The capacity-load model of non-communicable disease risk: understanding the effects of child malnutrition, ethnicity and the social determinants of health

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4999 words, 4 figures

Abstract

The capacity-load model is a conceptual model developed to improve understanding of the life-course aetiology of non-communicable diseases (NCDs) and their ecological and societal risk factors. The model addresses continuous associations of both (a) nutrition and growth patterns in early life and (b) lifestyle factors at older ages with NCD risk. Metabolic capacity refers to physiological traits strongly contingent on early nutrition and growth during the first 1000 days, which promote the long-term capacity for homeostasis in the context of fuel metabolism and cardiovascular health. Metabolic load refers to components of nutritional status and lifestyle that challenge homeostasis. The higher the load, and the lower the capacity, the greater the NCD risk. The model therefore helps understand dose-response associations of both early development and later phenotype with NCD risk. Infancy represents a critical developmental period, during which slow growth can constrain metabolic capacity, whereas rapid weight gain may elevate metabolic load. Severe-acute malnutrition in early childhood (stunting, wasting) may continue to deplete metabolic capacity, and confer elevated susceptibility to NCDs in the long-term. The model can be applied to associations of NCD risk with socio-economic position (SEP): lower SEP is generally associated with lower capacity, but often also with elevated load. The model can also help explain ethnic differences in NCD risk, as both early growth patterns and later body composition differ systematically between ethnic groups. Recent work has begun to clarify the role of organ development in metabolic capacity, which may further contribute to ethnic differences in NCD risk.

Keywords: developmental origins, non-communicable disease, capacity-load model, public health nutrition

Introduction

There is now compelling evidence that the risk of chronic non-communicable diseases (NCDs), such as cardiovascular disease, stroke, diabetes and hypertension, is associated both with lifestyle and living conditions in adulthood, and also with patterns of nutrition and growth during early development. These scenarios are central to the 'developmental origins of adult health and disease' (DOHaD) hypothesis.[1]

Diverse physiological mechanisms have been shown to underpin such life-course associations. These include developmental alterations in DNA expression (epigenetic marks), where the contributions of specific genes can be explored,[2] development of the gut microbiome,[3] growth of organs and tissues, and the setting of hormonal axes relating to growth, development, appetite and the stress response. DOHaD research has also pursued various study designs and experimental approaches, including prospective/retrospective epidemiological analyses, randomized trials, Mendelian randomization studies, and tightly controlled experiments on various animal species.

Mechanistic work is clearly crucial, but conceptual models are also needed to integrate data from diverse study designs and physiological mechanisms. Among the first such models were those proposing 'critical windows' of development, during which phenotype is particularly sensitive to ecological factors, and the 'thrifty phenotype' hypothesis of Hales and Barker.[4] The latter was the first to suggest *why*, rather than merely *how*, variability in adult NCD might be shaped by developmental experience.

The thrifty phenotype hypothesis has been influential, stimulating both empirical research and further conceptual development. Hales and Barker originally addressed type 2 diabetes risk, and proposed that malnutrition during fetal life and infancy compromised development of the pancreas. In the short term, the resulting energy-saving would help meet the obligatory metabolic requirements of the brain, but in the long term the cost would be poorer pancreatic function, reducing tolerance of adult obesity and energy-dense diets.[4]

Early malnutrition thus became emphasized as a key step in NCD aetiology. Initially, data appeared to support the hypothesis: low weight at birth or in infancy was associated with later diabetes risk in many cohorts,[5, 6] while animal experiments confirmed that exposure to low-protein diets during pregnancy affected insulin metabolism, pancreatic function and body fatness in the offspring.[7]

Nevertheless, early DOHaD studies did not formally test the thrifty phenotype hypothesis, rather they simply appealed to it when interpreting their findings. As larger epidemiological datasets became available, it became apparent that associations between early growth patterns and NCD risk were evident across the entire range of birth weight.[5, 8, 9] Broadly, every unit-increase in birth weight was associated with lower NCD risk. On this basis, overt fetal malnutrition could not be the primary mechanism linking developmental experience with NCD risk. Rather, simply *growing* during fetal life and infancy appeared broadly protective.[10, 11]

For several reasons, however, attention began to shift away from birth weight as an important marker of NCD risk. First, variability in gene expression attracted growing

attention, with studies showing that nutritional exposures during the peri-conceptual period generated epigenetic effects relevant to NCD risk.[12] Since size at birth is most closely associated with nutritional experience in later pregnancy, and relates poorly to growth variability in early pregnancy,[13] birth weight could not be easily linked with these epigenetic studies. Second, if the fetal development of organs such as the pancreas was important, then weight at birth and during infancy might represent an unreliable risk marker, due to confounding by variable fatness. Third, an influential statistical model was published, proposing that weight change between birth and adulthood was the primary component of growth predictive of NCD risk.[14] Seemingly consistent with that, randomized trials linked the composition of infant formula-milks with NCD risk in childhood.[15] These effects were independent of fetal growth patterns, as the trial groups had similar birth weight when the trial commenced.

However, none of these challenges actually refutes an important role of early growth variability in the aetiology of NCDs. The fact that epigenetic marks emerging in early pregnancy predict NCD risk does not preclude an independent contribution of growth variability. The statistical model emphasizing postnatal weight change should be reconsidered, because variability in body weight relates to physiology in very different ways at different life-course periods . Moreover, randomized trials of formula-milks can illustrate the role of infant nutrition in NCD aetiology, but provide no information on fetal nutrition because the intervention began at birth.

Since size both in early life and adulthood is strongly predictive of NCD risk, patterns of early growth merit further attention. To this end, the capacity-load model was developed.[10]

The capacity-load model

Many components of adult lifestyle and environment contribute to NCD risk, including diet, physical inactivity, psychosocial stress, smoking, air pollution, alcohol intake and exposure to infections. Collectively, all of these impose a 'metabolic load' that challenges the body's ability to maintain homoeostasis at the levels of cells, organs or tissues.[10, 11] The concept overlaps broadly with that of allostatic load,[16] but instead of emphasizing the stress response, 'metabolic load' highlights components of homoeostasis related to fuel metabolism and cardiovascular function. This makes it especially relevant to exploring the associations of dietary intake, physical activity behavior and body composition with NCD risk – in other words, the capacity-load model is designed with the key elements of public health nutrition in mind.

The ability to tolerate metabolic load is then considered to depend on a suite of traits, collectively termed 'metabolic capacity', that enable maintenance of homeostasis.[10, 11] Consistent with the thrifty phenotype hypothesis, these traits develop during early 'critical windows', meaning that they are strongly shaped by growth patterns (and hence nutritional supply) in fetal life and infancy. Importantly, nutrition in early life has very different effects on organ phenotype compared to later life, due to fundamental changes in the nature of growth.

