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Genetics

On the origin of obesity: identifying the biological, environmental and cultural drivers of genetic risk among human populations

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Summary

Genetic predisposition to obesity presents a paradox: how do genetic variants with a detrimental impact on human health persist through evolutionary time? Numerous hypotheses, such as the thrifty genotype hypothesis, attempt to explain this phenomenon yet fail to provide a justification for the modern obesity epidemic. In this critical review, we appraise existing theories explaining the evolutionary origins of obesity and explore novel biological and sociocultural agents of evolutionary change to help explain the modern-day distribution of obesity-predisposing variants. Genetic drift, acting as a form of 'blind justice,' may randomly affect allele frequencies across generations while gene pleiotropy and adaptations to diverse environments may explain the rise and subsequent selection of obesity risk alleles. As an adaptive response, epigenetic regulation of gene expression may impact the manifestation of genetic predisposition to obesity. Finally, exposure to malnutrition and disease epidemics in the wake of oppressive social systems, culturally mediated notions of attractiveness and desirability, and diverse mating systems may play a role in shaping the human genome. As an important first step towards the identification of important drivers of obesity gene evolution, this review may inform empirical research focused on testing evolutionary theories by way of population genetics and mathematical modelling.

Keywords: gene pleiotropy, genetic predisposition to obesity, mating systems, natural selection.

Abbreviations: ARA, arachidonic acid (20:4n-6); BAT, brown adipose tissue; BMD, bone mineral density; BMI, body mass index; DHA, docosahexaenoic acid (22:6n-3); DNA, deoxyribonucleic acid; PCOS, polycystic ovary syndrome; PWS, Prader-Willi syndrome; SNP, single nucleotide polymorphism; UVR, ultraviolet radiation; WAT, white adipose tissue; WHR, waist-to-hip ratio.

Introduction

The worldwide prevalence of overweight (body mass index, BMI≥ 25 kg/m^2) and obesity (BMI≥ 30 kg/m^2) has risen by over 27% in the last three decades, bringing the number of affected individuals to approximately 2.1 billion (1). Estimates indicate that approximately 50% of populations in many Persian Gulf countries and the Pacific Islands are obese (1). In developed nations, the rate of increase of obesity has slowed over the last decade (1). However, extreme forms of obesity are becoming more prevalent (2). As an established risk factor for numerous comorbidities including osteoarthritis, depression, type 2 diabetes, hypertension,

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cardiovascular disease and cancer (3), obesity is a growing concern for the medical community. In extreme cases, obesity may reduce life expectancy by 6–14 years (4). Behavioural and pharmacological interventions to manage obesity exist (5). However, these interventions seem to have little effect in tackling the epidemic. Bariatric surgery, though effective at reducing body weight and related comorbidities, and improving quality of life is invasive and is associated with a number of other complications (6). Without elucidating the biological, environmental and social causes of the current obesity epidemic, we will remain ill-equipped to prevent, manage and treat this complex disorder.

Excess adiposity is 'a normal response to an abnormal environment' (7). All organisms, from prokaryotes to mammals, have developed lipid storage mechanisms to overcome imbalance in nutrient availability (8). Many animals undergo periods of seasonal fat deposition during hibernation (9) or migration (10). Naturally fat animals are also common at high altitudes or deserts – environments characterized by severe conditions and unpredictability of food supply (11). Fat deposits may serve different functions. Blubber, for instance, acts as an insulator and energy reserve among marine mammals (12,13). Female great whales migrate to warmer waters to deliver their offspring, so stored fat is used as an energy source while lactating when food supplies are limited (14). The capacity for energy storage among animals may have a strong genetic basis. Mexican cavefish are highly adapted to nutrient-poor environments and consequently harbour *MC4R* mutations linked to increased appetite and resistance to starvation (15). Surprisingly, as the authors note, similar mutations in humans have been implicated in monogenic obesity because of MC4R deficiency.

Obesity among animals, however, is in stark contrast to human obesity: many animals exhibit a 'healthy obese' phenotype, free of the metabolic complications typically seen among morbidly obese humans (11). The Brandt's vole, for instance, undergoes phases of photoperiod-induced adiposity without any effect on glucose homeostasis (16). Even among animals bred to store maximum energy – such as cows and pigs – obesity exists without hyperglycaemia (17). Conversely, when animals adapted to environments with nutritional stress are displaced from their native habitat, symptoms of metabolic disease are obvious. When in environments with low energy expenditure and high-fat diets, wild pigs from Ossabaw Island exhibit characteristics of prediabetes and heart disease (18). Likewise, invasive lionfish living amid food overabundance in the Atlantic Ocean have markedly increased interstitial fat deposits and comorbid liver damage (19). Human obesity may be affected by a similar discord between our native habitat and the environment in which we currently reside.

The modern obesity epidemic is largely explained by environment factors, with excess energy intake and physical inactivity pinned as the main culprits. However, even in shared environments, only a subset of individuals develops obesity (20). There appears to be a differential propensity to obesity at the individual level, with biological factors such as sex, age and *in utero* environment contributing to this variability (20,21). Obesity rates also differ among ethnic groups living in similar environmental conditions (20). Though lifestyle choices may explain some of this variability, admixture studies demonstrate that specific genes also contribute to ethnic-dependent obesity risk (22). Heritability estimates of obesity from twin and family studies range from 0.25 to 0.90 (23), suggesting a large portion of obesity risk may be because of inherited factors. To date, genetic association studies have identified 63, 12 and 157 loci involved in monogenic syndromic, monogenic non-syndromic and polygenic forms of obesity, respectively (24,25).

