Body composition and susceptibility to Type 2 Diabetes: an evolutionary perspective

Jonathan CK Wells

Childhood Nutrition Research Centre

UCL Great Ormond Street Institute of Child Health

30 Guilford Street

London WC1N 1EH

Jonathan.Wells@ucl.ac.uk

4998 words, 7 figures, 1 table, 98 references

Abstract

Type 2 diabetes is rapidly increasing in prevalence worldwide, in concert with epidemics of obesity and sedentary behaviour that are themselves tracking economic development. Within this broad pattern, susceptibility to diabetes varies substantially in association with ethnicity and nutritional exposures through the life-course. An evolutionary perspective may help understand why humans are so prone to this condition in modern environments, and why this risk is unequally distributed. A simple conceptual model treats diabetes risk as the function of two interacting traits, namely 'metabolic capacity' which promotes glucose homeostasis, and 'metabolic load' which challenges glucose homoeostasis. This conceptual model helps understand how long-term and more recent trends in body composition can then be considered to have shaped variability in diabetes risk. Hominin evolution appears to have continued a broader trend evident in primates, towards lower levels of muscularity. In addition, hominins developed higher levels of body fatness, especially in females in relative terms. These traits most likely evolved as part of a broader reorganisation of human life history traits in response to growing levels of ecological instability, enabling both survival during tough periods and reproduction during bountiful periods. Since the emergence of *Homo sapiens*, populations have diverged in body composition in association with geographical setting and local ecological stresses. These long-term trends in both metabolic capacity and adiposity help explain the overall susceptibility of humans to diabetes in ways that are similar to, and exacerbated by, the effects of nutritional exposures during the life-course.

Keywords: evolution; public health; diabetes; body composition; capacity-load model

Introduction

Diabetes mellitus is an incurable chronic disease where blood sugar levels cannot be controlled. Conventionally, it has been broadly divided into two subcategories – Type 1, an autoimmune condition, and Type 2, an environmentally-induced condition. Type 2 diabetes (T2DM), the focus on this review, is currently increasing exponentially in prevalence worldwide. The classic explanatory model considers obesity (especially truncal fat) and physical inactivity the primary environmental causes.[1,2] The disease also clusters within families, indicating a heritable component of susceptibility.[3,4]

The utility of this model is limited, however, as it fails to explain major differences in T2DM prevalence across geographical regions, or between ethnic groups inhabiting relatively similar environments. For example, China and India have rapidly acquired high prevalences among urban populations,[5,6] despite low levels of obesity according to criteria developed in European populations. Recent, a leading diabetologist argued that 'Type 2 diabetes is a disease in search of a definition' and that our poor understanding of its heterogeneity is hindering global efforts to develop effective prevention strategies.[7]

The fact that T2DM risk is associated with each of (a) broader ecological factors (eg level of economic development), (b) population factors (eg ethnicity) and (c) developmental factors (eg growth patterns) indicates a very complex scenario. An evolutionary perspective can shed more light on this complexity and integrate our understanding, by identifying broader mechanisms through which variability in diabetes susceptibility emerges, and then applying this approach to hominins and past and present humans.

A metabolic model of diabetes risk

T2DM can be considered a 'two-hit' disease, involving both insulin resistance in muscle tissue, and failure of the pancreatic beta-cells to produce enough insulin to compensate for this resistance.[8] There is compelling evidence linking obesity with insulin resistance, although the connection may be bi-directional, involving positive feedback.[9] However, poor early growth also contributes by reducing beta-cell function, which is further undermined by oxidative stress. Eventually, beta-cell 'exhaustion' provokes the transition from insulin resistance to overt diabetes.

Early studies on the developmental origins of T2DM identified elevated susceptibility among those born with low birth weight, initially interpreted as 'fetal starvation'.[10] Hales and Barker proposed the 'thrifty phenotype' hypothesis, which assumed that in response to fetal malnutrition, growth of organs such as the liver and pancreas was sacrificed to protect the vulnerable brain. This would promote short-term survival, but at a cost of reduced ability to tolerate a high plane of nutrition in later life.[11]

However, many studies show inverse dose–response associations of birth weight with later glucose intolerance across almost the full range of birth weight, with similar associations evident for thinness (low ponderal index) and length at birth,[12-14] though T2DM risk increases again at high birth weights in some populations.[15,16] Thus, rather than overt fetal starvation provoking pathophysiology, there is a graded association between early growth and T2DM risk. Other non-communicable diseases show a very similar pattern.[17]

This spurred the development of a continuous 'capacity-load' model of disease risk, readily applied to T2DM. The approach emphasises the interaction of two fundamental traits: 'metabolic capacity', referring to factors indexing the life-long capacity for homeostasis, and 'metabolic load', referring to factors that challenge homeostasis.[18,19] For T2DM, the most relevant components of metabolic capacity are beta-cell function (insulin production) and muscle mass (glucose clearance).[20] Each of these traits is strongly contingent on fetal and infant growth patterns. The most relevant components of metabolic load are elevated adiposity (especially visceral adiposity), dietary glycemic load, and sedentary lifestyle, all of which perturb glycemic control and promote insulin resistance and chronic inflammation, deleterious to beta-cell function.[21,22] However, psychosocial stress is also relevant.

Figure 1 illustrates the basic model, showing how the capacity-load relationship impacts regulation of blood sugar levels. Variability in this relationship over time then shapes the risk of developing diabetes. Longitudinal cohort studies support the model (**Figure 2**), illustrating the interactive effects of birth weight (a proxy for metabolic capacity) with markers of an unhealthy lifestyle, proxied by traits such as high body mass index (BMI), unhealthy diet, smoking and physical inactivity. For adults with healthy lifestyle, the diabetes risk following low birth weight is relatively modest, whereas for those with unhealthy lifestyle, risk increases strongly as birth weight declines.[23]

Figures 1 and 2 near here

It should be emphasized that using *growth traits* to evaluate the capacity-load model does not address every mechanism through which adult disease susceptibility is shaped by developmental experience. For example, some fetal growth variability is not indexed by weight at birth or during infancy, while other mechanisms of developmental plasticity (eg epigenetic effects) are also important.[19] Nevertheless, interactive associations between early growth, adult phenotype and chronic disease risk have been widely replicated, and explain a substantial component of risk variance within and across populations.[23]

This simple model can be used to investigate T2DM risk in diverse ways, for example exploring life-course risk-accumulation, ethnic differences in diabetes susceptibility,[20,24] or longer-term evolutionary trends. Indices of body mass and activity patterns provide essential information about the magnitude of 'metabolic load', while stature or leg length represent simple markers of metabolic capacity, because they are associated with both birth weight and infant growth rate,[25] which encompass key periods of pancreatic development.[26,27] Supporting this, many studies show an increased risk of T2DM in association with short stature, though a few populations do not follow this pattern.[20] This inconsistency may emerge because in a few populations, taller individuals are also those most at risk of obesity.

Recently, this approach was used to provide an evolutionary perspective specifically on the elevated susceptibility of South Asian populations to T2DM.[20] Here, I extend it into a broader evolutionary perspective. First, I argue that long-term trends in hominin body size and physique may have made humans generically at greater risk of T2DM compared to other primates. Second, I consider how subsequent diversification in body composition may have shaped ethnic differences in T2DM risk. In this broader context, South Asian populations

appear to be merely at one extreme of a more general pattern of variability in T2DM susceptibility. Finally, I show how associations of phenotypic plasticity and T2DM can also be incorporated within an evolutionary perspective.

Long-term trends during human evolution

Through the 20th century, anthropologists assumed that hominin evolution had been driven primarily by adaptation to a relatively static savannah niche on the African continent. Most attention was directed to the emergence of traits shared by all humans, such as the large brain, bipedal locomotion and the capacities for language and material culture. Recently this perspective has undergone radical reappraisal, driven by growing awareness that hominin evolution occurred during a period when climate volatility steadily increased.[28] Thus, the key ecological challenge facing our hominin ancestors derived not from a specific niche, but rather from the *instability* of any geographical niche over short and long time periods.[29-31] From 3.4 million years ago, Australopithecines were already able to tolerate major climatic instability in East Africa.[32]

Many components of hominin phenotype are now considered to represent 'evolved solutions' to such ecological volatility, including body size and composition, reproductive strategy, ageing profile, encephalization and bipedal locomotion.[30,33]

Body composition can be considered a key component of this adaptive trend. Compared to other primates, including extent apes, contemporary humans have relatively low levels of muscle mass.[34] This pattern continues a broader evolutionary trend, for primates themselves

144 also show lower levels of muscle mass for their body mass compared to mammals in
145 general, a scenario attributed to their specialisation to arboreal habitats.[35] Complementary
146 to this trend in muscularity, adult humans of both sexes have greater adiposity than is
147 typical of other tropical mammals, especially in females.[36]
148
149 Reconstructing body size, shape and composition in past hominins is notoriously difficult, as
150 soft tissue does not preserve in the fossil record. The only option is to generate predictions
151 from contemporary humans or primates. Each of these approaches must inevitably be
152 imperfect, because hominins did not share associations between skeletal dimensions and
153 soft tissue with either of these groups of organisms. Nevertheless, it is still informative to
154 consider broader trends, using human data to interpret hominin skeletal characteristics.
155
156 Data on hominin size and shape have been reconstructed from fossilised skeletal
157 dimensions,[37,38] giving estimations of height and weight for a range of different species.
158 More recently, I developed an equation from diverse modern human populations that
159 predicted lean mass from weight and height in each sex, which could then be applied to
160 these hominin data.[36]
161
162 This approach identifies a broad decline among hominins in lean mass index (the lean
163 component of BMI), indicating increased 'gracility' from *Australopithecus/Paranthropus* to
164 *Homo*, especially in females (**Figure 3**). In addition, both lean mass and fat mass indices show
165 sexual dimorphism in most *Homo* species *(H. rudolfensis, H. erectus* and *H. Sapiens,* though
166 not in *H. habilis*) in the opposite direction to that predicted for Australopithecines. Since
167 brain expansion occurred in species post-dating *H. habilis*, the reduced musculature and

