

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

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4998 words, 7 figures, 1 table, 98 references

1 **Abstract**

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

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

23

24

25 **Introduction**

26

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

34

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

42

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

49

50 **A metabolic model of diabetes risk**

51

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

59

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

66

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

73

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

84

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

93

94

Figures 1 and 2 near here

95

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

103

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

113

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

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

123

124 **Long-term trends during human evolution**

125

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

136

137 Many components of hominin phenotype are now considered to represent ‘evolved
138 solutions’ to such ecological volatility, including body size and composition, reproductive
139 strategy, ageing profile, encephalization and bipedal locomotion.^{30,33}

140

141 Body composition can be considered a key component of this adaptive trend. Compared to
142 other primates, including extant apes, contemporary humans have relatively low levels of
143 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**

216

217 Modern humans probably emerged ~200,00 to ~150,000 years ago in Africa, although new
218 calculation methods and richer genomic material constantly fine-tune these estimations.^{48,49}
219 Around 100,000 to 60,000 years ago, some populations dispersed out of Africa and
220 progressively migrated across most of the global land mass. Australasia was reached at least
221 50,000 years ago, and the North American continent rather more recently.^{50,51} The pattern
222 of dispersal has clearly contributed to contemporary human diversity, mediated by the
223 regional geographical routes taken, contrasting selective pressures, and periodic local
224 isolations, all of which have promoted inter-group differences and some genetic
225 diversification.^{52,53} Despite this, our species is characterised by remarkably high levels of
226 genetic unity,⁵⁴ fundamentally linked with our high levels of phenotypic plasticity. The
227 selective pressures that favoured the capacity to tolerate ecological instability during
228 hominin evolution have made modern humans extremely well adapted to colonising diverse
229 environments.⁵⁵

230

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

236

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

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

246

247 Low levels of lean/muscle mass have been linked with elevated susceptibility of populations
248 such as South Asian and Australian aboriginals to insulin resistance in obesogenic
249 settings,^{19,20} and this scenario may apply to other populations with similar characteristics.

250 Hence, climatic adaptation is very likely to have shaped T2DM susceptibility.

251

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

257

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

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

267

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

278

279 *Figure 4 near here*

280

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

288

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

295

296 **Variability in diabetes susceptibility: genetics**

297

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

306

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

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

321

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

330

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

336 chronic under-nutrition over multiple generations causes profound changes in offspring
337 epigenetics, growth and metabolism.^{85,86}

338

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

345

346 **Variability in diabetes susceptibility: plasticity**

347

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

358

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

367

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

374

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

380

381 More generally, phenotypic plasticity in humans has been selected to allow accommodation
382 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

407

Figure 6 near here

408

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

420

421

Figure 7 near here

422

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

428

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

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

434

435 The study analysed UK birth weight data, stratifying by European or Indian ethnicity of each
436 parent. Compared to two European parents, two Indian parents produced a baby on average
437 ~400g lighter.⁹⁷ This describes the overall difference of Indians versus Europeans in a high-
438 income setting, but does not identify the underlying mechanism. Holding paternal ethnicity
439 constant, Indian mothers produced offspring on average ~250g lighter than European
440 mothers. Maternal phenotype clearly makes a key contribution, but whether via genotype or
441 metabolic phenotype remains unclear.

442

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

451

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

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

465

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

478

479 **Conclusions**

480

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

490

491

492

493

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.

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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/height² (FMI)
506 against lean mass/height² (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.
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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

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

<u>Trait</u>	<u>Ecological 'booms'</u>	<u>Ecological 'busts'</u>
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