The classic Minnesota starvation study, performed on adults during the Second World War, demonstrated ~70% loss of fat during restricted feeding, compared with only ~17% loss of

lean mass (27%, accounting for oedema).[17] During subsequent refeeding, the lean deficit was fully resolved. During early life, in contrast, deficits in organ growth appear impossible to reverse subsequently, even if body weight increases. Early growth comprises an increase in cell number through cell division, known as hyperplasia, whereas later growth comprises increases in cell size, or hypertrophy. The great majority of hyperplasic growth occurs during fetal life and early infancy. In the rat, for example, organ and tissue growth is entirely due to cell proliferation until ~17 days after birth, with minimal change in cell size; from ~17 to ~40 days cell proliferation proceeds but more slowly, and cell size increases in most organs; and from ~40 days cell proliferation slows substantially or ceases, while cells increase in size in most tissues, but minimally so in most organs.[18]

Extending this approach, the effects of subjecting rats to under-nutrition at different ages were investigated.[18] Even after refeeding, rats malnourished from birth had lighter organs and fewer cells in them. In contrast, those malnourished after 65 days of life managed to regain their organ masses and cell numbers after re-feeding. Hales and Barker suggested that it was through impacting hyperplasic growth and constraining cell division that early nutritional insults generated permanent metabolic defects.[4] From early childhood, the body becomes bigger, but it cannot reverse major structural 'decisions' already locked into physiology. This helps explain why early growth variability predicts NCD risk decades later.

The capacity-load model builds on these insights, but emphasizes dose-response associations between early growth variability and organ phenotype.[10, 11] Many specific physiological traits scale relatively linearly with birth weight, including neonatal lean mass, nephron number in the kidney, blood vessel caliber, airway size and metabolic functions

such as insulin secretion. Broadly, the larger lean mass at birth, the more enhanced are these traits, and hence the greater the long-term homeostatic capacity. Metabolic capacity is assumed to track from infancy into adulthood, but eventually deteriorates as part of the process of aging. Failure to maintain homeostasis allows the emergence of pathophysiology, eventually resulting in overt NCDs.

The duration of hyperplasic growth (effectively, the length of critical windows) may differ between specific organs. This may explain why low body weight at 1 year, indicating continued constraint of the pancreas, predicted greater diabetes risk in cohorts born in the early 20th century.[5] In contrast, nephrogenesis ceases at birth, hence greater weight gain at any time from birth onwards cannot enhance this physiological trait, and is instead associated with higher blood pressure.[19] These contrasts indicate that metabolic capacity continues to increase for some traits in early postnatal life, whereas for others metabolic load is already increasing after birth.

The risk of NCDs can then be modeled as a function of metabolic load relative to metabolic capacity.[10, 11] Holding constant capacity, increasing load is predicted to increase NCD risk in dose-response manner. Equally, holding constant load, decreasing capacity is predicted to increase risk in dose-response manner. The greatest NCD risk is predicted in those with both diminished capacity and elevated load. For example, a study of Swedish men showed that the blood pressure 'penalty' for low birth weight was minimal in those of small adult size, and largest in those both tall and heavy.[20] Recent large cohort studies provide stronger support, demonstrating exactly the predicted continuous relationships of both components of metabolism with diabetes (**Figure 1**) and hypertension risk.[9, 21] Among those maintaining a

185 healthy phenotype in adulthood, there is negligible elevated NCD risk in association with low
186 birth weight. This helps explain why despite low average birth weights, NCDs remained rare
187 in low-/middle-income countries (LMICs) until the obesity epidemic emerged.
188
189 *Figure 1 near here*
190
191 The key difference between the thrifty phenotype hypothesis and the capacity-load model is
192 that the former emphasis on early malnutrition is replaced by a continuous model of NCD
193 risk. This allows us to address an issue which has proved very challenging in public health,
194 namely that it is difficult to define specific risk thresholds for both adult nutritional status
195 and early growth variability. There is no clear subset of individuals with pathological traits,
196 rather statistical cut-offs are used to define high-risk groups (eg low birth weight, adult
197 obesity). In reality, there is a graded increase in disease risk in association with traits such as
198 adult BMI and birth weight, and the same scenario applies to the other components of load
199 (dietary intake, physical activity level etc).
200
201 In the largest datasets, these variables often display a J-shaped association with NCD risk.
202 For example, risk generally declines as birth weight rises, but in some populations it
203 increases again among those with the highest birth weights.[22] In the upper range, rising birth
204 weight is primarily attributable to adipose tissue (macrosomia, representing metabolic load)
205 rather than organs and tissue associated with metabolic capacity. Equally, the association
206 between BMI and NCD risk in adult life is J-shaped in the opposite direction. Over most of its
207 range, increasing BMI is associated with elevated NCD risk, however those with very low BMI
208 also have perturbed metabolism.[23] There is therefore an optimum range of birth weight and

BMI, and this scenario may apply to other traits such as dietary intake and physical activity level.

Recent studies highlight the importance of these traits in explaining NCD risk. Among three US cohorts, for example, it was estimated that 66% of hypertension cases, and 81% and 94% of diabetes cases in men and women respectively, could potentially have been prevented if people led healthy adult lifestyles (BMI, diet, physical activity, smoking, drinking) and had been born with a birth weight in the normal range.[9, 21] Whilst the capacity-load model may not fit the data equally successfully in every population, it appears useful for explaining unequal NCD risk in association with key nutritional traits within populations.

So far, I have emphasized the contribution of growth traits to metabolic capacity, where size in early life indicates homeostatic quality. This approach could potentially be extended to functional traits, though routinely obtaining such data in the fetus or infant remains challenging. Epigenetic marks could be explored in this context, as could various hormones or metabolic processes such as pancreatic beta-cell function or arterial distensibility.[2] However, the predictive success of the model as described above highlights the value of birth weight as a *composite* marker of early development. It is precisely because so many individual traits scale relatively linearly with birth weight that this outcome, in combination with markers of load, successfully predicts adult disease. Incorporating multiple detailed predictors should be tested empirically, but it would cost more, and might not perform substantially better. For both capacity and load, multiple traits could be incorporated by expressing outcomes as z-scores, and then averaging them. Alernatively, Li and colleagues

quantified a composite load using thresholds, and summed the traits per individual categorized as unhealthy.

