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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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Abstract

In their seminal book 'Worldwide variation in human growth', published in 1976, Eveleth and Tanner highlighted substantial variability within and between populations in the magnitude and schedule of human growth. In the four decades since then, research has clarified why growth variability is so closely associated with human health. First, growth patterns are strongly associated with body composition, both in the short- and long-term. Poor growth in early life constrains the acquisition of lean tissue, while compensatory 'catch-up' growth may elevate body fatness. Second, these data are examples of the fundamental link between growth and developmental plasticity. Growth is highly sensitive to ecological stresses and stimuli during early 'critical windows', but loses much of this sensitivity as it undergoes canalisation during early childhood. Crucially, the primary source of stimuli during early 'critical windows' is not the external environment itself, but rather maternal phenotype, which transduces the impact of ecological conditions. Maternal phenotype, representing many dimensions of 'capital', thus generates a powerful impact on the developmental trajectory of the offspring. There is increasing evidence that low levels of maternal capital impact the offspring's size at birth, schedule of maturation, and body composition and physiological function in adulthood. While evidence has accrued of substantial heritability in adult height, it is clear that the pathway through which it is attained has major implications for metabolic phenotype. Integrating these perspectives is important for understanding how developmental plasticity may on the one hand contribute to adaptation, while on the other shape susceptibility to non-communicable disease.

Key words: growth, body composition, developmental plasticity, inter-generational effects

Introduction

At the start of their seminal work '*Worldwide variation in human growth*', Eveleth and Tanner (1976) made two statements that are simultaneously complementary and yet seemingly antagonistic. The very first sentence of the book stated:

> *A child's growth rate reflects, better than any other single index, his state of health and nutrition; and often indeed his psychological situation also*.

On this basis, they argued, growth studies could be used to monitor the health of populations, or to identify subgroups particularly deserving of economic and social benefits. Elsewhere, Tanner developed the theme that growth monitoring provides unique insight into a population's living conditions. Many are familiar with his comment:

> *If you want to measure the classlessness of a society, and you are not interested in rhetoric but in actual conditions and facts, then looking at the growth of children … is perhaps the best way* (Tanner 1990).

This approach duly inspired a new discipline of 'anthropometric history' (Komlos 1991; 1994) - the analysis of variability in adult stature to provide an indication of environmental conditions in earlier life. This approach can broadly overcome the limitations of conventional indices of living standards such as wages or gross domestic product, which cannot take into account variability in mediating variables such as the price of food, or the differential agency of individuals to obtain resources. Variability in adult stature cannot index in detail the

underlying environmental causes impacting early growth, but the broader approach remains very valuable.

However, the second paragraph of '*Worldwide variation in human growth*' added a crucial cautionary note:

> *There is no guarantee, however, that all populations have the same growth potential* (Eveleth and Tanner 1976)

Several chapters of the book explored how ecological factors such as temperature or altitude are associated with growth patterns, and discussed genetic adaptation in this context. Here then is a key dilemma. How can we disentangle 'beneficial' variability in growth that could plausibly reflect adaptation to local ecological conditions from 'detrimental' variability in growth emerging from societal inequality, or from exposure to pathogens, parasites, pollution or malnutrition?

The book summarized with unprecedented detail the extraordinary diversity in size and shape that characterizes humans through the life course, much of it apparent across broader geographical regions. Tables and figures systematically demonstrated substantial between-population variability in growth outcomes, such as weight, height, body girths and skinfold thicknesses. Within-population studies further highlighted associations with environmental factors, yet the substantial heritability of growth traits was also described.

Eveleth and Tanner were very aware that adaptation could incorporate both developmental and genetic components. In their chapter focusing on variability associated with altitude and temperature, they observed:

> *The responses made by the human organism are physiological ones, but the limitations in making these responses are determined by the genotype. The analysis of growth physique encompasses both aspects of adaptability and may be seen both as the development of adaptive mechanisms and as the end product of growing up in a climatic extreme* (Eveleth and Tanner 1976).

Forty years later, what more have we learned about this profound variability in human growth, and in particular, what does it *mean* in relation to human health? On the one hand, growth variability is now accorded a central role in the 'developmental origins of adult disease' hypothesis (Hales and Barker 1992). Indeed, while much reference is made to under-nutrition as the key stress during development that predisposes to chronic disease in later life, much of the data pertains to growth – either birth weight as an index of fetal development, or post-natal gains in weight or length as an indication of growth faltering or compensatory catch-up (Barker et al., 1989; Hales et al., 1991; Eriksson et al., 1999). At the same time, studies repeatedly emphasise that components of size and shape are highly heritable, with some twin studies attributing as much as 80-90% of variability in adult stature to genetic factors (Silventoinen et al., 2003; Perola et al., 2007).

We are more aware than ever, therefore, that the study of growth carries vital messages about short- and long-term health variability. But it is also clear that growth itself is only a

marker for diverse other traits that are more direct determinants of health. 'Adding' a few centimetres of height to an individual cannot directly alter their risk of diabetes or heart disease, rather it must index underlying effects of developmental experience on the structure and function of cells and organs.

The last decade has seen another seminal publication, the World Health Organisation growth reference (Bhandari et al., 2002). This study, based on well-off individuals from six different populations, highlighted substantial consistency in early patterns of linear growth, giving a strong message that in good ecological conditions, humans grow relatively similarly in early life. More recent work has extended this approach to fetal life (Papageorghiou et al., 2014). It remains unclear, however, how relevant this scenario is to variability in adult size, or indeed to other somatic traits such as body shape, physique and body composition. A recent comprehensive survey of 200 countries reported substantial variability (20 cm between tallest and shortest countries) in adult height, and much of this variability has persisted despite secular trends in recent centuries (NCD Risk Factor Collaboration (NCD-RisC 2016).

The aim of this review is consider growth in more detail, in order to emphasise four issues relevant to the association between growth variability and health. First, I will summarise how growth patterns during different stages of development are associated with body composition. Second, I will suggest how these associations contribute to the 'developmental origins' of health and disease through the medium of developmental plasticity. Third, I will argue that growth is best considered a multi-generational phenomenon, bearing a strong

imprint of parental phenotype. Finally, I will reconsider the evidence that population variability in early growth may incorporate genetic effects.

