Review

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Re-examining heritability: genetics, life history and plasticity

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Human life-history traits (growth, maturation, nutritional status) are increasingly associated with risk of chronic degenerative disease. Twin studies suggest high heritability of such traits; however, although sophisticated approaches have identified genetic variation underlying a proportion of this heritability, studies also increasingly demonstrate significant plasticity, and many life-history traits are able to change by one standard deviation (SD) over 3–6 generations. Developments in our understanding of the contributions of genetics and plasticity to human life history are likely to improve understanding of the growing burden of chronic diseases. We argue that a life-history approach to understanding variation in the human phenotype must integrate these two risk components, and highlight the important contribution of plasticity to changes in disease prevalence.

Life history and the aetiology of disease

Much of the variability in human endocrinology and metabolism emerges from life-course processes of development, reproductive maturation and aging. During early life a variety of complementary hormonal processes regulate linear growth and tissue accretion and differentiation, with particular pathways dominating during corresponding windows of development. Sex hormones regulate pubertal maturation and the emergence of sexual dimorphism in body composition and reproductive biology, and also contribute to the changes taking place with maturation and reproduction [1,2]. Variability in early growth also has long-term consequences for the decreasing effectiveness of cellular repair mechanisms that underlies the aging process [3].

These developmental and reproductive traits are widely explored by evolutionary biologists using an integrative approach known as 'life-history theory', which assumes that inter- and intra-specific variability in life-history variables (e.g. size at birth, litter size, age at first birth, adult size) constitute a key means of adapting to ecological conditions [4]. In the past two decades a substantial volume of research has demonstrated that human life-history traits are also highly predictive of health and disease; for example, low birth weight is strongly associated with chronic degenerative disease risk [5], whereas age at menarche and body mass index (BMI) are associated with the risk of cardiovascular disease and reproductive cancers [6,7]. A key question is whether such traits are primarily under genetic control, or whether they are sensitive to environmental influences.

Answering this question will clarify the optimum approaches for improving public health by determining the extent to which phenotype can be manipulated by 'internal' molecular approaches, in contrast to 'external' manipulations of living conditions and behaviour. For example, drugs such as statins are successful because, on the basis of a single gene (*HMGCR*), they target a rate-limiting step in cholesterol metabolism [8], and hence generate a substantial reduction in cardiovascular disease risk. Many genes could be much less influential on phenotype, and could also exert multiple (pleitropic) effects, making molecular manipulations more challenging.

Many studies, as described in this review, have shown high levels of heritability in life-history traits, and in the chronic degenerative diseases associated with them. These findings have led to a widespread perception that strong genetic control underlies these diseases, and detailed studies are therefore currently investigating the genetic basis of diseases such as type 2 diabetes [9] and obesity [7].

Genotype and phenotype

It has generally been assumed that phenotypic variability within our species is the consequence of underlying genetic variation, arising via the impact of natural selection on ancestral generations. Recent advances in the study of variation in the nuclear genome have led to the ability to detect 'signatures' of past natural selection, operating on particular genes [10] within the last 10 000 years [11]. Evolution of genes governing lactose digestion in adulthood provides one of the best examples of recent natural selection in humans. To date four different alleles have been detected which influence the persistence of intestinal lactase production after weaning in humans from different geographic regions, suggesting that multiple independent episodes of natural selection have taken place in response to the origins of dairying [12].

Stature is a commonly studied trait because it is easily quantified and, being a normally distributed trait, offers the maximum statistical power to genome-wide association studies (GWAS). To date, no studies have shown a signature of selection in genes relating to stature; however, its genetic basis remains widely assumed on the basis of (i) twin studies, consistently indicating heritability coefficients of 80–90% for adult stature [13,14], and (ii) GWAS, which have

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Box 1. Variability in stature and its genetic basis

Stature provides a valuable example of the challenges of assessing heritability in humans [51]. The notion that stature was strongly heritable emerged from early studies of phenotypic correlations between parents and offspring [62]. Fisher proposed that the continuous nature of stature variability was consistent with many genes each exerting a relatively small effect [63]. Although family resemblance need not be due to genetic factors, twin studies seemingly provide strong evidence of genetic heritability. Recent large studies of European twins have estimated stature heritability at ~80–90% [13,14].