Each of capacity and load may change through the life-course, though to different degrees. Adults may adopt healthier lifestyles, and cohort studies indicate that these are associated with low risk of diabetes and hypertension, regardless of birth weight. High-risk groups (those with low capacity) clearly have most to gain from reducing their load. Some components of metabolic capacity are relatively fixed by early infancy, while other components will benefit from exercise and physical fitness throughout the life-course. Growth patterns in infancy and childhood are also very relevant.

Childhood under-nutrition

The capacity-load model was originally applied to understand associations of birth weight with NCD risk, and the findings have been relatively consistent across cohorts. The scenario for post-natal growth variability has received less attention, and the findings are more heterogeneous across populations.

In retrospective analyses of the UK Hertfordshire cohort, low weight at 1 year predicted elevated NCD risk.[5] This suggests that poor post-natal growth continues to constrain the development of metabolic capacity in early infancy, when hyperplasic growth is still occurring. The results of propsective randomized trials of infant formula-milk, in which groups with faster growth had higher NCD risk markers in childhood,[15] might appear to contradict this interpretation, but in fact they suggest that in this context, rapid infant

256 growth exacerbated metabolic load more than it benefited metabolic capacity.[11] The same
257 issue may apply to population-differences in the association between early post-natal
258 growth and adult body composition, discussed above. While the underlying physiological
259 mechanisms remains poorly understood, it appears that infant growth can impact both
260 metabolic capacity and metabolic load. Slow growth can constrain capacity, while rapid
261 growth can elevate load, and specific populations differ in the relative magnitudes of these
262 antagonistic effects.[11]
263
264 A further reason for extending the model to post-natal life is that birth weight is not
265 routinely measured in most LMIC populations, as the majority of births take place outside
266 hospital settings. Instead, data on nutritional status in early life relate primarily to stunting
267 (low height) and wasting (low weight-for-height). In this context, overt malnutrition in
268 childhood might indicate continued depletion of metabolic capacity, however this
269 hypothesis has received little attention.
270
271 A recent 7-year follow-up of children who had experienced severe acute malnutrition (SAM)
272 in early life provides unique data on this issue.[24] Markers of growth, adiposity, physical
273 function and NCD risk were compared between survivors of SAM and sibling/community
274 controls in rural Malawi. Compared to controls, SAM survivors demonstrated shorter stature
275 and leg length, lower lean mass, and weaker grip strength, all indicating reduced metabolic
276 capacity. Overall they had similar adiposity, but had reduced levels of peripheral adiposity,
277 and hence a more central fat distribution. There was little overt indication of increased NCD
278 risk at this timepoint.
279

In the absence of high metabolic load, therefore, deficits in metabolic capacity emerging in association with SAM may remain latent, but should this population be exposed to obesogenic factors later in life, they may demonstrate elevated susceptibility to NCDs.

So far, this review has described the capacity-load model and its potential to integrate data on diverse risk factors within a broader framework, to understand NCD aetiology. The next question is, can it help explain why NCD risk is so strongly associated with bio-social factors such as socio-economic position (SEP), ethnicity and geography?

Socio-economic status

Higher rates of chronic disease in those of lower SEP are now well established in high-income countries (HICs). Those of poorer backgrounds tend to die earlier from these conditions, and to experience more years of ill-health prior to death.[25] Importantly, disadvantaged groups tend to experience poorer nutrition and growth in early life, but may also demonstrate less healthy lifestyles in adulthood, thus demonstrating susceptibility to both components of NCD risk. The capacity-load model may therefore help understand the 'social determinants of health inequalities'.[26]

Most populations show an inverse social gradient in birth weight, as illustrated for a Brazilian city in **Figure 2a**.[27] In this population, the gradient persisted into post-natal life, with the offspring of low-income families gaining less weight in infancy. **Figure 2b** shows the consequences 19 years later, addressing any change in socioeconomic circumstances after birth.[28] In both sexes, those who had never experienced poverty were tallest, while those

304 who had remained poor throughout development were ~4 cm shorter. Those whose socio-
305 economic status had fallen since birth were taller than those who had started poor but
306 subsequently experienced better conditions. This study highlights the pernicious lifelong
307 effect on stature of being born into poverty.
308
309 *Figure 2 near here*
310
311 Many studies show a similar social gradient in adult height, established in early life. For
312 example, across 54 LMIC countries, women of higher status were found to be consistently
313 taller.[29] Whereas height increased over time in wealthier groups, suggesting improvements
314 in infant health, in poorer groups height either remained stable or declined over time. The
315 summed effect was increasing height inequality over time.
316
317 Associations of SEP with birth weight and adult height indicate significant social gradients in
318 metabolic capacity. One underlying mechanism is variability in organ phenotype, for
319 example height is associated with the size of various organs in adulthood.[30] However, poor
320 socio-economic circumstances during development have also been directly associated with
321 epigenetic effects.[31] Through such mechanisms, the effects of early poverty may become
322 locked into metabolism over the long-term. However, this reflects only the first of two
323 penalties, for many populations also show social gradients in metabolic load.
324
325 Until recently, obesity was restricted to affluent groups, and poorer groups remained
326 shorter and thinner throughout the life-course. By the late 20th century, the situation had
327 reversed in HICs. Here, obesity is now commoner amongst poorer groups, and tends to show

328 an inverse social gradient in adults and children, though adult data are more consistent in
329 men than women.[32] Poorer groups also consume less healthy diets, are more likely to
330 smoke, and have lower levels of leisure-time physical activity.
331
332 Looking beyond HICs, the picture is more complex. Amongst the poorest countries, chronic
333 disease risk factors remain clustered amongst the wealthy, and in the early stages of
334 economic development, this effect is magnified. In the 1990s, for example, an international
335 comparison of women and preschool children in LMICs found that obesity tended to
336 increase in proportion with gross national product (GNP) and, within populations, it was
337 characteristic of wealthier individuals.[33] Other studies also describe a strong association
338 between wealth and obesity in LMIC populations.[34]
339
340 As economic development consolidates, however, this pattern may reverse. One study 2004
341 reported that as GNP increases, obesity becomes commoner in those of low rather than high
342 SEP, with the effect stronger for women than men. Surprisingly, the GNP 'cross-over point'
343 at which the association between obesity and SEP shifted was not indicative of affluence,
344 being only $2500 per capita.[35] Other LMIC studies report that obesity remains commonest
345 among the affluent, though it may be increasing fastest in poorer groups.
346
347 Obesity is a useful marker for unhealthy diet and sedentary behaviour, and is closely
348 associated with the NCD epidemic. However, these studies indicate that obesity has a
349 complex association with economic development, and countries vary in terms of whether
350 the rich or poor acquire the greatest metabolic load from this source.
351

Beyond obesity, other components of metabolic load also show social patterning in LMICs, though again with heterogeneity across studies. In many cases, wealthier groups still have priority access to foods and lifestyles promoting NCD risk, but poorer groups are experiencing increased exposure to some risk factors. In India, for example, the diet of urban slum dwellers typically incorporates junk food, and predisposes to central adiposity and perturbed metabolism.[36] A study of informal settlements in Mumbai found that energy-dense snacks and sugary drinks were commonly given even to infants and toddlers.[37] More generally, smoking is more common among poor than rich groups, especially in men.