168 increased adiposity in *Homo* females may have helped meet the metabolic burden of
169 producing large-brained offspring.[39,40]
170
171 *Figure 3 near here*
172
173 If an alternative equation based on non-human primates is generated, only weight can be
174 used to predict hominin lean mass, greatly reducing accuracy. Using this approach, no sex-
175 differences are predicted in any hominin, hence the approach fails for the one species
176 (humans) where empirical evidence of body composition dimorphism is compelling.
177
178 Overall, this suggests that hominins would have become more prone to T2DM, by reducing
179 the mass of lean tissue that could clear glucose. Nonetheless, the tendency for foragers to
180 have at least moderate physical activity levels, combined with constraints on food supply,
181 suggests that the emergence of overt T2DM may have been very rare. Indeed, a similar
182 scenario can be seen in non-human primate species, where captivity typically elevates body
183 fat levels and physical inactivity, provoking the spontaneous development of T2DM.[41] This
184 suggests that the fundamental physiology of diabetes risk is shared across primates, and that
185 contemporary humans differ only in being more likely to experience environmental
186 exposures that provoke the disease.
187
188 It might appear paradoxical that despite on average having relatively greater adiposity
189 (metabolic load) and lower height and lean mass (markers of metabolic capacity),
190 contemporary human females develop T2DM at higher BMI values than males, and thus
191 appear somewhat protected.[42] This scenario can be explained by profound sex differences in

192 the anatomical distribution of body fat. Females store reproductive fat in gluteo-femoral
193 depots,[43,44] which in contrast to truncal and visceral fat are associated with insulin sensitivity
194 and low diabetic risk.[45-47] Thus, gender differences in fat distribution are themselves an
195 indication that its 'toxicity' was an intrinsic stress during hominin evolution, and that females
196 were selected to reduce this risk by storing fat in metabolically-inert depots.
197
198 These body composition trends can be considered components of a broader reorganisation
199 of hominin life history strategy, in order to tolerate ecological volatility. Adiposity and
200 plasticity in the schedule of growth and maturation (representing the sensitivity of both
201 'capacity' and 'load' to ecological stresses) emerged in combination with other components
202 of phenotypic flexibility, such as cooperative breeding and longer lifespans. Collectively, all
203 of these traits promote both (a) survival in tough conditions and (b) rapid reproduction
204 during bountiful conditions (**Table 1**).[33] The same traits are revisited later in this review, in
205 the context of how diabetes risk is related to phenotypic plasticity within the life-course.
206 Although hominin metabolism is often assumed to have adapted to guarantee the high
207 energy demands of the *Homo* brain, an alternative hypothesis is that successful adaptation
208 to stochastic environments generated a supply of energy sufficiently stable that
209 encephalization became viable.[33] From this broader *Homo* baseline, we can then consider
210 how variability in morphology and metabolism might have emerged within the human
211 species.
212
213 *Table 1 near here*
214
215 **The emergence of population variability**

Modern humans probably emerged ~200,00 to ~150,000 years ago in Africa, although new calculation methods and richer genomic material constantly fine-tune these estimations.[48,49] Around 100,000 to 60,000 years ago, some populations dispersed out of Africa and progressively migrated across most of the global land mass. Australasia was reached at least 50,000 years ago, and the North American continent rather more recently.[50,51] The pattern of dispersal has clearly contributed to contemporary human diversity, mediated by the regional geographical routes taken, contrasting selective pressures, and periodic local isolations, all of which have promoted inter-group differences and some genetic diversification.[52,53] Despite this, our species is characterised by remarkably high levels of genetic unity,[54] fundamentally linked with our high levels of phenotypic plasticity. The selective pressures that favoured the capacity to tolerate ecological instability during hominin evolution have made modern humans extremely well adapted to colonising diverse environments.[55]

Both these migrations, and long-term exposure to diverse ecological niches, are widely assumed to have shaped variability within our species in metabolism and body size, morphology and composition. A complete picture is still emerging, but likely ecological stresses include the thermal environment, energy availability, dietary quality, pathogen burden, and exposure to indices of volatility such as climate cycles.

Arguably the strongest evidence for adaptive variability in human body composition relates to the thermal environment. Since the 1950s, several studies have linked variation in human body size and shape with average annual temperature.[56,57] Physical laws suggest that

organisms can promote heat loss by increasing their surface area relative to their mass, whereas heat conservation can be promoted by decreasing this ratio.[58,59] Broadly, humans show larger area-mass ratios in tropical relative to polar environments, and the length of body extremities is also greater in hot environments, maximising heat loss from long slender limbs.[57,60,61] Unsurprisingly, these patterns extend beyond shape to body composition, with lean mass relative to height scaling inversely in association with annual temperature.

Low levels of lean/muscle mass have been linked with elevated susceptibility of populations such as South Asian and Australian aboriginals to insulin resistance in obesogenic settings,[19,20] and this scenario may apply to other populations with similar characteristics. Hence, climatic adaptation is very likely to have shaped T2DM susceptibility.

Body fatness also tends to increase in association with declining temperature, though in the past some polar populations had relatively low subcutaneous adiposity.[62] Intriguingly, sexual dimorphism in body composition is itself associated with climatic conditions: for example, at colder temperatures males show a greater excess of lean mass relative to females, whereas females show greater adiposity relative to males.[63]

Historically, human body fat was widely assumed to have been selected as a defence against starvation, but this view is now considered very simplistic. There are numerous 'fitness functions' of adiposity, demonstrated by recent findings that the hormone leptin plays critical regulatory roles in maturation, reproduction and immune function.[64-67] An eco-geographical analysis identified an inverse association between subscapular skinfold thickness and markers of the local pathogen burden, suggesting that populations with high

pathogen burdens metabolise central body fat to fund immune function.[68] There is mechanistic support for this hypothesis, as visceral fat has high expression of genes involved in the complement system.[69]

This proposed link between adiposity and immune function has two important implications for contemporary variability in T2DM risk. First, populations that have experienced long-term exposure to high pathogen burdens might have an elevated predisposition to gain central fat in obesogenic settings. This is consistent with strong associations between economic development in low-/middle-income countries, efforts to reduce infectious diseases, and rapid increases in waist circumference. Second, the specific diseases to which individual ethnic groups have experienced long-term exposure might have additionally shaped the metabolic profile of adipose tissue. The 'variable disease selection' hypothesis posits that humans may have adapted to specific pathogens by favouring energy storage in specific regional fat depots, and by developing specific cytokine profiles.[70]

Figure 4 near here

Regardless of whether this specific hypothesis is correct, ethnic differences in body fat distribution, lepin and cytokines are already well established.[62,68,71,72] In UK children, the association between adiposity and insulin resistance differs by ethnicity, so that body fat appears to be 'more toxic' in those of South Asian ancestry.[73] Since the energy-deficit imposed by starvation can be assumed to be a human 'constant', and since most starvation deaths occur via infection, the notion that ethnic differences in adipose tissue biology may have been shaped by local infectious disease burdens merits further consideration.[70]

Overall, therefore, broader geographical stresses such as climate and pathogen burden appear to have promoted human variability in physique, impacting components of both metabolic capacity and metabolic load.[19] However, the mechanisms underlying this variability remain poorly understood. It might be assumed that ethnic differences in physique and metabolism reflect genetic differences, but this issue is increasingly undergoing re-evaluation.

Variability in diabetes susceptibility: genetics

In a classic article, Neel proposed that populations exposed to regular cycles of 'feast and famine' adapted by developing 'thrifty genotypes', coding for traits favouring ready accumulation of fat stores during spikes in food supply.[74] Initially, such thriftiness was attributed to a fast insulin response, but others considered muscle insulin resistance the key mechanism, diverting excess energy to adipose issue.[75] Regardless, thrifty genes were predicted to increase T2DM susceptibility following exposure to 'permanent feast' conditions, equivalent today to energy-dense diets and physical inactivity following economic development.

Although this hypothesis has stimulated substantial research, adiposity is now well recognised to be a polygenic trait, and as yet, very few candidate genes linking obesity and T2DM risk have been identified. More generally, few examples of metabolic adaptation to local ecological conditions have been identified. Rather, genetic variability in human metabolic phenotype can largely be attributed to geographic variability in gene

frequencies.[76,77] For example, one study showed that the prevalence of T2DM 'risk-alleles' decreases in relation to the population's distance from Africa, suggesting that increasing exposure to non-African environments favoured cumulative 'diabetes protection'. Within that scenario, most T2DM risk-alleles appear to exert similar directions and magnitudes of effects in different ethnic groups,[78] though there are exceptions such as the FTO gene.[79] Most likely, geographical variability in human body composition derives in part from variability in the frequency of genes shaping early-life growth patterns and adult morphology and metabolism. However, the nature of any such adaptation is still being established.