Growth and body composition

Shortly after the publication of '*Worldwide variation in human growth*', another landmark article emerged - the 'reference child' of Fomon and colleagues (1982). This paper highlighted for the first time substantial aged-associated variability in pediatric body composition. Six months after birth, infants were typically over 25% fat, in contrast with around 14% at birth. Yet by mid childhood, the reference boy was barely 12% fat, and the girl around 17%. These data indicate that infants become adipose only temporarily, suggesting unique functions of body fat stores during early life. The same data indicated a steady acquisition of lean mass from birth onwards, though not consistently in proportion with height. In other words, the developmental profile of human body composition is quite complex, and like growth patterns, it too might very substantially between populations.

Since children grow at variable rates, it is ideal to adjust for this when assessing body composition. Fomon's data can be re-plotted as fat mass index (fat mass/height^2) against lean mass index (lean mass/height^2), which effectively splits body mass index into its two principal components (Hattori et al., 1997; Van Itallie et al., 1990; Wells 2001). This approach highlights the changes in body composition that occur with age, as well as sex differences (**Figure 1**). That both growth and body composition are sensitive to ecological influences in early life is clearly demonstrated through studies of infant feeding mode (Dewey et al., 1993; Butte et al., 2000).

Subsequent comparisons across ethnic groups have consistently shown population differences. For example, Ethiopian infants have less body fat than European infants at birth (Andersen et al., 2011), while at birth and in early infancy, South Asian infants in the UK have less lean mass but similar body fat compared to white European infants (Yajnik et al., 2003; Stanfield et al., 2012). During childhood, South Asian children continue to have lower lean mass index compared to European children, whereas Afro-Caribbean and black African children tend to have higher levels of lean mass index than European children, and similar body fat (Nightingale et al., 2011; Lee et al., 2015; D'Angelo et al., 2015). Though current living conditions undoubtedly contribute to such differences, their large magnitude also suggests potential genetic responses to ancestral ecological conditions.

Beyond body composition variability *per se*, it is now also clear that early growth variability has implications for body composition at later ages. Data from numerous studies are relatively consistent in showing an association between birth weight and later lean mass (Wells et al., 2007). Associations between birth weight and later adiposity in contrast are inconsistent across studies: in many populations, no such association is apparent, but in a few populations low birth weight predicts subsequent central adiposity whereas in others, a heavier birth weight also predicts greater adiposity in later life (Wells et al., 2007). This heterogeneity is most likely due to differences between populations in the rate of infant growth, for example some populations with low average birth weight may have undergone catch-up growth. In two large studies, birth weight was associated with later adiposity in females but not males (Sachdev et al., 2005; Rogers et al., 2006), suggesting contrasting life history strategies between the sexes. Broadly, these data indicate that fetal life is a key

period in the developmental trajectory of lean tissue mass, and this is consistent with similar associations between birth weight and later height.

The scenario for infancy is rather more complex. In high-income industrialised populations, a number of studies have demonstrated an association between rapid infant weight gain and later adiposity, or risk of obesity (Stettler et al., 2002; 2005; Ekelund et al., 2006; Chomtho et al., 2008). This in turn has identified infancy as a potential critical period in the developmental origins of obesity. However, data from low- and middle-income countries contrast markedly with these findings. In a number of studies, from both South American populations and India, faster weight gain during infancy has been associated with later lean mass, but not with later fat mass (Li et al., 2003; Sachdev et al., 2005; Wells et al., 2005; 2012; Kuzawa et al., 2012). However, whether interventions in early life invariably promote lean mass rather than fat accretion remains unclear (Rivera et al., 1995; Kulkarni et al., 2014). This may be because the optimal intervention may require the mediating influence of maternal nutrition, as discussed below.

The reasons underlying this population-contrast remain poorly understood. One possibility is that there are genetic differences between populations that directly affect the composition of tissue accretion, but this explanation is perhaps unlikely given that some of the studies from lower and middle-income countries derive from Brazil, where a substantial proportion of the population are of European origin. An alternative is that infants larger at birth and closer to their 'growth potential; have lower capacity to gain additional lean mass, and must therefore gain more fat. A more intriguing possibility is that populations differ in the duration of critical windows, during which nutrition regulates infant growth (Wells 2014).

Earlier closure of critical windows might direct energy intake to fat accretion rather than lean tissue. Possible underlying mechanisms may include hormonal factors in breast milk, differences in exposure to environmental agents such as pathogens, or genetic variability in the physiological mechanisms that regulate critical windows. Supporting evidence for these hypotheses is currently lacking and given the need to tackle both under-nutrition and obesity through public health efforts, this represents an important topic for further research.

Developmental plasticity

The complex associations between early growth patterns and later body composition highlight the mediating role of developmental plasticity. Indeed, it was classic animal studies of growth that first revealed the long-term impact of early-life nutrition on size and metabolic phenotype. If a rat were malnourished directly after birth, it would never fully recover the deficit in body size. If the insult was delayed until 9 weeks after birth, however, growth would only slow temporarily, and as soon as adequate supplies of food were restored, the rat would gain weight rapidly and regain the growth trajectory it had displayed prior to the insult (McCance and Widdowson 1956; McCance 1962). This implicated early infancy as a 'critical period' in the development of adult size and metabolism.

Critical windows of sensitivity in growth close in due course, after which growth becomes canalized, or 'self-correcting' under the genetic influence of growth hormone. The tendency of traits to remain relatively stable following periods of plasticity is often termed 'tracking'. This does not mean that growth is entirely immune from subsequent environmental effects.

Rather, the magnitude of tracking is best described on a continuous scale, for example the tendency of height to track after infancy is relatively high, whereas that of weight is lower.

