC, Broyles S, Smith SR, Wells JC, Katzmarzyk PT. A population-based approach to define body-composition phenotypes. Am J Clin Nutr 2014 Jun;99(6):1369-77.
29. Siervo M, Prado CM, Mire E, Broyles S, Wells JC, Heymsfield S, Katzmarzyk PT. Body composition indices of a load-capacity model: gender- and BMI-specific reference curves. Public Health Nutr 2015 May;18(7):1245-54.
30. Tyrovolas S, Koyanagi A, Olaya B, Ayuso-Mateos JL, Miret M, Chatterji S, Tobiasz-Adamczyk B, Koskinen S, Leonardi M, Haro JM. Factors associated with skeletal muscle mass, sarcopenia, and sarcopenic obesity in older adults: a multi-continent study. J Cachexia Sarcopenia Muscle. 2016 Jun;7(3):312-21.
31. WHO. Physical status: the use and interpretation of anthropometry, Report of a WHO Expert Committee. Geneva: World Health Organization; 1995.

Appendix 2. Malnutrition and the microbiome, and the effects of probiotics on cardio-metabolic risk markers

(A) Associations between different forms of malnutrition through the life-course with dysbiosis						
Form of malnutrition	Age	Population	Study design	n	Reported associations	Ref
Low birth weight	37-42w gestational age	Beijing, China	Case-control	24	Placenta of low birth weight neonates had significantly lower bacterial richness than that of normal birth weight neonates	1
Stunting	3–24m	Vellore, South India	Case-control	20	Chronically stunted children had lower microbiome enrichment in probiotic species and increased enrichment in inflammogenic taxa, but no difference in microbiome diversity	2
	M: 10m + 10 m follow-up B: 3m + 14m follow-up	Malawi, Bangladesh		36 twin pairs	Reduced microbiota diversity was associated with stunting severity, while increased relative abundance of some species predicted future growth faltering	3
Severe-acute malnutrition		Malawi, Bangladesh	Case- control	M: 19 B: 76	Severe-acute malnutrition is associated with relative microbiota immaturity, only partially ameliorated by nutritional therapy	4,5
	6-24m	Uganda	Comparison of 2 groups	87	Non-oedematous children had lower gut microbiome diversity than oedematous children	6
	13.4 ± 17.8m	Nigeria, Senegal		15	Severe-acute malnutrition was associated with globally decreased microbiome diversity, a depletion in oxygen-sensitive prokaryotes, and an enrichment in potentially pathogenic species	7
Sarcopenia	63-78y	HICs		Systematic review of 5 studies	4 of 5 studies associated physical frailty with reduced microbiome diversity	8
Anorexia nervosa	30 ± 8y	Japan		46	Lower amounts of total bacteria and altered microbiome composition in patients vs controls	9
Obesity	Range of means 26-61y	HICs/MICs	Comparison of 2 groups	Meta-analysis of 10 studies	Only weak evidence for a systematic association between obesity status and microbial communities	10
	18-27m	US		77	Maternal obesity is associated with less varied microbiome composition in the young child	11

(B) Effect of interventions using probiotics to reduce cardio-metabolic risk markers in adults						
Form of cardio-metabolic risk	Age	Population	Study design	n	Effect of interventions using probiotics	Ref
BMI and % fat	Adults	HICs/MICs	RCTs	Meta analysis of 15 studies	Probiotic supplements promoted loss of BMI and %fat, though the effect size was small	12
Waist girth	Adults	HICs/MICs	RCTs	Meta analysis of 4 studies	Consistent reduction in waist circumference across studies	13
Type 2 diabetes	Adults	HICs/MICs	RCTs	Meta analyses of 12 and 13 studies	Supplementation with probiotics reduced fasting blood glucose, insulin resistance and HDL cholesterol compared to placebo	14,15
Gestational diabetes	Adult women		RCTs	Meta analysis of 4 studies	Supplementation with probiotics reduced insulin resistance compared to placebo, but did not affect gestational weight gain	16
Hypertension	Adults	HICs/MICs	RCTs	Meta analysis of 9 studies	Supplementation with probiotics reduced systolic and diastolic blood pressure compared to placebo, with the effects stronger when multiple species of probiotic are consumed	17
LDL and HDL	Adults	HICs/MICs	RCTs	Meta analysis of 15 and 14 studies	Supplementation with probiotics reduced LDL, though results showed heterogeneity, but had no consistent effect on HDL	18
Triglycerides	Adults	HICs/MICs	RCTs	Meta analyses of 13 studies	Supplementation with probiotics had no consistent effect on triglycerides	18
Inflammatory markers	Adults	HICs/MICs	RCTs		Supplementation with probiotics reduced C-reactive protein but not TNF Alpha or IL6	19

(C) Effect of interventions using probiotics to improve growth in children						
Growth outcomes	Age	Population	Study design	n	Effect of interventions using probiotics	Ref
Weight and height for age	Children <5 y	HICs/LMICs	RCTs and non-randomized clinical trials	Systematic review of 10 RTCS and 2 non-randomized clinical trials	Positive effect of probiotics on child growth in 5 studies in developing countries with mostly under-nourished children, but no significant effect in 7 studies in developed countries	20

(D) Effect of interventions using fecal microbiota transplantation (FMT) to reduce cardio-metabolic risk markers in adults						
Form of cardio-metabolic risk	Age	Population	Donors	n	Effect of interventions using fecal transplant ation	Ref
Metabolic syndrome	55 (SD 8) y	Male obese participants of West European genetic background	Vegans	10 patients with 9 donors, vs 10 patients with autologous FMT	Changes in intestinal microbiota composition but no change in production capacity of an atherogenic metabolite, or markers of vascular inflammation	21
Metabolic syndrome	47 (SD 4) y	Male Caucasian obese subjects	Healthy lean men	9 patients with 9 donors, vs 9 patients with autologous FMT	Improved insulin sensitivity of recipients at 6 weeks, along with increased levels of butyrate-producing intestinal microbiota	22
Metabolic syndrome	54 (49-60) y	Male, omnivorous, Caucasian, obese subjects	Healthy lean men	26 patients with 11 donors, vs 12 patients with autologous FMT	Transient improvement in insulin sensitivity at 6 weeks (not sustained), associated with changes in microbiota composition and fasting plasma metabolites.	23

W – weeks; m – months; y – years; RCTs – Randomized controlled trials

HICs – High-income countries; MICs – Middle-income countries;

References to Appendix 2.

1. Zheng J, Xiao X, Zhang Q, Mao L, Yu M, Xu J. The placental microbiome varies in association with low birth weight in full-term neonates. Nutrients. 2015 Aug 17;7(8):6924-37.
2. Dinh DM, Ramadass B, Kattula D, Sarkar R, Braunstein P, Tai A et al. Longitudinal Analysis of the Intestinal Microbiota in Persistently Stunted Young Children in South India. PLoS One. 2016 May 26;11(5):e0155405.
3. Gough EK, Stephens DA, Moodie EE, Prendergast AJ, Stoltzfus RJ, Humphrey JH, et al. Linear growth faltering in infants is associated with Acidaminococcus sp. and community-level changes in the gut microbiota. Microbiome. 2015 Jun 13;3:24.
4. Subramanian S, Huq S, Yatsunenko T, Haque R, Mahfuz M, Alam MA, et al. Persistent gut microbiota immaturity in malnourished Bangladeshi children. Nature. 2014 Jun 19;510(7505):417-21.
5. Blanton LV, Charbonneau MR, Salih T, Barratt MJ, Venkatesh S, Ilkaveya O, et al. Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children. Science. 2016 Feb 19;351(6275). pii: aad3311
6. Kristensen KH, Wiese M, Rytter MJ, Özçam M, Hansen LH, Namusoke H, et al. Gut microbiota in children hospitalized with oedematous and non-oedematous severe acute malnutrition in Uganda. PLoS Negl Trop Dis. 2016 Jan 15;10(1):e0004369.
7. Tidjani Alou M, Million M, Traore SI, Mouelhi D, Khelaifia S, Bachar D, et al. Gut bacteria missing in severe acute malnutrition, can we identify potential probiotics by culturomics? Front Microbiol 2017;8:899.
8. Ticinesi A, Lauretani F, Milani C, Nouvenne A, Tana C, Del Rio D, et al. Aging gut microbiota at the cross-road between nutrition, physical frailty, and sarcopenia: is there a gut-muscle axis? Nutrients. 2017 Nov 30;9(12). pii: E1303.Morita
9. Sze MA, Schloss PD. Looking for a signal in the noise: revisiting obesity and the microbiome. MBio. 2016 Aug 23;7(4). pii: e01018-16.
10. Morita C, Tsuji H, Hata T, Gondo M, Takakura S, Kawai K, et al . Gut dysbiosis in patients with Anorexia Nervosa. PLoS One. 2015 Dec 18;10(12):e0145274.
11. Galley JD, Bailey M, Kamp Dush C, Schoppe-Sullivan S, Christian LM. Maternal obesity is associated with alterations in the gut microbiome in toddlers. PLoS One. 2014 Nov 19;9(11):e113026.
12. Borgeraas H, Johnson LK, Skattebu J, Hertel JK, Hjelmesaeth J. Effects of probiotics on body weight, body mass index, fat mass and fat percentage in subjects with overweight or obesity: a systematic review and meta-analysis of randomized controlled trials. Obes Rev 2018 Feb;19(2):219-232.

13. Sun J, Buys N. Effects of probiotics consumption on lowering lipids and CVD risk factors: a systematic review and meta-analysis of randomized controlled trials. Ann Med. 2015;47(6):430-40.
14. Li C, Li X, Han H, Cui H, Peng M, Wang G, et al. Effect of probiotics on metabolic profiles in type 2 diabetes mellitus: A meta-analysis of randomized, controlled trials. Medicine (Baltimore). 2016 Jun;95(26):e4088.
15. Akbari V, Hendijani F. Effects of probiotic supplementation in patients with type 2 diabetes: systematic review and meta-analysis. Nutr Rev. 2016 Dec;74(12):774-784.
16. Taylor BL, Woodfall GE, Sheedy KE, O'Riley ML, Rainbow KA, Bramwell EL, et al. Effect of probiotics on metabolic outcomes in pregnant women with gestational diabetes: a systematic review and meta-analysis of randomized controlled trials. Nutrients. 2017 May 5;9(5). E461.
17. Khalesi S, Sun J, Buys N, Jayasinghe R. Effect of probiotics on blood pressure: a systematic review and meta-analysis of randomized, controlled trials. Hypertension. 2014 Oct;64(4):897-903.
18. Wu Y, Zhang Q, Ren Y, Ruan Z. Effect of probiotic Lactobacillus on lipid profile: A systematic review and meta-analysis of randomized, controlled trials. PLoS One. 2017 Jun 8;12(6):e0178868.
19. Mazidi M, Rezaie P, Ferns GA, Vatanparast H. Impact of Probiotic Administration on Serum C-Reactive Protein Concentrations: Systematic Review and Meta-Analysis of Randomized Control Trials. Nutrients. 2017 Jan 3;9(1). pii: E20.
20. Onubi OJ, Poobalan AS, Dinnen B, Marais D, McNeill G. Effects of probiotics on child growth: a systematic review. J Health Pop Nutr 2015;34:8
21. A. Smits LP, Kootte RS, Levin E, Prodan A, Fuentes S, Zoetendal EG, Wang Z, Levison BS, Cleophas MCP, Kemper EM, Dallinga-Thie GM, Groen AK, Joosten LAB, Netea MG, Stroes ESG, de Vos WM, Hazen SL, Nieuwdorp M. Effect of Vegan Fecal Microbiota Transplantation on Carnitine- and Choline-Derived Trimethylamine-N-Oxide Production and Vascular Inflammation in Patients With Metabolic Syndrome. J Am Heart Assoc. 2018 Mar 26;7(7). pii: e008342.
22. B. Vrieze A, Van Nood E, Holleman F, Salojärvi J, Kootte RS, Bartelsman JF, et al.Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology. 2012 Oct;143(4):913-6.e7. doi: 10.1053/j.gastro.2012.06.031. Epub 2012 Jun 20.
23. C. Kootte RS, Levin E, Salojärvi J, Smits LP, Hartstra AV, Udayappan SD, et al. Improvement of Insulin Sensitivity after Lean Donor Feces in Metabolic Syndrome Is Driven by Baseline Intestinal Microbiota Composition. Cell Metab. 2017 Oct 3;26(4):611-619.e6.

Appendix 3: Expanded Panel 1

Mechanisms through which early nutrition impacts long-term phenotype

- Early nutrition generates long-term effects on organ size, structure and function. Mammalian growth in fetal life and early infancy comprises hyperplasia (cell proliferation), crucial for the development of organ structure, whereas from late infancy, growth shifts to hypertrophy (increases in cell size).[1] For example, low birth weight infants have altered cardiac structure[2] and small liver, kidneys and spleen,[3,4] while macrosomic infants may demonstrate organomegaly.[5]

- Early nutrition impacts various hormonal axes regulating growth and appetite. For example, both under- and over-nutrition in the perinatal period affect insulin metabolism[6-8] and hypothalamic circuits regulating food intake.[9] Low birth weight infants may be insulin-sensitive at birth, but are susceptible to insulin-resistance in association with faster childhood weight gain.

- Both inter-uterine growth retardation and maternal diabetes expose the fetus to oxidative stress, impacting cardiac structure, haemodynamics and endothelial dysfunction.[10]

- Maternal nutrition in pregnancy is associated with variability in offspring gene expression. For example, peri-conceptional exposure to maternal famine has been associated with epigenetic changes in IGF1 expression that persisted into early old-age,[11] while season of conception in a rural African population was associated with diverse epigenetic effects in infancy.[12] Maternal obesity and gestational diabetes is associated with epigenetic effects on genes associated with metabolic disease,[13,14] and dietary interventions in pregnancy may alter neonatal gene expression.[15] Some such epigenetic changes may have adverse long-term health effects.