More recent work has linked genes with both low birth weight and T2DM risk in adulthood.[80] It remains unclear if such genes generate specific pathophysiological effects, or whether they merely shape growth trajectory at a broader level. I have previously suggested that natural selection must have favoured a polygenic basis for fetal growth, where each gene must have a very small magnitude of effect. Any gene producing a large increment in birth weight would be under strong selection from the stress of cephalo-pelvic disproportion, through the tendency for mothers malnourished in early life to grow small pelvises by adulthood.[81]

Initially, the elevated T2DM susceptibility of Pima Indians living in the US was considered some of the best evidence supporting the thrifty genotype hypothesis.[82] Certainly, T2DM risk has a genetic component in this population, but recent studies suggest that chronic under-nutrition through the 20th century elevated their T2DM susceptibility through intergenerational plasticity.[83,84] This scenario is consistent with animal studies, where

chronic under-nutrition over multiple generations causes profound changes in offspring epigenetics, growth and metabolism.[85,86]

This scenario fits the 'capacity-load' model described above, which acknowledges that a component of T2DM risk derives from nutritional experience in development. Moreover, there is little doubt that the primary factor driving the global T2DM epidemic is the 'nutrition transition', driving changes in multiple forms of behaviour. Beyond genetics and selection, an evolutionary perspective can help understand why patterns of nutrition and growth through the life course have such profound impact on T2DM risk.

Variability in diabetes susceptibility: plasticity

One attempt to develop an evolutionary model of developmental plasticity and adult chronic disease was the 'predictive adaptive response' (PAR) hypothesis. This proposed that malnourished foetuses developed 'thrifty' traits that would be well adapted to famine, anticipated to persist in adult life. For T2DM, insulin resistance and central fat were specifically identified as 'predictive adaptive responses'. However, this hypothesis has been strongly criticized on several grounds. First, long-term ecological prediction is implausible.[87] Second, malnourished infants are not insulin resistant at birth, but rather acquire this phenotype if they develop overweight from childhood onwards.[88] Third, outside obesogenic settings, those born with low birth weight do not develop insulin resistance or central fat.[89] Alternative explanatory models are therefore required.

Unlike the PAR hypothesis, evolutionary biologists conventionally address plasticity using life history theory. This assumes that every organism has finite quantities of energy, and must invest it optimally across four competing functions: maintenance, growth, reproduction and defence against pathogens/predators.[90] Faster life histories are favoured in high-risk environments: for example, elevated extrinsic mortality risk accelerates the 'pace' at which the organism passes through the life course. Faster life histories inherently reduce investment in growth and long-term maintenance, prioritising instead survival and reproduction.[91,92]

From this perspective, a key benefit of 'maintenance' comprises protection against T2DM, through glucose homeostasis at the level of tissues and organs, and the suppression of oxidative stress at the molecular level.[93] Stresses during early life alter energy-allocation patterns, potentially reducing investment in 'maintenance' and growth with long-term detrimental effects on homeostasis. Such stresses may derive directly from inadequate energy supply, or indirectly from allocating more energy to immune function.

For example, ecological instability early in life limits the acquisition of lean tissue. In Peru, children born around the time of the 1998 El Niño event showed reduced height and lean mass later in childhood compared to those unexposed, but no difference in adiposity.[94] In other words, contemporary variability in physique tracks local ecological conditions along exactly the same lines as suggested for long-term hominin evolution.

More generally, phenotypic plasticity in humans has been selected to allow accommodation of prevailing ecological conditions in ways that maximise survival and reproduction (**Table 1**).

383 This constellation of plastic traits provides over-arching flexibility in life-history trajectory,
384 allowing individuals to select a 'slower' or 'faster' trajectory depending on the conditions
385 encountered during the life-course.
386
387 This is consistent with life-course research that has linked a series of developmental traits
388 with T2DM susceptibility. These include lower birth weight, poor infant growth, rapid
389 childhood weight gain, early puberty and short adult stature (**Figure 5**).[12,20,95,96] All these
390 traits are markers of a faster life history, indicating how T2DM risk is shaped by the
391 cumulative adjustment of developmental trajectory to ecological conditions to maximise
392 fitness.[19]
393
394 *Figure 5 near here*
395
396 T2DM develops over time, and overt disease typically occurs from middle-age onwards,
397 following the accumulation of metabolic damage. In environments with high extrinsic
398 mortality risk, such as the constant threat of fatal infectious disease, a high proportion of
399 individuals would not live long enough to benefit from investing in homeostasis to an extent
400 that would minimise metabolic deterioration in old age. Instead, fitness would be maximised
401 by investing in reproduction, at the cost of 'maintenance', and only a small proportion who
402 by random chance survived past middle-age would pay the long-term costs, for example by
403 developing T2DM at post-reproductive ages (**Figure 6**). This helps understand the 'thrifty
404 phenotype' as a developmental strategy, trading off short-term survival and reproduction
405 against longevity.
406

Figure 6 near here

However, low maternal investment may provoke exactly the same response in the offspring, by reducing the intrinsic 'somatic quality' of the offspring. During fetal life, when much developmental adjustment occurs, the primary environmental influence is maternal phenotype.[19] Low maternal investment constrains the offspring's long-term capacity for homeostasis, making it more vulnerable to diverse risks. Once again, the best response is to shunt energy towards reproduction, in order to maximise reproductive fitness before mortality occurs.[92] This hypothesis is supported by a study of South Asian women living in the UK. Those with low birth weight (indicating low maternal investment during early 'critical periods') showed faster maturation, shorter adult height, higher adiposity and higher blood pressure (**Figure 7**). This indicates a fast life history strategy: investing in maturation and storing energy for reproduction, at a cost to growth and homeostasis.

Figure 7 near here

In high-risk environments, where every offspring has a fair chance of random death, even well-nourished mothers will optimise their fitness by producing greater numbers of smaller offspring, rather than smaller numbers of large robust offspring. For multiple reasons, therefore, offspring size is expected to decrease in association with environmental risk, with implications for long-term T2DM risk.

Ethnic differences in birth weight are strongly implicated in differential susceptibility to T2DM, but it remains unclear whether, for example, relatively low birth weights in South

Asian populations indicate genetic adaptation to past environments, or more recent inter-generational plasticity mediated by chronic under-nutrition. A recent study of parental ethnicity shed some light on this issue.

The study analysed UK birth weight data, stratifying by European or Indian ethnicity of each parent. Compared to two European parents, two Indian parents produced a baby on average ~400g lighter.[97] This describes the overall difference of Indians versus Europeans in a high-income setting, but does not identify the underlying mechanism. Holding paternal ethnicity constant, Indian mothers produced offspring on average ~250g lighter than European mothers. Maternal phenotype clearly makes a key contribution, but whether via genotype or metabolic phenotype remains unclear.

Among Indian mothers, birth weight was averaged ~250g more if the father was European, rather than Indian. This indicates that the nutritional constraint imposed by Indian mothers is not fixed, and can be modulated by the father. Conversely, among European mothers, birth weight averaged ~100g lower if the father was Indian, rather than European. Thus, birth weight was apparently constrained by Indian paternity. Collectively, these results indicate some degree of paternal 'adaptation' in the Indian population to chronic maternal under-nutrition, involving either epigenetic or genetic mechanisms, through the medium of 'parent-offspring conflict' over fetal nutrition.[97]

Given that increased supplies of energy should promote investment in life-long 'maintenance', why are economic development and the nutrition transition so strongly implicated in the global epidemic of T2DM? There are several reasons. First, the acquisition

of fat stores is occurring much faster than reductions in the prevalence of low birth weight or stunting. In other words, changes in metabolic load are substantially greater and faster than changes in metabolic capacity.[98] Thus, each generation in chronically undernourished populations still starts life with an elevated *susceptibility* to T2DM, which is then activated by the impact of economic development via obesity and sedentary behaviour. Second, the nutrition transition is not simply a shift to greater energy supply, rather it has deep structural connections with power relations at many levels of society, both within populations and between nations.[19] The transition involves major changes in dietary quality, accompanied by exposure to multiple technologies that collectively promote sedentary lifestyles.

All of these changes are driven by the maximisation of profit through repetitive behaviour. In many cases, corporations based in high-income countries now sell to low/middle-income countries products (eg tobacco, or foodstuffs high in trans-fats or refined carbohydrate) that in the high-income country have already been banned outright, or strongly targeted by public health policies. These products are not metabolically 'neutral', rather they are characterised by properties that favour repetitive consumption, and thereby themselves *drive* the nutrition transition. In this sense, unhealthy commodities play a key role in the 'metabolic manufacturing of consent' for economic development: those consuming them appear to legitimise the underlying politico-economic system.[19] Populations of low/middle-income countries that, for reasons described above, have lower metabolic capacity are both more vulnerable to gaining excess metabolic load though the nutrition transition, and arguably less able to resist the corporate influences that drive the transition.

Conclusions

This article has presented a relatively simple evolutionary model of T2DM susceptibility, focusing on variability in two generic metabolic traits: those that help maintain homeostasis, and those that challenge homeostasis. My hypothesis is that both traits are prone to variation on several different timescales - long-term hominin evolution; the population-diversification that occurred as humans dispersed out of Africa into multiple ecological niches; and individual life-courses mediated by diverse ecological stresses, many transmitted across generations. The consequence is a wide spectrum of T2DM susceptibility within and across populations. Better understanding of this variability may improve the development of public health programs intended to reduce the burden of this disease.