The concepts of critical windows, plasticity and tracking allow a number of specific questions to be raised (**Table 1**), in terms of phenotypic targets, mechanisms, timing and reversibility (Wells 2016). The primary period of plasticity in humans comprises fetal life and infancy, though which of these periods is most sensitive depends on the trait. Recently, attention has been directed to adolescence as another sensitive period, particularly for reproductive physiology and behaviour (Prentice et al., 2013). Overall, the life-course profile of human plasticity remains poorly understood, because scientists have generally been quick to notice its implications, but slower to define its characteristics in detail.

The importance of developmental plasticity for human health rapidly became clear, in particular through the pioneering epidemiological studies of Barker and colleagues (Barker et al., 1989; 2005; Hales et al., 1991). Following up cohorts of individuals born in the first half of the 20th century, it was repeatedly found that low birth weight and poor weight gain during infancy were associated with the risk of chronic diseases in late adulthood, including ischaemic heart disease, type 2 diabetes, hypertension and stroke (Barker et al., 1989; 2005; Eriksson et al., 1999; 2001). These findings have subsequently been extended to low and middle-income countries (Adair et al., 2013), although there is also some heterogeneity between populations in the associations between early growth patterns and later health outcomes (Wells et al., 2007; Sterling et al., 2014).

The initial interpretation of these data was that fetal malnutrition induced pathophysiological development, which in the long term elevated chronic disease risk. Initially, it seemed logical that low birth weight was implicating maternal malnutrition, either directly or through compromised function of the placenta. Hales and Barker (1992) proposed the 'thrifty phenotype' hypothesis: that in malnourished fetuses, growth of organs such as the pancreas was sacrificed in order to protect the vulnerable energy-demanding brain. This would represent a survival strategy in the short term, but at the long-term cost of a reduced capacity to tolerate high-energy diets. Individuals developing such a thrifty phenotype were thus at high risk of developing type 2 diabetes and other chronic diseases in later adult life. Eveleth and Tanner duly acknowledged this rapidly developing research area in the revised edition of their book (Eveleth and Tanner 1991).

Nevertheless, these retrospective cohort studies provided no direct information on putative malnutrition in early life. Rather, everything 'nutritional' was inferred from data on birth weight, placental weight, or the size and shape of the mother (Barker et al., 1989; 1990; 2005; Martyn et al., 1996). Moreover, the supporting data repeatedly showed that associations between birth weight or early postnatal growth and later disease risk were not restricted to those at the lower extremes, but were rather evident across the whole range of birth weight. In other words, each additional increment in birth weight lowered the risk of chronic disease in adult life, and this draws attention back to the process of growth itself.

The capacity-load model

Building on the 'thrifty phenotype' hypothesis, I have developed a simpler model of developmental plasticity and long-term health, focusing on two generic traits, one that promotes homeostasis and one that impedes it (Wells, 2011; 2016). This approach places less emphasis on the extremes of nutritional status, such as low birth weight or adult obesity. Instead, I assume that the relevant traits are each characterised by a continuous distribution. Specifically, I assume that in early life, the fetus and infant gain 'metabolic capacity', a generic term for physiological traits that enhance the potential to maintain homeostasis. From late fetal life onwards, I assume that individuals can accumulate 'metabolic load', a generic term for traits that challenge the capacity for homeostasis. The risk of chronic disease in adult life is then predicted to scale inversely with capacity, and positively with load (Wells 2011). Of particular importance, metabolic capacity and load are closely associated with different stages of development and different components of growth.

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

Not all stresses that shape metabolic capacity necessarily act through fetal weight gain, as proxied by birth weight or infant weight gain. First, early fetal growth faltering may leave no signal in birth weight, as was apparent for offspring exposed *in utero* to maternal famine during the first trimester of pregnancy (Roseboom et al., 2001). Indeed, following such early growth faltering, neonatal adiposity may even be greater than normal, indicating that a degree of 'catch-up' has already occurred prior to birth (Hemachandra and Klebanoff 2006); but this would conceal reduced lean mass. Likewise, the high body fat content of macrosomic neonates reduces their metabolic capacity relative to their birth weight. Thus, maternal obesity may in fact constrain metabolic capacity in the offspring, despite the high levels of maternal energy stores.

Second, maternal nutritional status around the time of conception may affect fetal gene expression, independent of fetal growth (Waterland et al., 2010; Khulan et al., 2012). Third, non-nutritional factors such as maternal psychosocial stress may impact signalling systems in the brain or other organs (Entringer et al., 2009, 2011). Birth weight cannot index such effects, even though they may involve perturbations of metabolic capacity. We should not therefore assume that the developmental origins of chronic disease are explained entirely by growth patterns, or that early growth patterns have a simple relation with maternal nutrition. Nevertheless, birth weight has been repeatedly associated with adult chronic disease risk in diverse populations, and the fact that such data is increasingly widely available means that it is one of the most valuable proxies for the quality of fetal development.

As the process of growth shifts to hypertrophy, characterized by increasing in cell size, the regulatory systems change. Whereas fetal development is very sensitive to the delivery of nutrients and oxygen, post-natal growth gradually loses this sensitivity, and comes under the canalizing control of growth hormone. From this point onwards, non-brain organ growth closely follows growth in stature (**Figure 2**). The striking linearity of these relationships indicates a common regulatory system, and helps explain why metabolic capacity tracks from early life into adulthood, where height remains associated with organ masses in both sexes (de la Grandmaison et al., 2001).

Evidence from rats indicates that hyperplasic growth may extend into early infancy (Enesco and LeBlond, 1962). Markers of early post-natal nutritional experience might therefore also correlate with certain components of metabolic capacity that are still developing after birth. However, infant weight gain is a problematic way to assess the quality of post-natal growth, since it shows an inverse correlation with birth weight on account of small neonates tending to undergo 'catch-up' (Ong et al., 2000). Thus we cannot tell whether rapid infant weight gain represents continued 'good growth', or recovery from earlier 'poor growth', characterized by constrained fetal organ development. To resolve this, we need a marker of infant/childhood growth that is independent of fetal growth.