- Exposing infants and young children to a relatively narrow range of sweet and salty tastes in early life may also have long-term negative consequences by reducing the repertoire of foods these children learn to like, and thus shaping their future food choices towards obesogenic diets.[16-19]

- Telomeres provide a marker of cellular aging sensitive to early nutritional experience. For example, placental and/or neonatal telomere length is associated with some components of maternal nutritional status,[20,21] and predict post-natal body composition,[22] while exclusive breast-feeding may reduce telomere attrition.[23]

- The gut microbiome rapidly matures in early life, and early malnutrition disrupts this process.[24,25] For example, among twins discordant for kwashiorkor, the affected sibling developed narrower gut microbiome diversity, and transplanting this biota to germ-free mice induced

growth failure.[26] The microbiome shows both resilience within individuals over time,[27] with implications for health status and diease risk, but also the capacity to respond to dietary change,[28] use of pre- and pro-biotics, and fecal transplantation.[29]

- Collectively, these mechanisms generate a profound imprint of early malnutrition on later phenotype, impacting both the risk and the metabolic effects of subsequent overweight.

References to Appendix 3

1. Winick M, Noble A. Cellular response in rats during malnutrition at various ages. J Nutr 1966; 89(3): 300-6.
2. Jiang B, Godfrey KM, Martyn CN, Gale CR. Birth weight and cardiac structure in children. Pediatrics. 2006 Feb;117(2):e257-61.
3.Crispi F, Miranda J, Gratacos E. Long-term cardiovascular consequences of fetal growth restriction: biology, clinical implications, and opportunities for prevention of adult disease. Am J Obstet Gynecol 2018; 218(2S): S869-S79.
4. Latini G, De Mitri B, Del Vecchio A, Chitano G, De Felice C, Zetterstrom R. Foetal growth of kidneys, liver and spleen in intrauterine growth restriction: "programming" causing "metabolic syndrome" in adult age. Acta Paediatr 2004; 93(12): 1635-9.
5. Topcuoglu S, Karatekin G, Yavuz T, Arman D, Kaya A, Gursoy T, et al. The relationship between the oxidative stress and the cardiac hypertrophy in infants of diabetic mothers. Diabetes Res Clin Pract. 2015 Jul;109(1):104-9.
6. Bazaes RA, Salazar TE, Pittaluga E, Peña V, Alegría A, Iñiguez G, et al. Glucose and lipid metabolism in small for gestational age infants at 48 hours of age. Pediatrics. 2003 Apr;111(4 Pt 1):804-9.
7. Mericq V, Ong KK, Bazaes R, Peña V, Avila A, Salazar T, et al. Longitudinal changes in insulin sensitivity and secretion from birth to age three years in small- and appropriate-for-gestational-age children. Diabetologia. 2005 Dec;48(12):2609-14.
8. Dyer JS, Rosenfeld CR, Rice J, Rice M, Hardin DS. Insulin resistance in Hispanic large-for-gestational-age neonates at birth. J Clin Endocrinol Metab. 2007 Oct;92(10):3836-43.
9. Martin-Gronert MS, Ozanne SE. Metabolic programming of insulin action and secretion. Diabetes Obes Metab 2012; 14 Suppl 3: 29-39.
10. Rodríguez-Rodríguez P, Ramiro-Cortijo D, Reyes-Hernández CG, López de Pablo AL, González MC, Arribas SM. Implication of Oxidative Stress in Fetal Programming of Cardiovascular Disease. Front Physiol. 2018 May 23;9:602.
11. Heijmans BT, Tobi EW, Stein AD, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. ProcNatlAcadSciUSA 2008; 105(44): 17046-9.
12. Dominguez-Salas P, Moore SE, Baker MS, et al. Maternal nutrition at conception modulates DNA methylation of human metastable epialleles. Nature communications 2014; 5: 3746.
13. Hjort L, Martino D, Grunnet LG, Naeem H, Maksimovic J, Olsson AH, et al. Gestational diabetes and maternal obesity are associated with epigenome-wide methylation changes in children. JCI Insight. 2018 Sep 6;3(17). pii: 122572.
14. Ruchat SM, Houde AA, Voisin G, St-Pierre J, Perron P, Baillargeon JP, et al. Gestational diabetes mellitus epigenetically affects genes predominantly involved in metabolic diseases. Epigenetics. 2013 Sep;8(9):935-43.
15. Geraghty AA, Sexton-Oates A, O'Brien EC, Alberdi G, Fransquet P, Saffery R, et al. A Low Glycaemic Index Diet in Pregnancy Induces DNA Methylation Variation in Blood of Newborns: Results from the ROLO Randomised Controlled Trial. Nutrients. 2018 Apr 6;10(4). pii: E455.
16. Bazzano A, Potts K, Bazzano L, Mason J. The Life Course Implications of Ready to Use Therapeutic Food for Children in Low-Income Countries. Int J Environ Res Public Health 2017; 14: 403.
17. Luque V, Escribano J, Closa-Monasterolo R, et al. Unhealthy Dietary Patterns Established in Infancy Track to Mid-Childhood: The EU Childhood Obesity Project. J Nutr 2018; 148: 752–9.

18. De Cosmi V, Scaglioni S, Agostoni C. Early taste experiences and later food choices. Nutrients. 2017 Feb 4;9(2). pii: E107.
19. Mennella JA. Ontogeny of taste preferences: Basic biology and implications for health. Am J Clin Nutr 2014 Mar;99(3):704S-11S.
20. Martens DS, Plusquin M, Gyselaers W, De Vivo I, Nawrot TS. Maternal pre-pregnancy body mass index and newborn telomere length. BMC Med. 2016 Oct 18;14(1):148.
21. Entringer S, Epel ES, Lin J, Blackburn EH, Buss C, Shahbaba B, et al. Maternal Folate Concentration in Early Pregnancy and Newborn Telomere Length. Ann Nutr Metab. 2015;66(4):202-8.
22. de Zegher F, Diaz M, Lopez-Bermejo A, Ibanez L. Recognition of a sequence: more growth before birth, longer telomeres at birth, more lean mass after birth. Pediatr Obes 2017; 12(4): 274-9.
23. Wojcicki JM, Heyman MB, Elwan D, Lin J, Blackburn E, Epel E. Early exclusive breastfeeding is associated with longer telomeres in Latino preschool children. Am J Clin Nutr 2016; 104(2): 397-405.
24. Mueller NT, Bakacs E, Combellick J, Grigoryan Z, Dominguez-Bello MG. The infant microbiome development: mom matters. Trends Mol Med. 2015 Feb;21(2):109-17
25. Blanton LV, Barratt MJ, Charbonneau MR, Ahmed T, Gordon JI. Childhood undernutrition, the gut microbiota, and microbiota-directed therapeutics. Science. 2016 Jun 24;352(6293):1533.
26. Smith MI, Yatsunenko T, Manary MJ, et al. Gut microbiomes of Malawian twin pairs discordant for kwashiorkor. Science 2013; 339(6119): 548-54.
27. Sommer F, Anderson JM, Bharti R, Raes J, Rosenstiel P. The resilience of the intestinal microbiota influences health and disease. Nat Rev Microbiol. 2017 Oct;15(10):630-638.
28. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014 Jan 23;505(7484):559-63.
29. Khoruts A. Targeting the microbiome: from probiotics to fecal microbiota transplantation. Genome Med. 2018 Oct 30;10(1):80.

Appendix 4: Meta-analyses for inter-generational transmission of underweight and overweight, and how each form of malnutrition increases risk of the other

Outcome	Exposure and reference group	Studies (n)	Age range of outcome	Pooled effect (95% CI)	Confounding, effect modification and biases	Conclusions	Ref
Inter-generational cycle of under-nutrition							
Low birth weight	Maternal low BMI (vs normal BMI), defined variably across studies	78	Birth	RR 1.64 (1.39, 1.94)	Most studies from HICs, but effect size similar in HICs and LMICs	Increased risk of low birth weight in low BMI mothers	1
Low birth weight, SGA	Maternal low BMI (vs normal BMI), defined variably across studies	8	Birth	LBW: OR 1.66 (1.50,1.84) SGA: OR 1.85 (1.69, 2.02)	All studies from LMICs. BMI measured before or during early pregnancy	Low BMI mothers at increased risk of delivering LBW and SGA babies	2
Preterm birth	Maternal low BMI (vs normal BMI), defined variably across studies	78	Birth	RR 1.29 (1.15, 1.46)	Most studies from HICs, difference non-significant in LMICs	Increased risk of preterm delivery in low BMI mothers in HICs but not LMICs	1
Preterm birth	Maternal low BMI (vs normal BMI), defined variably across studies	11	Birth	OR 1.13 (1.01,1.27)	All studies from LMICs. BMI measured before or during early pregnancy	Low BMI mothers at high risk of delivering preterm babies	2
Low birth weight	Maternal short stature (vs normal stature) defined variably across studies	56	Birth	RR 1.81 (1.47, 2.23)	Studies from HICs and LMICs. Unadjusted effects reported, some heterogeneity in adjusted analyses	Increased risk of low birth weight offspring in mothers of short stature	3
Preterm birth	Maternal short stature (vs normal stature) defined variably across studies	56	Birth	RR 1.23 (1.11, 1.37)	Studies from HICs and LMICs. Unadjusted effects reported	Increased risk of preterm delivery in mothers of short stature	3
Low birth weight	Maternal anemia low haemoglobin) vs non anaemic in first 2 trimesters	17	Birth	RR 1.31 (1.13, 1.51)	Studies from LMICs	Maternal anaemia assessed by low haemoglobin is associated with increased risk of low birth weight	4
Preterm birth	Maternal anemia (low haemoglobin) vs non anaemic in first 2 trimesters	13	Birth	RR 1.63 (1.33, 2.01)	Studies from LMICs	Maternal anaemia assessed by low haemoglobin is associated with increased risk of preterm birth	4

Preterm birth	Gestational weight gain below IOM guidelines Vs weight gain within guidelines	4	Birth	OR 1.70 (1.32,2.20)	Effect modified by pre-pregnancy BMI. Weight self-reported or measured at first antenatal visit	Low gestational weight gain associated with increased risk of preterm delivery	5
SGA	Gestational weight gain below IOM guidelines vs weight gain within guidelines	4	Birth	OR 1.53 (1.44, 1.64)	Adjusted for sex, ethnicity and parity Effect modified by pre-pregnancy BMI	Low gestational weight gain associated with increased risk of SGA	5
Stunting	Low birth weight (<2.5kg) vs ≥2.5kg SGA (<10th percentile) vs ≥10th percentile	19	12-60 m	LBW: OR 2.92 (2.56, 3.33) SGA: OR 2.32 (2.12, 2.54)	Studies from LMICs. Wide age range of outcome (12-60 months)	Being born LBW or SGA increased the odds of stunting in early childhood	6
Stunting	Pre-term birth vs term delivery	19	12-60 m	OR 1.69 (1.48, 1.93)	Studies from LMICs. Wide age range of outcome (12-60 months)	Preterm birth increases the odds of stunting in early childhood	6
Wasting	Low birth weight (<2.5kg) vs ≥2.5kg SGA (<10th percentile) vs ≥10th percentile	19	12-60 m	LBW OR 2.68 (2.23, 3.21) SGA: OR 2.36 (2.14, 2.60)	Studies from LMICs. Wide age range of outcome (12-60 months)	Being LBW or SGA increased the odds of wasting in early childhood	6
Wasting	Pre-term birth vs term delivery	19	12-60 m	OR 1.55 (1.21, 1.97)	Studies from LMICs. Wide age range of outcome (12-60 months)	Preterm birth increases the odds of wasting in early childhood	6
Inter-generational cycle of overweight							
Macrosomia (>4 or >4.5 kg)	Pre-pregnancy obesity (BMI ≥30) vs nonobese	16	Birth	OR 1.93 (1.65, 2.27)	All studies from HIC or MICs. Adjusted for pregnancy weight gain, parity, ethnicity	Pre-pregnancy obesity is associated with increased risk of macrosomia	7
Macrosomia,, LGA, variably defined	Gestational weight gain below IOM guidelines vs weight gain within guidelines	11, 13	Birth	M: OR 1.95 (1.79, 2.11) LGA: OR 1.85 (1.76, 1.95)	Effect modified by pre-pregnancy BMI	Gestational weight gain above guidelines associated with increased risk of macrosomia and LGA	5
Macrosomia,, LGA, variably defined	Gestational diabetes vs non-diabetes	12	Birth	OR 1.71 (1.52,1.94)	Adjusted for pre-pregnancy BMI, gestational weight gain, parity and ethnicity	Gestational diabetes associated with increased risk of macrosomia independent of maternal BMI	8
Overweight in childhood	Pre-pregnancy overweight or obesity vs normal weight	4	Childhood 3.5-18 y	OVW: OR 1.95 (1.77, 2.13) OB: OR 3.06	Studies from 3 HICs and 1 LMICs	Pre-pregnancy overweight/ obesity increase the risk of overweight in the offspring	9