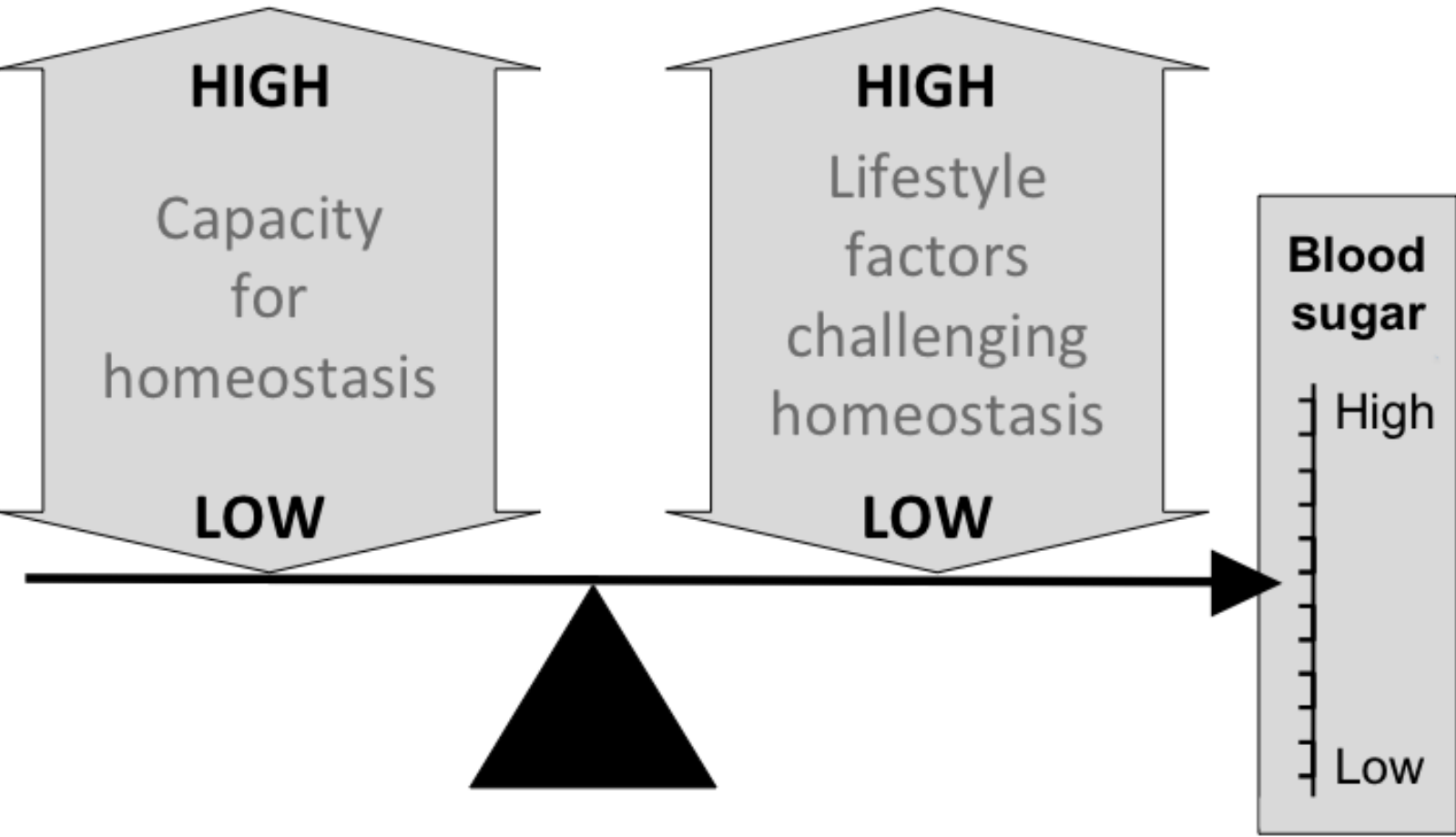