Approximately ~50 genetic loci were initially associated with stature, but their combined effects accounted for only 5% of the total variation, whereas the typical effect of each common allele on height was around 0.4 cm [51], in line with Fisher's predictions. The 'failure' to reveal much of the source of heritability was attributed to insufficient statistical power to identify the small effects of large numbers of variants, the possibility that rare genes with significant effects are missed by current approaches, and the need for larger sample sizes to detect gene–gene interactions [17]. There are also indications that a given locus could contribute both strong effects through rare variants, and weaker effects through commoner variants [51].

New work is proving more successful in identifying the genetic factors associated with stature. Early studies appear to have been conservative, over-correcting for 'multiple comparisons' when testing each single nucleotide polymorphism (SNP) individually, whereas a new analysis, simultaneously comparing almost 300 000 SNPs, avoided this problem and, in doing so, substantially increased the proportion of phenotypic variance explained to ~45% [16]. Other work is also uncovering biological pathways not previously known to affect growth [51]. Collectively, this work implies that much of the genetic basis of heritability involves complex and subtle gene–gene or gene–environment interactions [16]. A variety of non-sequence-based factors could also contribute and allow for more complex interactions of genes and environment.

The remaining 'missing' heritability could be encoded in the genome through factors such as minor allele frequencies and could be detectable in the future with new methods and larger samples [16]. Although a degree of such optimism is reasonable, it must also be qualified by new work challenging the interpretation of twin studies, because the greater similarity of monozygotic compared to dizygotic twins could reflect epigenetic as well as genetic factors [20]. Increasing understanding of life-history plasticity (Box 2) also suggests that genetic factors could be too readily invoked to explain trans-generational phenotypic correlations.

identified a large number of genes associated with stature, but nevertheless explain a much lower proportion of the phenotypic variance [15,16] (Box 1). The discrepancy between these two approaches has led to interest in the 'missing heritability' [16].

Recent studies are beginning to challenge accepted wisdom regarding the genetic component of phenotypic variability, and cause us to question what we know about the heritability of life-history traits. We argue below that there is evidence for substantial plasticity in these traits, indicating that a significant component of variability is not controlled directly by genomic variation, and therefore heritability could have been over-estimated. This issue is not unique to stature, and remains relevant to the aetiology of a variety of complex diseases [17]. Reconsideration of phenotypic traits with high heritability estimates, but where only a small proportion of this heritability is accounted for by known genetic variation, could clarify the underlying biology of phenotypic variability.

Re-examining heritability estimates

Heritability appears to be a relatively straightforward concept, colloquially referring to the proportion of phenotypic variation attributable to genotypic variation; nevertheless, its application is less than straightforward. Table 1 summarises evidence for genetic heritability in a variety of life-history traits. The heritability values appear to be variable, and this is due in part to inconsistency in study design. Family studies routinely show lower heritability values than twin studies – which typically produce values of 60–90%, though less for birth weight. These discrepancies offer important clues regarding how the genetic basis of heritability might have been over-estimated.

The longstanding primacy of twin studies for disentangling genetic and environmental components of heritability is based on a simple logic – that both monozygotic (MZ) and dizygotic (DZ) twins share their *in utero* environment, but the two types of twin differ in their genetic similarity. The influence of genotype on phenotypic variation can

Table 1. Life-history traits with high heritability but with few significant individual genetic markers

Trait	Population	Heritability	Ref.
Birth weight	UK twins	44%	[69]
	Norwegian families	31%	[70]
	Swedish twin pairs	25–40%	[71]
Age at menarche	Australian sister-pairs	69%	[72]
	Dutch families	70%	[73]
	US families (Fels study)	49%	[74]
Adult height	Gambian families	60%	[75]
	Indian families	74%	[76]
	European twins	81%	[13]
Body mass index	Finnish twins	80%	[77]
	Nigerian families	46%	[78]
	Chinese twins	61%	[79]
Age at menopause	US families (Framingham)	52%	[80]
	Dutch mother–daughter pairs	44%	[81]
	Dutch twins	71%	[82]

therefore be estimated by calculating the difference in correlations. However, recent research indicates that twin studies could overestimate the proportion of heritability directly attributable to variability in genotype.