				(2.68, 3.49)			
Overweight in childhood or adulthood	High birth weight (>4000g) vs <4000g	66	Infancy onwards 6 m - 79 y	OR 1.66 (1.55, 1.77)	Studies from HICs and MICs	High birth weight predisposes to later overweight	10
Infant body composition	Mothers with any diabetes vs non-diabetic mothers	10,8	Birth to 3 weeks	FM: Δ 83g (49g, 117g) FFM: -11g (-99.2g, 77.3g)	Unadjusted data presented Small observational studies Overall results influenced by large GDM group	Infants of diabetic mothers have higher fat mass but no difference in fat-free mass	11
Overweight in childhood	Gestational diabetes vs non-diabetic mothers	8	-11 years	OR 1.35 (1.01, 1.80)	Weak evidence, association only evident in 4 studies at >11 y	Offspring of diabetic mothers may have higher risk of childhood overweight	12
Overweight in childhood	Rapid weight gain 0-24 m (>0.67 z-scores) vs slower weight gain	14	Childhood (>24 m)	OR 3.66 (2.59, 5.17)	Studies from HICs and MICs. Wide age range at outcome. Covariates included sex, birth weight, breastfeeding and maternal BMI, education, SES	RWG in infancy was associated with overweight/obesity from childhood to adulthood	13
Overweight metabolic perturbation and elevated risk of markers of nutritional deficiency							
SGA	Gestational weight gain below IOM guidelines in obese women vs adequate weight gain	13	Birth	OR 1.28 (1.14, 1.43)	Studies from HICs. 9 studies self reported BMI	Inadequate gestational weight gain in obese women is associated with increased risk of SGA	14
Low birth weight	Maternal hypertension vs normal blood pressure	14	Birth	RR 2.7 (1.9, 3.8)	Heterogeneity across studies	Maternal hypertension increases risk of LBW	15
Preterm birth	Maternal hypertension vs normal blood pressure	30	Birth	RR 2.7 (1.9, 3.6)	Heterogeneity across studies	Maternal hypertension increases risk of preterm birth	15
Vitamin D deficiency	Obesity vs normal BMI	15	4-45 years	OR 3.43 (2.33, 5.06)	Studies from MICs to HICs. Wide age range at outcome. Results similar in Asian and European-American populations	Prevalence of vitamin D deficiency is greater in obese individuals	16
Iron Deficiency	Overweight/Obese vs normal BMI	15	1-57 years	OR 1.31 (1.01, 1.68)	Studies for middle and HICs Varied method used to diagnose iron deficiency	Overweight/obese persons had increased risk of iron deficiency	17
Initiation of breastfeeding,	Maternal obesity vs	81	Birth	RR 1.23 (1.03,	Studies from HICs	Obese mothers are less likely to initiate breast-feeding, and	18

delayed lactogenesis	normal BMI			1.47) RR 2.06 (1.18, 3.61)		to experience delayed lactogenesis	
Under-nutrition and elevated risk of subsequent metabolic perturbation							
Impaired insulin sensitivity	Catch-up vs no catch-up following low birth weight	2	3-30 m	Δ 2.54 (2.33, 2.76)	Only 2 studies analysed	Catch-up growth following LBW is associated with higher fasting insulin levels	19
Type 2 Diabetes	Low birth weight vs 2500-4000g	8	20-75 y	RR 1.55 (1.39, 1.73)	Studies from HICs	Low birth weight was associated elevated risk of T2DM	20
Hypertension	Low birth weight vs >2500g	9	4-84 y	OR 1.21 (1.3, 1.30)	Most studies from HICs, a few from LMICs	Low birth was associated with elevated risk of hypertension	21
Type 2 Diabetes	Short stature vs tall stature	17	18-85 years	RR 0.85 (0.76, 0.96)	Studies from MICs to HICs Significant in women but not men	Taller women have a lower likelihood of T2DM compared to shorter women.	22
Gestational diabetes	Height of diabetic vs non-diabetic women	38	Mean 31 y	Δ -1.13cm (-0.78, -1.50)	Screening for GDM varied among studies	Women with GDM were shorter than women without	23
Coronary heart disease and stroke	Per 6.5 cm decline in adult height	121	Mean age 55±10 y	CHD: HR 1.06 (1.06, 1.10) Stroke: HR 1.07 (1.04, 1.10)	Studies from HICs and LMICs Adjusted for age at baseline and smoking status, and stratified by decades of year of birth. Adjustment for adiposity, blood pressure, lipids, inflammation, diabetes and SES made little difference	Shorter adults are associated with increased risk of CHD morbidity and mortality than taller adults	24
Gestational diabetes	High iron status (haemoglobin, ferritin) in pregnancy vs low iron status	9,7	Mean 22-32 y	H: OR 1.52 (1.23, 1.88) F: OR 2.09 (1.48, 2.96)	Studies from HICs and LMICs	Elevated iron status increased the risk of GDM, and hence might be an adverse consequence of supplementation programmes	25

LBW – Low birth weight, birth weight <2.5 kg; Preterm birth – delivery <37 weeks gestation; SGA – Small-for-gestational age, <10th percentile

Stunting – Height-for-age z-score <-2; Wasting – Weight-for-age z-score <-2

T2DM – Type 2 diabetes; GDM Gestaitonal diabetes; CHD – Coronary heart disease

HIC – High income country; MIC – Middle-income country; LMIC – Low-/Middle-income country; SES – Socio-economic status

PR – Prevalence ratio; OR – Odds ratio; HR – Hazard ratio

References to Appendix 4

1. Han Z, Mulla S, Beyene J, Liao G, McDonald SD, Knowledge Synthesis Group. Maternal underweight and the risk of preterm birth and low birth weight: a systematic review and meta-analyses. Int J Epidemiol 2011;40(1):65-101.

2. Rahman MM, Abe SK, Kanda M, Narita S, Rahman MS, Bilano V, et al. Maternal body mass index and risk of birth and maternal health outcomes in low- and middle-income countries: a systematic review and meta-analysis. Obes Rev 2015;16(9):758-70.

3. Han Z, Lutsiv O, Mulla S, McDonald SD, Knowledge Synthesis G. Maternal height and the risk of preterm birth and low birth weight: a systematic review and meta-analyses. J Obstet Gynaecol Can 2012;34(8):721-46.

4. Rahman MM, Abe SK, Rahman MS, Kanda M, Narita S, Bilano V, et al. Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: systematic review and meta-analysis. Am J Clin Nutr 2016;103(2):495-504

5. Goldstein RF, Abell SK, Ranasinha S, Misso M, Boyle JA, Black MH, et al. Association of Gestational Weight Gain With Maternal and Infant Outcomes: A Systematic Review and Meta-analysis. JAMA. 2017;317(21):2207-25.

6. Christian P, Lee SE, Donahue Angel M, Adair LS, Arifeen SE, Ashorn P, et al. Risk of childhood undernutrition related to small-for-gestational age and preterm birth in low- and middle-income countries. Int J Epidemiol 2013;42(5):1340-55.

7. Dai RX, He XJ, Hu CL. Maternal pre-pregnancy obesity and the risk of macrosomia: a meta-analysis. Arch Gynecol Obstet 2018;297(1):139-45.

8. He XJ, Qin FY, Hu CL, Zhu M, Tian CQ, Li L. Is gestational diabetes mellitus an independent risk factor for macrosomia: a meta-analysis? Arch Gynecol Obstet 2015;291(4):729-35.

9. Yu Z, Han S, Zhu J, Sun X, Ji C, Guo X. Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis. PLoS One 2013;8(4):e61627.

10. Schellong K, Schulz S, Harder T, Plagemann A. Birth weight and long-term overweight risk: systematic review and a meta-analysis including 643,902 persons from 66 studies and 26 countries globally. PLoS One 2012;7(10):e47776.

11. Logan KM, Gale C, Hyde MJ, Santhakumaran S, Modi N. Diabetes in pregnancy and infant adiposity: systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2017;102(1):F65-F72.

12. Kawasaki M, Arata N, Miyazaki C, Mori R, Kikuchi T, Ogawa Y, et al. Obesity and abnormal glucose tolerance in offspring of diabetic mothers: A systematic review and meta-analysis. PLoS One 2018;13(1):e0190676.

13. Zheng M, Lamb KE, Grimes C, Laws R, Bolton K, Ong KK, et al. Rapid weight gain during infancy and subsequent adiposity: a systematic review and meta-analysis of evidence. Obes Rev 2018;19(3):321-32.

14. Xu Z, Wen Z, Zhou Y, Li D, Luo Z. Inadequate weight gain in obese women and the risk of small for gestational age (SGA): a systematic review and meta-analysis. J Matern-Fetal Neonat Med 2017;30(3):357-67.

15. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. BMJ 2014;348:g2301.

16. Yao Y, Zhu L, He L, Duan Y, Liang W, Nie Z, et al. A meta-analysis of the relationship between vitamin D deficiency and obesity. Inty J Clin Exp Med 2015;8(9):14977-84.

17. Zhao L, Zhang X, Shen Y, Fang X, Wang Y, Wang F. Obesity and iron deficiency: a quantitative meta-analysis. Obes Rev. 2015;16(12):1081-93.

18. Garcia AH, Voortman T, Baena CP, Chowdhurry R, Muka T, Jaspers L, et al. Maternal weight status, diet, and supplement use as determinants of breastfeeding and complementary feeding: a systematic review and meta-analysis. Nutr Rev 2016;74(8):490-516.

19. Martin A, Connelly A, Bland RM, Reilly JJ. Health impact of catch-up growth in low-birth weight infants: systematic review, evidence appraisal, and meta-analysis. Matern Child Nutr 2017;13(1).

20. Mi D, Fang H, Zhao Y, Zhong L. Birth weight and type 2 diabetes: A meta-analysis. Exp Ther Med 2017;14(6):5313-20.

21. Mu M, Wang SF, Sheng J, Zhao Y, Li HZ, Hu CL, et al. Birth weight and subsequent blood pressure: a meta-analysis. Arch Cardiovasc Dis 2012;105(2):99-113.

22. Janghorbani M, Momeni F, Dehghani M. Hip circumference, height and risk of type 2 diabetes: systematic review and meta-analysis. Obes Rev 2012;13(12):1172-81.

23. Brite J, Shiroma EJ, Bowers K, Yeung E, Laughon SK, Grewal JG, et al. Height and the risk of gestational diabetes: variations by race/ethnicity. Diabet Med 2014;31(3):332-40.

24. Emerging Risk Factors Collaboration. Adult height and the risk of cause-specific death and vascular morbidity in 1 million people: individual participant meta-analysis. Int J Epidemiol. 2012 Oct;41(5):1419-33.

25. Fernandez-Cao JC, Aranda N, Ribot B, Tous M, Arija V. Elevated iron status and risk of gestational diabetes mellitus: A systematic review and meta-analysis. Matern Child Nutr 2017;13(4). doi: 10.1111/mcn.12400. Epub 2016 Dec 14.

Appendix 5: Expanded Panel 2

Developmental links between stunting, obesity and cardio-metabolic risk in Brazil

- Under-nutrition in early life promotes survival by energy-sparing, selectively preserving some tissues and organs over others.[1-3] This is achieved by endocrine changes impacting growth, energy expenditure and body composition, which then interact with the composition and energy content of the diet.

- Among children from Brazilian shanty-towns, prospective studies have shown that stunting is associated with a decrease in Resting Metabolic Rate associated with a higher velocity of weight gain, as well as a diminished fasting and post-prandial fat oxidation.[4] These changes are associated with an increase in adiposity, especially truncal fat, at the expenses of a decrease in lean body mass, mediated by a higher insulin sensitivity at this age although beta cell production and plasma insulin concentration are low.[5,6] Altogether, these changes preserve body energy, especially central body fat, mediated by higher cortisol[7] and insulin sensitivity[5], with lower thyroid activity[7].

- By adulthood, the adverse effects of overweight on cardio-metabolic traits are exacerbated among those also stunted. Among overweight adults, stunting is associated with lower T3, higher insulin resistance, and higher glycated haemoglobin. In overweight women, stunting is also associated with dyslipidaemia and higher blood pressure.[8,9]

- Adequate treatment of under-nutrition during childhood requires both appropriate diet and the treatment of infections.[10] Recovery in height and weight leads to normalization of insulin activity,[11] leptin,[12] cortisol stress response, body composition and bone mineral density.[13] Conflicting results that demand further investigation revealed either high[14,15] or low[16] blood pressure among Brazilian children recovered from malnutrition.

References to Appendix 5

1. Dulloo AG. Regulation of body composition during weight recovery: integrating the control of energy partitioning and thermogenesis. ClinNutr 1997; 16 Suppl 1: 25-35.
2. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia 1992; 35(7): 595-601.
3. Latini G, De Mitri B, Del Vecchio A, Chitano G, De Felice C, Zetterstrom R. Foetal growth of kidneys, liver and spleen in intrauterine growth restriction: "programming" causing "metabolic syndrome" in adult age. Acta Paediatr 2004; 93(12): 1635-9.
4. Hoffman DJ, Sawaya AL, Verreschi I, Tucker KL, Roberts SB. Why are nutritionally stunted children at increased risk of obesity? Studies of metabolic rate and fat oxidation in shantytown children from Sao Paulo, Brazil. Am J Clin Nutr 2000; 72(3): 702-7.
5. Martins PA, Sawaya AL. Evidence for impaired insulin production and higher sensitivity in stunted children living in slums. Brit J Nutr 2006; 95: 996-1001.

6. Hoffman DJ, Martins PA, Roberts SB, Sawaya AL. Body fat distribution in stunted compared with normal-height children from the shantytowns of São Paulo, Brazil. Nutrition 2007; 23: 640-646.
7. Martins VJB, Neves APO, Garcia MC, et al. Normal cortisol response to cold pressor test, but lower free thyroxine, after recovery from undernutrition. Brit J Nutr 2015; 115: 14-23.
8. Florêncio TT, Ferreira HS, Cavalcante JC, Stux GR, Sawaya AL. Short stature, abdominal obesity, insulin resistance and alterations in lipid profile in very low-income women living in Maceió, north-eastern Brazil. Eur J Cardiovasc Prev Rehabil 2007; 14: 346-348.
9. Florêncio TT, Ferreira HS, Cavalcante JC, Sawaya AL. Short stature, obesity and arterial hypertension in very low income population in North-eastern Brazil. Nutr Metab Cardiovasc Dis 2004; 14: 26-33.
10. Martins VJ, de Albuquerque MP, Sawaya AL. Endocrine changes in undernutrition, metabolic programming, and nutritional recovery. In: Preedy VR, Patel VB, eds. Handbook of famine, starvation, and nutritional deprivation. Switzerland: Springer International Publishing AG; 2017: 1-21.
11. Martins VJB, Martins PA, Neves J, Sawaya AL. Children recovered from malnutrition exhibit normal insulin production and sensitivity. Brit J Nutr 2008; 99: 297-302.
12. Martins VJB, Neves APO, Franco MCP, Clemente APG, Sawaya AL. Impact of nutritional recovery with linear growth on the concentrations of adipokines in undernourished children living in Brazilian slums. Brit J Nutr 2014; 112: 937-944.
13. Neves J, Martins PA, Sesso R, Sawaya AL. Malnourished children treated in day-hospital or outpatient clinics exhibit linear catch-up and normal body composition. J Nutr 2006; 136: 648-655.
14. Sesso R, Barreto GP, Neves J, Sawaya AL. Malnutrition is associated with increased blood pressure in childhood. Nephron Clin Pract 2004; 97: c61-c66.
15. Clemente AP, Santos CD, Silva AA, et al. Mild stunting is associated with higher blood pressure in overweight adolescents. Arq Bras Cardiol 2012; 98(1): 6-12.
16. Martins VJB, Sesso R, Clemente APG, Fernandes MBF, Sawaya AL. Albuminuria, renal function and blood pressure in undernourished children recovered from undernutrition. Pediatr Nephrol 2017; 32: 1555-1563.