In HICs, there is a clearer inverse social gradient in NCD risk, and yet here too there is complexity, for socio-economic position in many of these countries is associated with the ethnic composition of the population. The capacity-load model can likewise help explain ethnic variability in NCD risk.

Ethnicity

Ethnic differences in birth weight are well recognized in countries like Australia, South Africa, UK and US. **Figure 3a** shows differences of ethnic minorities relative to white European infants in a UK cohort born 2000-2002. Average weight was lower, though variably so, in every ethnic minority, and the prevalence of low birth weight was greater.[38] Smaller maternal size, higher parity, and slightly shorter pregnancies accounted for much of the difference in the Indian and Bangladeshi populations, while SEP and educational status also contributed for all groups.[38] This indicates that variability in metabolic capacity reflects the cumulative experience of earlier generations.

Figure 3 near here

These differences, averaging 9-10% lower values in the South Asian populations, indicate deficits in metabolic capacity. Moreover, the magnitude of depletion of metabolic capacity may be greater than that in birth weight. Indian neonates from the city of Pune were found to be on average almost 1 kg lighter than British neonates of European ancestry, but this deficit was unequally distributed across body components. Whilst head circumference was reduced by ~1.2 z-scores, weight and length were ~1.5 z-scores lower, and abdominal circumference ~2.3 z-scores lower. In contrast, triceps skinfold was reduced by ~0.8 z-scores, and subscapular skinfold by only ~0.3 z-scores.[39] Similar findings emerged from a UK study: at 3 months, South Asian infants were ~220 g lighter than European infants, but had ~340 g less lean mass, and this deficit could be largely explained by their ~500 g lower birth weight.[40] Indian babies have been described as having a 'thin-fat' phenotype, preserving their brain growth and adiposity at a cost to other organs and muscle mass.[39] This can be considered an extreme form of the 'thrifty phenotype', implying a major deficit in metabolic capacity.

More generally, birth weight varies substantially across populations and systematically by global region, being higher in Western industrialized than in Asian, African or Central/South American populations.[11] Again, this implies variability in metabolic capacity. Although this may incorporate genetic effects, as indicated by studies of babies of mixed ethnic ancestry, environmental factors undoubtedly play a crucial role. Restricting analysis to high SEP populations, variability in fetal growth across countries is very modest, suggesting that

cumulative exposure to contrasting environments across generations is the primary cause of inter-country variability.

As with birth weight, human populations also show substantial variability in adult nutritional status. Turkana pastoralists from Kenya average 168 and 177 cm in height in females and males respectively, but have BMI below 18.5 kg/m^2. Tongan Islanders differ negligibly in height from the Turkana, but with BMI of ~30 kg/m^2 they have ~70% more weight, much of the difference comprising adipose tissue.[11] Since organs track stature more strongly than weight, Tongan Islanders must impose a substantially greater metabolic load on their homeostatic capacity than the Turkana.

Both the amount and distribution of adipose tissue vary between ethnic groups. Imaging studies have demonstrated low levels of visceral fat in African Americans relative to Europeans, whereas South Asians have both higher total body fat content for a given BMI (**Figure 3b**), and greater visceral fat.[41] Along with their lower birth weight, this excess adiposity is considered to account for much of the elevated NCD risk of South Asians relative to Europeans.

Beyond variability in the quantity and distribution of adipose tissue, ethnic groups also vary in its metabolic impact. In British schoolchildren, the association between adipose tissue and insulin resistance was stronger in South Asians compared to those of African/Caribbean or European ethnicity.[42] In other words, excess adiposity appears to be more 'toxic' for some ethnic groups. A plausible explanation may lie in the inflammatory factors secreted by adipose tissue, which promote immune function but also elevate cardiovascular risk. Several

studies have reported ethnic differences in leptin and cytokine levels, which may reflect variability in both the anatomical distribution of adipose tissue and its inflammatory activity.

Overall, such differences in body composition are strongly implicated in the variability in NCD risk that characterizes ethnic minority groups such as South Asians in the UK, African and Hispanic Americans in the US, aboriginal or first nation populations in Canada and Australia, and Maori populations in New Zealand. Some populations seem to pay a greater metabolic penalty for obesity than others. In addition, ethnic groups may also vary in their lifestyles, though the heterogeneity is very complex, and individual groups may change behaviour at different rates over time. Finally, ethnic minorities have often faced long-term prejudice and psychosocial stress, which may elevate metabolic load via chronic activation of the stress response.

Broadly, therefore, ethnic minority groups in HICs are characterized by lower metabolic capacity, and this is often exacerbated by elevated metabolic load. Ethnic differences in cytokine biology may exacerbate these effects, so that migrants born in pathogen-rich conditions who live as adults in industrialized settings may have three sources of elevated cardio-metabolic risk: lower capacity, elevated load, and a predisposition to inflammation.

Which of capacity and load is more important?

We should not expect the epidemiology observed in HICs to be replicated exactly in other regions, for several reasons.[11] First, the relative contributions of capacity and load may differ. In HICs, the obesity epidemic in combination with western diets and sedentary

448 behaviour indicates relatively high load in the majority of adults. Under this scenario,
449 variability in birth weight helps explain variability disease risk, by indicating how well each
450 individual can tolerate the high load.
451
452 In LMICs, in contrast, individuals vary substantially in the magnitude of metabolic load. In
453 urban environments, many are overweight or obese, whereas in rural settings, average BMI
454 remains much lower and chronic energy deficiency remains prevalent. Conversely, the
455 majority were born with lower birth weights than HIC populations. This indicates a generic
456 reduction in metabolic capacity, and increases the susceptibility of entire populations to any
457 elevation in metabolic load. In this scenario, NCD risk may be predicted better by load than
458 capacity, and is strongly associated with urbanization. This may explain the high prevalence
459 of diabetes in urban India, despite high BMI remaining relatively uncommon.
460
461 Second, infant growth patterns may shape NCD risk in contrasting ways. In HICs with high
462 average birth weight, rapid infant weight gain is associated with later adiposity and elevated
463 NCD risk. In India, Brazil and Guatemala, however, where average birth weight is lower,
464 rapid infant weight gain was associated with greater height and lean mass in adulthood, but
465 negligbly with adiposity.[43] Infant weight gain may therefore benefit metabolic capacity in
466 chronically undernourished populations, but elevate load in populations that are already
467 relatively well nourished.
468
469 As yet, most data are observational, and more studies are needed to determine whether
470 promoting infant growth in LMIC populations would indeed reduce NCD risk. Two studies
471 offer some support for this hypothesis. First, a community supplementation program