First, heritability is essentially calculated as the variation due to genetic factors expressed as a proportion of total variability. In populations occupying relatively homogenous environments, the contribution of genetic factors to total heritability is artificially inflated [18]. For example, studies in healthy European populations subject to several decades of high quality nutrition (e.g. [13]) are likely to over-estimate the heritability of height characteristic of humans as a species, because environmental variability has been constrained. Twin studies therefore require very careful interpretation because heritability can vary substantially between populations, a scenario difficult to interpret in terms of fundamental physiology or molecular biology.

Second, MZ twins share particular environmental factors as well as their DNA content. Both twins subjected to the same maternal pregnancy physiology could pick up similar or identical epigenetic influences *in utero* [19]. DZ twins could similarly pick up such epigenetic effects, but their different genotypes could reduce the homogeneity of these influences. It is therefore possible that the apparent genetic similarity of MZ twins is inflated by their more similar epigenetic profile [20,21].

From genes to life-history plasticity

All organisms have a unified life-history trajectory, with individual traits contributing to common developmental and reproductive strategies. Natural selection acts not on physical traits, therefore, but on these life-cycle strategies [22]; for example, in the case of stature, natural selection does not act on final size but instead on the strategy of growing [22]. Using stature as an example, the human growth process is unusually complex, with its distribution across several distinct developmental periods [23]; this complexity could help to explain the polygenic basis of stature variability. Adult stature furthermore reflects multiple life-history events, including size at birth, infant growth rate, and the timing and duration of puberty, hence genes affecting one trait could also affect others [24,25]. However, such variability need not only have a genetic basis.

Growth rates in human foraging populations demonstrate substantial variability in age of maturation, final size and duration of reproductive career [26]. It remains unclear how much of this variability represents longer-term genetic adaptation to selective pressures, and how much represents the shorter-term optimisation of growth in relation to more stochastic aspects of local ecology. Favourable conditions (increased availability of food) and unfavourable conditions (increased risk of mortality) are each associated with faster maturation and early sexual maturity [26].

That life-history variability need not be genetic is demonstrated by substantial secular trends observed in numerous human populations. For example, over the 20th century, many industrialised populations experienced upward trends in stature [27], although in populations exposed to poor conditions, downward trends were also observed [28]. There has also been a trend towards earlier puberty, for example from 17 to 14 years in the US between the mid 19th and mid 20th centuries [29]. More subtle trends are evident in other life-history traits, such as birth weight. Here, the driving force might be changes in maternal height and weight in previously under-nourished populations [30] and maternal obesity in well-nourished populations [31], the effects on body composition at birth could differ according to these pathways. Trends in increasing age of menopause have also been identified [32]; therefore, combined with earlier menarche, the female reproductive career has lengthened in both directions. These trends vary in their duration and magnitude, for example the increase in birth weight in industrialised populations could be tailing off [33].

These data, arising primarily from environmental influences rather than population genetic change, therefore illustrate that human phenotype is characterised by norms of reaction – the capacity of any genotype to give rise to variable phenotype according to the environmental conditions during development [4]. Norms of reaction allow