Appendix 6: Methods for logistic regression analyses illustrated in Figure 2

We conducted logistic regression analysis to explore the associations of maternal phenotype with two outcomes, (a) the risk of giving birth to a child that was stunted between the age of 18 and 60 months, and (b) the risk of the mother delivering by caesarean section. We analysed data from a number of countries from different geographical regions using the most recent DHS surveys.

In each case, generalised linear models were used to estimate the risk (odds) of the outcome for each of the combinations of maternal short stature (yes/no) and maternal overweight and obesity. The reference group comprised women with normal stature and low-to-normal body mass index (BMI). Exposures were therefore short women with normal BMI; overweight women of normal stature; obese women of normal stature; short overweight women; and short obese women.

The analyses excluded twin births (except for Nigeria that had no information on twin births and thus included both single and twin births). The analyses were adjusted for wealth index, maternal age, rural/urban residence, birth order and offspring sex. Low to normal BMI, overweight and obesity were defined as having a BMI <25 kg/m2, BMI ≥25 & <30 kg/m^2 and BMI ≥30 kg/m^2, respectively. For the Asian countries (Cambodia, India and Nepal), low to normal BMI, overweight and obesity were defined as having a BMI <23 kg/m^2, BMI ≥23 & <27 kg/m^2 and BMI ≥27 kg/m^2, respectively. For all countries, maternal short stature was defined as having a height in the bottom quartile of the population sample.

An overall Odds Ratio (OR) estimate was estimated using Linear (Mixed-Effects) Models. We used a restricted maximum likelihood estimator to estimate the between country variance t^2. The function 'rma.uni' in the R – package 'Metafor' was used to estimate the overall OR value and associated confidence intervals. All analyses were carried out in R version 3.4.1 (The R foundation for Statistical Computing).

Appendix 7. The capacity-load conceptual model of non-communicable disease risk

The capacity-load model is a conceptual model intended to aid interpretation of studies on nutrition, growth and the developmental origins of adult non-communicable diseases (NCDs). It builds on the ground-breaking thrifty phenotype hypothesis of Hales and Barker,[1] but has some differences. Obesity is widely recognised as a key physical factor driving the global NCD epidemic, though it is also associated with unhealthy diets, physical inactivity and smoking.[2] Since the late 1980s, however, variability in early growth patterns has also been understood to contribute to NCD risk.[3,4]

The thrifty phenotype hypothesis focused on the elevated NCD risk of adults born with low birth weight (<2500g), and proposed that *in utero* under-nutrition caused the fetus to constrain growth of some organs/tissues (eg pancreas, liver) to protect others such as the brain.[1] These differences in organ growth would track into later life, so that the smaller organs of those under-nourished in fetal life would reduce tolerance of high-energy diets and obesity in adult life, predisposing to diabetes and other NCDs. Early support for the hypothesis was given by a study showing that a low birth weight relative to adult height, indicating *failure* to grow in fetal life relative to growth potential, was associated with elevated risk of hypertension in middle-age.[5] Follow-up studies of the Dutch Hunger Winter, which exposed fetuses to maternal starvation, also supported the hypothesis,[6,7] while numerous animal studies have shown that maternal dietary restriction in pregnancy elevated cardio-metabolic risk in the offspring.[8]

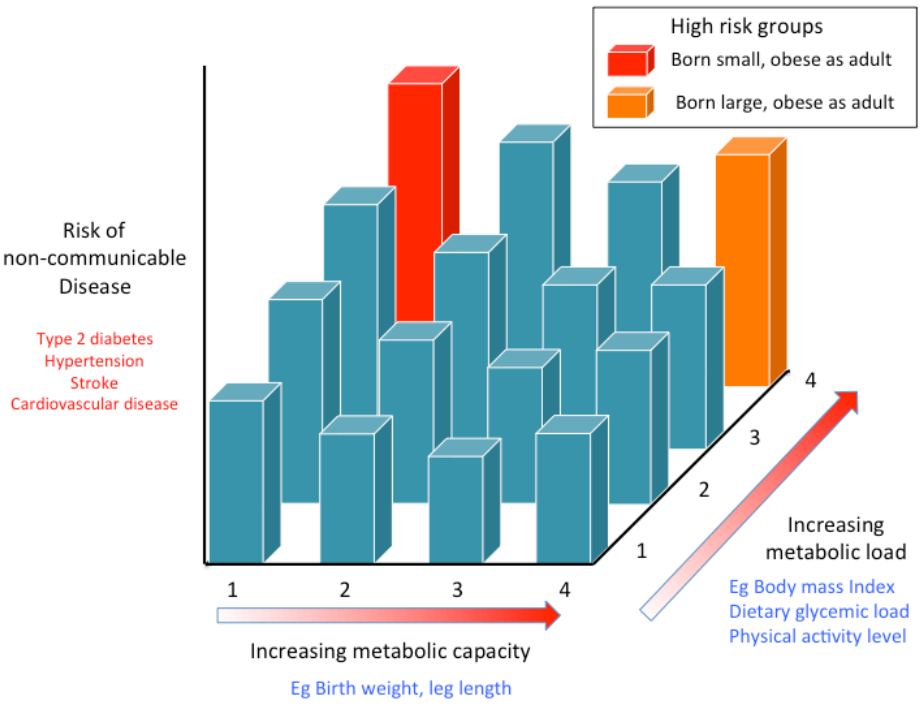
However, it is increasingly recognised inverse associations of birth weight with later NCD risk are not restricted to those born small, but apply across most of the birth weight spectrum. Each additional unit of birth weight is associated with lower NCD risk.[4,9,10] In many studies, therefore, the highest risk is found in those born large who remain normal BMI in adult life, whereas the lowest risk is found in those born small who become obese in adult life.[9,10] These continuous associations require explanation.

Because associations of birth weight with NCD risk often emerge most strongly, or depend on, statistical adjustment for adult size, some have suggested that NCD risk is entirely explained by change in size between birth and adulthood.[11] However, among a large sample of adults of identical size, who had therefore had similar rates of weight gain from birth onwards, NCD risk remained strongly inversely associated with birth weight.[12] Thus, the magnitude of growth achieved by birth is a critical factor in NCD risk variability.

The capacity-load model[13,14] focuses on two generic traits, each of which has broadly continuous associations with NCD susceptibility, but which act together to determine actual risk. ‘ Metabolic capacity’ refers to physiological traits developing during early life, which promote the life-long capacity for homeostasis. This in turn prevents the manifestation of metabolic damage that leads to NCDs. Specific components of metabolic capacity include a variety of traits, each of which broadly scales with birth weight across the entire birth weight range. These include nephron number in the kidney, pancreatic beta cell mass, the size of organs such as the liver and kidney, airway and blood vessel diameter. The continuous nature of these scaling associations is assumed to explain why greater size at birth has a dose-response inverse association with NCD risk.

A second set of traits, termed 'metabolic load', and primarily developing from early post-natal life onwards, challenges this capacity for homeostasis. Relevant traits include adiposity, an energy-dense diet, physical inactivity, psychosocial stress and behaviours such as smoking. All of these perturb metabolism, and the lower the metabolic capacity, the greater the deleterious effects of elevated load.

Non-communicable disease risk is then predicted to scale negatively with capacity, and positively with load.[13,14] The greatest risk is expected in those with low capacity and high load, in other words those born small who become obese and lead an unhealthy lifestyle in adult life. The lowest risk is expected and those who have achieved healthy rates of growth in early life, and who maintain a normal BMI and lead a healthy lifestyle in adult life. This is consistent with cohort studies from diverse settings.[9,10,15]



However, some studies show a U-shaped association between birth weight and NCD risk.[16] The heaviest infants have high adiposity (macrosomia) in combination with less lean tissue than expected for their high birth weight, indicating both elevated load but also constrained capacity. Fetuses of mothers with gestational diabetes may initially demonstrate poor growth, followed by catch-up weight gain in the third trimester.[17] Such individuals are prone to subsequent obesity and elevated NCD risk.[18] The capacity-load model is illustrated in **Supplementary Figure 1**, demonstrating these two high-risk groups.

Metabolic capacity may continue to increase in post-natal life, for example organs such as pancreatic beta-cell mass contribute to increase during infancy,[19] and this may explain why poor infant weight gain also predicts NCD risk.[4] On this basis, child stunting and wasting in low-middle-income countries are predicted to reduce metabolic capacity further, and elevate susceptibility to NCDs. However, this *susceptibility* is only predicted to progress to overt NCDs only if metabolic load subsequently increases. Consistent with this, survivors of severe-acute malnutrition in Malawi who remained thin had lower height, leg length, lean mass and grip strength than controls, but did not show elevated cardio-metabolic risk.[20] In contrast, survivors of exposure to the Biafran famine during pregnancy or infancy, who were typically overweight in middle age (increased load), showed elevated NCD

risk compared to those non-exposed.[21] A useful marker of nutritional experience in post-natal life may therefore be relative leg length (leg length/height), which is independent of birth weight.[22] Various studies have linked short leg length with elevated NVCD risk,[23,24] supporting the hypothesis that it indicates constraint of metabolic capacity. However, not all studies are consistent and the association between post-natal growth variability and NCD is less well understood compared to fetal growth.

Recent studies have linked nutritional intakes during the peri-conceptional period with subsequent epigenetic variability in gene expression,[25] while most components of metabolic load elevate oxidative stress. Both capacity and load could therefore be approached at more mechanistic levels. Indeed, birth weight has limitations as a marker of metabolic capacity, as it may be confounded by variability in adiposity, and it reflects growth variability in late but not early fetal life. For example, growth faltering in the first trimester is associated with slightly elevated birth weight.[26] Nevertheless, birth weight provides a valuable composite indicator of fetal nutritional experience, and it explains a substantial component of adult NCD risk when analysed in combination with markers of metabolic load.[4,5,9,10]

In the absence of a higher metabolic load, a low metabolic capacity need not necessarily lead to high NCD risk. This is supported by studies of low-/middle-income populations that have linked the emergence of the global NCD risk epidemic with nutrition transition and the obesity epidemic. Low average birth weights and child malnutrition have long characterised such populations, but in the absence of acquiring high metabolic load the risk of NCDs remains relatively low.

Which of capacity or load matters more may vary between settings. In high-income countries, where a large proportion of the population have acquired high load (overweight/obesity), then variability in capacity may explain a substantial component of NCD risk variability. In low-/middle-income countries, where the majority of the population have relatively low birth weights, and hence reduced metabolic capacity, then the magnitude of metabolic load acquired by individuals may be the best predictor of NCD risk. This scenario also helps understand why NCDs typically develop at lower BMI thresholds and younger age in low-/middle-income country populations compared to high-income country populations – metabolic capacity is systematically lower.

References to Appendix 7

1. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia 1992; 35(7): 595-601.

2. World Health Organization. Global health risks: mortality and burden of disease attributable to selected major risks. Geneva: World Health Organization. 2009.

3. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet. 1989 Sep 9;2(8663):577-80.

4. Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, Winter PD. Fetal and infant growth and impaired glucose tolerance at age 64. BMJ. 1991 Oct 26;303(6809):1019-22.

5. Leon DA, Koupilova I, Lithell HO, Berglund L, Mohsen R, Vagero D, Lithell UB, McKeigue PM. Failure to realise growth potential in utero and adult obesity in relation to blood pressure in 50 year old Swedish men. BMJ. 1996 Feb 17;312(7028):401-6.

6. Ravelli AC, van Der Meulen JH, Osmond C, Barker DJ, Bleker OP. Obesity at the age of 50 y in men and women exposed to famine prenatally. Am J Clin Nutr. 1999 Nov;70(5):811-6.

7. Roseboom TJ, Painter RC, van Abeelen AF, Veenendaal MV, de Rooij SR. Hungry in the womb: what are the consequences? Lessons from the Dutch famine. Maturitas. 2011 Oct;70(2):141-5.

8. McMillen IC, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. Physiol Rev. 2005 Apr;85(2):571-633.

9. Li Y, Ley SH, Tobias DK, et al. Birth weight and later life adherence to unhealthy lifestyles in predicting type 2 diabetes: prospective cohort study. BMJ 2015; 351: h3672.

10. Li Y, Ley SH, VanderWeele TJ, et al. Joint association between birth weight at term and later life adherence to a healthy lifestyle with risk of hypertension: a prospective cohort study. BMC Med 2015; 13: 175.

11. Lucas A, Fewtrell MS, Cole TJ. Fetal origins of adult disease-the hypothesis revisited. BMJ. 1999 Jul 24;319(7204):245-9.

12. Lawlor DA, Leon DA, Rasmussen F. Growth trajectory matters: interpreting the associations among birth weight, concurrent body size, and systolic blood pressure in a cohort study of 378,707 Swedish men. Am J Epidemiol. 2007 Jun 15;165(12):1405-12.

13. Wells JC. The thrifty phenotype: An adaptation in growth or metabolism? Am J Hum Biol. 2011 Jan-Feb;23(1):65-75.

14. Wells JCK. The metabolic ghetto: an evolutionary perspective on nutrition, power relations and chronic disease. Cambridge: Cambridge University Press. 2016.

15. Bavdekar A, Yajnik CS, Fall CH, Bapat S, Pandit AN, Deshpande V, Bhave S, Kellingray SD, Joglekar C.Insulin resistance syndrome in 8-year-old Indian children: small at birth, big at 8 years, or both? Diabetes. 1999 Dec;48(12):2422-9.