The best candidate currently appears to be relative leg length (leg length/height), for while each component of birth length is associated with birth weight, the ratio between them is not, indicating that relative leg length is primarily determined in post-natal life (Gunnell et al., 1999; Bogin and Baker, 2012; Pomeroy et al., 2014). After birth, leg length typically shows stronger associations than trunk length with environmental factors such as infant or

early childhood diet (Gunnell et al., 1998; Wadsworth et al., 2002). In turn, relatively shorter legs have been associated with poorer metabolic function in adult life, including higher blood pressure and blood lipids, insulin resistance, thickened carotid arteries, and greater risk of coronary disease and diabetes (Asao et al., 2006; Gunnell et al., 2003; Tilling et al., 2006; Fraser et al., 2008; Lawlor et al., 2002a). Collectively, these findings indicate that components of metabolic capacity may continue to be compromised after birth under adverse conditions, in association with poorer leg growth.

As in fetal life, some post-natal growth traits may be protected during adverse conditions at a cost to others. This is supported by a recent study in Peru, which compared children from a high altitude rural setting, exposed to various ecological stresses, with children from a more favourable lowland urban setting. While the high altitude children were shorter, the growth deficit varied according by anatomical region. Whereas lower leg length was ~1.3 z-scores shorter, foot length was ~1 z-score shorter, and the combined length of the head and trunk, incorporating the brain and vital organs, was only ~0.7 z-scores shorter (Pomeroy et al., 2012). The thrifty phenotype thus appears to apply to body proportions as well as organs, and this supports the use of growth outcomes such as leg length as developmental markers of chronic disease risk. For example, height explained 25% of the variability in kidney length in pre-pubertal children from lowland Nepal, though in this case sitting height and leg length showed similar associations (Wells et al., 2016a).

Obesity, itself manifesting as excessive somatic growth, is a key factor challenging homeostasis in later life. One reason for this, according to autopsy studies, is that adult organ masses scale with total body weight much more weakly than with height (de la

Grandmaison et al., 2001). This means that as adults gain weight, their organs cannot keep up, and bear a relatively heavier metabolic burden. Thus, the second element of my model comprises 'metabolic load', referring to traits or behaviours that challenge the capacity for homeostasis.

This concept is clearly analogous to that of 'allostatic load' developed by McEwen and colleagues (McKewan and Stellar 1993; McEwan 1998), but contrasting with their emphasis on 'psychosocial stress' and its impact on neuroendocrine function, my focus is specifically on nutritional/metabolic exposures. Beyond central abdominal obesity, metabolic load also links closely with various 'adult lifestyle' risk factors for chronic diseases such as lipogenic diets, sedentary behaviour, psychosocial stress and tobacco smoking, as well as infectious disease and a variety of toxins and pollutants, all of which challenge homeostasis (Wells 2011, 2016). Metabolic load develops primarily during the period of hypertrophic growth, though elevated adiposity in newborns of obese mothers (Sewell et al., 2006) suggests that load may rise even during fetal life. At the cellular level, metabolic load may cause insulin resistance, oxidative stress and telomere attrition (Wells 2016), and this helps understand why catch-up growth is associated not only with adult size and body composition, but also longevity (Metcalfe and Monaghan 2001).

Consistent with the capacity-load model, interactive effects of birth weight and current weight have now been described for a variety of traits (Wells 2011). The greatest chronic disease risk is predicted in those who have diminished capacity and elevated load. For example, a study of Swedish men showed that the blood pressure 'penalty' associated with low birth weight was minimal in those of small adult size, but large in those who were both

tall and heavy (Leon et al., 1996). In other words, the penalty for diminished capacity was greatest in those with elevated load, while the penalty for high load was greatest in those with diminished capacity. Moreover, recent data from three US cohorts demonstrate continuous interactive associations of birth weight and unhealthy adult lifestyle with the risk of diabetes and hypertension (Li et al., 2015a,b), exactly as the capacity-load model predicts (**Figure 3**).

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

Intergenerational effects

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

The fact that growth represents an inter-generational process makes it challenging to understand how developmental plasticity can contribute to adaptation. The 'predictive adaptive response' hypothesis assumed that early-life plasticity allows metabolic adaptation directly to local ecological conditions (Gluckman and Hanson 2004). This perspective has been challenged for several reasons: first, early-life cues in long-lived species such as humans are highly likely to go 'out-of-date', making long-term adaptation implausible (Wells 2007) and second, the nature of placental nutrition and lactation is such that the primary ecological influence during early critical windows is not the external environment but maternal capital (Wells 2010). This means that early growth trajectory is profoundly imprinted by maternal phenotype, and within any given environment, mothers will vary amongst themselves in their physiological condition.

In pregnancy, the quality and quantity of blood reaching the placental interface determines the supply of nutrients (Haig 1993). The human placenta presents a relatively thin barrier of cells separating maternal and fetal blood. It is highly permeable and efficient at passing certain nutrients to the fetus, in particular free fatty acids which are important in building the large human brain, and glucose which provides fuel for fetal energy metabolism (Rurak 2001). This high permeability potentially makes the fetus very sensitive to variability in maternal metabolism, but in healthy mothers, homeostatic mechanisms buffer the fetus from short-term metabolic fluctuations, so that the fetus is exposed to more stable metabolic signals, such as maternal lean mass (Mongelli 1996; Kulkarni et al., 2006). Although mothers typically gain weight during pregnancy, this energy is primarily stored for lactation, and has modest effect on fetal growth unless the mother has impaired fuel homeostasis. Other components of maternal metabolism that may impact fetal growth

include physical activity level (Tafari et al., 1970), the presence of infections such as malaria (Guyatt and Snow 2004), and micronutrient status. For example, in rural India, low maternal intake of vitamin B12 in the first trimester was associated with adiposity and insulin resistance in the offspring at 6 years (Yajnik et al., 2008).

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

Although short-term nutritional supplementation of mothers has relatively modest effects on birth weight of the offspring (Ceesay et al., 1997), sustained nutritional supplementation initiated before pregnancy begins has been associated with more favourable growth in the offspring, including lower risk of stunting (Martorell, 1995). Thus, increasing maternal capital can be very beneficial for the offspring.