Table 2. Evidence for secular trends in life-history traits

Trait	Population	Rate of change per decade	Decades per SD change[a]	Ref.
Birth weight (g)	Canada (m,f[b])	95.4	5.2	[83]
	Norway (m,f)	36.8	13.6	[84]
	India (m,f)	32.2	15.5	[30]
Age at menarche (yr)	Spain	0.26	3.8	[85]
	South Africa (black)	0.50	2.0	[86]
	India	0.20	4.9	[87]
Height (cm)	Czech (f)	1.1	5.4	[88]
	India (f)	2.2	2.1	[87]
	Portugal (m)	1.0	6.1	[89]
Body mass index (kg/m^2)	Sweden (f)	1.2	2.5	[34]
	Greece (m)	0.6	5.3	[90]
	US (m)	0.8	3.7	[35]
Age at menopause (yr)	Spain	0.34	11.7	[91]
	Sweden	1.00	4.0	[32]
	United States	0.59	6.8	[92]

[a]SD was simulated as follows: birth weight 500 g; age at menarche 1 yr; height 6 cm; BMI 3 kg/m^2; age at menopause 4 yr.

[b]m, male; f, female.

phenotypic change across a certain range, hence the potential for secular trends is not unlimited.

For each life-history trait, we calculated the rate of change per decade and the approximate number of decades of change at this rate required to induce a one SD difference in the trait (Table 2). Owing to the lack of available data in many of the studies, we used estimated 'typical' SD scores. Our estimates of the time required to alter phenotype by one SD are therefore imperfect, and in reality would be expected to vary more between populations. Nevertheless, the studies are fairly consistent in showing that life-history traits can alter at a rate of one SD over 3–6 decades for most traits, but with a longer period typically demonstrated for birth weight. Importantly, obesity itself increases much faster than average BMI [34,35]. These data highlight the plasticity in human life-history traits.

Trans-generational phenotypic plasticity

Secular trends are most evident by comparisons across generations, but their phenotypic effects are not restricted to a single generation and, instead, often propagate forward to subsequent generations, thereby generating trans-generational phenotypic covariance that does not arise through direct transmission of DNA. Known to biomedical researchers as 'intergenerational effects' [36], and to zoologists as 'parental or maternal effects' [37], trans-generational transmission of phenotype is fundamental to life-history traits such as birth size, the rate of childhood growth and maturation, adult size, nutritional status and duration of the reproductive career, each of which is sensitive to nutritional influences. For example, in industrialised populations, approximately 10% of foetal growth restriction is attributable to the impact of maternal birth weight, indicating that low birth weight in one generation constrains growth in the next [38].

Various mechanisms could account for non-genetic co-variance of parental and offspring phenotype [31]. These include the behavioural transfer of environmental circumstances, *in utero* hormonal programming [39], and epigenetic marks – which comprise alterations to gene expression through molecular mechanisms such as DNA methylation, histone modification and RNA transmission [40,41]. It is helpful to differentiate epigenetic effects, which incorporate all non-genomic influences of the parent on the offspring, from epigenetic inheritance, which refers specifically to the transmission of epigenetic marks across generations [41]. The different potential influences of parents on their offspring are discussed in Box 2, and all could contribute to secular trends, illustrated for maternal and offspring body weights in macaques in Figure 1. The vast majority of epigenetic marks arise *de novo* through environmental influence each generation, hence phenotypic effects transmitted to grandchildren generally imply direct exposure of the F2 generation to the environmental stimulus acting in the F0 generation [41], potentially mediated by phenotypic effects expressed in the F1 generation.

Maternal effects are most clearly demonstrated in studies of MZ twins, which reveal effects of the uterine environment with confidence because genotype is identical. Even in MZ twins, birth weight discordance is common, and some of this intra-pair difference continues into adulthood, as demonstrated for stature and weight [42]. Recent research on the impact of maternal age at menarche on offspring phenotype [43] also suggests complex effects of such trans-generational transmission, which are furthermore integrated across diverse life-history traits (Box 2). Crucially, such plastic effects on growth rate also translate into differential risk of degenerative diseases such as type 2 diabetes [44].

The distribution of secular trends across several generations indicates that ecological cues need to be experienced in multiple generations to generate significant effects on population phenotype. This means that although they involve plasticity, such traits maintain consistency across generations unless ecological conditions alter systematically. Accelerating the rate of such secular trends appears to inflate the deleterious metabolic consequences. For example, increases in childhood weight in rapidly modernising populations such as India are greater than increases in stature [45], and the resulting BMI increases are associated with increased risk of diabetes in adulthood [46].