16. Tam CH, Wang Y, Luan J, Lee HM, Luk AO, Tutino GE, Tong PC, Ko GT, Ozaki R, Tam WH, Kong AP, So WY, Chan JC, Ma RC. Non-linear relationship between birthweight and cardiometabolic risk factors in Chinese adolescents and adults. Diabet Med. 2015 Feb;32(2):220-5

17. Sletner L, Jenum AK, Yajnik CS, Mørkrid K, Nakstad B, Rognerud-Jensen OH, Birkeland KI, Vangen S. Fetal growth trajectories in pregnancies of European and South Asian mothers with and without gestational diabetes, a population-based cohort study. PLoS One. 2017 Mar 2;12(3):e0172946.

18. Dabelea D. The predisposition to obesity and diabetes in offspring of diabetic mothers. Diabetes Care. 2007 Jul;30 Suppl 2:S169-74.

19. Bouwens L & Rooman I. Regulation of pancreatic beta-cell mass. Physiol Rev 2005;85:1255–1270.

20. Lelijveld N, Seal A, Wells JC, et al. Chronic disease outcomes after severe acute malnutrition in Malawian children (ChroSAM): a cohort study. Lancet Glob Health 2016; 4(9): e654-62.

21. Hult M, Tornhammar P, Ueda P, Chima C, Bonamy AK, Ozumba B, Norman M. Hypertension, diabetes and overweight: looming legacies of the Biafran famine. PLoS One. 2010 Oct 22;5(10):e13582.

22. Gunnell D, Smith GD, McConnachie A, Greenwood R, Upton M, Frankel S. Separating in-utero and postnatal influences on later disease. Lancet. 1999 Oct 30;354(9189):1526-7.

23. Gunnell D, Whitley E, Upton MN, McConnachie A, Smith GD, Watt GC. Associations of height, leg length, and lung function with cardiovascular risk factors in the Midspan Family Study. J Epidemiol Community Health. 2003 Feb;57(2):141-6.

24. Lawlor DA, Ebrahim S, Davey Smith G. The association between components of adult height and Type II diabetes and insulin resistance: British Women's Heart and Health Study. Diabetologia. 2002 Aug;45(8):1097-106.

25. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, Slagboom PE, Lumey LH. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci U S A. 2008 Nov 4;105(44):17046-9.

26. Hemachandra AH, Klebanoff MA. Use of serial ultrasound to identify periods of fetal growth restriction in relation to neonatal anthropometry. Am J Hum Biol. 2006 Nov-Dec;18(6):791-7.

Appendix 8. Findings from longitudinal studies from low-/middle-income countries in Asia and sub-Saharan Africa on interactive associations of early growth patterns and later nutritional status with cardio-metabolic (CM) risk markers or non-communicable disease, and interpretation using the capacity-load conceptual model

Population	Ref	Location	n	Key findings	Interpretation
Asia					
India	1,2	Rural	631+663 vs controls	Compared to European neonates, Indian neonates weighed 0.5 to 0.8 kg less and had smaller abdominal and mid-arm girths but relatively similar skinfolds	Indian infants have substantially reduced metabolic capacity at birth compared to Europeans, and divert energy to truncal adiposity, a marker of metabolic load
India	3,4	Urban	477 + 539	CM risk at 8-9 y was associated with weight and inversely with birth weight. Lower birth weight was associated with increased insulin resistance and BP but not with B-cell function.	In urban populations characterized by faster post-natal weight gain, CM risk is associated with both higher load and reduced capacity
India	5	Rural	698	CM risk at 6 y was associated with current body size and adiposity, and with faster post-infancy growth, and inversely with birth weight for BP but not insulin resistance. Smaller mid-arm girth at 6 m predicted insulin resistance at 6 y.	In a rural population characterized by slower growth, CM risk is associated with higher load, but only weakly with lower capacity. Low muscle accretion in infancy may indicate poor development of capacity in post-natal life
India	6,7	Rural children, urban men	631 and	Markers of lean mass are lower in Indian children and South Asian adults compared to European, and markers of adiposity higher, even after holding constant for BMI	Indians maintain a relatively higher metabolic load per unit weight compared to Europeans from early life through to adult life.
South Asia	8	Multi-ethnic study in UK	1266 vs controls	Adiposity was positively associated with HOMA-IR in all ethnic groups, but more strongly among South Asian compared to black African-Caribbean and white European children	Body fat imposes a more toxic metabolic load in South-Asian children compared to other ethnic groups
India	9	Urban	486	Growth in weight and length before 2 y was associated with later height but not CM risk at 13 y. Gains in fatness after 2 y were associated with insulin resistance at 13 y	Early growth benefits metabolic capacity, from early childhood weight gain elevates adiposity and metabolic load
India	10-12	Urban	1492 and 2218	Impaired glucose tolerance or diabetes was associated with rapid BMI gain in childhood and adolescence but with thinness at birth and lower	Diabetes risk was associated with rapid elevation of load during childhood, and with low capacity developing in fetal life and

				BMI in infancy	infancy
	13	Rural	378	Risk of high BP increased in association with BMI. Those with high BP had low BMI up to 2 y, low height at 3 y, and accelerated gain in BMI after 3 y	High BP was associated with high load and with poor development of capacity before 3 y. Child stunting may indicate post-natal constraint of capacity.
India	14	Urban	2076	High systolic BP was associated with high adiposity in high-SES girls, whereas high diastolic BP was associated with short leg length in low-SES girls	High BP was linked with high load in a high-SES population, but with a marker of low capacity in a low-SES population
India	15	Urban	517	Birth weights were very low, with 29% below 2500g, while adult BMI was relatively low. Prevalence of coronary heart disease was associated with low weight, length and head circumference at birth, and with low maternal pregnancy weight	A low metabolic capacity increased risk of coronary heart disease, even though metabolic load was relatively modest
China	16	Urban	2085	Number of adult non-communicable diseases was inversely associated with birth weight	Chronic disease risk increased inversely in dose-response association with metabolic capacity
China	17,18	Urban	2019	Risk of impaired glucose tolerance and metabolic syndrome was associated with adult central obesity and unhealthy life-style, and inversely association with birth weight	Diabetes risk was associated in dose-response manner both with adult load, and inversely with capacity developing in fetal life
China	19	Urban	973	Risk of diabetes and hypertension was associated with abdominal obesity. Birth weight was inversely associated with abdominal obesity, fasting glucose and BP	Risk of diabetes and hypertension increased in dose-response manner with adult load, and inversely with capacity developing in fetal life
China	20	Urban	745	Risk of CVD events (nonfatal coronary heart disease or cerebrovascular disease, cardiovascular death) was associated with abdominal adiposity, and inversely with birth weight	Risk of CVD was associated with adult load and inversely with capacity developing in fetal life
Sub-Saharan Africa					
Gambia	21	Rural	219	Neither season of birth (a proxy for fetal nutritional experience) nor childhood weight was associated with CM risk markers in early adulthood.	In a lean and fit population, with negligible metabolic load and low levels of overall CM risk, variability in capacity was unrelated to CN risk variability

Malawi	22	Rural/Urban	352	Severe-acute malnutrition in early childhood was associated with reduced growth markers, lean mass and grip strength, but not directly with CM risk	In later childhood, survivors of severe-acute malnutrition have reduced capacity, but in the absence of elevated load CM risk is unaffected
South Africa	23	Urban	849	At 5 years, systolic BP was associated with weight and height, and inversely associated with birth weight	Systolic BP was associated in dose-response manner both with childhood load, and inversely with capacity developing in fetal life
DR Congo	24	Urban	2648	Birth weight inversely associated with BP and low birth weight was associated with increased risk of hypertension for SBP and DBP.	High BP was associated in dose-response manner both with childhood load, and inversely with capacity developing in fetal life
Multiple	25	Rural and urban	16 studies	Birth weight was inversely associated with later BP in studies of children, but in adolescents the results were inconsistent	Studies on blood pressure from Africa are consistent with the capacity-load model in children, but not adolescence.
DR Congo	26	Urban	407	Risk of the metabolic syndrome was associated with high BMI in both sexes, but also with low BMI in men, and with low birth weight in both sexes.	Risk of the metabolic syndrome increased in association with high adult load, and inversely with capacity developing in fetal life. However, thin men (low load) also had elevated risk compared to those of normal weight
Nigeria	27	Urban	1339	Exposure in early life to famine was associated with short adult height, elevated CM risk markers and greater risk of hypertension, IGT and overweight compared to those unexposed. Fetal vs infant exposure could not be differentiated.	Early malnutrition reduced capacity and elevated load, and was associated with elevated CM risk. Capacity may have been impaired during fetal life, infancy or both.
Multi-country studies					
COHORTS *	28	Urban	6511	Lower birth weight and accelerated weight gain after 48 months were risk factors for adult glucose intolerance. Adjusting for adult waist girth, birth weight was inversely related to insulin resistance	Diabetes risk was associated with the rapid accumulation of load from early childhood onwards, and with reduced capacity developing in early life.
COHORTS *	29	Urban	4335	BP was associated with adult BMI, and inversely with birth weight. Weight gain at any period from birth to adulthood was associated with higher BP	BP was associated positively with adult load, and inversely with capacity developing in fetal life. Weight gain elevates load throughout post-natal life
COHORTS *	30	Urban	3432	Birth weight and weight gain before 24 m were more strongly associated with adult fat-free mass	Growth in fetal life and infancy is beneficial for tissues associated with capacity, whereas load

				than fat mass, whereas weight gain from mid-childhood predicted both fat and fat-free masses	is more strongly associated with weight gain after 24 m
Young Lives**	31	Rural and urban	3999	Birth weight was a strong predictor of child height, despite some attenuation of effect	Poor fetal growth indicates long term constraint of metabolic capacity, as indexed by height

BMI – body mass index; SES – socio-economic status; BP – blood pressure; m – months; y – years

* COHORTS countries: Brazil, Guatemala, India, Philippines, South Africa

** YOUNG LIVES countries: Ethiopia, India, Peru, and Vietnam

References to Appendix 8

1. Yajnik CS, Fall CH, Coyaji KJ, Hirve SS, Rao S, Barker DJ, et al. Neonatal anthropometry: the thin-fat Indian baby. The Pune Maternal Nutrition Study. Int J Obes 2003 Feb;27(2):173-80.
2. Krishnaveni GV, Hill JC, Veena SR, Leary SD, Saperia J, Chachyamma KJ, et al. Truncal adiposity is present at birth and in early childhood in South Indian children. Indian Pediatr. 2005 Jun;42(6):527-38.
3. Bavdekar A, Yajnik CS, Fall CH, Bapat S, Pandit AN, Deshpande V, et al. Insulin resistance syndrome in 8-year-old Indian children: small at birth, big at 8 years, or both? Diabetes 1999 Dec;48(12):2422-9.
4. Krishnaveni GV, Veena SR, Wills AK, Hill JC, Karat SC, Fall CH. Adiposity, insulin resistance and cardiovascular risk factors in 9-10-year-old Indian children: relationships with birth size and postnatal growth. J Dev Orig Health Dis 2010 Dec;1(6):403-11.
5. Joglekar CV, Fall CH, Deshpande VU, Joshi N, Bhalerao A, Solat V, et al. Newborn size, infant and childhood growth, and body composition and cardiovascular disease risk factors at the age of 6 years: the Pune Maternal Nutrition Study. Int J Obes 2007 Oct;31(10):1534-44.
6. D'Angelo S, Yajnik CS, Kumaran K, Joglekar C, Lubree H, Crozier SR, et al. Body size and body composition: a comparison of children in India and the UK through infancy and early childhood. J Epidemiol Community Health. 2015 Dec;69(12):1147-53.
7. Chandalia M, Lin P, Seenivasan T, Livingston EH, Snell PG, Grundy SM, et al. Insulin resistance and body fat distribution in South Asian men compared to Caucasian men. PloS one 2007;2(8):e812.
8. Nightingale CM, Rudnicka AR, Owen CG, Wells JC, Sattar N, Cook DG, et al. Influence of adiposity on insulin resistance and glycemia markers among U.K. Children of South Asian, black African-Caribbean, and white European origin: child heart and health study in England. Diabetes Care 2013 Jun;36(6):1712-9.
9. Krishnaveni GV, Veena SR, Srinivasan K, Osmond C, Fall CH. Linear Growth and Fat and Lean Tissue Gain during Childhood: Associations with Cardiometabolic and Cognitive Outcomes in Adolescent Indian Children. PLoS One 2015 Nov 17;10(11):e0143231.
10. Bhargava SK, Sachdev HS, Fall CH, Osmond C, Lakshmy R, Barker DJ, et al. Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. N Engl J Med 2004 Feb 26;350(9):865-75.
11. Fall CH, Sachdev HS, Osmond C, Lakshmy R, Biswas SD, Prabhakaran D, et al. Adult metabolic syndrome and impaired glucose tolerance are associated with different patterns of BMI gain during infancy: Data from the New Delhi Birth Cohort. Diabetes Care 2008;31(12):2349-56.
12. Raghupathy P, Antonisamy B, Geethanjali FS, Saperia J, Leary SD, Priya G, et al. Glucose tolerance, insulin resistance and insulin secretion in young south Indian adults: Relationships to parental size, neonatal size and childhood body mass index. Diabetes Res Clin Pract 2010 Feb;87(2):283-92.
13. Kanade A, Deshpande S, Patil K, Rao S. Prevalence of high blood pressure among young rural adults in relation to height in childhood and adult body mass index. J Am Coll Nutr 2011 Jun;30(3):216-23.
14. Rao S, Kanade A. Somatic disproportion predicts risk of high blood pressure among adolescent girls in India. J Hypertens. 2007 Dec;25(12):2383-9.