Inter-generational effects are not limited to undernourished mothers, and are also evident in those who are overweight. Maternal obesity has been consistently associated with high risk of adverse metabolic traits in the offspring, including high birth weight, childhood obesity and components of the metabolic syndrome (Boney et al., 2005; Phillips et al., 2005). A study found that each 5-year increase in maternal age increased the risk of obesity in the

offspring by 14%, most likely because older mothers were fatter (Patterson et al., 1997). Following bariatric surgery to reduce body fat, mothers have a lower risk of delivering large infants, and offspring born after maternal surgery have lower adiposity, insulin resistance and blood pressure than their siblings born before the surgery (Roos et al., 2013; Guenard et al., 2013).

Significantly, the development of obesity in one generation may be more likely if under-nutrition occurred in previous generations. Short maternal stature following early growth retardation carries an increased risk of gestational diabetes, which shapes phenotype in the offspring. The likelihood of maternal obesity predicting offspring obesity in a Swedish cohort was increased three-fold if the mother was herself born small (Cnattingius et al., 2012). As the metabolic syndrome becomes more prevalent in populations, it manifests as yet another pathway whereby maternal metabolism can impact the offspring (Wells 2007). Maternal diabetes is associated with larger neonates, through the excessive transfer of glucose. However, this 'overexposure' to fuel does not promote healthy growth in the offspring, rather it alters the structure and function of the pancreas, leading to perturbed insulin metabolism and excess adiposity (Garcia Carrapato 2003). The breast-milk of diabetic mothers also promotes rapid weight gain in the offspring, due to excess milk glucose and insulin content (Plagemann et al., 2002).

These data indicate the mother's capacity for homeostasis may be considered a crucial component of maternal capital, helping understand the inter-generational basis of health variability. The chronically-undernourished mother and the obese diabetic mother both have in common impaired maternal capital, reducing the quality of growth in the offspring. This

may help explain why markers of both maternal under-nutrition and maternal obesity have been associated with elevated obesity risk in the offspring (Yajnik et al., 2008; Cnattingius et al., 2012; Patel et al., 2015).

What we consider maternal phenotype also includes her gut biota. Even *in utero*, the fetus experiences exposure to the maternal microbial community. A further major inoculation occurs through vaginal delivery, which has long-term effects on the offspring's metabolism (Rautava et al., 2012). Beyond such direct effects, the maternal biota are integral to maternal metabolism, and hence indirectly affect the nutrient supply to the fetus. For example, giving a probiotic supplement during pregnancy may reduce both the risk of gestational diabetes in the mother, and the risk of high birth weight and obesity in her offspring (Luoto et al., 2010a, b).

Thus fetal nutrition derives from the composite metabolic milieu of the mother, integrating multiple ecological exposures. Some of these are immediate, some reflect a modest time lag and others occurred in previous generations (**Figure 4**). Finally, we must not forget that fathers also impact the phenotype of their offspring through similar pathways. Paternal diet may transmit epigenetic effects through imprinting of the sperm, as has been shown in observational studies of humans, and experimentally in rats (Pembrey, 2010; Pembrey et al., 2006; Ng et al., 2010).

Adaptation to maternal capital

Barker and colleagues produced novel evidence that factors constraining maternal investment during pregnancy impaired the long-term health of their offspring. For example, mothers with flattened bony pelvis produced babies whose birth weight and placental weight were reduced relative to their head circumference. These traits predicted an increased risk of stroke in old age (Martyn et al., 1996). In terms of the maternal capital model, this can be interpreted as mothers who experienced nutritional constraint in their own development having reduced capacity to transfer nutritional resources to their offspring during pregnancy. In turn, the altered body proportions of the offspring can be interpreted as an unhealthy fetal growth profile, broadly consistent with the thrifty phenotype hypothesis (Hales and Barker, 1992) in showing preservation of head growth at the expense of somatic tissue growth.

More recent work has demonstrated how low levels of maternal capital impact not only somatic growth itself, but also the entire developmental schedule of the offspring. In South Asian women born in the UK, low birth weight (a proxy for lower maternal investment) was associated with a suite of traits in the daughters, including short adult height, earlier menarche, higher body fatness, and higher blood pressure (**Figure 5**) (Wells et al., 2016b). These data indicate that female offspring receiving lower maternal investment adopt a faster life history strategy, prioritising reproduction at the expense of maintenance and growth. To the extent that these offspring are responding adaptively to cues early in their life, they appear to be tailoring their reproductive scheduling to the magnitude of maternal investment, rather than directly to the external environment.

How could it be adaptive to tailor life history strategy to a constraint in early life? Consistent with life history theory (Hill 1993) and the disposable soma theory (Kirkwood and Rose 1991), developing a lower metabolic capacity in early life predicts more rapid failure of homeostasis in adulthood and thus shorter lifespan, which increases the value of shunting energy towards earlier reproduction (Wells 2016). This helps understand why compensatory catch-up growth is associated not only with earlier puberty and elevated adiposity on girls (Ong et al., 2009) but also in animal models with telomere attrition (Metcalfe and Mongahan et al., 2001).

Revisiting heritability

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

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

dizygotic and monozygotic twins are characterised by similar degrees of shared environment within families, an assumption that is not strictly true at this stage of development: whereas dizygotic twins have two different placentas, monozygotic twins typically share a single placenta, and hence have greater environmental similarity. However, this scenario is unlikely to explain the substantial changes in heritability estimated to occur through late gestation or early infancy). Remarkably, heritability is relatively high in mid pregnancy, but drops to barely 20% around the time of birth, before increasing again to around 60% by two years of age, increasing more slowly subsequently. This pattern of variability gives a strong indication that the influences of genes on growth are systematically relaxed around the time of birth, likely to relate to the challenge of delivery through the maternal pelvis (Wells 2015). In turn, we recognise this as the primary period of growth plasticity.

Disentangling the contributions of genotype and plasticity to height variability was of interest to Eveleth and Tanner (1976), and they highlighted the value of studying 'mixed ethnic' individuals in this context, showing for example that during adolescence, individuals of mixed Japanese-European ancestry had heights intermediate between those of homogenous parental ethnicity. This study design has recently been applied to birth weight.

