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**Worldwide variability in growth and its association with health: incorporating body composition, developmental plasticity, and intergenerational effects**

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**Worldwide variability in growth and its association with health: incorporating body composition, developmental plasticity, and intergenerational effects**

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2  
3 1 **Abstract**  
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8 3 In their seminal book 'Worldwide variation in human growth', published in 1976, Eveleth  
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10 4 and Tanner highlighted substantial variability within and between populations in the  
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12 5 magnitude and schedule of human growth. In the four decades since then, research has  
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14 6 clarified why growth variability is so closely associated with human health. First, growth  
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16 7 patterns are strongly associated with body composition, both in the short- and long-term.  
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18 8 Poor growth in early life constrains the acquisition of lean tissue, while compensatory 'catch-  
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20 9 up' growth may elevate body fatness. Second, these data are examples of the fundamental  
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22 10 link between growth and developmental plasticity. Growth is highly sensitive to ecological  
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24 11 stresses and stimuli during early 'critical windows', but loses much of this sensitivity as it  
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26 12 undergoes canalisation during early childhood. Crucially, the primary source of stimuli during  
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28 13 early 'critical windows' is not the external environment itself, but rather maternal  
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30 14 phenotype, which transduces the impact of ecological conditions. Maternal phenotype,  
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32 15 representing many dimensions of 'capital', thus generates a powerful impact on the  
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34 16 developmental trajectory of the offspring. There is increasing evidence that low levels of  
35  
36 17 maternal capital impact the offspring's size at birth, schedule of maturation, and body  
37  
38 18 composition and physiological function in adulthood. While evidence has accrued of  
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40 19 substantial heritability in adult height, it is clear that the pathway through which it is  
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42 20 attained has major implications for metabolic phenotype. Integrating these perspectives is  
43  
44 21 important for understanding how developmental plasticity may on the one hand contribute  
45  
46 22 to adaptation, while on the other shape susceptibility to non-communicable disease.  
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48 23  
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50 24 **Key words:** growth, body composition, developmental plasticity, inter-generational effects  
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3 25 **Introduction**  
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8 27 At the start of their seminal work 'Worldwide variation in human growth', Eveleth and  
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10 28 Tanner (1976) made two statements that are simultaneously complementary and yet  
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12 29 seemingly antagonistic. The very first sentence of the book stated:  
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17 31 *A child's growth rate reflects, better than any other single index, his state of health*  
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19 32 *and nutrition; and often indeed his psychological situation also.*  
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24 34 On this basis, they argued, growth studies could be used to monitor the health of  
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26 35 populations, or to identify subgroups particularly deserving of economic and social benefits.  
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28 36 Elsewhere, Tanner developed the theme that growth monitoring provides unique insight  
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30 37 into a population's living conditions. Many are familiar with his comment:  
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36 39 *If you want to measure the classlessness of a society, and you are not interested in*  
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38 40 *rhetoric but in actual conditions and facts, then looking at the growth of children ... is*  
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40 41 *perhaps the best way* (Tanner 1990).  
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45  
46 43 This approach duly inspired a new discipline of 'anthropometric history' (Komlos 1991; 1994)  
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48 44 - the analysis of variability in adult stature to provide an indication of environmental  
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50 45 conditions in earlier life. This approach can broadly overcome the limitations of conventional  
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52 46 indices of living standards such as wages or gross domestic product, which cannot take into  
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54 47 account variability in mediating variables such as the price of food, or the differential agency  
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56 48 of individuals to obtain resources. Variability in adult stature cannot index in detail the  
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3 49 underlying environmental causes impacting early growth, but the broader approach remains  
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5 50 very valuable.  
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10 52 However, the second paragraph of '*Worldwide variation in human growth*' added a crucial  
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12 53 cautionary note:  
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17 55 *There is no guarantee, however, that all populations have the same growth potential*  
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19 56 (Eveleth and Tanner 1976)  
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24 58 Several chapters of the book explored how ecological factors such as temperature or  
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26 59 altitude are associated with growth patterns, and discussed genetic adaptation in this  
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28 60 context. Here then is a key dilemma. How can we disentangle 'beneficial' variability in  
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30 61 growth that could plausibly reflect adaptation to local ecological conditions from  
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32 62 'detrimental' variability in growth emerging from societal inequality, or from exposure to  
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34 63 pathogens, parasites, pollution or malnutrition?  
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40 66 The book summarized with unprecedented detail the extraordinary diversity in size and  
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42 67 shape that characterizes humans through the life course, much of it apparent across broader  
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44 68 geographical regions. Tables and figures systematically demonstrated substantial between-  
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46 69 population variability in growth outcomes, such as weight, height, body girths and skinfold  
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48 70 thicknesses. Within-population studies further highlighted associations with environmental  
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50 71 factors, yet the substantial heritability of growth traits was also described.  
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3 72 Eveleth and Tanner were very aware that adaptation could incorporate both developmental  
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5 73 and genetic components. In their chapter focusing on variability associated with altitude and  
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8 74 temperature, they observed:  
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12 76 *The responses made by the human organism are physiological ones, but the*  
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14 77 *limitations in making these responses are determined by the genotype. The analysis*  
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17 78 *of growth physique encompasses both aspects of adaptability and may be seen both*  
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20 79 *as the development of adaptive mechanisms and as the end product of growing up in*  
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22 80 *a climatic extreme* (Eveleth and Tanner 1976).  
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27 82 Forty years later, what more have we learned about this profound variability in human  
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29 83 growth, and in particular, what does it *mean* in relation to human health? On the one hand,  
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31 84 growth variability is now accorded a central role in the 'developmental origins of adult  
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33 85 disease' hypothesis (Hales and Barker 1992). Indeed, while much reference is made to  
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36 86 under-nutrition as the key stress during development that predisposes to chronic disease in  
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38 87 later life, much of the data pertains to growth – either birth weight as an index of fetal  
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41 88 development, or post-natal gains in weight or length as an indication of growth faltering or  
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43 89 compensatory catch-up (Barker et al., 1989; Hales et al., 1991; Eriksson et al., 1999). At the  
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46 90 same time, studies repeatedly emphasise that components of size and shape are highly  
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48 91 heritable, with some twin studies attributing as much as 80-90% of variability in adult  
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50 92 stature to genetic factors (Silventoinen et al., 2003; Perola et al., 2007).  
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55 94 We are more aware than ever, therefore, that the study of growth carries vital messages  
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57 95 about short- and long-term health variability. But it is also clear that growth itself is only a  
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3 96 marker for diverse other traits that are more direct determinants of health. 'Adding' a few  
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5 97 centimetres of height to an individual cannot directly alter their risk of diabetes or heart  
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7 98 disease, rather it must index underlying effects of developmental experience on the  
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10 99 structure and function of cells and organs.  
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15 101 The last decade has seen another seminal publication, the World Health Organisation  
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17 102 growth reference (Bhandari et al., 2002). This study, based on well-off individuals from six  
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19 103 different populations, highlighted substantial consistency in early patterns of linear growth,  
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21 104 giving a strong message that in good ecological conditions, humans grow relatively similarly  
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23 105 in early life. More recent work has extended this approach to fetal life (Papageorghiou et al.,  
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25 106 2014). It remains unclear, however, how relevant this scenario is to variability in adult size,  
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27 107 or indeed to other somatic traits such as body shape, physique and body composition. A  
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29 108 recent comprehensive survey of 200 countries reported substantial variability (20 cm  
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31 109 between tallest and shortest countries) in adult height, and much of this variability has  
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33 110 persisted despite secular trends in recent centuries (NCD Risk Factor Collaboration (NCD-  
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35 111 RisC 2016).  
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43 113 The aim of this review is consider growth in more detail, in order to emphasise four issues  
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45 114 relevant to the association between growth variability and health. First, I will summarise  
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47 115 how growth patterns during different stages of development are associated with body  
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49 116 composition. Second, I will suggest how these associations contribute to the 'developmental  
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51 117 origins' of health and disease through the medium of developmental plasticity. Third, I will  
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53 118 argue that growth is best considered a multi-generational phenomenon, bearing a strong  
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3 119 imprint of parental phenotype. Finally, I will reconsider the evidence that population  
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5 120 variability in early growth may incorporate genetic effects.  
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10 122 **Growth and body composition**