472 targeting pregnant women and children <7 years in Guatemala was associated both with
473 improved childhood growth, and with modest reductions in adult NCD risk. Further follow-
474 ups are testing whether these benefits amplify with increasing age of the cohort.[44] Second, a
475 similar supplementation program in India was associated with reduced NCD risk in
476 adolescents.[45] In each case, supplementation appeared to promote metabolic capacity
477 without elevating load. The main limitation is that these studies did not involve
478 randomization at the individual level, and hence might be confounded by background
479 differences between those supplemented versus controls.
480
481 **Incorporating organ phenotype**
482
483 The capacity-load model assumes that the structure and function of organs makes a key
484 contribution to variability in NCD risk. Until recently, this was difficult to test empirically, but
485 data are increasingly available. In the rat, a variety of organs were found to be smaller
486 following fetal under-nutrition, whereas the brain was relatively protected.[46] In humans,
487 growth-retarded neonates likewise had reduced volumes of the kidney, liver and spleen.[47] A
488 recent study in Nepal demonstrated that independent of weight at birth and childhood fat
489 mass, dimensions of the kidneys also explained variability in systolic blood pressure at 8
490 years.[48]
491
492 Whereas fetal organ development is very sensitive to the delivery of nutrients and oxygen, in
493 post-natal life linear growth gradually loses sensitivity to nutrition, and eventually comes
494 under the canalizing control of growth hormone. From this point, organ growth closely
495 follows growth in stature (**Figure 4a**).[49] The striking linearity of the relationships indicates a

common regulatory system, and helps explain why metabolic capacity tracks from early life into adulthood, where height remains associated with organ masses (**Figure 4b**).[30]

Figure 4 near here

Such associations may also extend to ethnic differences. Autopsy data indicate that Indians have smaller organs than Europeans, even after adjusting for their shorter height, indicating a generic lower metabolic capacity.[50] Substantial variability in height and weight across ethnic groups may therefore index variability in organ mass, and hence metabolic capacity, as well as adipose tissue distribution, representing metabolic load, but this hypothesis requires further investigation.

Conclusion

The capacity-load model represents a broad conceptual framework for understanding the development of NCDs and their key risk factors. It complements detailed mechanistic research highlighting the role of very specific traits, enabling the integration of diverse types of data from multiple study designs. It may prove particularly valuable for research on the social determinants of health, the inter-generational transmission of NCD risk, and understanding geographical and ethnic variability in NCD susceptibility. Future work will apply it to other NCD outcomes such as cancer and infectious disease.

Conflict of interest statement

The author declares no conflict of interest.

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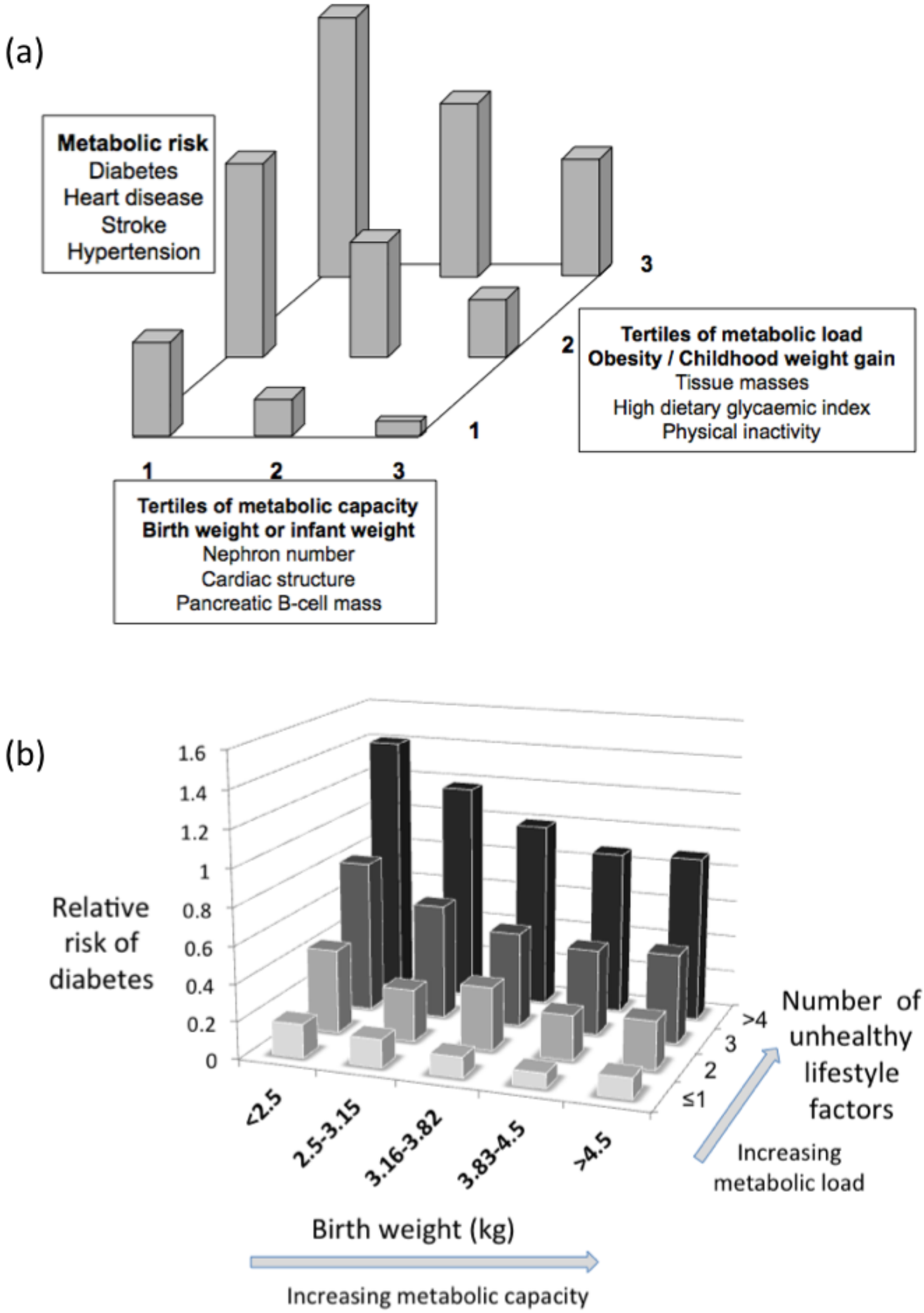
Legends for illustrations