494 **Legends for illustrations**

495

496 **Figure 1**. Schematic diagram illustrating the basic capacity-load model of glycemic control, in
497 which blood sugar levels rise in association with factors such as a high glycaemic diet,
498 sedentary behaviour and high body fatness, and decrease in proportion to the homeostatic
499 capacity of the body, indexed by traits such as pancreatic beta cell mass and muscle mass.
500 Reprinted with permission from Wells et al., 2016.[20]

501

502 **Figure 2**. The capacity-load model illustrated for the prospective risk of developing Type 2
503 diabetes in three US cohorts. Data from Li et al.[23]

504

505 **Figure 3**. Simulated trends in hominin body composition, plotting fat mass/height^2 (FMI)
506 against lean mass/height^2 (LMI) which add up to body mass index (BMI). There is a broad
507 trend to lower LMI in more recent hominins, especially in females, and the emergence of
508 dimorphism in LMI and FMI in the main members of the genus *Homo*. Based on data from
509 Wells 2010.[36]

510

511 **Figure 4**. Schematic diagram illustrating the 'variable disease selection' hypothesis, positing
512 that different local infectious disease burdens select for contrasting anatomical distributions
513 and cytokine profiles of adipose tissue.

514

515 **Figure 5**. Schematic diagram (not to scale) illustrating the accelerated life history trajectory
516 associated with chronic diseases (dotted line) relative to the slower and healthier trajectory
517 (continuous line). While the second part of the healthy trajectory builds a larger body, this

518 occurs slowly, and follows higher growth rates during fetal life. The faster life history
519 trajectory superimposes a high metabolic load on a diminished metabolic capacity.
520 Reprinted with permission from Wells 2016.[19]
521
522 **Figure 6**. Schematic diagram of extrinsic risk, life history strategy and metabolic phenotype.
523
524 **Figure 7**. Empirical associations between maternal investment (proxied by birth size),
525 maturation rate and adult phenotype in adult south Asian women. (a) Birth weight is
526 inversely associated with age at menarche. (b) Earlier menarche is associated with lower
527 adult stature. (c) Earlier menarche is associated with higher adult subscapular skinfold. (d)
528 Subscapular skinfold is positively associated with adult systolic blood pressure. Reprinted
529 with permission from Wells et al. 2016.[92]
530

References

1. Astrup A, Finer N. Redefining type 2 diabetes: 'diabesity' or 'obesity dependent diabetes mellitus'? Obesity reviews : an official journal of the International Association for the Study of Obesity 2000;1:57-9.
2. Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS, Jr. Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. N Engl J Med 1991;325:147-52.
3. Hong Y, Rice T, Gagnon J, et al. Familial clustering of insulin and abdominal visceral fat: the HERITAGE Family Study. J Clin Endocrinol Metab 1998;83:4239-45.
4. Willemsen G, Ward KJ, Bell CG, et al. The Concordance and Heritability of Type 2 Diabetes in 34,166 Twin Pairs From International Twin Registers: The Discordant Twin (DISCOTWIN) Consortium. Twin Res Hum Genet 2015;18:762-71.
5. Jayawardena R, Ranasinghe P, Byrne NM, Soares MJ, Katulanda P, Hills AP. Prevalence and trends of the diabetes epidemic in South Asia: a systematic review and meta-analysis. BMC Public Health 2012;12:380.
6. International Diabetes Federation. IDF Diabetes Atlas, 6th edition: International Diabetes Federation; 2013.
7. Gale EA. Is type 2 diabetes a category error? Lancet 2013;381:1956-7.
8. Bergman RN, Ader M, Huecking K, Van CG. Accurate assessment of beta-cell function: the hyperbolic correction. Diabetes 2002;51 Suppl 1:S212-S20.
9. Lustig RH. Which comes first? The obesity or the insulin? The behavior or the biochemistry? JPediatr 2008;152:601-2.
10. Ravelli AC, van der Meulen JH, Michels RP, et al. Glucose tolerance in adults after prenatal exposure to famine. Lancet 1998;351:173-7.
11. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia 1992;35:595-601.
12. Hales CN, Barker DJ, Clark PM, et al. Fetal and infant growth and impaired glucose tolerance at age 64. BMJ 1991;303:1019-22.
13. Phillips DI, Barker DJ, Hales CN, Hirst S, Osmond C. Thinness at birth and insulin resistance in adult life. Diabetologia 1994;37:150-4.
14. Rich-Edwards JW, Colditz GA, Stampfer MJ, et al. Birthweight and the risk for type 2 diabetes mellitus in adult women. Ann Intern Med 1999;130:278-84.
15. Whincup PH, Kaye SJ, Owen CG, et al. Birth weight and risk of type 2 diabetes: a systematic review. JAMA 2008;300:2886-97.
16. Fall CH, Stein CE, Kumaran K, et al. Size at birth, maternal weight, and type 2 diabetes in South India. Diabet Med 1998;15:220-7.
17. Rich-Edwards JW, Stampfer MJ, Manson JE, et al. Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. BMJ 1997;315:396-400.
18. Wells JC. The thrifty phenotype: An adaptation in growth or metabolism? Am J Hum Biol 2011;23:65-75.
19. Wells JC. The metabolic ghetto: an evolutionary perspective on nutrition, power relations and chronic disease. Cambridge: Cambridge University Press; 2016.
20. Wells JC, Pomeroy E, Walimbe SR, Popkin BM, Yajnik CS. The Elevated Susceptibility to Diabetes in India: An Evolutionary Perspective. Front Public Health 2016;4:145.

21. Hu FB. Globalization of diabetes: the role of diet, lifestyle, and genes. Diabetes Care 2011;34:1249-57.
22. Gupta D, Krueger CB, Lastra G. Over-nutrition, obesity and insulin resistance in the development of beta-cell dysfunction. Current diabetes reviews 2012;8:76-83.
23. Li Y, Ley SH, Tobias DK, et al. Birth weight and later life adherence to unhealthy lifestyles in predicting type 2 diabetes: prospective cohort study. BMJ 2015;351:h3672.
24. Wells JC. Ethnic variability in adiposity, thrifty phenotypes and cardiometabolic risk: addressing the full range of ethnicity, including those of mixed ethnicity. Obesity reviews : an official journal of the International Association for the Study of Obesity 2012;13 Suppl 2:14-29.
25. Wells JC, Chomtho S, Fewtrell MS. Programming of body composition by early growth and nutrition. ProcNutrSoc 2007;66:423-34.
26. Cook JT, Levy JC, Page RC, Shaw JA, Hattersley AT, Turner RC. Association of low birth weight with beta cell function in the adult first degree relatives of non-insulin dependent diabetic subjects. BMJ 1993;306:302-6.
27. Bouwens L, Rooman I. Regulation of pancreatic beta-cell mass. Physiological reviews 2005;85:1255-70.
28. Lisiecki LE, Raymo ME. A plio-pleistocene stack of 57 globally distributed benthic $\delta^{18}O$ records. Paleoceanography 2005;20.
29. Potts R. Environmental hypotheses of hominin evolution. Am J PhysAnthropol 1998;Suppl 27:93-136.
30. Potts R. Humanity's descent: the consequences of ecological instability. New York: William Morrow & Co.; 1996.
31. Potts R. Environmental and behavioral evidence pertaining to the evolution of early Homo. Curr Anthropol 2012;53 Suppl. 6:S299-S318.
32. Bonnefille R, Potts R, Chalie F, Jolly D, Peyron O. High-resolution vegetation and climate change associated with Pliocene Australopithecus afarensis. Proc Natl Acad Sci U S A 2004;101:12125-9.
33. Wells JC. Ecological volatility and human evolution: a novel perspective on life history and reproductive strategy. Evol Anthropol 2012;21:277-88.
34. Leonard WR, Robertson ML, Snodgrass JJ, Kuzawa CW. Metabolic correlates of hominid brain evolution. Comp BiochemPhysiol A MolIntegrPhysiol 2003;136:5-15.
35. Muchlinski MN, Snodgrass JJ, Terranova CJ. Muscle mass scaling in primates: an energetic and ecological perspective. American journal of primatology 2012;74:395-407.
36. Wells JC. The evolutionary biology of human body fat: thrift and control. Cambridge: Cambridge University Press; 2010.
37. McHenry HM. How big were early hominids? EvolAnthropol 1992;1:15-20.
38. McHenry HM. Body size and proportions in early hominids. Am J PhysAnthropol 1992;87:407-31.
39. Aiello LC, Key C. Energetic consequences of being a Homo erectus female. AmJHumBiol 2002;14:551-65.
40. Aiello LC, Wells JC. Energetics and the evolution of the genus *Homo*. AnnRevAnthropol 2002;31:323-38.
41. Campbell BC, Cajigal A. Diabetes: energetics, development and human evolution. MedHypotheses 2001;57:64-7.
42. Logue J, Walker JJ, Colhoun HM, et al. Do men develop type 2 diabetes at lower body mass indices than women? Diabetologia 2011;54:3003-6.