Based on analysis of individuals born in the UK, those with two Indian parents were found to have birth weights on average ~350 g lower than those with two European parents. Depending on the ethnicity of the father, Indian mothers were found to produce babies ~150 to ~250 g lighter than the offspring of European mothers. This clearly indicates that lower maternal capital contributes to the lower birth weight of the Indian baby, but without differentiating ecological versus genetic influences. Compared to two Indian parents, the

combination of an Indian mother and a European father produced a baby on average ~250 g heavier, suggesting that the lower investment of Indian mothers is not 'fixed', but can rather be modified by paternal influence. Compared to two European parents, the combination of a European mother and an Indian father produced a baby on average ~100 g lighter (Wells et al., 2013). This suggests that although European mothers are capable of producing large babies, Indian fathers contribute 'lower growth potential' to their offspring, though this could occur either through genetic factors, or through epigenetic effects.

As yet this question has not been answered, but given the long-term decline in Indian stature over the last 10,000 years (Wells 2010), genetic differences between these populations are at least plausible. If long-term falls in maternal height occurred through natural selection, and if this decline impacted the dimensions of the pelvis as well (Wells 2015), selection could have favoured alleles constraining birth weight likewise.

Growth as an index of social conditions

This review strongly supports the pioneering argument of Eveleth and Tanner that human growth fundamentally reflects living conditions, with major implications for health. What has become clearer over the last four decades however is the complex intergenerational nature of this association. The capacity-load model may help understand its life-course aetiology. Many studies have shown inverse associations between levels of deprivation and birth weight or weight gain during infancy (Victora et al., 1987; Wilcox et al., 1995). Recent studies have shown striking dose response associations of childhood obesity with the level of deprivation (**Figure 7**). The composite effect is that metabolic capacity declines in association

with worsening deprivation even as metabolic load increases, so that those from the poorest backgrounds have the highest ratio of load to capacity. This represents a fast track to chronic disease in adulthood.

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

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Legends for illustrations

Figure 1. Hattori charts illustrating average age-associated changes in body composition adjusted for height in (a) infancy and (b) childhood, based on data from the reference child of Fomon et al., 1982. Sequential data points are as follows: (a) monthly from birth to 6 months, and then at 9 and 12 months; (b) 1 years, 1.5 years, and then yearly from 2 to 10 years. Movement across the graph over time indicates whether changes in body mass index are due to differences in fat-free mass (FFM), fat mass (FM) or both. Reproduced with permission from Wells (2000).

Figure 2. Associations between body length and mass of the kidney, liver and brain, based on autopsy data from children between birth and 12 years. Data from Coppoletta and Wolbach 1932, reproduced with permission from Wells (2016).

Figure 3. Interactive associations of birth weight (indexing metabolic capacity) and components of an unhealthy adult lifestyle (indexing metabolic load) in relation to the prospective risk of developing diabetes in three US cohorts. Data from Li et al., 2015b.

Figure 4. Schematic diagram summarizing the multiple nutritional influences acting on the developmental origins of chronic diseases. Reproduced with permission from Wells (2016).

Figure 5. Associations between maternal investment (proxied by birth size) and offspring phenotype in South Asian women in the UK. (a) Birth weight is positively associated with age at menarche. (b) Earlier menarche is associated with lower adult stature. (c) Earlier

menarche is associated with higher adult subscapular skinfold. (d) Subscapular skinfold is positively associated with adult systolic blood pressure. Reproduced with permission from Wells et al., 2016b.

Figure 6. Figure 4. Estimates of heritability in weight and length/height in The Netherlands Twin Register study, with data from another study of late pregnancy added. Data from Mook-Kanamori et al., 2012 and Gielen et al., 2008. Reproduced with permission from Wells 2015.

Figure 7. Association between obesity prevelance and level of deprivation (categorized in deciles) in UK children in reception class or Year 6. Data from UK National Obesity Observatory. Reproduced with permission from Wells (2016).

Table 1. Key questions concerning critical windows of plasticity and human growth outcomes relevant to health

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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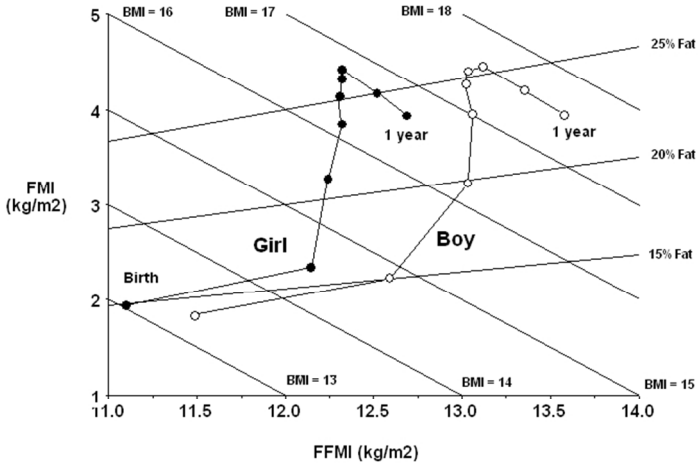

Fig 1a

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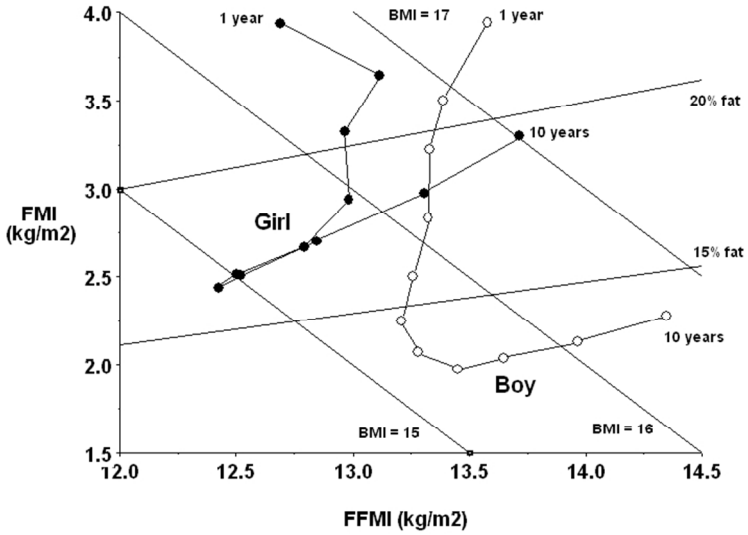