15. Stein CE, Fall CH, Kumaran K, Osmond C, Cox V, Barker DJ. Fetal growth and coronary heart disease in south India. Lancet 1996 Nov 9;348(9037):1269-73.
16. Zeng Y, Zhang Z, Xu T, Fan Z, Xiao X, Chen X, et al. Association of Birth Weight with Health and Long-Term Survival up to Middle and Old Ages in China. J Popul Ageing 2010 Dec;3(3-4):143-159.
17. Xiao X, Zhang ZX, Cohen HJ, Wang H, Li W, Wang T et al. Evidence of a relationship between infant birth weight and later diabetes and impaired glucose regulation in a Chinese population. Diabetes Care 2008 Mar;31(3):483-7.
18. Xiao X, Zhang ZX, Li WH, Feng K, Sun Q, Cohen HJ, et al. Low birth weight is associated with components of the metabolic syndrome. Metabolism 2010 Sep;59(9):1282-6.
19. Tian JY, Cheng Q, Song XM, Li G, Jiang GX, Gu YY, et al. Birth weight and risk of type 2 diabetes, abdominal obesity and hypertension among Chinese adults. Eur J Endocrinol 2006 Oct;155(4):601-7.
20. Tian J, Qiu M, Li Y, Zhang X, Wang H, Sun S, et al. Contribution of birth weight and adult waist circumference to cardiovascular disease risk in a longitudinal study. Sci Rep 2017 Aug 29;7(1):9768.
21. Moore SE, Halsall I, Howarth D, Poskitt EM, Prentice AM. Glucose, insulin and lipid metabolism in rural Gambians exposed to early malnutrition. Diabet Med 2001 Aug;18(8):646-53.
22. Lelijveld N, Seal A, Wells JC, Kirkby J, Opondo C, Chimwezi E, et al. Chronic disease outcomes after severe acute malnutrition in Malawian children (ChroSAM): a cohort study. Lancet Glob Health 2016 Sep;4(9):e654-62.
23. Levitt NS, Steyn K, De Wet T, Morrell C, Edwards R, Ellison GT, et al. An inverse relation between blood pressure and birth weight among 5 year old children from Soweto, South Africa. J Epidemiol Community Health 1999 May;53(5):264-8.
24. Longo-Mbenza B, Ngiyulu R, Bayekula M, Vita EK, Nkiabungu FB, Seghers KV, et al. Low birth weight and risk of hypertension in African school children. J Cardiovasc Risk. 1999 Oct;6(5):311-4.
25. Lule SA, Elliott AM, Smeeth L, Webb EL. Is birth weight associated with blood pressure among African children and adolescents? A systematic review. J Dev Origins Health Dis, 2018, e-pub ahead of print.
26. Longo-Benza B, Vangu Ngoma D, Mbungu Fuele S. Low birth weight, metabolic syndrome and their associations with the global crisis of 1930 - 1945, rapidly growing economy and coronary heart disease in Central Africa. Int J Nutr Metab 2010;2(1):2-10.
27. Hult M, Tornhammar P, Ueda P, Chima C, Bonamy AK, Ozumba B, Norman M. Hypertension, diabetes and overweight: looming legacies of the Biafran famine. PLoS One. 2010 Oct 22;5(10):e13582.
28. Norris SA, Osmond C, Gigante D, Kuzawa CW, Ramakrishnan L, Lee NR, et al. Size at birth, weight gain in infancy and childhood, and adult diabetes risk in five low- or middle-income country birth cohorts. Diabetes Care 2012 Jan;35(1):72-9.
29. Adair LS, Martorell R, Stein AD, Hallal PC, Sachdev HS, Prabhakaran D, et al. Size at birth, weight gain in infancy and childhood, and adult blood pressure in 5 low- and middle-income-country cohorts: when does weight gain matter? Am J Clin Nutr 2009 May;89(5):1383-92.
30. Kuzawa CW, Hallal PC, Adair L, Bhargava SK, Fall CH, Lee N, et al. Birth weight, postnatal weight gain, and adult body composition in five low and middle income countries. Am J Hum Biol. 2012 Jan-Feb;24(1):5-13.
31. Krishna A, Fink G, Berkman LF, Subramanian SV. Short- and long-run associations between birth weight and children's height. Econ Hum Biol. 2016 May;21:156-66.

Appendix 9a: Meta-analyses of associations of adult height with risk of various cardio-metabolic diseases

Type of cardio-metabolic disease	Number of studies	Height exposure	Risk (95% CI)	Ref
Gestational diabetes	38	> 168 vs < 157 cm (Asian/Pacific Islander)	OR 0.18 (0.09, 0.36)	1
Gestational diabetes	38	> 168 vs < 157 cm (non-Hispanic white)	OR 0.33 (0.29, 0.38)	1
Gestational diabetes	38	> 168 vs < 157 cm (Hispanic)	OR 0.39 (0.31, 0.51)	1
Gestational diabetes	38	> 168 vs < 157 cm (non-Hispanic black)	OR 0.59 (0.47, 0.75)	1
Type 2 diabetes (men)	8	Highest vs lowest height category	RR 0.87 (0.71, 1.07)	2
Type 2 diabetes (men)	9	Highest vs lowest height category	RR 0.85 (0.76, 0.96)	2
Non-fatal myocardial infarction	121	Per 6.5 cm increase	HR 0.91 (0.89, 0.93)	3
Coronary death	121	Per 6.5 cm increase	HR 0.93 (0.90, 0.96)	3
Coronary heart disease (M)	30 Asia	Per standard deviation increase	HR 0.95 (0.89, 1.01)	4
Coronary heart disease (F)	30 Asia	Per standard deviation increase	HR 1.00 (0.90, 1.10)	4
Ischaemic stroke	121	Per 6.5 cm increase	HR 0.94 (0.90, 0.97)	3
Ischaemic stroke (M)	30 Asia	Per standard deviation increase	HR 0.98 (0.92, 1.04)	4
Ischaemic stroke (F)	30 Asia	Per standard deviation increase	HR 0.98 (0.89, 1.07)	4
Haemorrhagic stroke	121	Per 6.5 cm increase	HR 0.90 (0.85, 0.95)	3
Haemorrhagic stroke (M)	30 Asia	Per standard deviation increase	HR 0.90 (0.84, 0.96)	4
Haemorrhagic stroke (F)	30 Asia	Per standard deviation increase	HR 0.86 (0.78, 0.95)	4

HR – Hazard ratio; OR – Odds ratio; RR – Relative risk

References to Appendix 9a

1. Brite J, Shiroma EJ, Bowers K, Yeung E, Laughon SK, Grewal JG, Zhang C. Height and the risk of gestational diabetes: variations by race/ethnicity. Diabet Med 2014 Mar;31(3):332-40.
2. Janghorbani M, Momeni F, Dehghani M. Hip circumference, height and risk of type 2 diabetes: systematic review and meta-analysis. Obes Rev 2012 Dec;13(12):1172-81.
3. Emerging Risk Factors Collaboration. Adult height and the risk of cause-specific death and vascular morbidity in 1 million people: individual participant meta-analysis. Int J Epidemiol 2012 Oct; 41(5): 1419–1433.
4. Lee CM, Barzi F, Woodward M, Batty GD, Giles GG, Wong JW, Jamrozik K, Lam TH, Ueshima H, Kim HC, Gu DF, Schooling M, Huxley RR; Asia Pacific Cohort Studies Collaboration. Adult height and the risks of cardiovascular disease and major causes of death in the Asia-Pacific region: 21,000 deaths in 510,000 men and women. Int J Epidemiol 2009 Aug;38(4):1060-71

Appendix 9b. Meta-analyses of associations of adult height with risk of various cancers

Type of cancer	Number of studies	Height exposure	Risk (95% CI)	Ref
Head and neck cancer	20	Per 5 cm increase	HR 1.02 (1.00, 1.05)	1
Thyroid cancer	15	Per 5 cm increase	RR 1.16 (1.09, 1.23)	2
Lung cancer	16	Per 10 cm increase	RR 1.06, (1.03, 1.09)	3
Kidney cancer	14	Per 10 cm increase	RR 1.23 (1.18, 1.28)	4
Pancreatic cancer	12	Per 5 cm increase	RR 1.07 (1.03, 1.12)	5
Gallbladder cancer	19	Per 5 cm increase	HR 1.10 (1.03, 1.17)	6
Colorectal cancer	47	Per 5 cm increase	RR 1.04 (1.02, 1.05)	7
Osteosarcoma	7	51^{st} - 89^{th} centile vs ≤50^{th} centile	OR 1.35 (1.18, 1.54)	8
Ovarian cancer	16	Per 10 cm increase	RR 1.16 (1.11, 1.21)	9
Endometrial cancer	30	Per 10 cm increase	RR 1.15 (1.09, 1.22)	10
Breast cancer (women)	159	Per 10 cm increase	RR 1.17 (1.15, 1.19)	11
Breast cancer (men)	21	Highest vs lowest tertile	1.18 (1.01, 1.38)	12
Testicular cancer	14	Per 5 cm increase	OR 1.13 (1.07, 1.19)	13
Prostate cancer	58	Per 10 cm increase	OR 1.06 (1.03, 1.09)	14

HR – Hazard ratio; OR – Odds ratio; RR – Relative risk

References to Appendix 9b

1. Gaudet MM, Kitahara CM, Newton CC, et al. Anthropometry and head and neck cancer:a pooled analysis of cohort data. Int J Epidemiol 2015 Apr;44(2):673-81.
2. Jing Z, Hou X, Liu Y, Yan S, Wang R, Zhao S, Wang Y. Association between height and thyroid cancer risk: a meta-analysis of prospective cohort studies. Int J Cancer 2015 Sep 15;137(6):1484-90.
3. Wang F, Xu X, Yang J, Min L, Liang S, Chen Y. Height and lung cancer risk: A meta-analysis of observational studies. PLoS One 2017 Sep 26;12(9):e0185316.
4. Liang S, Lv G, Chen W, Jiang J, Wang J. Height and kidney cancer risk: a meta-analysis of prospective studies. J Cancer Res Clin Oncol 2015 Oct;141(10):1799-807.
5. Aune D, Vieira AR, Chan DS, Navarro Rosenblatt DA, Vieira R, Greenwood DC, Cade JE, Burley VJ, Norat T. Height and pancreatic cancer risk: a systematic review and meta-analysis of cohort studies. Cancer Causes Control. 2012 Aug;23(8):1213-22.
6. Campbell PT, Newton CC, Kitahara CM, et al. Body Size Indicators and Risk of Gallbladder Cancer: Pooled Analysis of Individual-Level Data from 19 Prospective Cohort Studies. Cancer Epidemiol Biomarkers Prev 2017 Apr;26(4):597-606.
7. Abar L, Vieira AR, Aune D, et al.Height and body fatness and colorectal cancer risk: an update of the WCRF-AICR systematic review of published prospective studies. Eur J Nutr. 2017 Oct 28. doi: 10.1007/s00394-017-1557-1. [Epub ahead of print]

8. Mirabello L, Pfeiffer R, Murphy G, Daw NC, Patiño-Garcia A, Troisi RJ, Hoover RN, Douglass C, Schüz J, Craft AW, Savage SA. Height at diagnosis and birth-weight as risk factors for osteosarcoma. Cancer Causes Control 2011 Jun;22(6):899-908.
9. Aune D, Navarro Rosenblatt DA, Chan DS, Abar L, Vingeliene S, Vieira AR, Greenwood DC, Norat T. Anthropometric factors and ovarian cancer risk: a systematic review and nonlinear dose-response meta-analysis of prospective studies. Int J Cancer 2015 Apr 15;136(8):1888-98.
10. Aune D, Navarro Rosenblatt DA, Chan DS, Vingeliene S, Abar L, Vieira AR, Greenwood DC, Bandera EV, Norat T. Anthropometric factors and endometrial cancer risk: a systematic review and dose-response meta-analysis of prospective studies. Ann Oncol 2015 Aug;26(8):1635-48.
11. Zhang B, Shu XO, Delahanty RJ, et al. Height and Breast Cancer Risk: Evidence From Prospective Studies and Mendelian Randomization. J Natl Cancer Inst 2015 Aug 20;107(11).
12. Brinton LA, Cook MB, McCormack V, et al. Anthropometric and hormonal risk factors for male breast cancer: male breast cancer pooling project results. J Natl Cancer Inst 2014 Mar;106(3):djt465.
13. Lerro CC, McGlynn KA, Cook MB. A systematic review and meta-analysis of the relationship between body size and testicular cancer. Br J Cancer 2010 Oct 26;103(9):1467-74.
14. Zuccolo L, Harris R, Gunnell D, Oliver S, Lane JA, Davis M, Donovan J, Neal D, Hamdy F, Beynon R, Savovic J, Martin RM. Height and prostate cancer risk: a large nested case-control study (ProtecT) and meta-analysis. Cancer Epidemiol Biomarkers Prev 2008 Sep;17(9):2325-36. doi: 10.1158/1055-9965.EPI-08-0342.

Appendix 10. Associations of breast-feeding with mechanisms of plasticity listed in Panel 1

For many of these mechanisms, evidence is only just beginning to emerge of how they respond to components of variability in breast-feeding. However, there is some supportive evidence for each of the mechanisms listed in Panel 1, though currently it is weakest for epigenetic effects and for telomere attrition.

Mechanism	Population	Study design	n	Reported association	Ref
Differential organ growth	Bangladesh	Birth cohort participating in RCT	2094	Longer duration of exclusive breast-feeding associated with larger thymus volume at 1 year	1
	Denmark	Cross-sectional study	47	Mean thymic index was 38.3 in exclusively breastfed infants, 27.3 in partially breastfed infants and 18.3 in formula fed infants at 4 mo ($p<0.001$)	2
Hormonal axes	Spain	Longitudinal study	28	Milk leptin concentration at 1 month of lactation was negatively correlated with infant BMI at 18 and 24 mo.	3
	Canada	Birth cohort	430	Higher breast milk leptin was associated with lower infant WFL z-score at 4 months and 1 year	4
Oxidative stress	US	Longitudinal study	56	Markers of oxidative stress in breast-milk were associated with greater infant WHZ in offspring of obese mothers but not normal weight mothers	5
	Iran	Longitudinal study	140	Breast-milk total anti-oxidant capacity was greater than that of formula-milk, and individual variability predicted infant length but not weight at 1 year	6
Epigenetic effects	HICS	Systematic review	7 studies	Breastfeeding might be associated with DNA methylation, but evidence is very limited and more research is needed	7
	Philippines	Birth cohort	494	Duration of breast-feeding was associated DNA methylation of inflammatory genes in young adulthood	8
Taste preference	US	RCT	97	A relatively brief experience (1 mo) with vegetable flavors in mothers' milk was associated with preference for carrot but not broccoli flavour after weaning	9
	Australia	Longitudinal cohort study	1905	Breastfeeding duration was associated with core and vegetable variety scores at 2 years	10
Telomere attrition	US	Longitudinal study		Exclusive breastfeeding at 4-6 wk was associated withy longer telomeres at 4 and 5 y of age	11
	Philippines	Birth cohort	1759	Duration of exclusive breast-feeding was not associated with telomere length at young adulthood	12

Gut microbiome development	US	Longitudinal study	107	During the first 30 days of life, predominantly breast-fed infants received bacteria from both breast milk and areolar skin, seeding the infant gut	13
	US	Longitudinal study	323	Breastfeeding was associated with infant intestinal microbial diversity, including individual taxa previously linked to early-life diet and health outcomes	14

References to Appendix 10

1. Moore SE, Prentice AM, Wagatsuma Y, Fulford AJ, Collinson AC, Raqib R, et al. Early-life nutritional and environmental determinants of thymic size in infants born in rural Bangladesh. Acta Paediatr. 2009 Jul;98(7):1168-75.