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14 124 Shortly after the publication of '*Worldwide variation in human growth*', another landmark  
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17 125 article emerged - the 'reference child' of Fomon and colleagues (1982). This paper  
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20 126 highlighted for the first time substantial aged-associated variability in pediatric body  
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22 127 composition. Six months after birth, infants were typically over 25% fat, in contrast with  
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24 128 around 14% at birth. Yet by mid childhood, the reference boy was barely 12% fat, and the  
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26 129 girl around 17%. These data indicate that infants become adipose only temporarily,  
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29 130 suggesting unique functions of body fat stores during early life. The same data indicated a  
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31 131 steady acquisition of lean mass from birth onwards, though not consistently in proportion  
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33 132 with height. In other words, the developmental profile of human body composition is quite  
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35 133 complex, and like growth patterns, it too might vary substantially between populations.  
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40 135 Since children grow at variable rates, it is ideal to adjust for this when assessing body  
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42 136 composition. Fomon's data can be re-plotted as fat mass index ( $\text{fat mass}/\text{height}^2$ ) against  
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44 137 lean mass index ( $\text{lean mass}/\text{height}^2$ ), which effectively splits body mass index into its two  
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46 138 principal components (Hattori et al., 1997; Van Itallie et al., 1990; Wells 2001). This approach  
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48 139 highlights the changes in body composition that occur with age, as well as sex differences  
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50 140 (**Figure 1**). That both growth and body composition are sensitive to ecological influences in  
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52 141 early life is clearly demonstrated through studies of infant feeding mode (Dewey et al., 1993;  
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54 142 Butte et al., 2000).  
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5 144 Subsequent comparisons across ethnic groups have consistently shown population  
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7 145 differences. For example, Ethiopian infants have less body fat than European infants at birth  
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9 146 (Andersen et al., 2011), while at birth and in early infancy, South Asian infants in the UK have  
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11 147 less lean mass but similar body fat compared to white European infants (Yajnik et al., 2003;  
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13 148 Stanfield et al., 2012). During childhood, South Asian children continue to have lower lean  
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15 149 mass index compared to European children, whereas Afro-Caribbean and black African  
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17 150 children tend to have higher levels of lean mass index than European children, and similar  
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19 151 body fat (Nightingale et al., 2011; Lee et al., 2015; D'Angelo et al., 2015). Though current  
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21 152 living conditions undoubtedly contribute to such differences, their large magnitude also  
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23 153 suggests potential genetic responses to ancestral ecological conditions.  
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31 155 Beyond body composition variability *per se*, it is now also clear that early growth variability  
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33 156 has implications for body composition at later ages. Data from numerous studies are  
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35 157 relatively consistent in showing an association between birth weight and later lean mass  
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37 158 (Wells et al., 2007). Associations between birth weight and later adiposity in contrast are  
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39 159 inconsistent across studies: in many populations, no such association is apparent, but in a  
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41 160 few populations low birth weight predicts subsequent central adiposity whereas in others, a  
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43 161 heavier birth weight also predicts greater adiposity in later life (Wells et al., 2007). This  
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45 162 heterogeneity is most likely due to differences between populations in the rate of infant  
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47 163 growth, for example some populations with low average birth weight may have undergone  
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49 164 catch-up growth. In two large studies, birth weight was associated with later adiposity in  
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51 165 females but not males (Sachdev et al., 2005; Rogers et al., 2006), suggesting contrasting life  
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53 166 history strategies between the sexes. Broadly, these data indicate that fetal life is a key  
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3 167 period in the developmental trajectory of lean tissue mass, and this is consistent with similar  
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5 168 associations between birth weight and later height.  
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10 170 The scenario for infancy is rather more complex. In high-income industrialised populations, a  
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12 171 number of studies have demonstrated an association between rapid infant weight gain and  
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14 172 later adiposity, or risk of obesity (Stettler et al., 2002; 2005; Ekelund et al., 2006; Chomtho et  
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17 173 al., 2008). This in turn has identified infancy as a potential critical period in the  
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19 174 developmental origins of obesity. However, data from low- and middle-income countries  
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21 175 contrast markedly with these findings. In a number of studies, from both South American  
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23 176 populations and India, faster weight gain during infancy has been associated with later lean  
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25 177 mass, but not with later fat mass (Li et al., 2003; Sachdev et al., 2005; Wells et al., 2005;  
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27 178 2012; Kuzawa et al., 2012). However, whether interventions in early life invariably promote  
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29 179 lean mass rather than fat accretion remains unclear (Rivera et al., 1995; Kulkarni et al.,  
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31 180 2014). This may be because the optimal intervention may require the mediating influence of  
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33 181 maternal nutrition, as discussed below.  
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40 183 The reasons underlying this population-contrast remain poorly understood. One possibility is  
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42 184 that there are genetic differences between populations that directly affect the composition  
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44 185 of tissue accretion, but this explanation is perhaps unlikely given that some of the studies  
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46 186 from lower and middle-income countries derive from Brazil, where a substantial proportion  
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48 187 of the population are of European origin. **An alternative is that infants larger at birth and**  
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50 188 **closer to their 'growth potential; have lower capacity to gain additional lean mass, and must**  
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52 189 **therefore gain more fat.** A more intriguing possibility is that populations differ in the  
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55 190 duration of critical windows, during which nutrition regulates infant growth (Wells 2014).  
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3 191 Earlier closure of critical windows might direct energy intake to fat accretion rather than  
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5 192 lean tissue. Possible underlying mechanisms may include hormonal factors in breast milk,  
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7 193 differences in exposure to environmental agents such as pathogens, or genetic variability in  
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9 194 the physiological mechanisms that regulate critical windows. Supporting evidence for these  
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11 195 hypotheses is currently lacking and given the need to tackle both under-nutrition and  
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13 196 obesity through public health efforts, this represents an important topic for further research.  
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### 198 **Developmental plasticity**