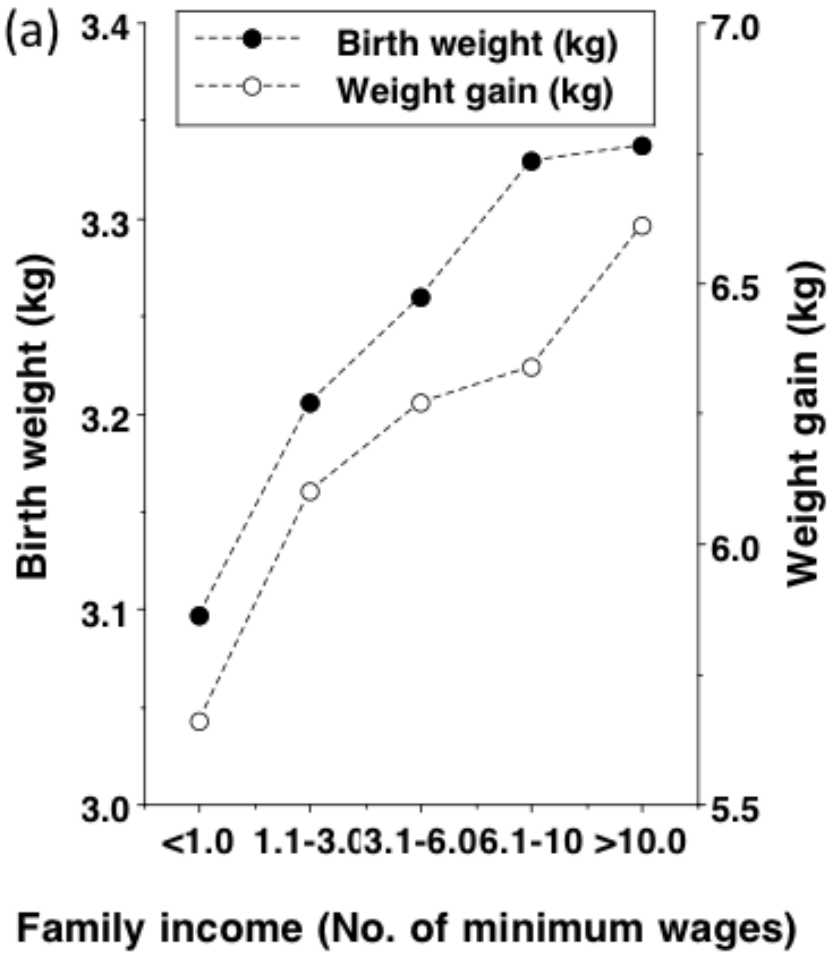
Figure 1. (a) Basic architecture of the capacity-load conceptual model (reproduced with permission from ref 10). (b) The model illustrated for the prospective risk of developing diabetes in three US cohorts. The right hand y-axis counts an increasing number of unhealthy adult traits (high BMI, smoking, physical inactivity, high alcohol consumption, unhealthy diet).[9]

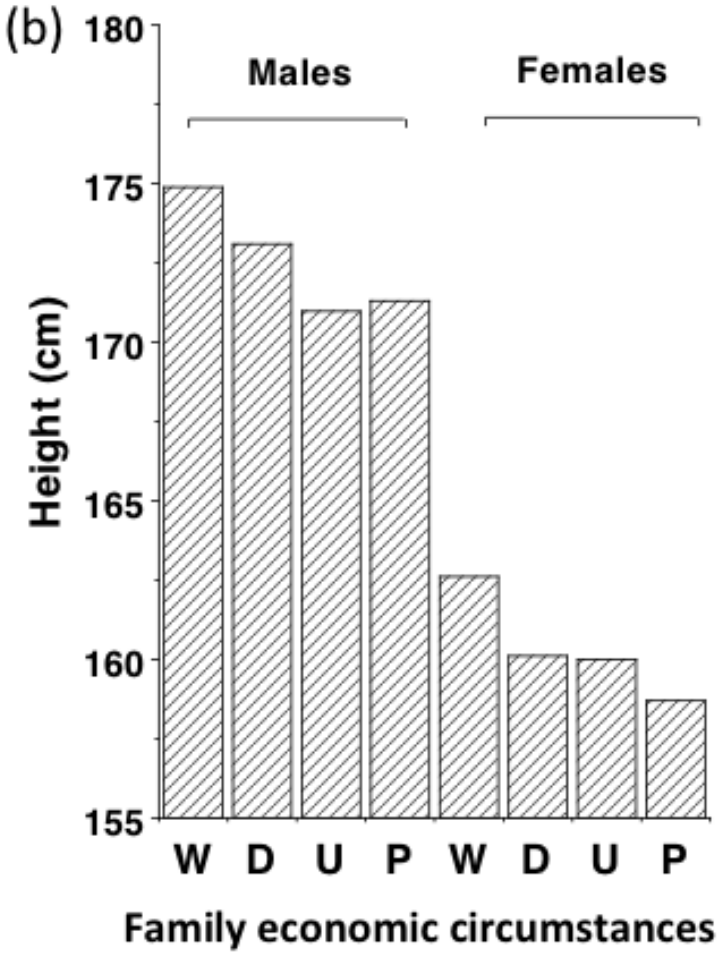
Figure 2. Poverty and metabolic capacity in Brazil. (a) Association of birth weight and infant weight gain with family income, assessed in 'minimum wages'.[27] (B) Adult height according to whether the individual had always been wealthy (W), always poor (P), or had undergone improvement (U) or deterioration (D) between birth and adulthood.[28]