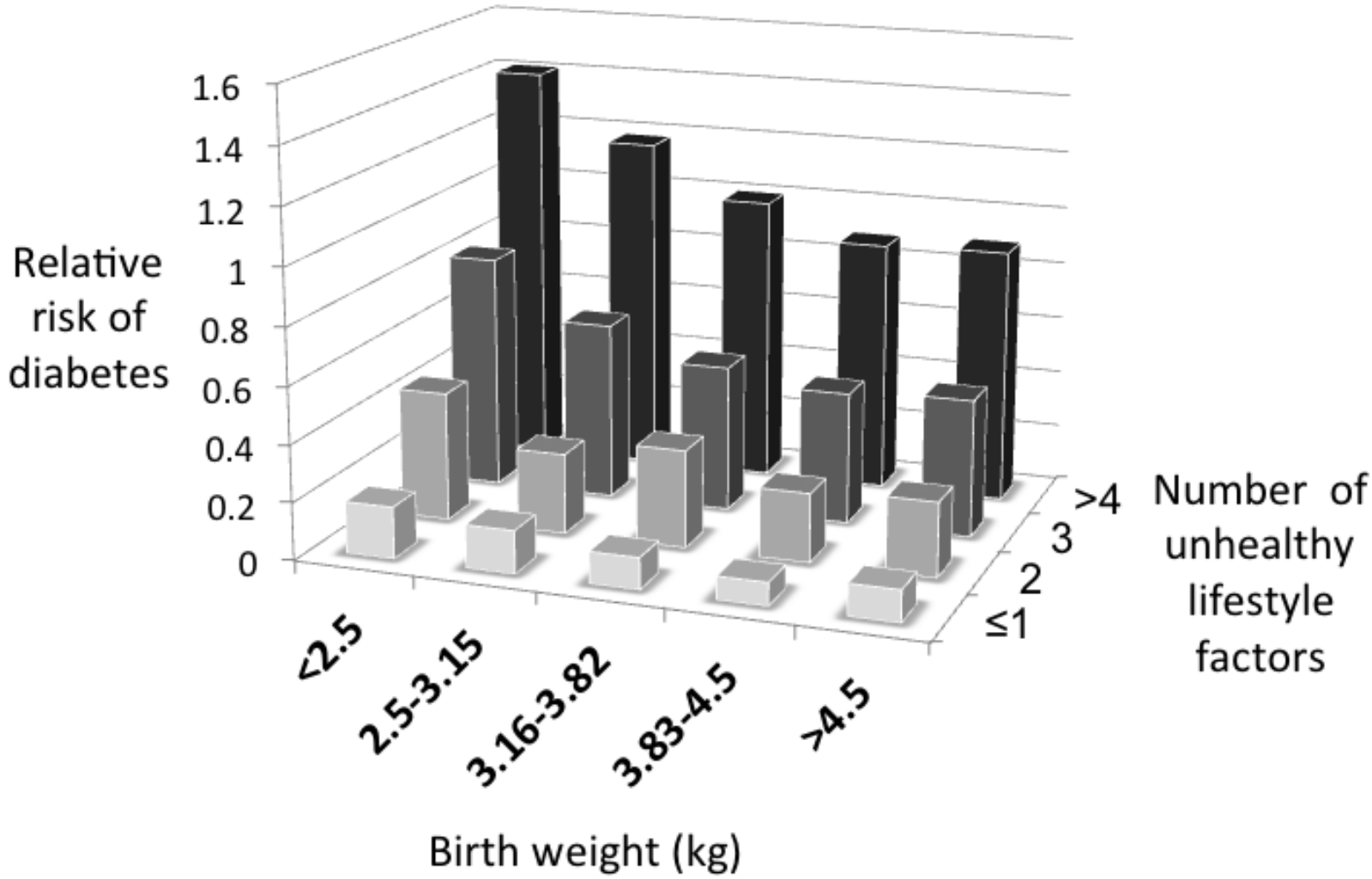