Plasticity in life-history traits is not contradictory to their genetic basis, instead the two sources of variability are complementary. Plastic traits (e.g. weight gain, rate of maturation) absorb ecological pressures and thereby buffer other traits (e.g. brain growth) which are less flexible. These less flexible or 'canalised' traits are subject to

Box 2. Life-history plasticity in growth and maturation

Although secular trends within populations that are relatively stable in terms of the gene pool offer strong evidence for life-history plasticity (Table 2), the propagation of phenotypic effects across generations is of particular interest. These epigenetic effects could arise through a variety of mechanisms (Figure 1).

In an experimental study of rhesus macaques (*Macaca mulatta*), improvements in nutritional supply induced a secular trend first in maternal size, and then in offspring birth weight, especially that of female offspring, over five generations (Figure 1) [64]. This showed that the impact of ecological change on phenotype can be distributed across several generations, with variable time-lags [31].

Recent work on the Avon Longitudinal Study of Parents and Children in Bristol, UK, revealed unexpected complexity in the impact of maternal life-history traits on offspring phenotype. Maternal age at menarche was associated with offspring size at birth, infant growth rate, age at puberty and adolescent body composition [43,65], with probable effects on adult stature in due course. Although such trans-generational phenotypic effects could incorporate genetic effects, the central role of early growth patterns in such associations strongly suggests the involvement of non-genetic factors. Growth in early life is highly sensitive to nutritional supply, and maternal obesity is itself correlated with maternal age at menarche [43]. Thus, the maternal life-history profile could 'drive' life-history trajectory in the next generation through mechanisms that allow phenotype to change across several generations depending on ecological cues such as food availability.

Trans-generational phenotypic plasticity is clearly advantageous in species occupying unpredictable environments, where genetic adaptation risks 'over-commitment', in other words a reduced flexibility to address short-term environmental change. Human evolution is increasingly understood to have taken place in such ecologically unstable circumstances [66], whereas human reproductive patterns and flexible subsistence patterns prone to boom–bust dynamics could similarly have exacerbated ecological stochasticity [67]. From an evolutionary perspective, we therefore expect both (i) constraints on the extent of, and capacity for, genetic adaptation in human life-history, together with (ii) phenotypic plasticity.