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24 200 The complex associations between early growth patterns and later body composition  
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26 201 highlight the mediating role of developmental plasticity. Indeed, it was classic animal studies  
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28 202 of growth that first revealed the long-term impact of early-life nutrition on size and  
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30 203 metabolic phenotype. If a rat were malnourished directly after birth, it would never fully  
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32 204 recover the deficit in body size. If the insult was delayed until 9 weeks after birth, however,  
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34 205 growth would only slow temporarily, and as soon as adequate supplies of food were  
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36 206 restored, the rat would gain weight rapidly and regain the growth trajectory it had displayed  
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38 207 prior to the insult (McCance and Widdowson 1956; McCance 1962). This implicated early  
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40 208 infancy as a 'critical period' in the development of adult size and metabolism.  
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47 210 Critical windows of sensitivity in growth close in due course, after which growth becomes  
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49 211 canalized, or 'self-correcting' under the genetic influence of growth hormone. The tendency  
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51 212 of traits to remain relatively stable following periods of plasticity is often termed 'tracking'.  
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54 213 This does not mean that growth is entirely immune from subsequent environmental effects.  
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3 214 Rather, the magnitude of tracking is best described on a continuous scale, for example the  
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5 215 tendency of height to track after infancy is relatively high, whereas that of weight is lower.  
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10 217 The concepts of critical windows, plasticity and tracking allow a number of specific questions  
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12 218 to be raised (**Table 1**), in terms of phenotypic targets, mechanisms, timing and reversibility  
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14 219 (Wells 2016). The primary period of plasticity in humans comprises fetal life and infancy,  
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16 220 though which of these periods is most sensitive depends on the trait. Recently, attention has  
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18 221 been directed to adolescence as another sensitive period, particularly for reproductive  
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20 222 physiology and behaviour (Prentice et al., 2013). Overall, the life-course profile of human  
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22 223 plasticity remains poorly understood, because scientists have generally been quick to notice  
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24 224 its implications, but slower to define its characteristics in detail.  
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31 226 The importance of developmental plasticity for human health rapidly became clear, in  
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33 227 particular through the pioneering epidemiological studies of Barker and colleagues (Barker  
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35 228 et al., 1989; 2005; Hales et al., 1991). Following up cohorts of individuals born in the first half  
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37 229 of the 20th century, it was repeatedly found that low birth weight and poor weight gain  
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39 230 during infancy were associated with the risk of chronic diseases in late adulthood, including  
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41 231 ischaemic heart disease, type 2 diabetes, hypertension and stroke (Barker et al., 1989; 2005;  
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43 232 Eriksson et al., 1999; 2001). These findings have subsequently been extended to low and  
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45 233 middle-income countries (Adair et al., 2013), although there is also some heterogeneity  
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47 234 between populations in the associations between early growth patterns and later health  
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49 235 outcomes (Wells et al., 2007; Sterling et al., 2014).  
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3 237 The initial interpretation of these data was that fetal malnutrition induced  
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5 238 pathophysiological development, which in the long term elevated chronic disease risk.  
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7 239 Initially, it seemed logical that low birth weight was implicating maternal malnutrition, either  
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9 240 directly or through compromised function of the placenta. Hales and Barker (1992) proposed  
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11 241 the 'thrifty phenotype' hypothesis: that in malnourished fetuses, growth of organs such as  
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13 242 the pancreas was sacrificed in order to protect the vulnerable energy-demanding brain. This  
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15 243 would represent a survival strategy in the short term, but at the long-term cost of a reduced  
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17 244 capacity to tolerate high-energy diets. Individuals developing such a thrifty phenotype were  
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19 245 thus at high risk of developing type 2 diabetes and other chronic diseases in later adult life.  
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21 246 Eveleth and Tanner duly acknowledged this rapidly developing research area in the revised  
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23 247 edition of their book (Eveleth and Tanner 1991).  
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31 249 Nevertheless, these retrospective cohort studies provided no direct information on putative  
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33 250 malnutrition in early life. Rather, everything 'nutritional' was inferred from data on birth  
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35 251 weight, placental weight, or the size and shape of the mother (Barker et al., 1989; 1990;  
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37 252 2005; Martyn et al., 1996). Moreover, the supporting data repeatedly showed that  
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39 253 associations between birth weight or early postnatal growth and later disease risk were not  
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41 254 restricted to those at the lower extremes, but were rather evident across the whole range of  
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43 255 birth weight. In other words, each additional increment in birth weight lowered the risk of  
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45 256 chronic disease in adult life, and this draws attention back to the process of growth itself.  
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52 258 **The capacity-load model**  
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3 260 Building on the 'thrifty phenotype' hypothesis, I have developed a simpler model of  
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5 261 developmental plasticity and long-term health, focusing on two generic traits, one that  
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7 262 promotes homeostasis and one that impedes it (Wells, 2011; 2016). This approach places  
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10 263 less emphasis on the extremes of nutritional status, such as low birth weight or adult  
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12 264 obesity. Instead, I assume that the relevant traits are each characterised by a continuous  
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15 265 distribution. Specifically, I assume that in early life, the fetus and infant gain 'metabolic  
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17 266 capacity', a generic term for physiological traits that enhance the potential to maintain  
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19 267 homeostasis. From late fetal life onwards, I assume that individuals can accumulate  
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21 268 'metabolic load', a generic term for traits that challenge the capacity for homeostasis. The  
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24 269 risk of chronic disease in adult life is then predicted to scale inversely with capacity, and  
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27 270 positively with load (Wells 2011). Of particular importance, metabolic capacity and load are  
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29 271 closely associated with different stages of development and different components of  
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31 272 growth.

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36 274 Metabolic capacity derives from key components of organ structure and function that  
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38 275 develop during the period of hyperplastic growth, characterized by increasing in cell number  
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40 276 (Bogin 1999). Specific examples include nephron number in the kidney, muscle mass,  
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42 277 pancreatic beta-cell mass, blood vessel diameter, and the size of the airways in the lungs.  
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45 278 Each of these traits scales relatively linearly with birth weight – the heavier the neonate, the  
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47 279 larger or more productive the physical trait (Wells 2011; 2016). Because these traits often  
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49 280 have little capacity to change subsequently, their functional properties tend to track on into  
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51 281 adult life. For example, the long-term inverse association between birth weight and blood  
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54 282 pressure may be due to the fact that nephron number, fundamental to kidney function,  
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57 283 changes negligibly after term birth (Hinchliffe et al., 1991).

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5 285 Not all stresses that shape metabolic capacity necessarily act through fetal weight gain, as  
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7 286 proxied by birth weight or infant weight gain. First, early fetal growth faltering may leave no  
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9 287 signal in birth weight, as was apparent for offspring exposed *in utero* to maternal famine  
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11 288 during the first trimester of pregnancy (Roseboom et al., 2001). Indeed, following such early  
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13 289 growth faltering, neonatal adiposity may even be greater than normal, indicating that a  
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15 290 degree of 'catch-up' has already occurred prior to birth (Hemachandra and Klebanoff 2006);  
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17 291 but this would conceal reduced lean mass. Likewise, the high body fat content of  
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19 292 macrosomic neonates reduces their metabolic capacity relative to their birth weight. Thus,  
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21 293 maternal obesity may in fact constrain metabolic capacity in the offspring, despite the high  
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23 294 levels of maternal energy stores.  
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31 296 Second, maternal nutritional status around the time of conception may affect fetal gene  
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33 297 expression, independent of fetal growth (Waterland et al., 2010; Khulan et al., 2012). Third,  
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35 298 non-nutritional factors such as maternal psychosocial stress may impact signalling systems in  
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37 299 the brain or other organs (Entringer et al., 2009, 2011). Birth weight cannot index such  
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39 300 effects, even though they may involve perturbations of metabolic capacity. We should not  
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41 301 therefore assume that the developmental origins of chronic disease are explained entirely by  
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43 302 growth patterns, or that early growth patterns have a simple relation with maternal  
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45 303 nutrition. Nevertheless, birth weight has been repeatedly associated with adult chronic  
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47 304 disease risk in diverse populations, and the fact that such data is increasingly widely  
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49 305 available means that it is one of the most valuable proxies for the quality of fetal  
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51 306 development.  
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3 308 As the process of growth shifts to hypertrophy, characterized by increasing in cell size, the  
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5 309 regulatory systems change. Whereas fetal development is very sensitive to the delivery of  
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8 310 nutrients and oxygen, post-natal growth gradually loses this sensitivity, and comes under the  
9  
10 311 canalizing control of growth hormone. From this point onwards, non-brain organ growth  
11  
12 312 closely follows growth in stature (**Figure 2**). The striking linearity of these relationships  
13  
14 313 indicates a common regulatory system, and helps explain why metabolic capacity tracks  
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17 314 from early life into adulthood, where height remains associated with organ masses in both  
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19 315 sexes (de la Grandmaison et al., 2001).