43. Lassek WD, Gaulin SJ. Waist-hip ratio and cognitive ability: is gluteofemoral fat a privileged store of neurodevelopmental resources? EvolHumBehav 2007;29:26-34.
44. Wells JC. Sexual dimorphism of body composition. BestPractRes ClinEndocrinolMetab 2007;21:415-30.
45. Snijder MB, Dekker JM, Visser M, et al. Trunk fat and leg fat have independent and opposite associations with fasting and postload glucose levels: the Hoorn study. Diabetes Care 2004;27:372-7.
46. Snijder MB, Visser M, Dekker JM, et al. Low subcutaneous thigh fat is a risk factor for unfavourable glucose and lipid levels, independently of high abdominal fat. The Health ABC Study. Diabetologia 2005;48:301-8.
47. Snijder MB, Zimmet PZ, Visser M, Dekker JM, Seidell JC, Shaw JE. Independent and opposite associations of waist and hip circumferences with diabetes, hypertension and dyslipidemia: the AusDiab Study. IntJ ObesRelat Metab Disord 2004;28:402-9.
48. Cann RL, Stoneking M, Wilson AC. Mitochondrial-Dna and Human-Evolution. Nature 1987;325:31-6.
49. Harpending H, Rogers A. Genetic perspectives on human origins and differentiation. AnnuRev Genomics Hum Genet 2000;1:361-85.
50. Mellars P. Why did modern human populations disperse from Africa ca. 60,000 years ago? A new model. ProcNatlAcadSciUSA 2006;103:9381-6.
51. Bowler JM, Johnston H, Olley JM, et al. New ages for human occupation and climatic change at Lake Mungo, Australia. Nature 2003;421:837-40.
52. Lahr MM, Foley R. Towards a theory of modern human origins: geography, demography, and diversity in recent human evolution. YrbkPhysAnthropol 1998;41:137-76.
53. Watson E, Forster P, Richards M, Bandelt HJ. Mitochondrial footprints of human expansions in Africa. Am J Hum Genet 1997;61:691-704.
54. Gagneux P, Wills C, Gerloff U, et al. Mitochondrial sequences show diverse evolutionary histories of African hominoids. Proc Natl Acad Sci U S A 1999;96:5077-82.
55. Wells JC, Stock JT. The biology of the colonizing ape. Am J PhysAnthropol 2007;Suppl 45:191-222.
56. Roberts DF. Body weight, race and climate. AmJPhysAnthropol 1953;11:533-58.
57. Roberts DF. Climate and human variability. An Addison-Wesley module in anthropology, No. 34. Reading, MA: Addison-Wesley Publishing Co, Inc; 1973.
58. Bergmann C. Über die Verhältnisse der wärmeökonomie der Thiere zu ihrer Grösse. Göttinger Studien 1847;3:595-708.
59. Allen JA. The influence of physical conditions on the genesis of species. Radical Rev 1877;1:108-40.
60. Crognier E. Climate and anthropometric variations in Europe and the Mediterranean area. AnnHumBiol 1981;8:99-107.
61. Hiernaux J, Froment A. The correlations between anthropobiological and climatic variables in sub-Saharan Africa: revised estimates. Hum Biol 1976;48:757-67.
62. Wells JC. Ecogeographical associations between climate and human body composition: analyses based on anthropometry and skinfolds. Am J Phys Anthropol 2012;147:169-86.
63. Wells JC. Sexual dimorphism in body composition across human populations: associations with climate and proxies for short- and long-term energy supply. Am J Hum Biol 2012;24:411-9.

64. Wade GN, Schneider JE, Li HY. Control of fertility by metabolic cues. The American journal of physiology 1996;270:E1-19.
65. Demas GE, Sakaria S. Leptin regulates energetic tradeoffs between body fat and humoural immunity. ProcBiol Sci 2005;272:1845-50.
66. Lord G. Role of leptin in immunology. NutrRev 2002;60:S35-S8.
67. Matarese G, Moschos S, Mantzoros CS. Leptin in immunology. J Immunol 2005;174:3137-42.
68. Wells JC, Cortina-Borja M. Different associations of subscapular and triceps skinfold thicknesses with pathogen load: an ecogeographical analysis. Am J Hum Biol 2013;25:594-605.
69. Gabrielsson BG, Johansson JM, Lonn M, et al. High expression of complement components in omental adipose tissue in obese men. ObesRes 2003;11:699-708.
70. Wells JC. Ethnic variability in adiposity and cardiovascular risk: the variable disease selection hypothesis. IntJ Epidemiol 2009;38:63-71.
71. Cox ED, Hoffmann SC, DiMercurio BS, et al. Cytokine polymorphic analyses indicate ethnic differences in the allelic distribution of interleukin-2 and interleukin-6. Transplantation 2001;72:720-6.
72. Zabaleta J, Schneider BG, Ryckman K, et al. Ethnic differences in cytokine gene polymorphisms: potential implications for cancer development. Cancer Immunol Immunother 2008;57:107-14.
73. Nightingale CM, Rudnicka AR, Owen CG, et al. Influence of Adiposity on Insulin Resistance and Glycemia Markers Among United Kingdom Children of South Asian, Black African-Caribbean, and White European Origin: Child Heart and Health Study in England. Diabetes Care 2013.
74. Neel V. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? AmJHumGenet 1962;14:353-62.
75. Reaven GM. Hypothesis: muscle insulin resistance is the ("not-so") thrifty genotype. Diabetologia 1998;41:482-4.
76. Hancock AM, Alkorta-Aranburu G, Witonsky DB, Di Rienzo A. Adaptations to new environments in humans: the role of subtle allele frequency shifts. Philos Trans R Soc Lond B Biol Sci 2010;365:2459-68.
77. Hancock AM, Witonsky DB, Ehler E, et al. Human adaptations to diet, subsistence, and ecoregion are due to subtle shifts in allele frequency. Proc Natl Acad Sci U S A 2010;107 Suppl 2:8924-30.
78. Sohani ZN, Deng WQ, Pare G, Meyre D, Gerstein HC, Anand SS. Does genetic heterogeneity account for the divergent risk of type 2 diabetes in South Asian and white European populations? Diabetologia 2014;57:2270-81.
79. Li H, Kilpelainen TO, Liu C, et al. Association of genetic variation in FTO with risk of obesity and type 2 diabetes with data from 96,551 East and South Asians. Diabetologia 2012;55:981-95.
80. Horikoshi M, Beaumont RN, Day FR, et al. Genome-wide associations for birth weight and correlations with adult disease. Nature 2016;538:248-52.
81. Wells JC. Between Scylla and Charybdis: renegotiating resolution of the 'obstetric dilemma' in response to ecological change. Philos Trans R Soc Lond B Biol Sci 2015;370.
82. Knowler WC, Pettitt DJ, Bennett PH, Williams RC. Diabetes mellitus in the Pima Indians: genetic and evolutionary considerations. Am J Phys Anthropol 1983;62:107-14.
83. Taubes G. The diet delusion. London: Vermillion; 2008:-.

84. Esparza-Romero J, Valencia ME, Urquidez-Romero R, et al. Environmentally Driven Increases in Type 2 Diabetes and Obesity in Pima Indians and Non-Pimas in Mexico Over a 15-Year Period: The Maycoba Project. Diabetes Care 2015;38:2075-82.
85. Martin JF, Johnston CS, Han CT, Benyshek DC. Nutritional origins of insulin resistance: a rat model for diabetes-prone human populations. J Nutr 2000;130:741-4.
86. Hardikar AA, Satoor SN, Karandikar MS, et al. Multigenerational Undernutrition Increases Susceptibility to Obesity and Diabetes that Is Not Reversed after Dietary Recuperation. Cell metabolism 2015;22:312-9.
87. Wells JC. A critical appraisal of the predictive adaptive response hypothesis. Int J Epidemiol 2012;41:229-35.
88. Soto N, Bazaes RA, Pena V, et al. Insulin sensitivity and secretion are related to catch-up growth in small-for-gestational-age infants at age 1 year: results from a prospective cohort. J ClinEndocrinolMetab 2003;88:3645-50.
89. Moore SE, Halsall I, Howarth D, Poskitt EM, Prentice AM. Glucose, insulin and lipid metabolism in rural Gambians exposed to early malnutrition. Diabet Med 2001;18:646-53.
90. Hill K. Life history theory and evolutionary anthropology Evol Anthropol 1993;2:78-89.
91. Wells JC, Nesse RM, Sear R, Johnstone RA, Stearns SC. Evolutionary public health: introducing the concept. Lancet 2017;in press.
92. Wells JC, Yao P, Williams JE, Gayner R. Maternal investment, life-history strategy of the offspring and adult chronic disease risk in South Asian women in the UK. Evolution, medicine, and public health 2016;2016:133-45.
93. Hoehn KL, Salmon AB, Hohnen-Behrens C, et al. Insulin resistance is a cellular antioxidant defense mechanism. Proc Natl Acad Sci U S A 2009;106:17787-92.
94. Danysh HE, Gilman RH, Wells JC, et al. El Niño adversely affected childhood stature and lean mass in northern Peru. Climate Change Responses 2014;1:7.
95. Eriksson JG, Forsen T, Tuomilehto J, Jaddoe VW, Osmond C, Barker DJ. Effects of size at birth and childhood growth on the insulin resistance syndrome in elderly individuals. Diabetologia 2002;45:342-8.
96. Hwang E, Lee KW, Cho Y, Chung HK, Shin MJ. Association between age at menarche and diabetes in Korean post-menopausal women: results from the Korea National Health and Nutrition Examination Survey (2007-2009). Endocr J 2015;62:897-905.
97. Wells JC, Sharp G, Steer PJ, Leon DA. Paternal and maternal influences on differences in birth weight between Europeans and Indians born in the UK. PLoS One 2013;8:e61116.
98. Wells JC, Stock JT. Re-examining heritability: genetics, life history and plasticity. Trends Endocrinol Metab 2011;22:421-8.