2. Hasselbalch H, Jeppesen DL, Engelmann MD, Michaelsen KF, Nielsen MB. Decreased thymus size in formula-fed infants compared with breastfed infants. Acta Paediatr. 1996 Sep;85(9):1029-32.

3. Miralles O, Sánchez J, Palou A, Picó C. A physiological role of breast milk leptin in body weight control in developing infants. Obesity (Silver Spring). 2006 Aug;14(8):1371-7.

4. Chan D, Goruk S, Becker AB, Subbarao P, Mandhane PJ, Turvey SE, et al. Adiponectin, leptin and insulin in breast milk: associations with maternal characteristics and infant body composition in the first year of life. Int J Obes (Lond). 2018 Jan;42(1):36-43.

5. Young BE, Patinkin ZW, Pyle L, de la Houssaye B, Davidson BS, Geraghty S, et al. Markers of Oxidative Stress in Human Milk do not Differ by Maternal BMI But are Related to Infant Growth Trajectories. Matern Child Health J. 2017 Jun;21(6):1367-1376.

6. Oveisi MR, Sadeghi N, Jannat B, Hajimahmoodi M, Behfar AO, Jannat F, et al. Human breast milk provides better antioxidant capacity than infant formula. Iran J Pharm Res. 2010 Fall;9(4):445-9.

7. Hartwig FP, Loret de Mola C, Davies NM, Victora CG, Relton CL. Breastfeeding effects on DNA methylation in the offspring: A systematic literature review. PLoS One. 2017 Mar 3;12(3):e0173070

8. McDade TW, Ryan C, Jones MJ, MacIsaac JL, Morin AM, Meyer JM, et al. Social and physical environments early in development predict DNA methylation of inflammatory genes in young adulthood. Proc Natl Acad Sci U S A. 2017 Jul 18;114(29):7611-7616.

9. Mennella JA, Daniels LM, Reiter AR. Learning to like vegetables during breastfeeding: a randomized clinical trial of lactating mothers and infants. Am J Clin Nutr. 2017 Jul;106(1):67-76. d

10. Scott JA, Chih TY, Oddy WH. Food variety at 2 years of age is related to duration of breastfeeding. Nutrients. 2012 Oct 15;4(10):1464-74.

11. Wojcicki JM, Heyman MB, Elwan D, Lin J, Blackburn E, Epel E. Early exclusive breastfeeding is associated with longer telomeres in Latino preschool children. Am J Clin Nutr. 2016 Aug;104(2):397-405.

12. Eisenberg DTA, Borja JB, Hayes MG, Kuzawa CW. Early life infection, but not breastfeeding, predicts adult blood telomere lengths in the Philippines. Am J Hum Biol. 2017 Jul 8;29(4).

13. Pannaraj PS, Li F, Cerini C, Bender JM, Yang S, Rollie A, et al. Association Between Breast Milk Bacterial Communities and Establishment and Development of the Infant Gut Microbiome. JAMA Pediatr. 2017 Jul 1;171(7):647-654.

14. Savage JH, Lee-Sarwar KA, Sordillo JE, Lange NE, Zhou Y, O'Connor GT, Sandel M, Bacharier LB, Zeiger R, Sodergren E, Weinstock GM, Gold DR, Weiss ST, Litonjua AA. Diet during Pregnancy and Infancy and the Infant Intestinal Microbiome. J Pediatr. 2018 Aug 30. pii: S0022-3476(18)30975-2.

Appendix 11: Maternal diabetes and breast-feeding

Given the many benefits of breast-feeding for mothers and their offspring, it should be recommended as widely as possible. However, two issues require attention in obese and diabetic mothers. First, they may find breast-feeding more difficult as they tend to experience delayed onset of lactation, and in diabetic mothers this is exacerbated by poorer metabolic control, pre-pregnancy obesity and insulin control.[1,2] Second, studies report that breast-milk of diabetic mothers has altered concentrations of glucose, insulin and other hormones, and higher energy content, compared to non-diabetic mothers.[3] This could potentially have metabolic effects on the offspring, with implications for future risk of overweight and diabetes. In a study from Singapore, for example, infants of non-diabetic mothers who were breast-fed exclusively or predominantly to 4 months gained less weight and BMI than those not breast-fed. However, this constraint of weight gain by breast-feeding was not observed among the offspring of mothers with gestational diabetes, potentially placing them at increased risk of childhood overweight.[4]

Nevertheless, there is growing evidence that neither of these issues precludes successful breastfeeding among diabetic mothers. Within a cohort of both Type 1 and Type 2 diabetic mothers in Canada, breast-feeding was still associated with a significantly reduced risk of obesity in the offspring.[5] Similarly, in studies from the US, the association of *in utero* exposure to maternal diabetes with childhood BMI and central adiposity was negated if the child was breastfed for ≥6 months.[6-8] The resolution to the apparent paradox that breast-milk of diabetic mothers can be metabolically different altered and yet still beneficial appears to lie in counter-balancing metabolic effects during different periods of lactation.

More detailed studies compared the effects of breast-milk from diabetic mothers (DBM), versus banked breast-milk (BBM) from unrelated non-diabetic women, on the offspring's BMI status and glucose tolerance at 2 years. Regarding intake in the first 7 days of life, the risks of child overweight and impaired glucose tolerance increased in dose-response manner in association with the proportion of DBM, and fell with the proportion of BBM.[9] However, a similar study focusing on the later neonatal period found that the associations of DBM with adverse outcomes disappeared if statistical adjustment was made for the volume of DBM in the first 7 days.[10] Together, these studies suggest that the first week of post-natal life is a 'critical period' for the programming effect of DBM on offspring metabolism.

Overall, when diabetic mothers breast-feed for >6 months, the impact of *in utero* exposure to maternal diabetes appears to be substantially attenuated, and breast-feeding protects against rather than elevates the risk of childhood overweight.[5-8] Moreover, another study showed that components of breast-feeding associated with maternal diabetes, such as short breast-feeding duration, are important mediators of the link between maternal diabetes and child overweight.[11] Increasing the support for extended breast-feeding by diabetic mothers is therefore key to maximising the health benefits for both mother and offspring.

References to Appendix 11

1. De Bortoli J, Amir LH. Is onset of lactation delayed in women with diabetes in pregnancy? A systematic review. Diabet Med. 2016 Jan;33(1):17-24.

2. Matias SL, Dewey KG, Quesenberry CP Jr, Gunderson EP. Maternal prepregnancy obesity and insulin treatment during pregnancy are independently associated with delayed lactogenesis in women with recent gestational diabetes mellitus. Am J Clin Nutr. 2014 Jan;99(1):115-21.

3. Dugas C, Perron J, Kearney M, Mercier R, Tchernof A, Marc I, et al. Postnatal Prevention of Childhood Obesity in Offspring Prenatally Exposed to Gestational Diabetes mellitus: Where Are We Now? Obes Facts. 2017;10(4):396-406.

4. Aris IM, Soh SE, Tint MT, Saw SM, Rajadurai VS, Godfrey KM, et al. Associations of infant milk feed type on early postnatal growth of offspring exposed and unexposed to gestational diabetes in utero. Eur J Nutr. 2017 Feb;56(1):55-64.

5. Feig DS, Lipscombe LL, Tomlinson G, Blumer I. Breastfeeding predicts the risk of childhood obesity in a multi-ethnic cohort of women with diabetes. J Matern Fetal Neonatal Med. 2011 Mar;24(3):511-5.

6. Crume TL, Ogden L, Maligie M, Sheffield S, Bischoff KJ, McDuffie R, et al. Long-term impact of neonatal breastfeeding on childhood adiposity and fat distribution among children exposed to diabetes in utero. Diabetes Care. 2011 Mar;34(3):641-5.

7. Mayer-Davis EJ, Rifas-Shiman SL, Zhou L, Hu FB, Colditz GA, Gillman MW. Breast-feeding and risk for childhood obesity: does maternal diabetes or obesity status matter? Diabetes Care. 2006 Oct;29(10):2231-7.

8. Crume TL, Ogden LG, Mayer-Davis EJ, Hamman RF, Norris JM, Bischoff KJ, et al. The impact of neonatal breast-feeding on growth trajectories of youth exposed and unexposed to diabetes in utero: the EPOCH Study. Int J Obes (Lond). 2012 Apr;36(4):529-34.

9. Plagemann A, Harder T, Franke K, Kohlhoff R. Long-term impact of neonatal breast-feeding on body weight and glucose tolerance in children of diabetic mothers. Diabetes Care. 2002 Jan;25(1):16-22.

10. Rodekamp E, Harder T, Kohlhoff R, Franke K, Dudenhausen JW, Plagemann A. Long-term impact of breast-feeding on body weight and glucose tolerance in children of diabetic mothers: role of the late neonatal period and early infancy. Diabetes Care. 2005 Jun;28(6):1457-62.

11. Hummel S, Pflüger M, Kreichauf S, Hummel M, Ziegler AG. Predictors of overweight during childhood in offspring of parents with type 1 diabetes. Diabetes Care. 2009 May;32(5):921-5.

Appendix 12: Examples of populations at high risk of the double burden of malnutrition and its co-morbidities

Country	Population	Early growth	Adult body composition	Non-communicable disease profile
Ethnic minority groups within high-income nations				
Canada	Aboriginal and First Nations populations, compared to those of European ancestry	High prevalence of high birth weights associated with high prevalence of gestational diabetes	High levels of obesity, high levels of truncal abdominal fat even after adjusting for BMI, similar levels of lean mass	Higher rates of death from cardiovascular disease within each income quintile and level of education, greater lifetime risk of developing diabetes and higher rates of gestational diabetes
Australia	Aboriginal populations, compared to those of European ancestry	Relatively lower average birth weight and greater risk of low birth weight and preterm birth	Low average BMI in communities living traditional lifestyle, but high child and adult obesity rates in urban populations, and high susceptibility to abdominal obesity	High prevalence of diabetes and hypertension, and high incidence of cardiovascular events. Non-communicable diseases develop at relatively low BMI levels and young age.
New Zealand	Maori and Pacific Islander populations, compared to those of European ancestry	High prevalence of high birth weights and high weights in early infancy. Proposal that low birth weight in these populations should be categorized <3000g.	Faster weight gain, higher BMI and adiposity develop early in childhood. BMI, fat mass, lean mass and central abdominal fat are all high in adulthood	High rates of diabetes, chronic kidney disease and cardiovascular risk, associated with higher age-standardised mortality rates
UK	South Asian populations, compared to those of European ancestry	Lower average birth weight and greater prevalence of low birth weight	Higher body fat and lower muscle mass per BMI value, higher abdominal adiposity, and faster rates of increased in childhood obesity after adjusting for ethnic differences in physique	Higher rates of diabetes and coronary heart disease, however these are not fully explained by conventional cardio-metabolic risk factors
UK	African and Caribbean populations, compared to those of European ancestry	Lower average birth weight and greater prevalence of low birth weight	Lower levels of visceral fat, but higher levels of truncal obesity in women though not men, as well as higher lean mass, all contributing to higher BMI	Higher rates of diabetes and stroke but lower rates of coronary heart disease, however these are not fully explained by conventional cardio-metabolic risk factors
US	African American populations, compared to those of European ancestry	Lower average birth weight and greater prevalence of low birth weight and preterm birth	High lean-fat ratio per unit weight, less central fat deposition in men, higher total BMI in women. Smaller mass of homeostatic organs (liver, heart, spleen, kidneys)	Higher rates of diabetes, stroke and cardiovascular disease, mediated by high blood pressure and insulin resistance. Body composition only accounts for some of these differences
US	Hispanic American populations, compared to those of European ancestry	Little difference in birth weight, higher rate of preterm birth	High fat-lean ratio per unit weight, more central fat distribution	Higher rates of diabetes and cardiovascular disease, strongly mediated by central adiposity, high blood pressure and insulin resistance

Rural-urban migration				
Peru	Rural-urban migrants compared to rural and urban populations	Higher rates of stunting in rural populations, indicating poorer growth of migrants relative to urban populations	Rural-to-urban migrants almost match urban populations in prevalence of obesity and truncal obesity, with much lower prevalence in rural populations. Obesity increases with duration of urban residence.	Rural-to-urban migrants have intermediate cardiovascular risk factors between rural and urban populations, with higher levels if they migrated after 1 age. Migrants have lower mortality rates than urban populations.
India	Rural-urban migrants compared to rural and urban populations	Lower average birth weights and higher rates of stunting in rural populations, indicating poorer growth of migrants relative to urban populations	Urban populations have higher rates of obesity in childhood and adulthood, and migrants rapidly converge on this pattern.	Cardio-metabolic risk factors increase more slowly following migration than adiposity, but migrants show elevated rates of diabetes, hypertension and cardiovascular disease.

References to Appendix 12

1. Chen L, Xiao L, Auger N, Torrie J, McHugh NG, Zoungrana H, et al. Disparities and Trends in Birth Outcomes, Perinatal and Infant Mortality in Aboriginal vs. Non-Aboriginal Populations: A Population-Based Study in Quebec, Canada 1996-2010. PLoS One 2015 Sep 23;10(9):e0138562.