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21 316  
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24 317 Evidence from rats indicates that hyperplastic growth may extend into early infancy (Enesco  
25  
26 318 and LeBlond, 1962). Markers of early post-natal nutritional experience might therefore also  
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28 319 correlate with certain components of metabolic capacity that are still developing after birth.  
29  
30 320 However, infant weight gain is a problematic way to assess the quality of post-natal growth,  
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32 321 since it shows an inverse correlation with birth weight on account of small neonates tending  
33  
34 322 to undergo 'catch-up' (Ong et al., 2000). Thus we cannot tell whether rapid infant weight  
35  
36 323 gain represents continued 'good growth', or recovery from earlier 'poor growth',  
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38 324 characterized by constrained fetal organ development. To resolve this, we need a marker of  
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40 325 infant/childhood growth that is independent of fetal growth.  
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47 327 The best candidate currently appears to be relative leg length (leg length/height), for while  
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49 328 each component of birth length is associated with birth weight, the ratio between them is  
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51 329 not, indicating that relative leg length is primarily determined in post-natal life (Gunnell et  
52  
53 330 al., 1999; Bogin and Baker, 2012; Pomeroy et al., 2014). After birth, leg length typically  
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55 331 shows stronger associations than trunk length with environmental factors such as infant or  
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3 332 early childhood diet (Gunnell et al., 1998; Wadsworth et al., 2002). In turn, relatively shorter  
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5 333 legs have been associated with poorer metabolic function in adult life, including higher  
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7 334 blood pressure and blood lipids, insulin resistance, thickened carotid arteries, and greater  
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9 335 risk of coronary disease and diabetes (Asao et al., 2006; Gunnell et al., 2003; Tilling et al.,  
10  
11 336 2006; Fraser et al., 2008; Lawlor et al., 2002a). Collectively, these findings indicate that  
12  
13 337 components of metabolic capacity may continue to be compromised after birth under  
14  
15 338 adverse conditions, in association with poorer leg growth.  
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22 340 As in fetal life, some post-natal growth traits may be protected during adverse conditions at  
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24 341 a cost to others. This is supported by a recent study in Peru, which compared children from a  
25  
26 342 high altitude rural setting, exposed to various ecological stresses, with children from a more  
27  
28 343 favourable lowland urban setting. While the high altitude children were shorter, the growth  
29  
30 344 deficit varied according by anatomical region. Whereas lower leg length was ~1.3 z-scores  
31  
32 345 shorter, foot length was ~1 z-score shorter, and the combined length of the head and trunk,  
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34 346 incorporating the brain and vital organs, was only ~0.7 z-scores shorter (Pomeroy et al.,  
35  
36 347 2012). The thrifty phenotype thus appears to apply to body proportions as well as organs,  
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38 348 and this supports the use of growth outcomes such as leg length as developmental markers  
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40 349 of chronic disease risk. For example, height explained 25% of the variability in kidney length  
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42 350 in pre-pubertal children from lowland Nepal, though in this case sitting height and leg length  
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44 351 showed similar associations (Wells et al., 2016a).  
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52 353 Obesity, itself manifesting as excessive somatic growth, is a key factor challenging  
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54 354 homeostasis in later life. One reason for this, according to autopsy studies, is that adult  
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56 355 organ masses scale with total body weight much more weakly than with height (de la  
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3 356 Grandmaison et al., 2001). This means that as adults gain weight, their organs cannot keep  
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5 357 up, and bear a relatively heavier metabolic burden. Thus, the second element of my model  
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8 358 comprises 'metabolic load', referring to traits or behaviours that challenge the capacity for  
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10 359 homeostasis.

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14 361 This concept is clearly analogous to that of 'allostatic load' developed by McEwen and  
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16  
17 362 colleagues (McKewan and Stellar 1993; McEwan 1998), but contrasting with their emphasis  
18  
19 363 on 'psychosocial stress' and its impact on neuroendocrine function, my focus is specifically  
20  
21 364 on nutritional/metabolic exposures. Beyond central abdominal obesity, metabolic load also  
22  
23 365 links closely with various 'adult lifestyle' risk factors for chronic diseases such as lipogenic  
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25 366 diets, sedentary behaviour, psychosocial stress and tobacco smoking, as well as infectious  
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27 367 disease and a variety of toxins and pollutants, all of which challenge homeostasis (Wells  
28  
29 368 2011, 2016). Metabolic load develops primarily during the period of hypertrophic growth,  
30  
31 369 though elevated adiposity in newborns of obese mothers (Sewell et al., 2006) suggests that  
32  
33 370 load may rise even during fetal life. At the cellular level, metabolic load may cause insulin  
34  
35 371 resistance, oxidative stress and telomere attrition (Wells 2016), and this helps understand  
36  
37 372 why catch-up growth is associated not only with adult size and body composition, but also  
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39 373 longevity (Metcalf and Monaghan 2001).

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43 375 Consistent with the capacity-load model, interactive effects of birth weight and current  
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45 376 weight have now been described for a variety of traits (Wells 2011). The greatest chronic  
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47 377 disease risk is predicted in those who have diminished capacity and elevated load. For  
48  
49 378 example, a study of Swedish men showed that the blood pressure 'penalty' associated with  
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51 379 low birth weight was minimal in those of small adult size, but large in those who were both  
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3 380 tall and heavy (Leon et al., 1996). In other words, the penalty for diminished capacity was  
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5 381 greatest in those with elevated load, while the penalty for high load was greatest in those  
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7 382 with diminished capacity. Moreover, recent data from three US cohorts demonstrate  
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10 383 continuous interactive associations of birth weight and unhealthy adult lifestyle with the risk  
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12 384 of diabetes and hypertension (Li et al., 2015a,b), exactly as the capacity-load model predicts  
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14  
15 385 **(Figure 3).**

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20 387 This approach breaks down simplistic categorical differentiations, and provides a more  
21  
22 388 realistic life-course model of chronic disease risk. Whilst nutrition is clearly a key  
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24 389 determinant of both metabolic capacity and metabolic load, we can see that growth also  
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26 390 plays a central role in their interaction.

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### 30 31 392 **Intergenerational effects**

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36 394 Barker and colleagues were quick to acknowledge the importance of maternal phenotype in  
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38 395 relation to the offspring's growth trajectory during early life (Barker et al., 1990; Martyn et  
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40 396 al., 1996). Building on the embodied capital model of Kaplan and colleagues (2003),  
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42 397 components of maternal phenotype that impact development of the offspring have been  
43  
44 398 termed 'maternal capital' (Wells 2010). Recent studies have shown that many different  
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46 399 components of maternal phenotype are relevant, some of them (eg micronutrient status,  
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48 400 adiposity) reflecting current maternal condition, while others (eg height) reflect ecological  
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50 401 conditions during the mother's own period of development.

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3 403 The fact that growth represents an inter-generational process makes it challenging to  
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5 404 understand how developmental plasticity can contribute to adaptation. The 'predictive  
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7 405 adaptive response' hypothesis assumed that early-life plasticity allows metabolic adaptation  
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9 406 directly to local ecological conditions (Gluckman and Hanson 2004). This perspective has  
10  
11 407 been challenged for several reasons: first, early-life cues in long-lived species such as  
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13 408 humans are highly likely to go 'out-of-date', making long-term adaptation implausible (Wells  
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15 409 2007) and second, the nature of placental nutrition and lactation is such that the primary  
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17 410 ecological influence during early critical windows is not the external environment but  
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19 411 maternal capital (Wells 2010). This means that early growth trajectory is profoundly  
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21 412 imprinted by maternal phenotype, and within any given environment, mothers will vary  
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23 413 amongst themselves in their physiological condition.  
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31 415 In pregnancy, the quality and quantity of blood reaching the placental interface determines  
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33 416 the supply of nutrients (Haig 1993). The human placenta presents a relatively thin barrier of  
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35 417 cells separating maternal and fetal blood. It is highly permeable and efficient at passing  
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37 418 certain nutrients to the fetus, in particular free fatty acids which are important in building  
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39 419 the large human brain, and glucose which provides fuel for fetal energy metabolism (Rurak  
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41 420 2001). This high permeability potentially makes the fetus very sensitive to variability in  
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43 421 maternal metabolism, but in healthy mothers, homeostatic mechanisms buffer the fetus  
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45 422 from short-term metabolic fluctuations, so that the fetus is exposed to more stable  
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47 423 metabolic signals, such as maternal lean mass (Mongelli 1996; Kulkarni et al., 2006).  
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49 424 Although mothers typically gain weight during pregnancy, this energy is primarily stored for  
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51 425 lactation, and has modest effect on fetal growth unless the mother has impaired fuel  
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53 426 homeostasis. Other components of maternal metabolism that may impact fetal growth  
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3 427 include physical activity level (Tafari et al., 1970), the presence of infections such as malaria  
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5 428 (Guyatt and Snow 2004), and micronutrient status. For example, in rural India, low maternal  
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8 429 intake of vitamin B12 in the first trimester was associated with adiposity and insulin  
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10 430 resistance in the offspring at 6 years (Yajnik et al., 2008).