Table 1. Components of phenotypic plasticity and flexibility promoting adaptation to stochastic environments

Trait	Ecological 'booms'	Ecological 'busts'
Growth	Rapid	Slow Brain-sparing at cost to other organs
Maturation	Early puberty	Delayed puberty
Body fat	Rapid accretion Fund reproduction	Buffer starvation Fund immune function
Reproduction	Short-birth intervals	Amenorrhea
Cognitive capacity	Cooperative breeding	Locate fall-back foods

Figure 1

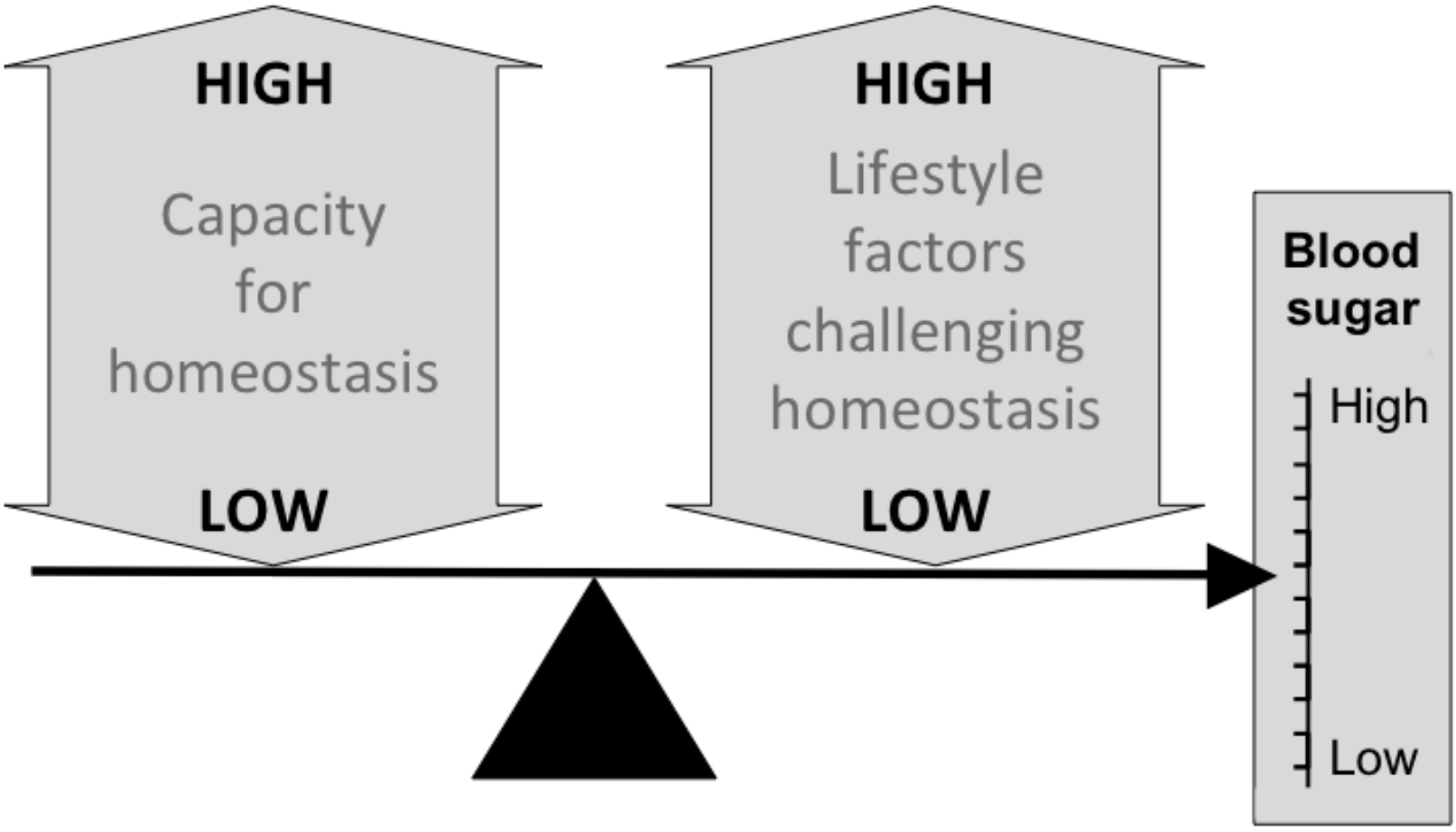
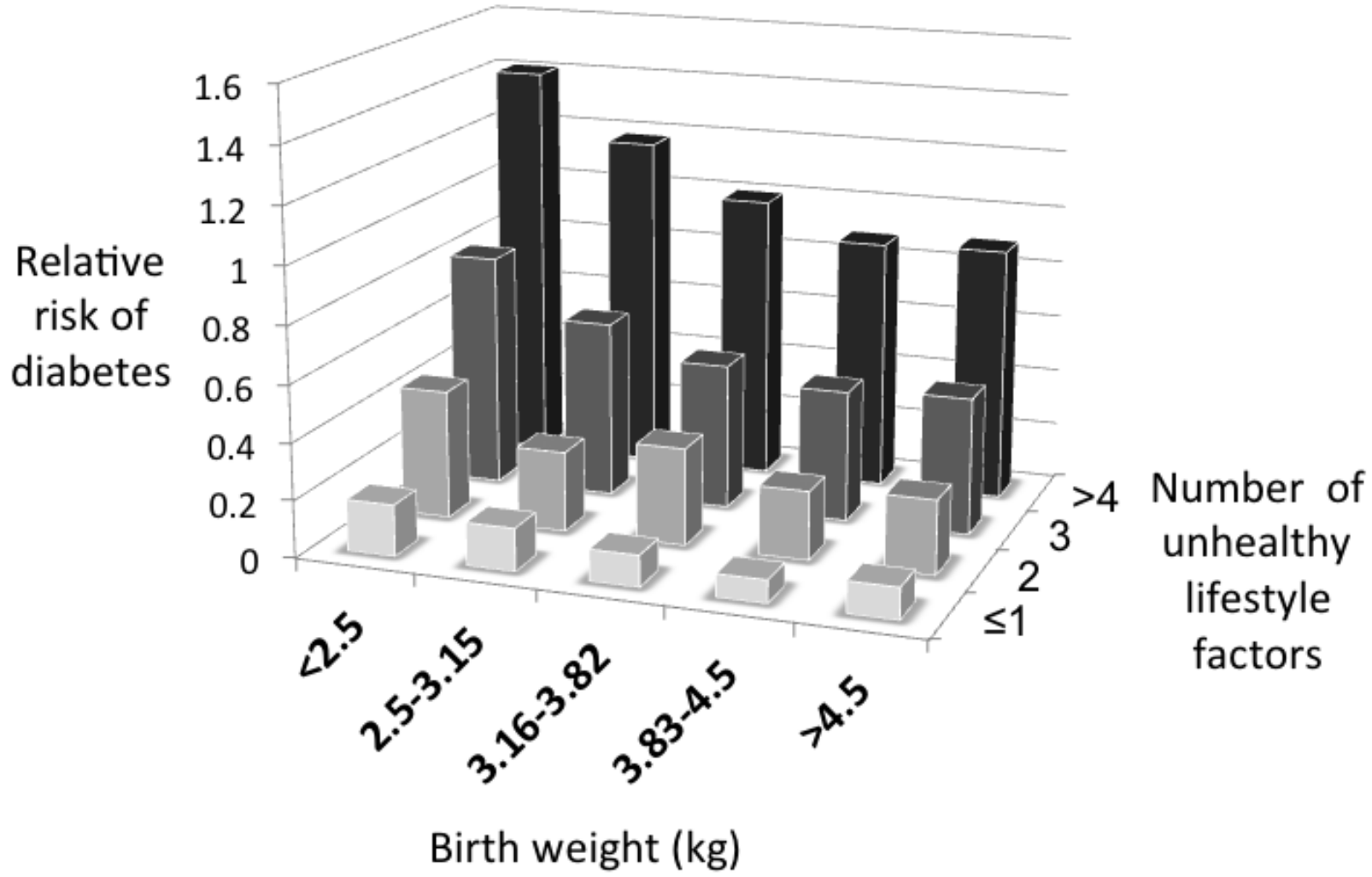

HIGH
Capacity for homeostasis
LOW
HIGH
Lifestyle factors challenging homeostasis
LOW
Blood sugar
High
Low

Figure 2


Relative risk of diabetes
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
<2.5
2.5-3.15
3.16-3.82
3.83-4.5
>4.5
Birth weight (kg)
≤1
2
3
>4
Number of unhealthy lifestyle factors

Key			
	afa – Australopithecus afarensis	hab – Homo habilis	sap – Homo sapiens
	afr – Australopithecus africanus	rud – Homo rudolfensis	
	rob – Paranthropus robustus	dma – Homo erectus (Dmanisi)	
	boi – Paranthropus boisei	ere – Homo erectus (late)	