2. Dyck RF, Karunanayake C, Pahwa P, Osgood ND. The hefty fetal phenotype hypothesis revisited: high birth weight, type 2 diabetes and gestational diabetes in a Saskatchewan cohort of First Nations and non-First Nations women. J Dev Orig Health Dis. 2017 Dec 22:1-7.

3. Leslie WD, Weiler HA, Nyomba BL. Ethnic differences in adiposity and body composition: the First Nations bone health study. Appl Physiol Nutr Metab 2007 Dec;32(6):1065-72.

4. Oster RT, King M, Morrish DW, Mayan MJ, Toth EL. Diabetes in pregnancy among First Nations women in Alberta, Canada: a retrospective analysis. BMC Pregnancy Childbirth 2014 Apr 10;14:136.

5. Tjepkema M, Wilkins R, Goedhuis N, Pennock J. Cardiovascular disease mortality among First Nations people in Canada, 1991-2001. Chronic Dis Inj Can. 2012 Sep;32(4):200-7.

6. Turin TC, Saad N, Jun M, Tonelli M, Ma Z, Barnabe CC, et al. Lifetime risk of diabetes among First Nations and non-First Nations people. CMAJ. 2016 Nov 1;188(16):1147-1153.

7. Sayers S, Singh G, Mott S, McDonnell J, Hoy W. Relationships between birthweight and biomarkers of chronic disease in childhood: Aboriginal Birth Cohort Study 1987-2001. Paediatr Perinat Epidemiol. 2009 Nov;23(6):548-56.

8. Kildea S, Stapleton H, Murphy R, Kosiak M, Gibbons K. The maternal and neonatal outcomes for an urban Indigenous population compared with their non-Indigenous counterparts and a trend analysis over four triennia. BMC Pregnancy Childbirth. 2013 Aug 30;13:167. doi: 10.1186/1471-2393-13-167.

9. Kim S, Macaskill P, Baur LA, Hodson EM, Daylight J, Williams R, et al. The differential effect of socio-economic status, birth weight and gender on body mass index in Australian Aboriginal Children. Int J Obes (Lond). 2016 Jul;40(7):1089-95

10. McDermott R, Campbell S, Li M, McCulloch B. The health and nutrition of young indigenous women in north Queensland - intergenerational implications of poor food quality, obesity, diabetes, tobacco smoking and alcohol use. Public Health Nutr. 2009 Nov;12(11):2143-9.

11. Chamberlain C, Banks E, Joshy G, Diouf I, Oats JJ, Gubhaju L, et al. Prevalence of gestational diabetes mellitus among Indigenous women and comparison with non-Indigenous Australian women: 1990-2009. Aust N Z J Obstet Gynaecol. 2014 Oct;54(5):433-40.

12. Wang Z, Knight S, Wilson A, Rowley KG, Best JD, McDermott R, et al. Blood pressure and hypertension for Australian Aboriginal and Torres Strait Islander people. Eur J Cardiovasc Prev Rehabil. 2006 Jun;13(3):438-43.

13. Sundborn G, Schluter PJ, Schmidt-Uili M, Paterson J. What defines 'low birth weight' in Pacific infants born in New Zealand? Pac Health Dialog. 2011 Sep;17(2):23-31.

14. Howe LD, Ellison-Loschmann L, Pearce N, Douwes J, Jeffreys M, Firestone R. Ethnic differences in risk factors for obesity in New Zealand infants. J Epidemiol Community Health 2015 Jun;69(6):516-22.

15. Rush E, Reed PW, McLennan S, Coppinger T, Simmons D, Graham D. Tracking of body mass indices over 2 years in Māori and European children. Eur J Clin Nutr. 2012 Feb;66(2):143-9.

16. Rush EC, Plank LD, Mitchelson E, Laulu MS. Central obesity and risk for type 2 diabetes in Maori, Pacific, and European young men in New Zealand. Food Nutr Bull. 2002 Sep;23(3 Suppl):82-6.

17. Joshy G, Simmons D. Epidemiology of diabetes in New Zealand: revisit to a changing landscape. N Z Med J. 2006 Jun 2;119(1235):U1999.

18. Sundborn G, Metcalf PA, Gentles D, Scragg RK, Schaaf D, Dyall L, et al R. Ethnic differences in cardiovascular disease risk factors and diabetes status for Pacific ethnic groups and Europeans in the Diabetes Heart and Health Survey (DHAH) 2002-2003, Auckland New Zealand. N Z Med J. 2008 Sep 5;121(1281):28-39.

19. Kelly Y, Panico L, Bartley M, Marmot M, Nazroo J, Sacker A. Why does birthweight vary among ethnic groups in the UK? Findings from the Millennium Cohort Study. J Public Health (Oxf). 2009 Mar;31(1):131-7.

20. Leon DA, Moser KA. Low birth weight persists in South Asian babies born in England and Wales regardless of maternal country of birth. Slow pace of acculturation, physiological constraint or both? Analysis of routine data. J Epidemiol Community Health. 2012 Jun;66(6):544-51.

21. Hudda MT, Nightingale CM, Donin AS, Owen CG, Rudnicka AR, Wells JCK, et al. Reassessing Ethnic Differences in Mean BMI and Changes Between 2007 and 2013 in English Children. Obesity 2018 Feb;26(2):412-419.

22. Tillin T, Hughes AD, Godsland IF, Whincup P, Forouhi NG, Welsh P, et al. Insulin resistance and truncal obesity as important determinants of the greater incidence of diabetes in Indian Asians and African Caribbeans compared with Europeans: the Southall And Brent REvisited (SABRE) cohort. Diabetes Care. 2013 Feb;36(2):383-93.

23. Eastwood SV, Tillin T, Dehbi HM, Wright A, Forouhi NG, Godsland I, et al. Ethnic differences in associations between fat deposition and incident diabetes and underlying mechanisms: the SABRE study. Obesity (Silver Spring). 2015 Mar;23(3):699-706.

24. Tillin T, Hughes AD, Mayet J, Whincup P, Sattar N, Forouhi NG, et al. The relationship between metabolic risk factors and incident cardiovascular disease in Europeans, South Asians, and African Caribbeans: SABRE (Southall and Brent Revisited) -- a prospective population-based study. J Am Coll Cardiol. 2013 Apr 30;61(17):1777-86.

25. Morisaki N, Kawachi I, Oken E, Fujiwara T. Social and anthropometric factors explaining racial/ethnical differences in birth weight in the United States. Sci Rep. 2017; 7: 46657.

26. Heymsfield SB, Peterson CM, Thomas DM, Heo M, Schuna JM. Why are there race/ethnic differences in adult body mass index–adiposity relationships? A quantitative critical review. Obes Rev. 2016 Mar; 17(3): 262–275

27. Gallagher D, Albu J, He Q, Heshka S, Boxt L, Krasnow N, Elia M. Small organs with a high metabolic rate explain lower resting energy expenditure in African American than in white adults. Am J Clin Nutr. 2006 May; 83(5): 1062–1067.

28. Spanakis EK, Golden SH. Race/ethnic difference in diabetes and diabetic complications. Curr Diab Rep. 2013 Dec;13(6):814-23.

29. Graham G. Disparities in cardiovascular disease risk in the United States. Curr Cardiol Rev. 2015;11(3):238-45.

30. Loret de Mola C, Quispe R, Valle GA, Poterico JA. Nutritional transition in children under five years and women of reproductive age: a 15-years trend analysis in Peru. PLoS One. 2014 Mar 18;9(3):e92550.

31. Urke HB, Mittelmark MB, Valdivia M. Trends in stunting and overweight in Peruvian pre-schoolers from 1991 to 2011: findings from the Demographic and Health Surveys. Public Health Nutr. 2014 Nov;17(11):2407-18.

32. Carrillo-Larco RM, Bernabé-Ortiz A, Pillay TD, Gilman RH, Sanchez JF, Poterico JA, et al. Obesity risk in rural, urban and rural-to-urban migrants: prospective results of the PERU MIGRANT study. Int J Obes (Lond). 2016 Jan;40(1):181-5.

33. Antiporta DA, Smeeth L, Gilman RH, Miranda JJ. Length of urban residence and obesity among within-country rural-to-urban Andean migrants. Public Health Nutr. 2016 May;19(7):1270-8.

34. Miranda JJ, Gilman RH, Smeeth L. Differences in cardiovascular risk factors in rural, urban and rural-to-urban migrants in Peru. Heart. 2011 May;97(10):787-96.

35. Burroughs Pena MS, Bernabé-Ortiz A, Carrillo-Larco RM, Sánchez JF, Quispe R, Pillay TD, et al. Migration, urbanisation and mortality: 5-year longitudinal analysis of the PERU MIGRANT study. J Epidemiol Community Health. 2015 Jul;69(7):715-8.

36. Bharati P, Bharati S, Pal M, Chakrabarty S, Som S, Gupta R. Growth and nutritional status of pre-school children in India: rural-urban and gender differences. Coll Antropol. 2009 Mar;33(1):7-21.

37. Antonisamy B, Sivaram M, Richard J, Rao PS. Trends in intra-uterine growth of single live births in southern India. J Trop Pediatr. 1996 Dec;42(6):339-41.

38. Raj M, Sundaram KR, Paul M, Sudhakar A, Kumar RK. Dynamics of growth and weight transitions in a pediatric cohort from India. Nutr J. 2009 Nov 23;8:55.

39. Ebrahim S, Kinra S, Bowen L, Andersen E, Ben-Shlomo Y, Lyngdoh T, et al. The effect of rural-to-urban migration on obesity and diabetes in India: a cross-sectional study. PLoS Med. 2010 Apr 27;7(4):e1000268.

40. Kinra S, Andersen E, Ben-Shlomo Y, Bowen L, Lyngdoh T, Prabhakaran D, et al. Association between urban life-years and cardiometabolic risk: the Indian migration study. Am J Epidemiol. 2011 Jul 15;174(2):154-64.

41. Kusuma Y, Gupta S, Pandav C. Migration and hypertension: a cross-sectional study among neo-migrants and settled-migrants in Delhi, India. Asia Pac J Public Health. 2009 Oct;21(4):497-507.

Appendix 13: Secular declines in age at menarche in low and middle-income countries

Country	Period of measurement	Rate of change (years/decade)	Reference
The Gambia	1989-2008	-0.65	1
Cameroon (rural)	1925-1994	no change	2
Cameroon (urban)	1925-1994	-0.21	2
South Africa (black)	1956-2004	-0.50	3
South Africa (white)	1956-2004	-0.22	3
India (rural)	1955-1989	-0.03	4
Indian (urban)	1955-1989	-0.12	4
Southeast China (rural)	1955-1985	-0.34	5
Southeast China (urban)	1955-1985	-0.27	5
China (Beijing rural)	1980-2004	-0.35	6
China (Beijing urban)	1980-2004	-0.80	6
Korea	1920-1986	-0.64	7
Thailand	1975-2012	-0.12	8
Mexico	1940-2000	-0.26	9
Mexico	1960-1980	-0.78	10
Brazil (Rio de Janeiro)	1920-1940	-0.12	11
Brazil (Rio de Janeiro)	1960-1980	-0.22	11
Brazil (Amazonia)	1930-1980	-0.24	12
Colombia	1941-1989	-0.55	13

References to Appendix 13

1. Prentice S, Fulford AJ, Jarjou LM, Goldberg GR, Prentice A. Evidence for a downward secular trend in age of menarche in a rural Gambian population. Ann Hum Biol 2010 Sep-Oct;37(5):717-21.

2. Pasquet P, Biyong AM, Rikong-Adie H, Befidi-Mengue R, Garba MT, Froment A. Age at menarche and urbanization in Cameroon: current status and secular trends. Ann Hum Biol 1999 Jan-Feb;26(1):89-97.

3. Jones LL, Griffiths PL, Norris SA, Pettifor JM, Cameron N. Age at menarche and the evidence for a positive secular trend in urban South Africa. Am J Hum Biol 2009 Jan-Feb;21(1):130-2.

4. Pathak PK, Tripathi N, Subramanian SV. Secular trends in menarcheal age in India-evidence from the Indian human development survey. PLoS One 2014 Nov 4;9(11):e111027.

5. Lyu Y, Mirea L, Yang J, Warre R, Zhang J, Lee SK, Li Z. Secular trends in age at menarche among women born between 1955 and 1985 in Southeastern China. BMC Womens Healt. 2014 Dec 12;14:155.

6. Chen FF, Wang YF, Mi J. Timing and secular trend of pubertal development in Beijing girls. World J Pediatr. 2014 Feb;10(1):74-9.

7. Hwang JY, Shin C, Frongillo EA, Shin KR, Jo I. Secular trend in age at menarche for South Korean women born between 1920 and 1986: the Ansan Study. Ann Hum Biol 2003 Jul-Aug;30(4):434-42.

8. Jaruratanasirikul S, Sriplung H. Secular trends of growth and pubertal maturation of school children in Southern Thailand. Ann Hum Biol 2015;42(5):447-54.

9. Marván ML, Catillo-López RL, Alcalá-Herrera V, Callejo DD. The Decreasing Age at Menarche in Mexico. J Pediatr Adolesc Gynecol. 2016 Oct;29(5):454-457.

10. Malina RM, Peña Reyes ME, Tan SK, Little BB. Secular change in age at menarche in rural Oaxaca, southern Mexico: 1968-2000. Ann Hum Biol 2004 Nov-Dec;31(6):634-46.

11. Kac G, Auxiliadora de Santa Cruz Coel, Velasquez-Melendez G. Secular trend in age at menarche for women born between 1920 and 1979 in Rio de Janeiro, Brazil. Ann Hum Biol. 2000 Jul-Aug;27(4):423-8.

12. Silva HP, Padez C. Secular trends in age at menarche among Caboclo populations from Pará, Amazonia, Brazil: 1930-1980. Am J Hum Biol. 2006 Jan;18(1):83-92.

13. Villamor E, Chavarro JE, Caro LE. Growing up under generalized violence: an ecological study of homicide rates and secular trends in age at menarche in Colombia, 1940s-1980s. Econ Hum Biol. 2009 Jul;7(2):238-45.