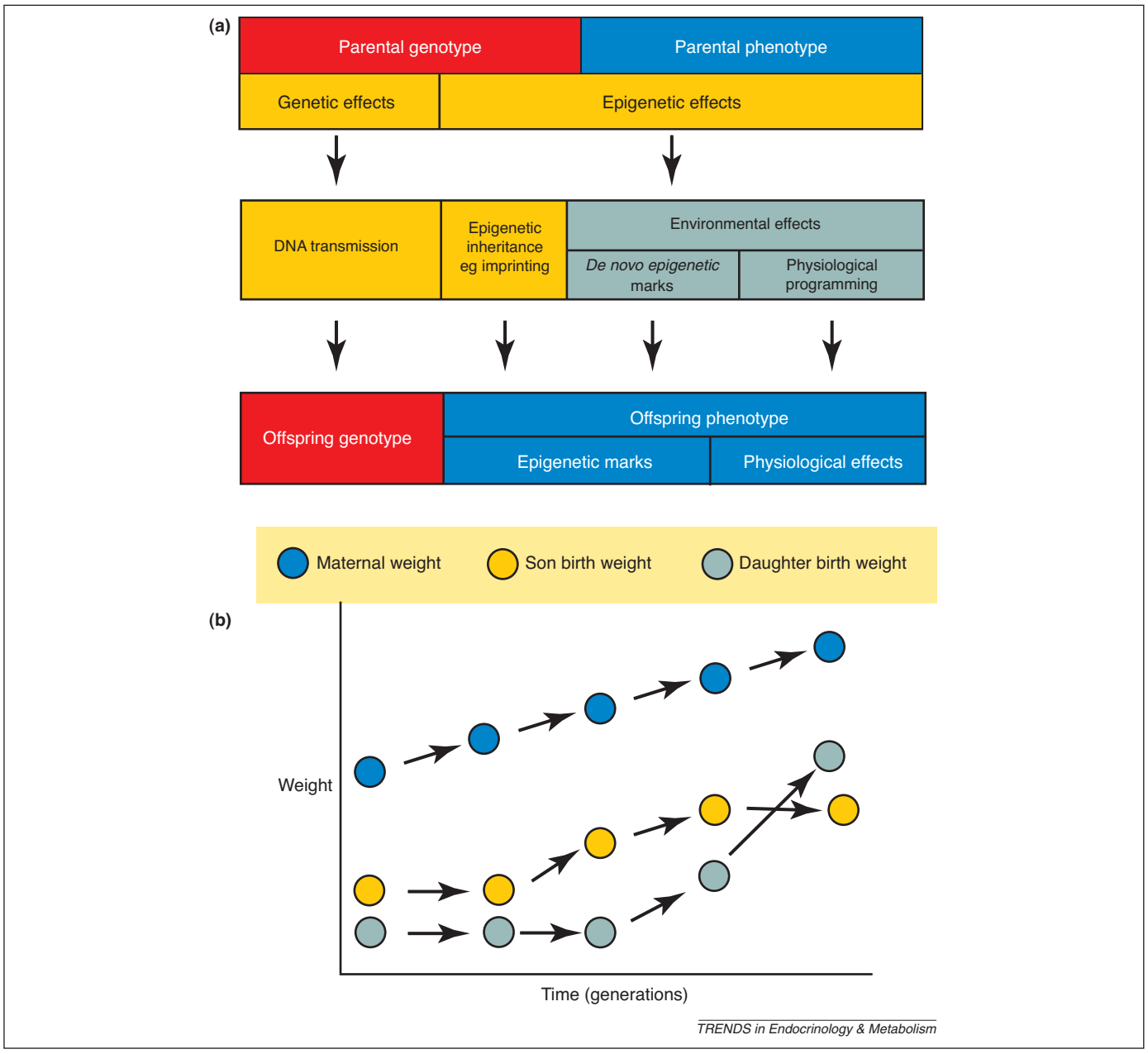

Figure 1. **(a)** Alternative pathways through which parental genotype and phenotype could impact on offspring genotype and phenotype. In addition to direct transmission of DNA, there are several components of epigenetic transmission, including the transmission of epigenetic marks (e.g. genomic imprinting), the generation of *de novo* epigenetic marks, and the transmission of broader environmental effects. Epigenetic factors account for secular trends across generations, for example **(b)** over five generations in macaques, first maternal weight and then offspring birth weight increased, although at different rates in sons and daughters [64].

stronger control by the genome or by transgenerational influences [47]. In turn, canalised traits offer a developmental 'scaffolding' around which plastic traits can vary [47]. Individuals could vary genetically in their sensitivity to epigenetically derived environmental effects [48]. Furthermore, the role of epigenesis remains open to question because it might be as important in stimulating phenotypic variation as it is in transmitting information [49]. However, their plasticity also renders life-history traits vulnerable to ecological effects (such as exposure to starvation or the obesogenic niche), such that cumulative compensatory adjustments over the life-course (e.g. low birth weight, early menarche, adult obesity) could translate in contemporary populations into elevated chronic disease risk.