Figure 2



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)	

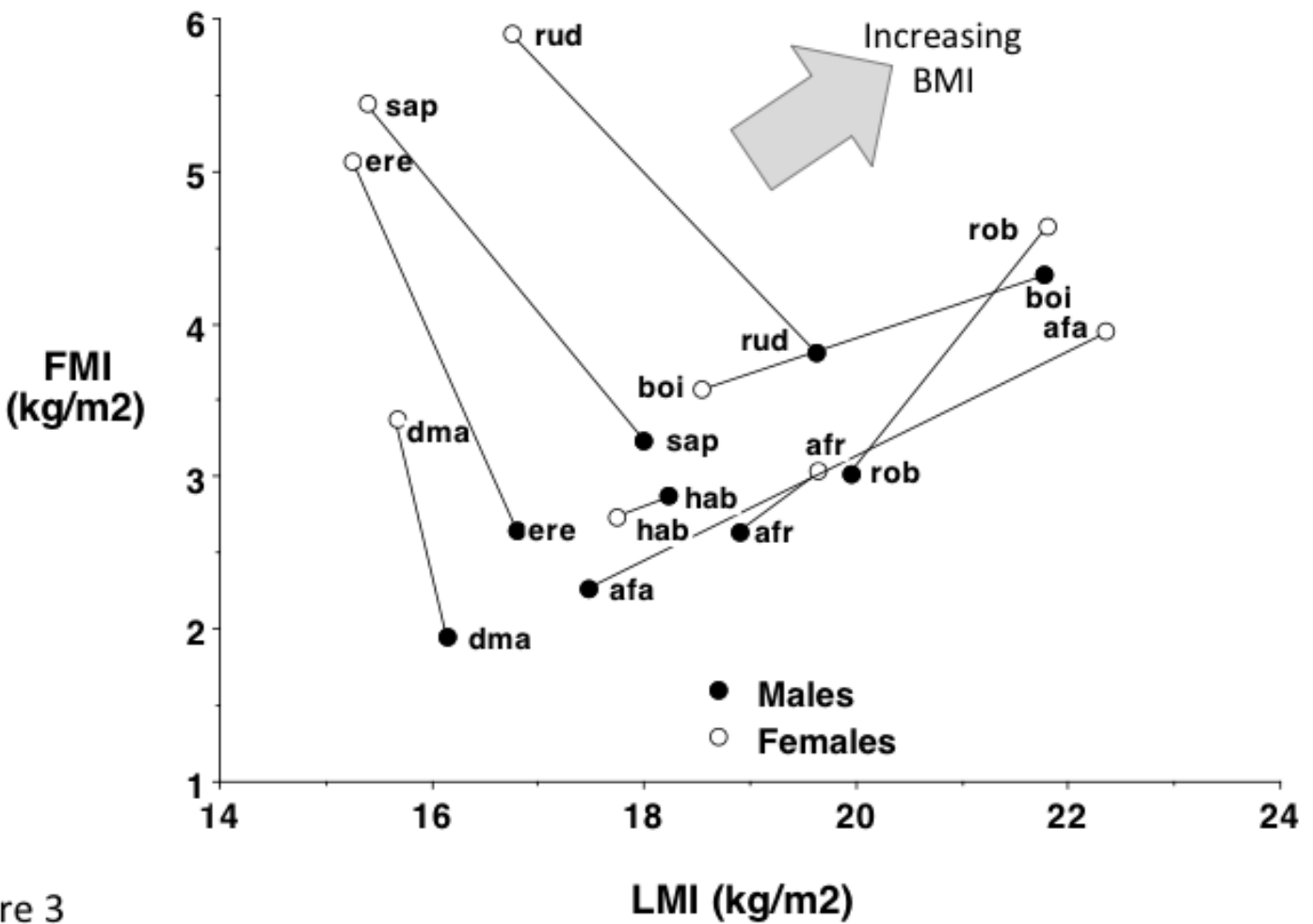




Figure 3

A  Geographical region  B

Eg: Red blood cell pathogen

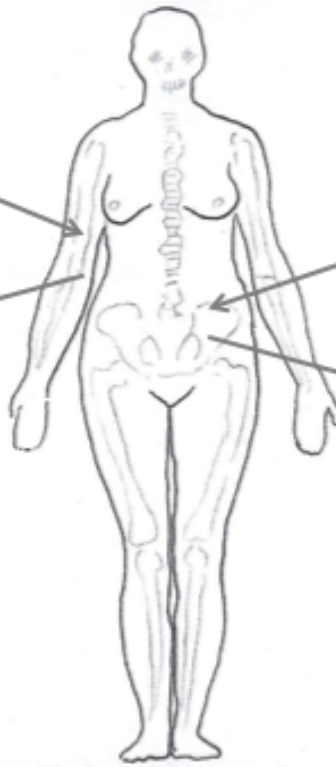