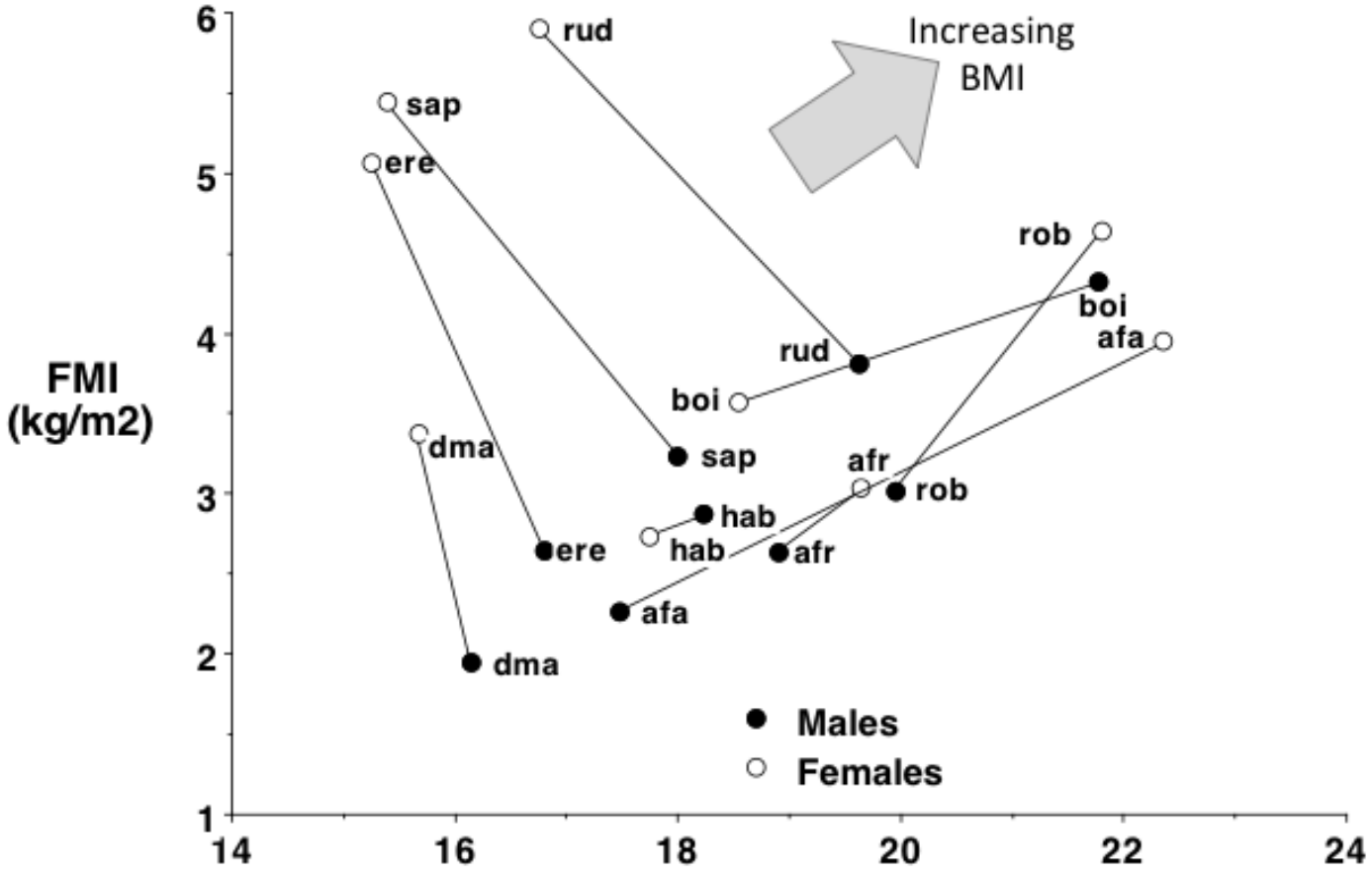


Figure 3

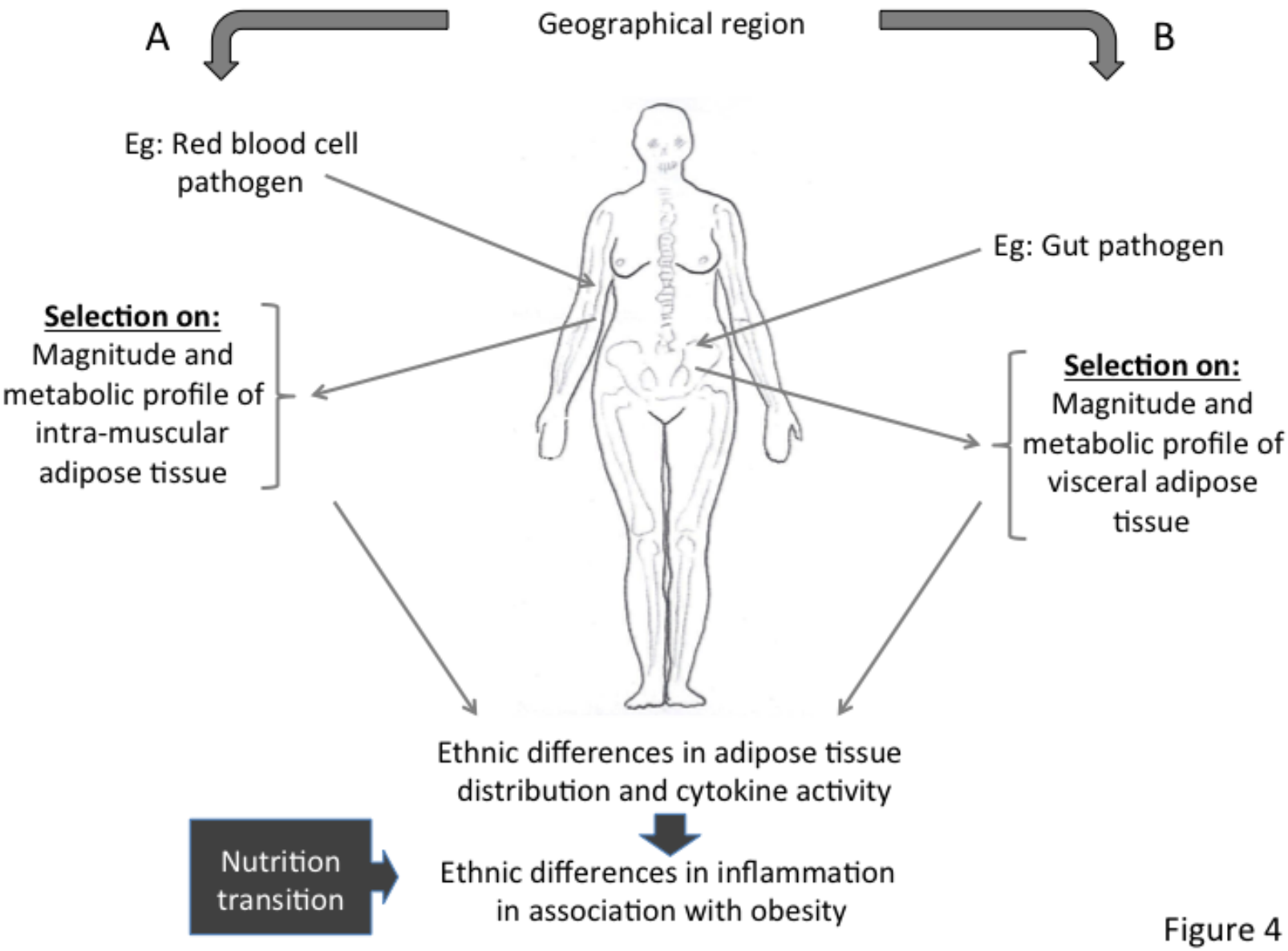

A
Geographical region
B
Eg: Red blood cell pathogen
Eg: Gut pathogen
Selection on:
Magnitude and metabolic profile of intra-muscular adipose tissue
Selection on:
Magnitude and metabolic profile of visceral adipose tissue
Ethnic differences in adipose tissue distribution and cytokine activity
Nutrition transition
Ethnic differences in inflammation in association with obesity

Figure 4

Figure 5

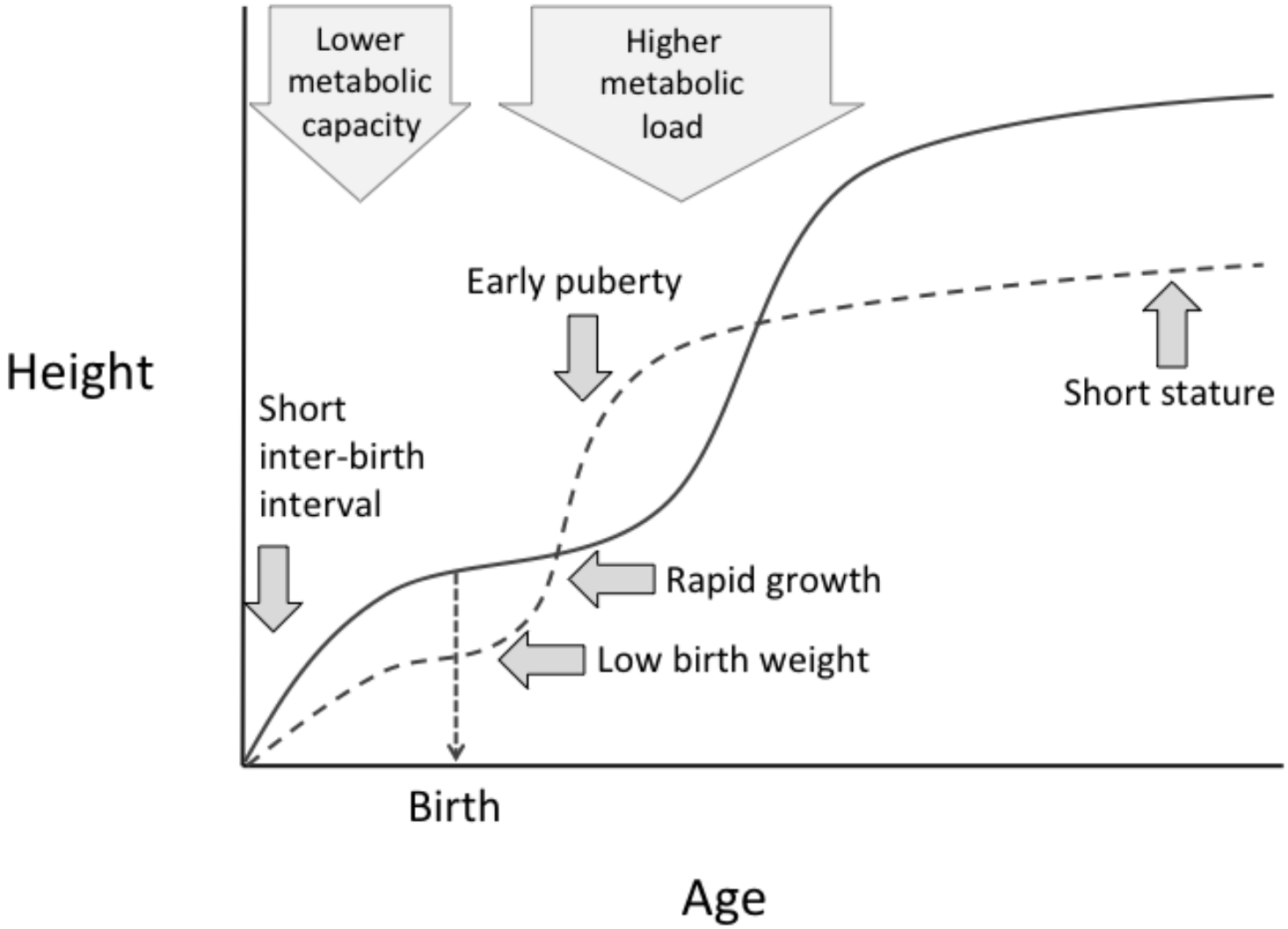

Lower metabolic capacity
Higher metabolic load
Early puberty
Short stature
Short inter-birth interval
Rapid growth
Low birth weight
Height
Birth
Age