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14 432 Beyond the effects of current maternal nutritional status, the offspring is also sensitive to  
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17 433 ecological stresses that impacted its mothers when she herself was developing. Studies from  
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19 434 Mexico and India show that the offspring of shorter or lighter mothers tend to replicate  
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21 435 these traits (Varela-Silva et al., 2009; Yajnik 2009). These associations may span multiple  
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23 436 generations: in an African-American community from Illinois, grand-maternal exposure to  
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25 437 poverty was associated with an increased risk of their daughters producing low birth weight  
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27 438 grandchildren (Collins et al., 2009).

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33 440 Although short-term nutritional supplementation of mothers has relatively modest effects  
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35 441 on birth weight of the offspring (Ceesay et al., 1997), sustained nutritional supplementation  
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37 442 initiated before pregnancy begins has been associated with more favourable growth in the  
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39 443 offspring, including lower risk of stunting (Martorell, 1995). Thus, increasing maternal capital  
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41 444 can be very beneficial for the offspring.  
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47 446 Inter-generational effects are not limited to undernourished mothers, and are also evident  
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49 447 in those who are overweight. Maternal obesity has been consistently associated with high  
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51 448 risk of adverse metabolic traits in the offspring, including high birth weight, childhood  
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53 449 obesity and components of the metabolic syndrome (Boney et al., 2005; Phillips et al., 2005).

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56 450 A study found that each 5-year increase in maternal age increased the risk of obesity in the  
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3 451 offspring by 14%, most likely because older mothers were fatter (Patterson et al., 1997).  
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5 452 Following bariatric surgery to reduce body fat, mothers have a lower risk of delivering large  
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7 453 infants, and offspring born after maternal surgery have lower adiposity, insulin resistance  
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9 454 and blood pressure than their siblings born before the surgery (Roos et al., 2013; Guenard et  
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11 455 al., 2013).  
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14 456  
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17 457 Significantly, the development of obesity in one generation may be more likely if under-  
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19 458 nutrition occurred in previous generations. Short maternal stature following early growth  
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21 459 retardation carries an increased risk of gestational diabetes, which shapes phenotype in the  
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23 460 offspring. The likelihood of maternal obesity predicting offspring obesity in a Swedish cohort  
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25 461 was increased three-fold if the mother was herself born small (Cnattingius et al., 2012). As  
26  
27 462 the metabolic syndrome becomes more prevalent in populations, it manifests as yet another  
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29 463 pathway whereby maternal metabolism can impact the offspring (Wells 2007). Maternal  
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31 464 diabetes is associated with larger neonates, through the excessive transfer of glucose.  
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33 465 However, this 'overexposure' to fuel does not promote healthy growth in the offspring,  
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35 466 rather it alters the structure and function of the pancreas, leading to perturbed insulin  
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37 467 metabolism and excess adiposity (Garcia Carrapato 2003). The breast-milk of diabetic  
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39 468 mothers also promotes rapid weight gain in the offspring, due to excess milk glucose and  
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41 469 insulin content (Plagemann et al., 2002).  
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50 471 These data indicate the mother's capacity for homeostasis may be considered a crucial  
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52 472 component of maternal capital, helping understand the inter-generational basis of health  
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54 473 variability. The chronically-undernourished mother and the obese diabetic mother both have  
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56 474 in common impaired maternal capital, reducing the quality of growth in the offspring. This  
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3 475 may help explain why markers of both maternal under-nutrition and maternal obesity have  
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5 476 been associated with elevated obesity risk in the offspring (Yajnik et al., 2008; Cnattingius et  
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7 477 al., 2012; Patel et al., 2015).  
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12 479 What we consider maternal phenotype also includes her gut biota. Even *in utero*, the fetus  
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14 480 experiences exposure to the maternal microbial community. A further major inoculation  
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16 481 occurs through vaginal delivery, which has long-term effects on the offspring's metabolism  
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18 482 (Rautava et al., 2012). Beyond such direct effects, the maternal biota are integral to  
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20 483 maternal metabolism, and hence indirectly affect the nutrient supply to the fetus. For  
21  
22 484 example, giving a probiotic supplement during pregnancy may reduce both the risk of  
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24 485 gestational diabetes in the mother, and the risk of high birth weight and obesity in her  
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26 486 offspring (Luoto et al., 2010a, b).  
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33 488 Thus fetal nutrition derives from the composite metabolic milieu of the mother, integrating  
34  
35 489 multiple ecological exposures. Some of these are immediate, some reflect a modest time lag  
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37 490 and others occurred in previous generations (**Figure 4**). Finally, we must not forget that  
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39 491 fathers also impact the phenotype of their offspring through similar pathways. Paternal diet  
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41 492 may transmit epigenetic effects through imprinting of the sperm, as has been shown in  
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43 493 observational studies of humans, and experimentally in rats (Pembrey, 2010; Pembrey et al.,  
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45 494 2006; Ng et al., 2010).  
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52 496 **Adaptation to maternal capital**  
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3 498 Barker and colleagues produced novel evidence that factors constraining maternal  
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5 499 investment during pregnancy impaired the long-term health of their offspring. For example,  
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8 500 mothers with flattened bony pelvis produced babies whose birth weight and placental  
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10 501 weight were reduced relative to their head circumference. These traits predicted an  
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12 502 increased risk of stroke in old age (Martyn et al., 1996). In terms of the maternal capital  
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14 503 model, this can be interpreted as mothers who experienced nutritional constraint in their  
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16 504 own development having reduced capacity to transfer nutritional resources to their  
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18 505 offspring during pregnancy. In turn, the altered body proportions of the offspring can be  
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20 506 interpreted as an unhealthy fetal growth profile, broadly consistent with the thrifty  
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22 507 phenotype hypothesis (Hales and Barker, 1992) in showing preservation of head growth at  
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24 508 the expense of somatic tissue growth.  
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31 510 More recent work has demonstrated how low levels of maternal capital impact not only  
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33 511 somatic growth itself, but also the entire developmental schedule of the offspring. In South  
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35 512 Asian women born in the UK, low birth weight (a proxy for lower maternal investment) was  
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37 513 associated with a suite of traits in the daughters, including short adult height, earlier  
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39 514 menarche, higher body fatness, and higher blood pressure (Figure 5) (Wells et al., 2016b).  
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41 515 These data indicate that female offspring receiving lower maternal investment adopt a  
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43 516 faster life history strategy, prioritising reproduction at the expense of maintenance and  
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45 517 growth. To the extent that these offspring are responding adaptively to cues early in their  
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47 518 life, they appear to be tailoring their reproductive scheduling to the magnitude of maternal  
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49 519 investment, rather than directly to the external environment.  
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3 521 How could it be adaptive to tailor life history strategy to a constraint in early life? Consistent  
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5 522 with life history theory (Hill 1993) and the disposable soma theory (Kirkwood and Rose  
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7 523 1991), **developing** a lower metabolic capacity **in early life** predicts more rapid failure of  
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9 524 homeostasis **in adulthood and thus shorter lifespan, which** increases the value of shunting  
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11 525 energy **towards earlier** reproduction (Wells 2016). This helps understand why compensatory  
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13 526 catch-up growth is associated not only with earlier puberty and elevated adiposity on girls  
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15 527 (Ong et al., 2009) but also in animal models with telomere attrition (Metcalf and Mongahan  
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17 528 et al., 2001).