Eg: Gut pathogen

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

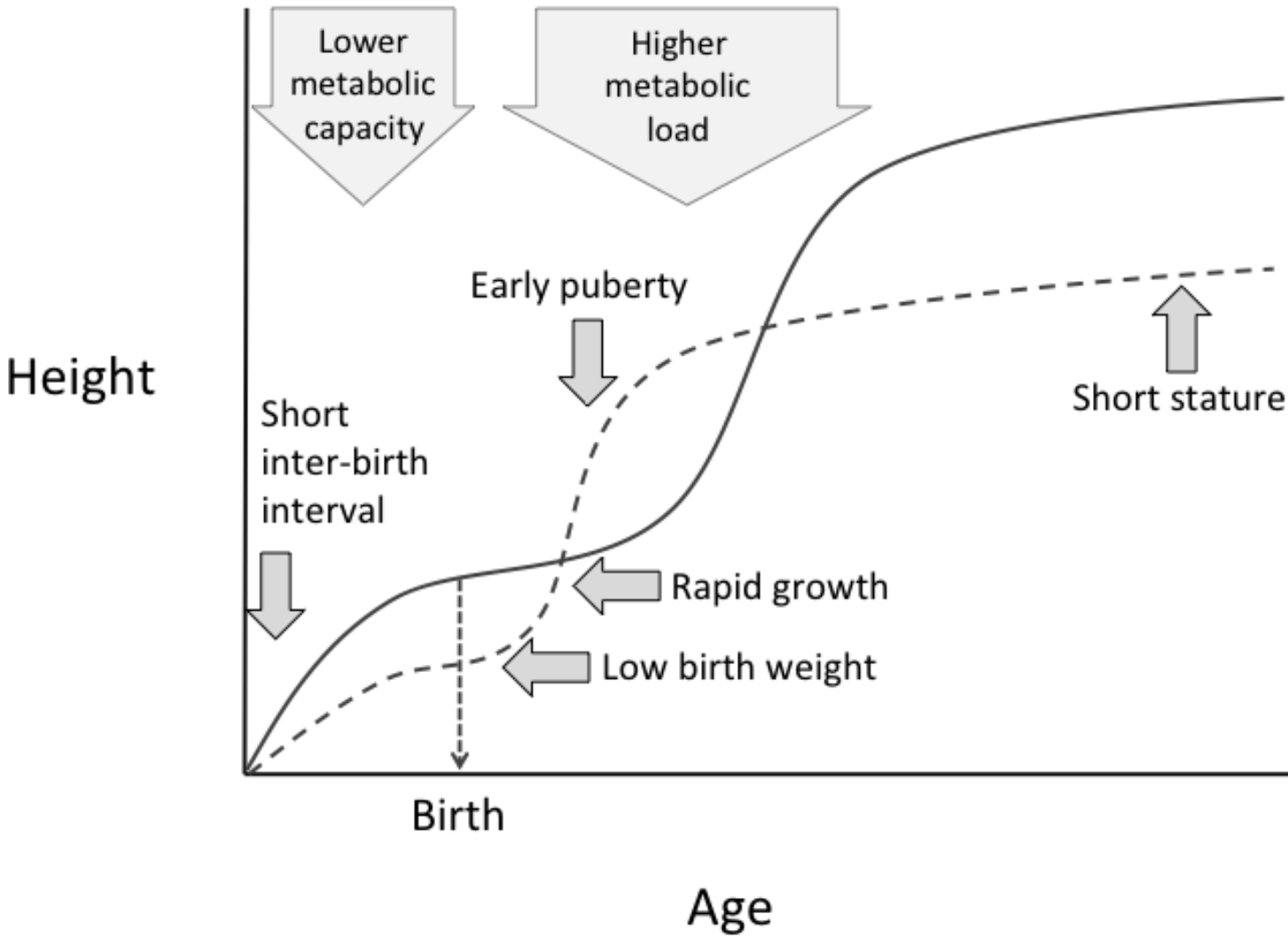
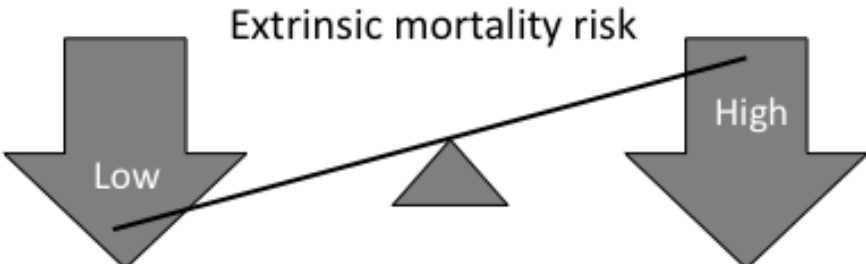


Figure 6



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

Figure 7