Implications for understanding chronic disease risk

The potential to understand the complexity of the heritability of stature is encouraging for those probing the heritability of complex disease traits. Nevertheless, the significance of this approach for tackling the increasing global prevalence of chronic degenerative diseases has been questioned [50]. For example, recent studies have identified many individual genes associated with stature, but the effect of each gene remains very small [51]. To date, the overwhelming finding from genetic investigations is that no commonly occurring allele has a powerful effect on either stature or chronic disease risk. Instead, individuals accrue their risk by accumulating multiple 'risk fragments' [25], and no 'rate-limiting step' gene has been discovered

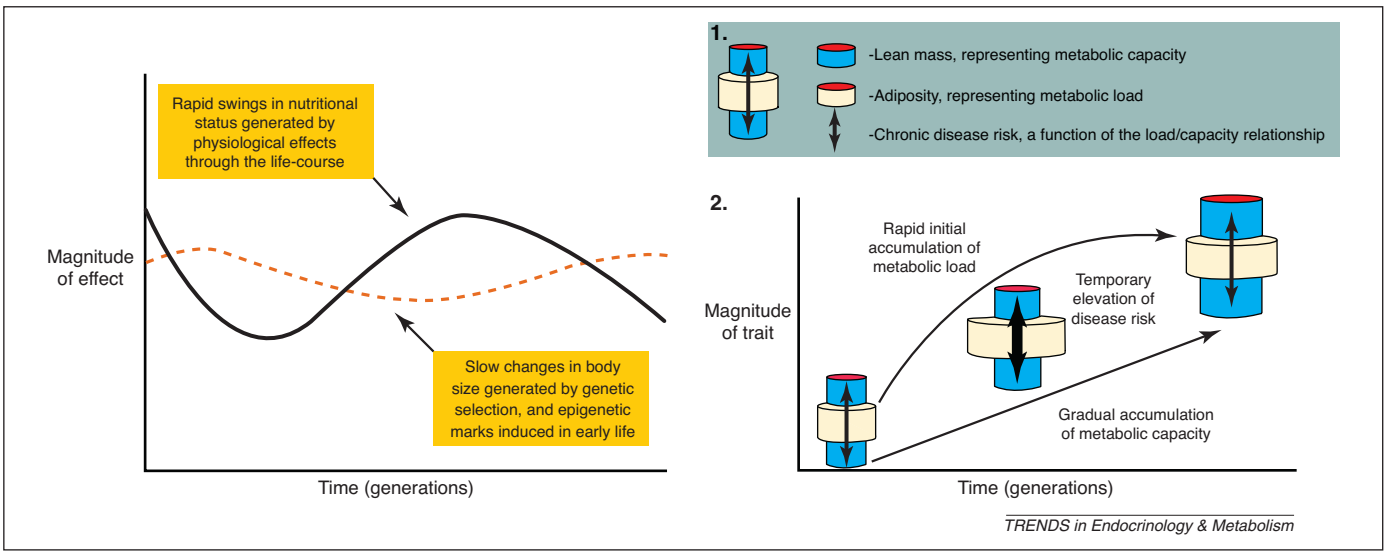

Figure 2. **(a)** Nutritional status (BMI) remains flexible across the life-course, whereas body size (height) is plastic primarily in early life only, and hence is much less variable through the life course [68]. **(b)** Metabolic capacity closely tracks height and changes with small increments across generations, whereas metabolic load can change substantially within a single life course. Environmental perturbations (e.g. starvation, the obesogenic niche) can engineer large disparities between metabolic capacity and metabolic load, exposing some generations to elevated disease risk.

for obesity or diabetes, in contrast to cholesterol metabolism. Although such risk accumulations are easily calculated from genomic data, it remains uncertain how the information could be used to improve health.

If the *in vivo* risk associated with a given gene variant is small, we must ask how strong a treatment effect might be generated by manipulating the underlying metabolic pathway. For example, if a single 'obesity allele' increases childhood BMI by 0.08 BMI SDs, as appears typical [25], is the treatment effect based on this allele similarly constrained? This question is particularly important because many genes generate multiple phenotypic effects, and treatments aggressively targeting one trait could induce adverse effects elsewhere in phenotype.

Another challenge stems from the possibility that, if no individual gene exerts a strong effect, identifying those 'best candidate' genes could be difficult. This dilemma is emphasised when contrasted with the predictive power of a holistic life-history approach, where each trait incorporates multiple genetic and environmental factors. Furthermore, the strongest predictions of chronic disease risk are generated from more than one life-history parameter. Most notably, the predictive power of low birth weight for disease risk emerges most strongly when subsequent BMI is taken into account, and *vice versa* [52].