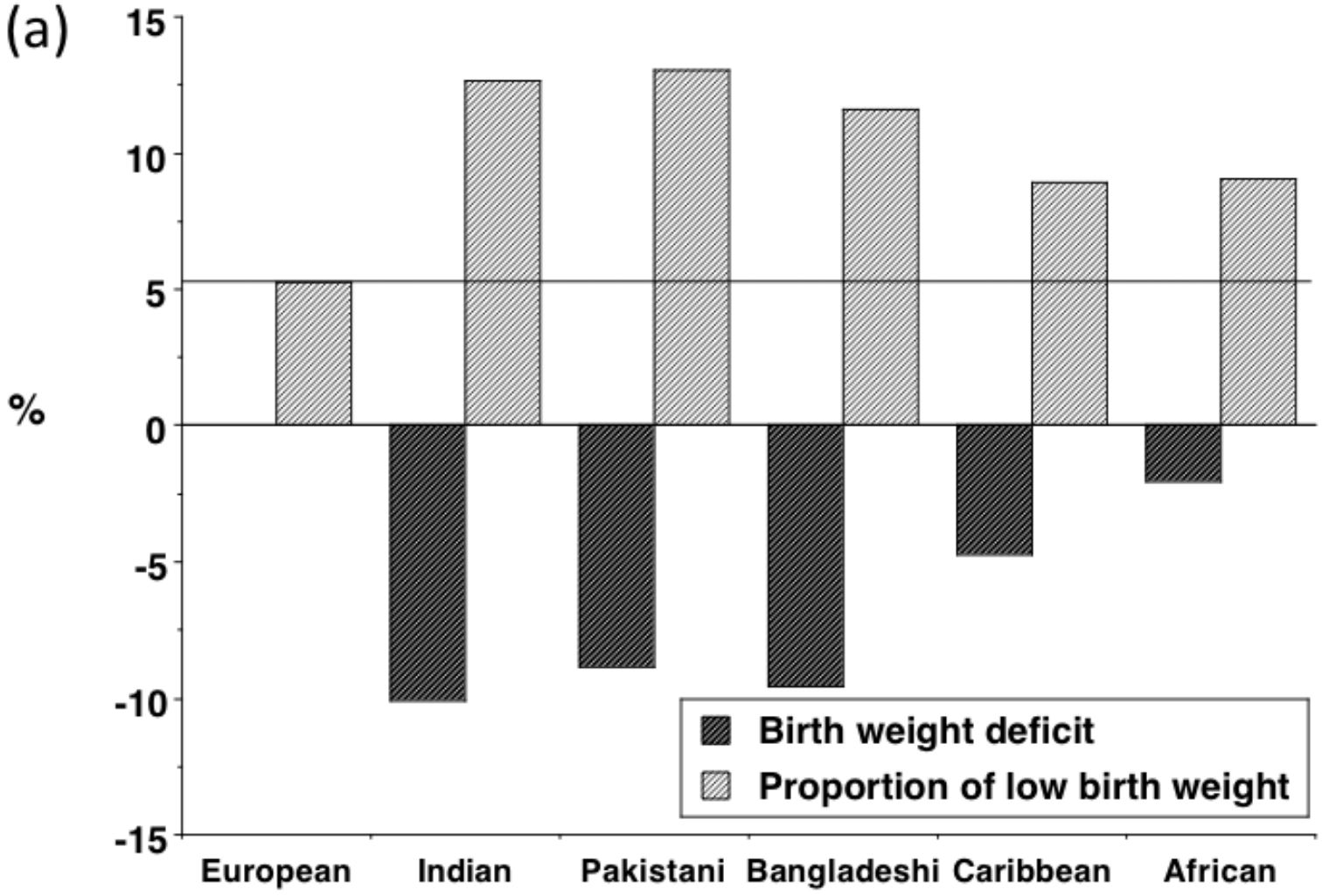
Figure 3. Ethnicity and the capacity-load model. (a) Deficits in birth weight, and increased proportion of low birth weight (<2500g) in ethnic minority groups relative to white Europeans in the UK Millennium cohort.[38] (b) Elevated fat mass for a given weight in UK infants of South Asian ancestry relative to Europeans.[40]

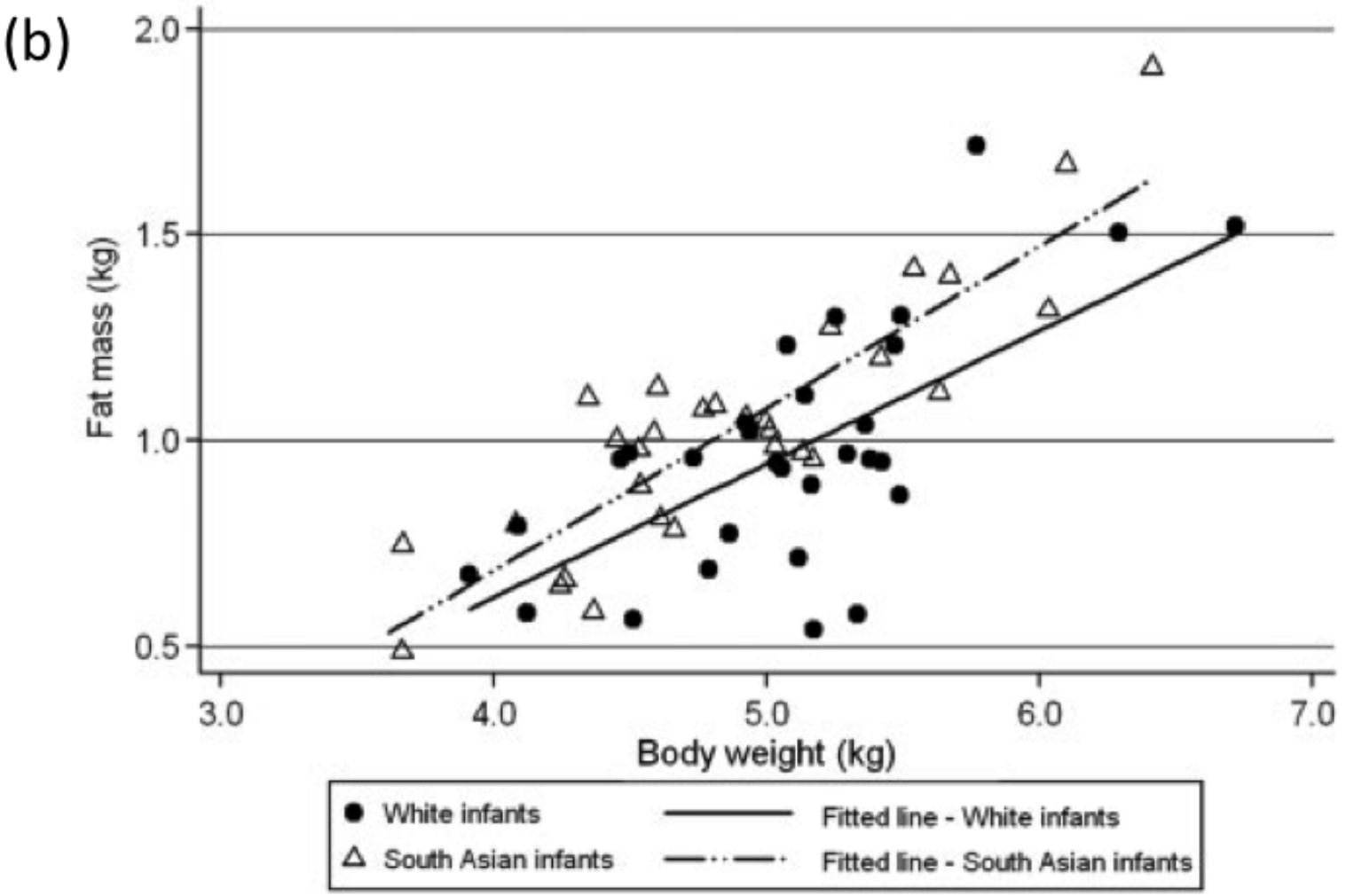
Figure 4. Organ growth and linear growth. (a) Associations between height and mass of the kidney, liver and brain, based on autopsy data from children between birth and 12 years.[49] (b) Associations between height and mass of the pancreas, spleen and kidney in adult men and women.[30]