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### 23 24 530 **Revisiting heritability**

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29 532 Up until now, I have focused primarily on plasticity in growth. Yet variability in adult size has  
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31 533 long been assumed primarily to reflect genetic influences. Twin studies routinely indicate  
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33 534 that the majority of variability in adult stature can be attributed to genotype, though family  
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35 535 studies indicate lower coefficients of heritability (Wells and Stock 2010). Genome-wide  
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37 536 association studies have now associated hundreds genes with height variability, and  
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39 537 although early such studies could account for only a small minority of the total variability in  
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41 538 stature, more recent studies account for a much greater percentage (Wood et al., 2014).

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47 540 To understand how growth can be simultaneously highly sensitive to ecological factors and  
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49 541 yet also powerfully influenced by genetic factors, it is valuable to focus on how heritability of  
50  
51 542 growth rates changes profoundly through the life course. **Figure 6** illustrates the heritability  
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53 543 of height and weight from mid pregnancy through to 40 months after birth, **based on twin**  
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55 544 **studies. (Note that estimates of genetic heritability from twin studies generally assume that**

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3 545 dizygotic and monozygotic twins are characterised by similar degrees of shared environment  
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5 546 within families, an assumption that is not strictly true at this stage of development: whereas  
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7 547 dizygotic twins have two different placentas, monozygotic twins typically share a single  
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9 548 placenta, and hence have greater environmental similarity. However, this scenario is unlikely  
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11 549 to explain the substantial changes in heritability estimated to occur through late gestation  
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13 550 or early infancy). Remarkably, heritability is relatively high in mid pregnancy, but drops to  
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15 551 barely 20% around the time of birth, before increasing again to around 60% by two years of  
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17 552 age, increasing more slowly subsequently. This pattern of variability gives a strong indication  
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19 553 that the influences of genes on growth are systematically relaxed around the time of birth,  
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21 554 likely to relate to the challenge of delivery through the maternal pelvis (Wells 2015). In turn,  
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23 555 we recognise this as the primary period of growth plasticity.  
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31 557 Disentangling the contributions of genotype and plasticity to height variability was of  
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33 558 interest to Eveleth and Tanner (1976), and they highlighted the value of studying 'mixed  
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35 559 ethnic' individuals in this context, showing for example that during adolescence, individuals  
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37 560 of mixed Japanese-European ancestry had heights intermediate between those of  
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39 561 homogenous parental ethnicity. This study design has recently been applied to birth weight.  
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45 563 Based on analysis of individuals born in the UK, those with two Indian parents were found to  
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47 564 have birth weights on average ~350 g lower than those with two European parents.

48 565 Depending on the ethnicity of the father, Indian mothers were found to produce babies  
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50 566 ~150 to ~250 g lighter than the offspring of European mothers. This clearly indicates that  
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52 567 lower maternal capital contributes to the lower birth weight of the Indian baby, but without  
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54 568 differentiating ecological versus genetic influences. Compared to two Indian parents, the  
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3 569 combination of an Indian mother and a European father produced a baby on average ~250 g  
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5 570 heavier, suggesting that the lower investment of Indian mothers is not 'fixed', but can rather  
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7 571 be modified by paternal influence. Compared to two European parents, the combination of a  
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10 572 European mother and an Indian father produced a baby on average ~100 g lighter (Wells et  
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12 573 al., 2013). This suggests that although European mothers are capable of producing large  
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14 574 babies, Indian fathers contribute 'lower growth potential' to their offspring, though this  
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16 575 could occur either through genetic factors, or through epigenetic effects.  
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22 577 As yet this question has not been answered, but given the long-term decline in Indian  
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24 578 stature over the last 10,000 years (Wells 2010), genetic differences between these  
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26 579 populations are at least plausible. If long-term falls in maternal height occurred through  
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28 580 natural selection, and if this decline impacted the dimensions of the pelvis as well (Wells  
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30 581 2015), selection could have favoured alleles constraining birth weight likewise.  
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### 35 36 583 **Growth as an index of social conditions**

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40 585 This review strongly supports the pioneering argument of Eveleth and Tanner that human  
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42 586 growth fundamentally reflects living conditions, with major implications for health. What has  
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44 587 become clearer over the last four decades however is the complex intergenerational nature  
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46 588 of this association. The capacity-load model may help understand its life-course aetiology.  
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48 589 Many studies have shown inverse associations between levels of deprivation and birth  
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50 590 weight or weight gain during infancy (Victora et al., 1987; Wilcox et al., 1995). Recent studies  
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52 591 have shown striking dose response associations of childhood obesity with the level of  
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54 592 deprivation (**Figure 7**). The composite effect is that metabolic capacity declines in association  
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3 593 with worsening deprivation even as metabolic load increases, so that those from the poorest  
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5 594 backgrounds have the highest ratio of load to capacity. This represents a fast track to chronic  
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8 595 disease in adulthood.

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12 597 Nutrition and growth play a crucial mediating role in the impact of the structure of society  
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15 598 on health. This is no mere coincidence, for I have argued elsewhere that nutrition is the  
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17 599 primary arena in which societal power relations are expressed. Social hierarchies emerge  
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20 600 from differential control over nutrition in its broadest sense: the availability of food, the  
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22 601 kinds of activity people undertake, and the level of agency that characterises their lifestyle  
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24 602 (Wells 2016). We should not be surprised therefore that the more hierarchical a society, the  
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26  
27 603 stronger the social gradient in growth and height.

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30  
31 605 **Acknowledgements**

32  
33 606 I very much appreciate the invitation of Robin Miriam Bernstein and Darna Dufour to  
34  
35  
36 607 participate in the Human Biology Symposium 'Worldwide variation in human growth: 40  
37  
38 608 years later'. I declare no conflict of interest.

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3 609 **Legends for illustrations**  
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8 611 **Figure 1.** Hattori charts illustrating **average** age-associated changes in body composition  
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10 612 adjusted for height in (a) infancy and (b) childhood, based on data from the reference child  
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12 613 of Fomon et al., 1982. **Sequential data points are as follows: (a) monthly from birth to 6**  
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14 614 **months, and then at 9 and 12 months; (b) 1 years, 1.5 years, and then yearly from 2 to 10**  
15  
16 615 **years. Movement across the graph over time indicates whether changes in body mass index**  
17  
18 616 **are due to differences in fat-free mass (FFM), fat mass (FM) or both.** Reproduced with  
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20 617 permission from Wells (2000).  
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26 619 **Figure 2.** Associations between body length and mass of the kidney, liver and brain, based  
27  
28 620 on autopsy data from children between birth and 12 years. Data from Coppoletta and  
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30 621 Wolbach 1932, reproduced with permission from Wells (2016).  
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35 623 **Figure 3.** Interactive associations of birth weight (indexing metabolic capacity) and  
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37 624 components of an unhealthy adult lifestyle (indexing metabolic load) in relation to the  
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39 625 prospective risk of developing diabetes in three US cohorts. Data from Li et al., 2015b.  
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45 627 **Figure 4.** Schematic diagram summarizing the multiple nutritional influences acting on the  
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47 628 developmental origins of chronic diseases. Reproduced with permission from Wells (2016).  
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51 630 **Figure 5.** Associations between maternal investment (proxied by birth size) and offspring  
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53 631 phenotype in South Asian women in the UK. (a) Birth weight is positively associated with age  
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55 632 at menarche. (b) Earlier menarche is associated with lower adult stature. (c) Earlier  
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3 633 menarche is associated with higher adult subscapular skinfold. (d) Subscapular skinfold is  
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5 634 positively associated with adult systolic blood pressure. Reproduced with permission from  
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8 635 Wells et al., 2016b.