In their classic article which challenged the notion that type 2 diabetes is primarily a genetic condition, Hales and Barker proposed the thrifty phenotype hypothesis, arguing that the small baby develops a survival phenotype in early life through reduced investment in particular vital organs such as the pancreas and liver [53]. These adaptations aid survival when faced with low energy supply during foetal life, but increase susceptibility to diabetes if exposed to a high glycaemic load in later life. We recently built on this model, arguing that chronic disease risk is exacerbated by an elevated ratio of metabolic load (high body weight and adiposity, rich diet, sedentary behaviour, each of which challenges cellular homeostasis) to metabolic capacity (characteristics of organ structure and function which confer homeostatic capability) [54,55]. Metabolic capacity is disproportionately influenced by growth during early developmental periods, whereas metabolic load emerges primarily through genetic and environmental exposures from childhood onwards. Both metabolic capacity and load therefore might reflect genotypic variation, and each could also incorporate phenotypic plasticity and respond to environmental factors.

One might assume that genetic and life-course risk assessments might be equally successful in predicting disease risk, although this can only be proven from long-term prospective studies capitalizing on both genetic and physiological data at baseline. However, because cardiovascular disease, stroke, hypertension, type 2 diabetes and cancers were relatively rare in Western populations before the 20th century, and remain rare in non-Western populations with minimal economic development, environmental change impacting upon life-course plasticity is assumed to be their primary cause. It appears that average phenotypes and not average genotypes have changed over time, and with them the population disease risk. The faster the rate of life-history change, the greater the increase in chronic disease risk, as demonstrated by the escalating risk of diabetes in populations such as urban India, in which BMI is increasing rapidly [56].

Of all the traits reviewed in Table 2, birth weight appears to change most slowly across generations, whereas other phenotypic traits respond more rapidly. This implies that secular trends in metabolic load take place more rapidly than those in metabolic capacity, and this helps to explain why recent secular trends in post-natal growth and maturational schedule, induced by exposure to the obesogenic niche, are so strongly associated with increased disease risk (Figure 2) [57]. However, over longer time periods, secular trends in metabolic capacity (more subtle than those in birth weight alone) could catch up trends in load, and this might account for the fact that several indices of cardiovascular risk have declined in industrialised populations in recent decades [58–60].

Box 3. Outstanding questions

- How is heritability encoded in the genome?
- How much of the greater phenotypic concordance within MZ as compared to DZ twin pairs (including disease risk) is due to epigenetic as opposed to genetic similarity?
- What is the magnitude of genetic heritability in phenotype, including that for chronic disease risk, when twin studies address such epigenetic effects?
- How much does the genetic component of heritability vary across populations?
- How can genomic information on disease risk, fragmented across numerous genes each with a small effect on phenotype, be used to improve health?
- How should public health programmes address phenotypic variability that is not genetic but which changes through plasticity across rather than within generations?

Equally, it is of interest that the majority of genetic factors associated with type 2 diabetes relate to β cell function, an index of metabolic capacity, whereas few genes have been identified for insulin resistance, an index of metabolic load [61]. Thus, the exacerbation of metabolic load that is so strongly linked with disease risk appears to be primarily of environmental origin, consistent with epidemiological findings of rapid changes in disease prevalence [56].

Concluding remarks

Several growth and maturational traits, predictive of chronic disease risk, have been reported to have high heritability. Although such traits are characterised by a substantial magnitude of heritability, this magnitude remains uncertain and difficult to interpret in terms of public health implications. The same traits are highly sensitive to ecological change. For several reasons, we argue that a life-history approach to disease risk is more informative than one based on genotype alone, and aids the integration of both genetic and plastic components of risk. Thus, while evidence for the heritability of phenotypic variability accrues, factors impacting on life-course plasticity within and across generations merit substantially more research (Box 3).

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