Fig 1b

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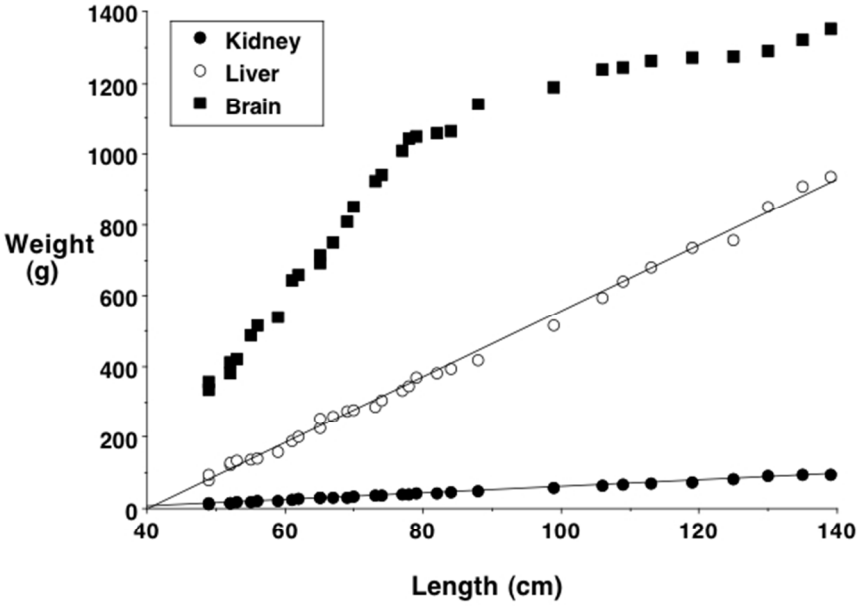

Fig 2

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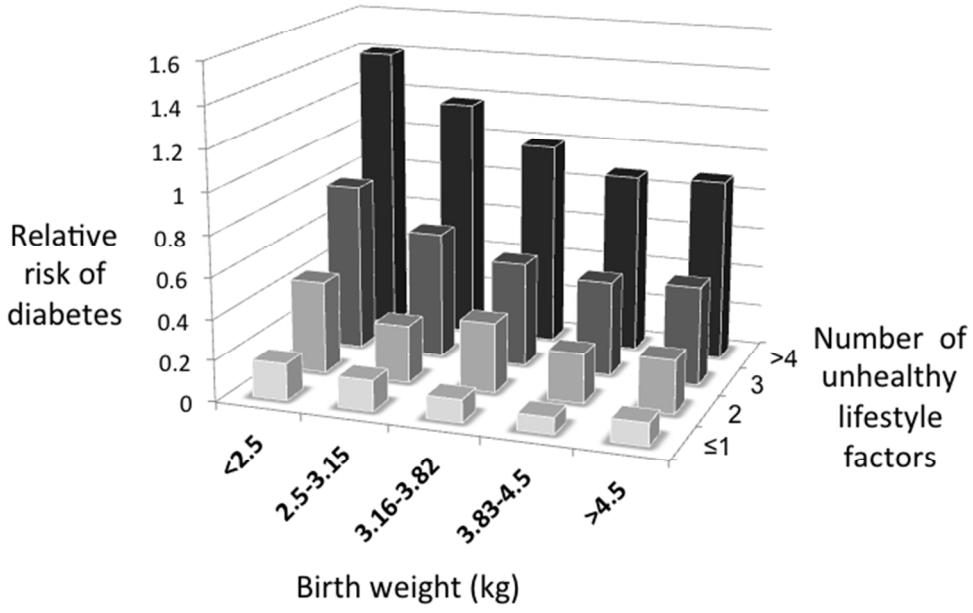

Fig 3

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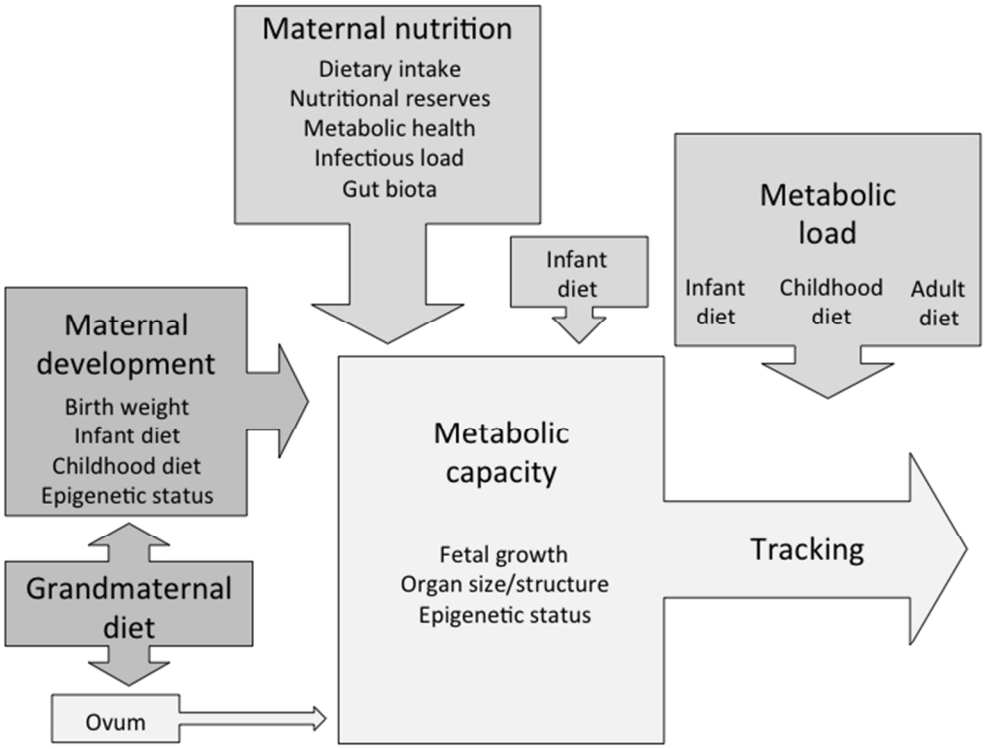