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12 637 **Figure 6.** Figure 4. Estimates of heritability in weight and length/height in The Netherlands  
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15 638 Twin Register study, with data from another study of late pregnancy added. Data from  
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17 639 Mook-Kanamori et al., 2012 and Gielen et al., 2008. Reproduced with permission from Wells  
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24 642 **Figure 7.** Association between obesity prevalence and level of deprivation (categorized in  
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26 643 deciles) in UK children in reception class or Year 6. Data from UK National Obesity  
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28 644 Observatory. Reproduced with permission from Wells (2016).

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3 646 **Table 1. Key questions concerning critical windows of plasticity and human growth**  
4 647 **outcomes relevant to health**  
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Issue	Research question
Responsiveness	What phenotypic trait is affected?
Environmental agent	What stress or stimuli impacts the trait?
Timing	When do critical windows of sensitivity open and close?
Reversibility	How immutable are the environmental effects
Mechanism	What is the mechanism through which phenotype responds?

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For Peer Review

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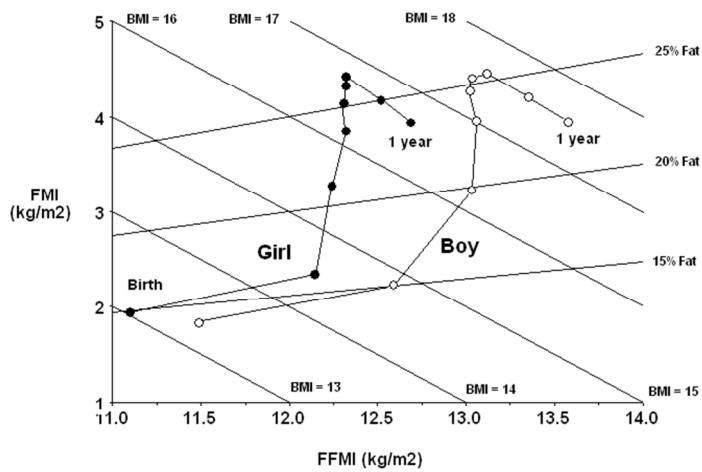


Fig 1a

254x190mm (96 x 96 DPI)

review

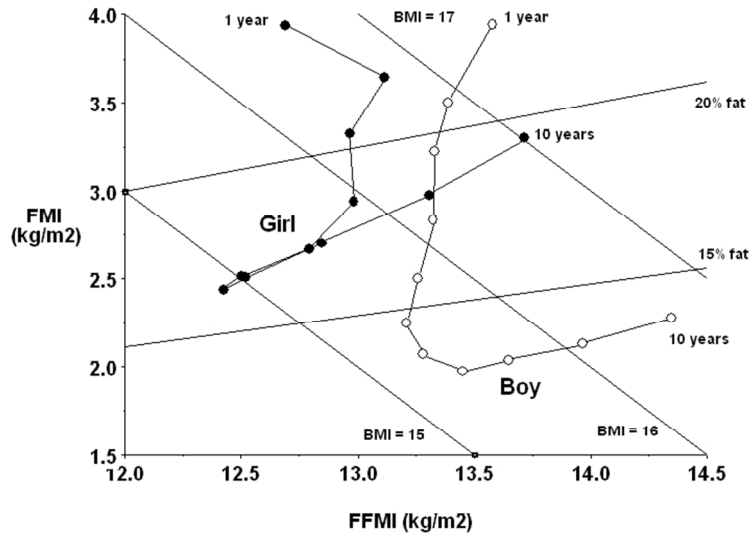


Fig 1b

254x190mm (96 x 96 DPI)

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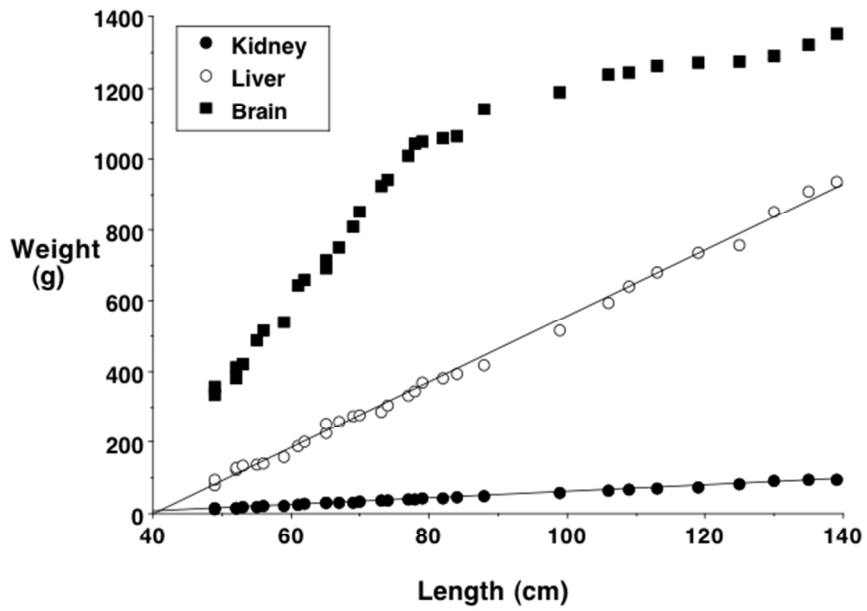


Fig 2

254x190mm (72 x 72 DPI)

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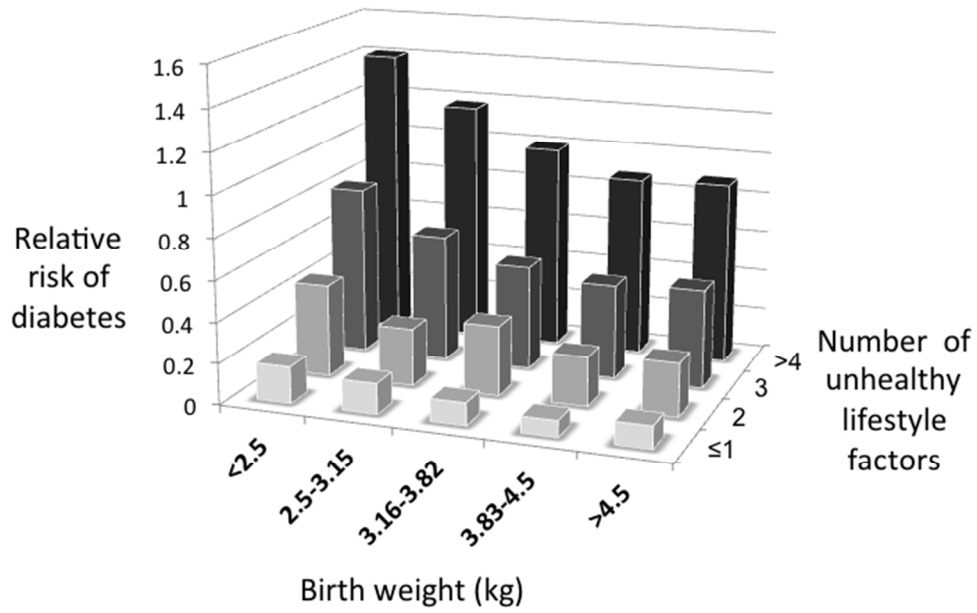


Fig 3

254x190mm (72 x 72 DPI)