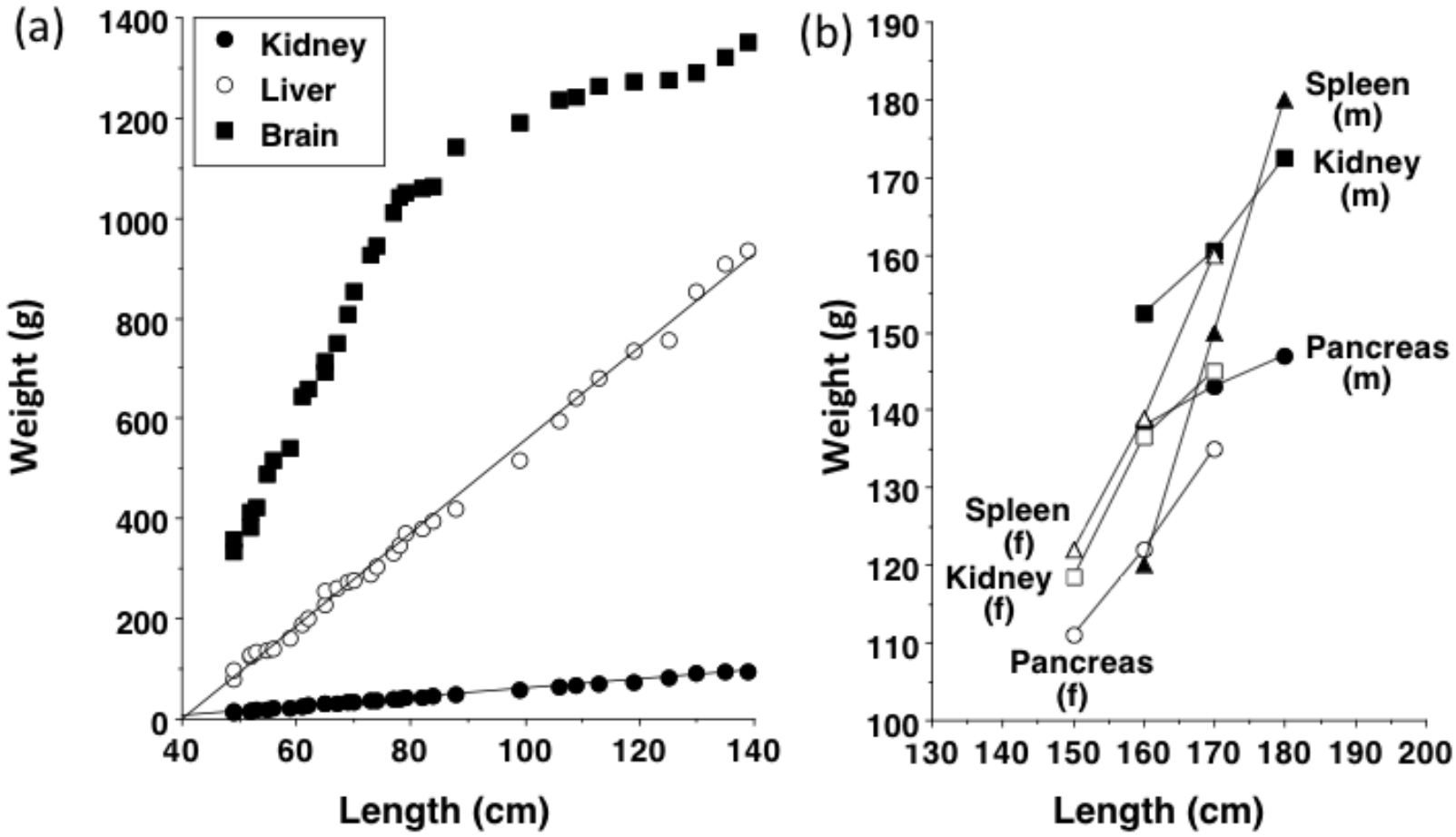

(a)
Metabolic risk
Diabetes
Heart disease
Stroke
Hypertension
3
2
1
Tertiles of metabolic load
Obesity / Childhood weight gain
Tissue masses
High dietary glycaemic index
Physical inactivity
1
2
3
Tertiles of metabolic capacity
Birth weight or infant weight
Nephron number
Cardiac structure
Pancreatic B-cell mass
(b)
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)
Increasing metabolic capacity
≤1
2
3
>4
Number of unhealthy lifestyle factors
Increasing metabolic load


(a)
Birth weight (kg)
Weight gain (kg)
3.4
3.3
3.2
3.1
3.0
7.0
6.5
6.0
5.5
<1.0
1.1-3.0
3.1-6.0
6.1-10
>10.0
Family income (No. of minimum wages)


(b)
Males
Females
180
175
170
165
160
155
Height (cm)
W
D
U
P
W
D
U
P
Family economic circumstances


(a)
15
10
5
0
-5
-10
-15
%
Birth weight deficit
Proportion of low birth weight
European
Indian
Pakistani
Bangladeshi
Caribbean
African


(b)
2.0
1.5
1.0
0.5
Fat mass (kg)
3.0
4.0
5.0
6.0
7.0
Body weight (kg)
White infants
South Asian infants
Fitted line - White infants
Fitted line - South Asian infants


(a)
Kidney
Liver
Brain
Weight (g)
Length (cm)
0
200
400
600
800
1000
1200
1400
40
60
80
100
120
140
(b)
Spleen (m)
Kidney (m)
Pancreas (m)
Spleen (f)
Kidney (f)
Pancreas (f)
Weight (g)
Length (cm)
100
110
120
130
140
150
160
170
180
190
130
140
150
160
170
180
190
200