Figure 6

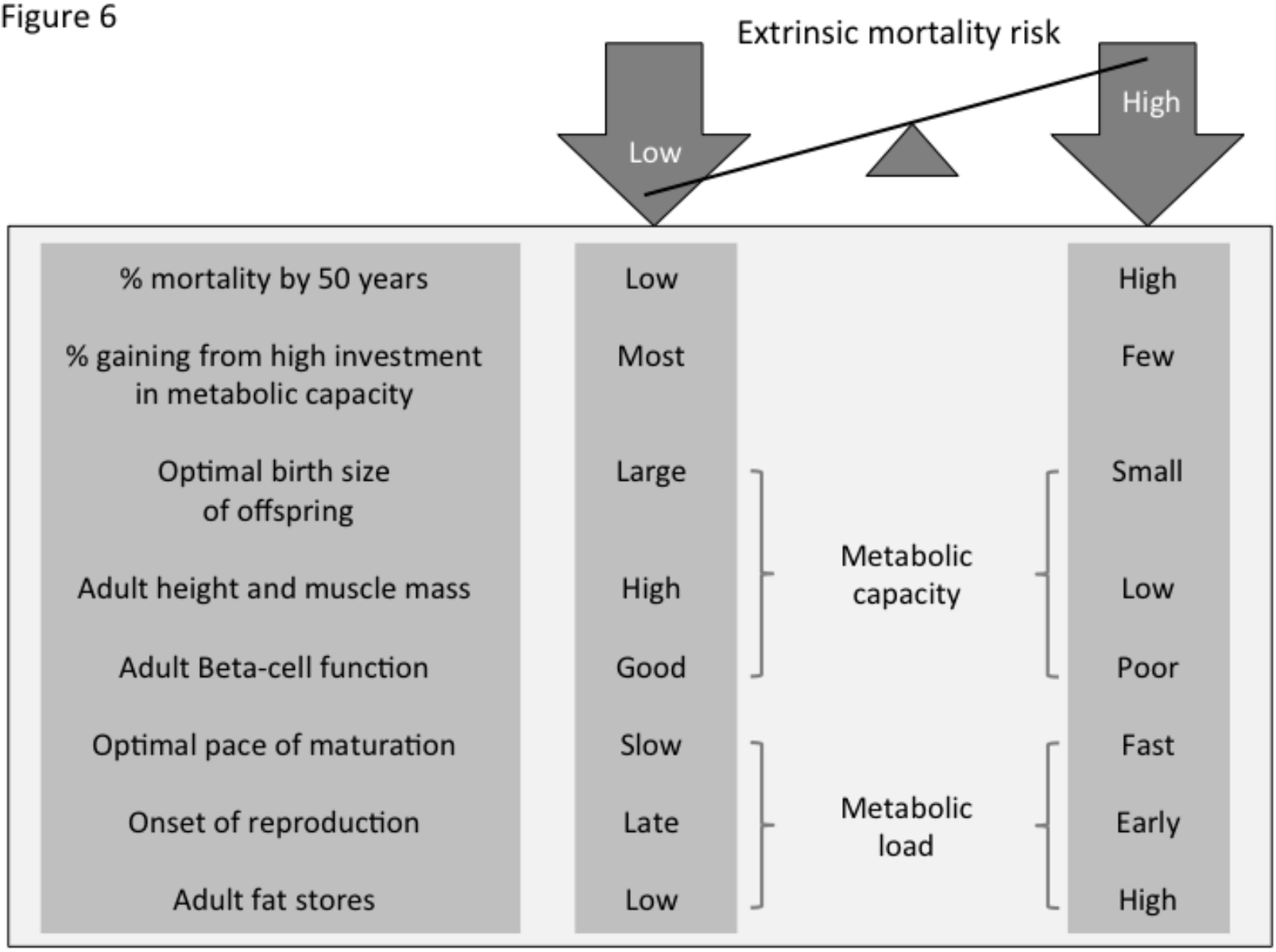
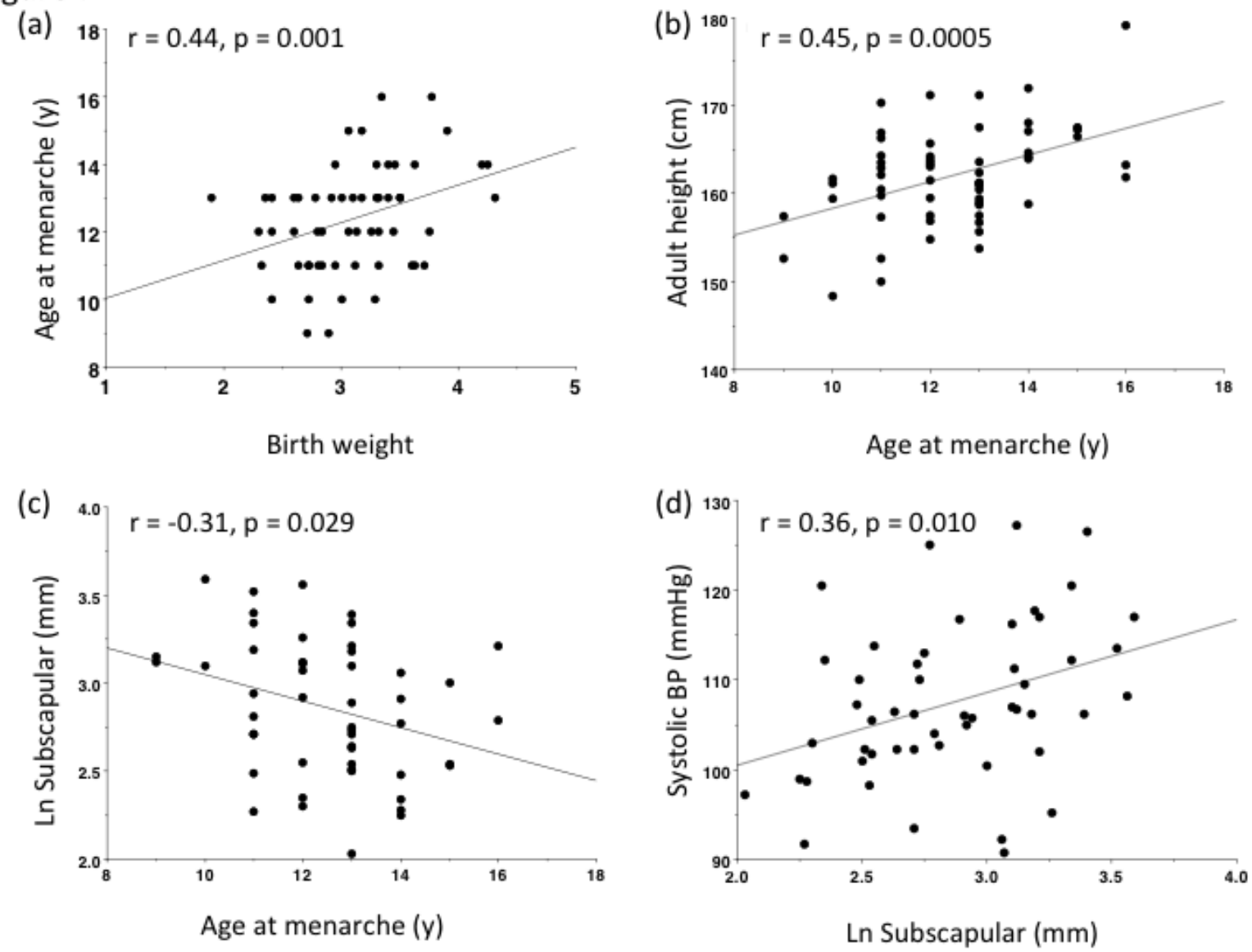

Extrinsic mortality risk
Low
High
% mortality by 50 years
Low
High
% gaining from high investment in metabolic capacity
Most
Few
Optimal birth size of offspring
Large
Small
Adult height and muscle mass
High
Low
Adult Beta-cell function
Good
Poor
Metabolic capacity
Optimal pace of maturation
Slow
Fast
Onset of reproduction
Late
Early
Adult fat stores
Low
High
Metabolic load

Figure 7


(a)
r = 0.44, p = 0.001
Age at menarche (y)
Birth weight
(b)
r = 0.45, p = 0.0005
Adult height (cm)
Age at menarche (y)
(c)
r = -0.31, p = 0.029
Ln Subscapular (mm)
Age at menarche (y)
(d)
r = 0.36, p = 0.010
Systolic BP (mmHg)
Ln Subscapular (mm)