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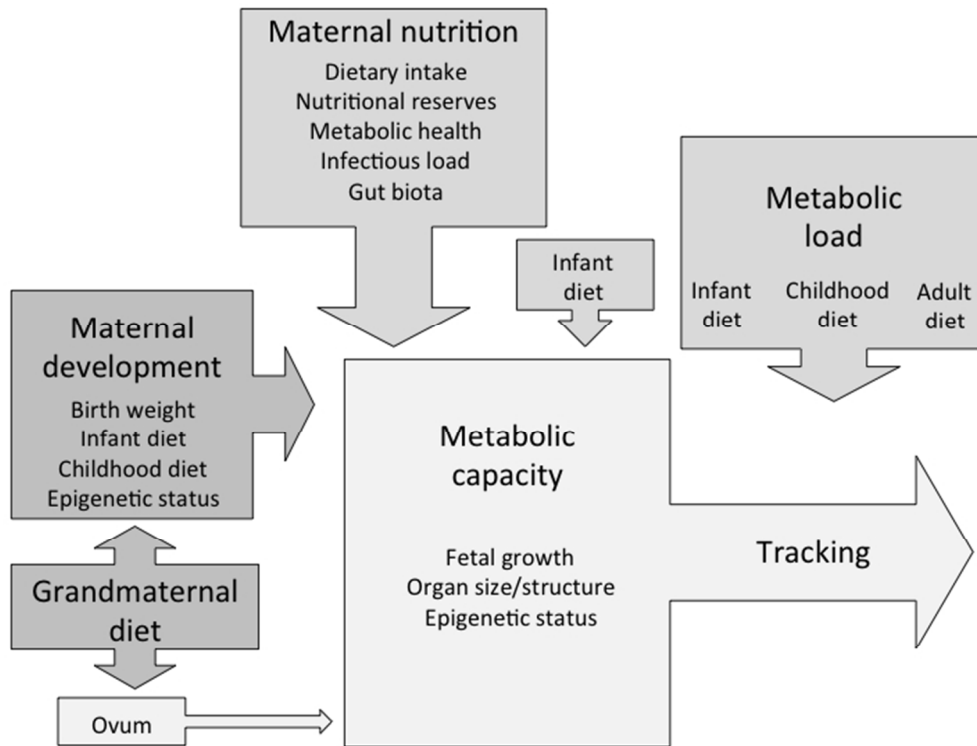


Fig 4

254x190mm (72 x 72 DPI)

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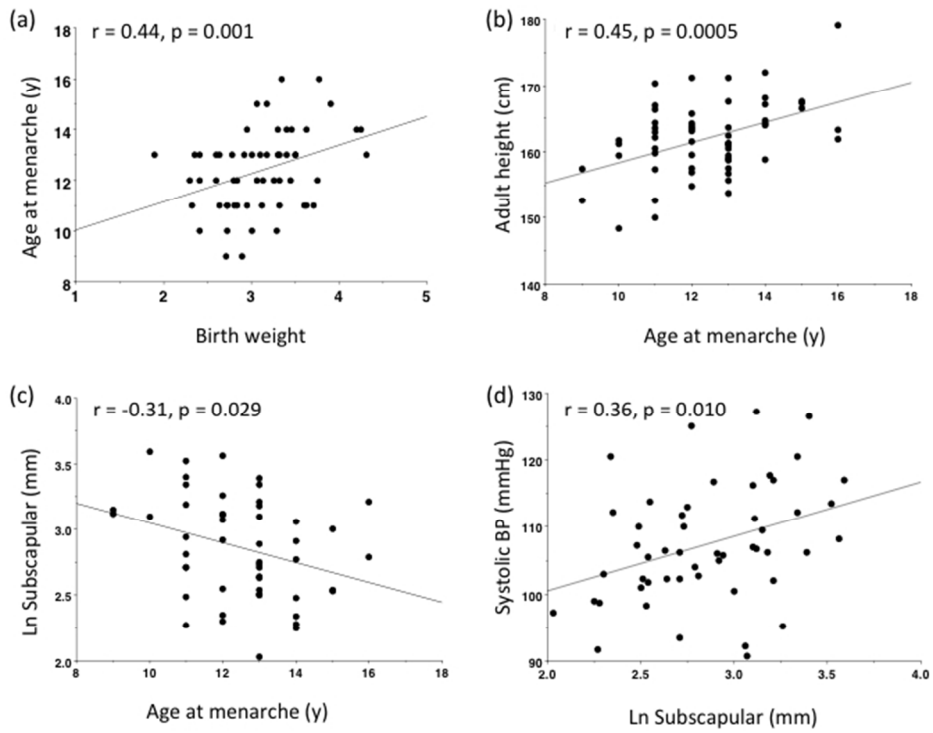


Fig 5

254x190mm (72 x 72 DPI)

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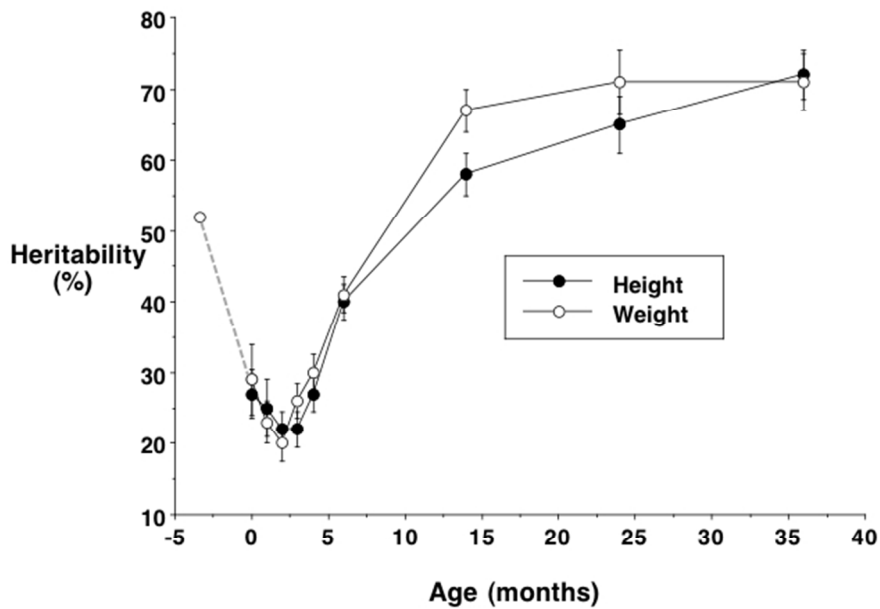


Fig 6

254x190mm (72 x 72 DPI)

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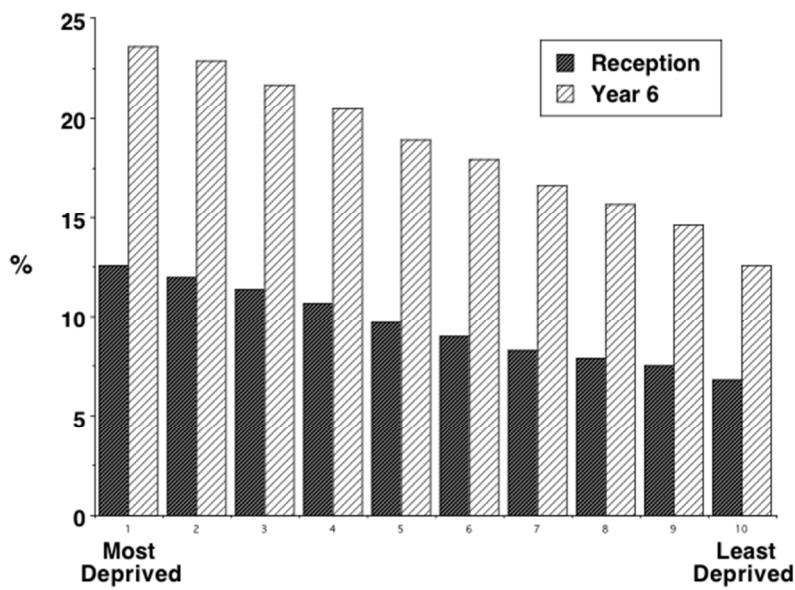


Fig 7

254x190mm (72 x 72 DPI)

review