Fig 4

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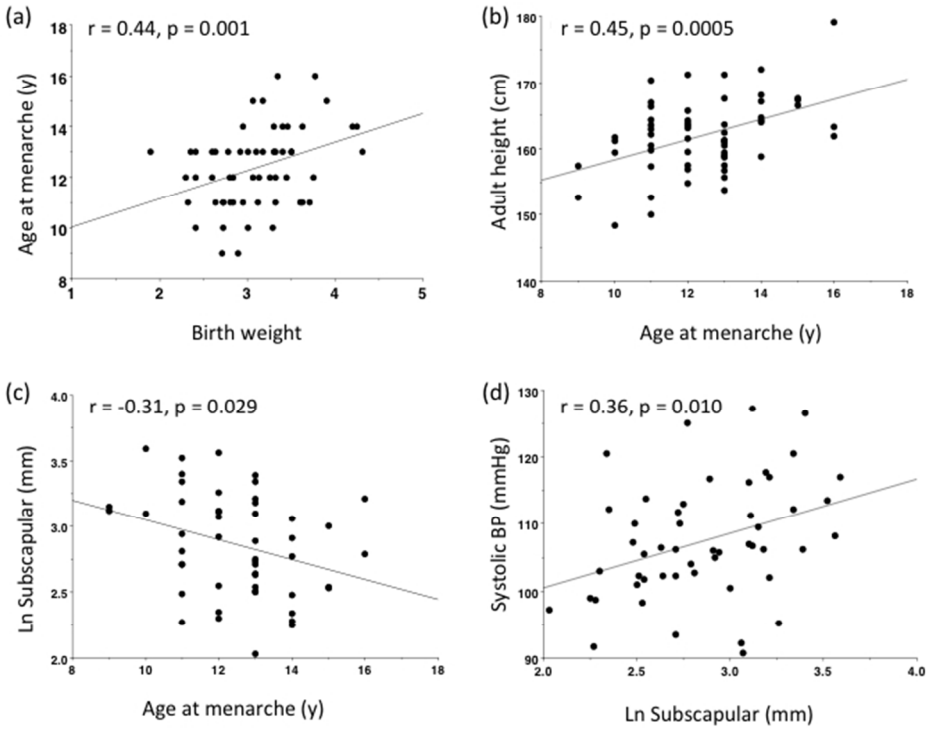

Fig 5

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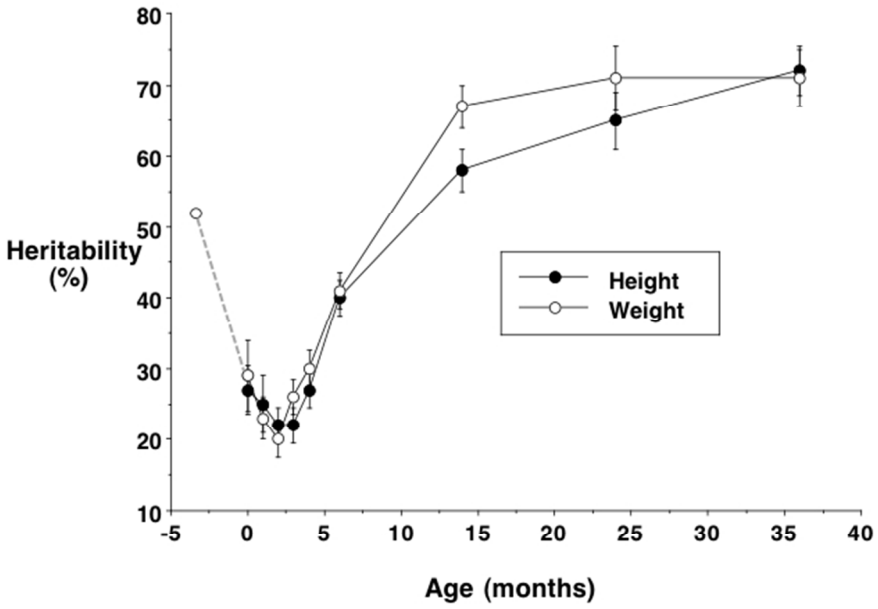

Fig 6

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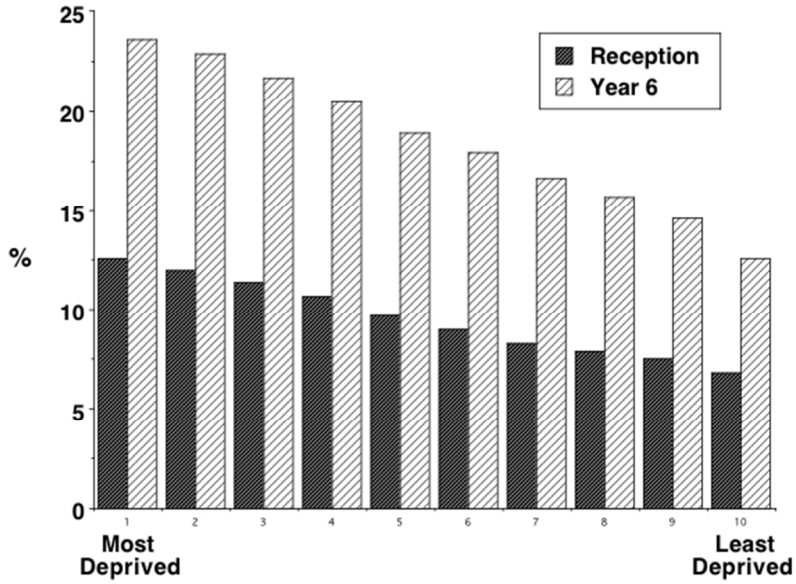

Fig 7

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