Over the past 50 years, numerous hypotheses have emerged to explain human propensity to obesity (26). Neel's thrifty genotype hypothesis, for instance, posits that extra adipose tissue enabled our ancestors to survive in the face of feast–famine cycles (27). This hypothesis, however, oversimplifies the matter: if obesity susceptibility variants were advantageous for survival, such variants would be likely fixed in humans, and obesity would be the norm in modern populations (28). This, however, is not the case. In fact, genetic variants conferring protection against obesity have been identified in humans (29,30).

Theories building on the thrifty genotype hypothesis attempt to capture the complexity in the modern obesity phenomenon. The thrifty phenotype hypothesis advances the notion that inadequate nutrition in early life alters the structure and function of organs and tissues, such that energy abundance experienced later in life leads to increased risk of cardiovascular disease and hyperglycaemia (31). The thrifty epigenotype hypothesis proposes that all humans possess a thrifty genotype; environmental cues, however, lead to phenotypic variability within a range of acceptable phenotypes via epigenetic modifications (32). Although many 'thrifty' theories exist framing adiposity as an adaptive trait, non-adaptive theories also exist. The predation release hypothesis, for instance, proposes that relaxation of predation pressures and random genetic drift contributed to the actual variability in genetic predisposition to obesity (28).

In reality, no single theory can explain the evolutionary origins of obesity. The history of our species is complex. Since the dispersion of modern humans out of Africa over 1.8 million years ago, the environmental and social conditions faced by our species have been in constant flux. Every human population has a unique genetic history, resulting from founder effects, genetic drift, admixture events and diverse ecological challenges.

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Jointly, these forces have shaped human genetic architecture. The objective of the present critical review is to identify these biological, environmental and cultural drivers of evolutionary change. Drawing on basic principles of population and evolutionary genetics, we highlight mechanisms that may explain the observed diversity in obesity- and leanness-predisposing genetic variants among modern human populations (Figs 1 and 2).

Methods

Much of the literature on obesity evolution has rested on concepts of metabolic thrift and fitness advantages of adipose tissue. Random genetic drift, as opposed to natural selection, has also been used to explain the obesity epidemic. Pleiotropic effects of obesity risk alleles, however, have rarely been incorporated into an evolutionary framework for obesity. Although the demographic history of human populations is embedded within some evolutionary theories (33), the impact of human agency and culture on the genetic landscape are also largely absent from explanations as to why obesity risk alleles persist (34). For these reasons, a critical review methodology (35) was adopted

1. to summarize and critically evaluate the merit of existing theories about the evolutionary origins of obesity; and
2. to incorporate the role of genetic pleiotropy and sociocultural phenomena such as mating rituals, and 'artificial' selection pressures, such as slavery, into an interdisciplinary framework explaining the evolution of the obesity epidemic.

Comprehensive searches were conducted using PubMed to identify existing evolutionary hypotheses and develop new theories about the evolutionary origins of obesity. Literature searches encompassed several major themes, including: fitness and adiposity, benefits of fat tissue, gene pleiotropy, evolutionary theories of obesity, animal models of obesity, mate/sexual selection, body image ideals and the impacts of colonialism and slavery on human health. A 'snowball' search strategy was employed, such that the list of search terms developed as the search progressed (Supporting Information).

Evolution and the 'bases' of human genetic diversity

Before developing our evolutionary framework for obesity, we provide a primer in evolution for the non-geneticist, with the hope that a review of basic genetic theory will enable a deeper understanding of the hypotheses we present in later chapters of this manuscript.

What is evolution?

Evolution is a change in the genetic makeup of a population, manifest in the variance or average value of a phenotype (36). Natural selection, gene flow (caused by in/out migration, admixture of different groups of people) and random genetic drift (random fluctuations in allele frequencies) are mechanisms by which evolution occurs (36,37). Natural selection is the opposite of chance, referring instead to non-random differences in average reproductive success and survival of individuals based on inherited characteristics (36). The ability to survive and reproduce in a given environment, and thereby transmit genes to the next generation, is termed fitness (38). Fitness can be thought of in terms of viability, mating success and fecundity – factors that affect the number of offspring an individual is able to produce. Traits that confer fitness are not universal over time or place. Phenotypes that confer reproductive success and survival in one environment may reduce fitness in another environment as a result of biological and physical environmental changes (38).

From where does genetic variation arise?

Natural selection, gene flow and genetic drift act upon variation that arises from recombination or mutation (36). Recombination occurs during meiosis, as a result of crossing over of homologous chromosomes (37). A *de novo* mutation can be expected at a rate of 1×10^{-4} to 1×10^{-6} mutations per gamete for a particular gene, arising from errors in the process of deoxyribonucleic acid (DNA) replication during cell division (39). Mutations may also result from environmental exposures such as excessive ultraviolet radiation (UVR) (39). Increasing parental age may also lead to genetic abnormalities, for instance increased rate of mutation in the germ line or aneuploidy (abnormal number of chromosomes), in males and females, respectively (40). A type 2 diabetes risk haplotype in Mexican and Latin Americans in *SLC16A11* has been traced back to Neanderthals (41). Thus, genomic introgression, movement of genes from one species to another, may be another source of genetic variation in the modern human genome, resulting from hybridization or admixture with archaic human species.

Genetic diversity can take the form of alterations that affect a single base or substitutions, insertions and deletions and rearrangements of whole genomic segments (36,42). The nature and location of these changes are critical in understanding the impact on organismal function. For example, a single nucleotide polymorphism (SNP) that occurs in a protein coding region that results in a change in encoded amino acids (i.e. nonsynonymous/missense) or affects the regulatory region of a gene (e.g. promoter) may have greater implications for fitness than a variant that does not affect

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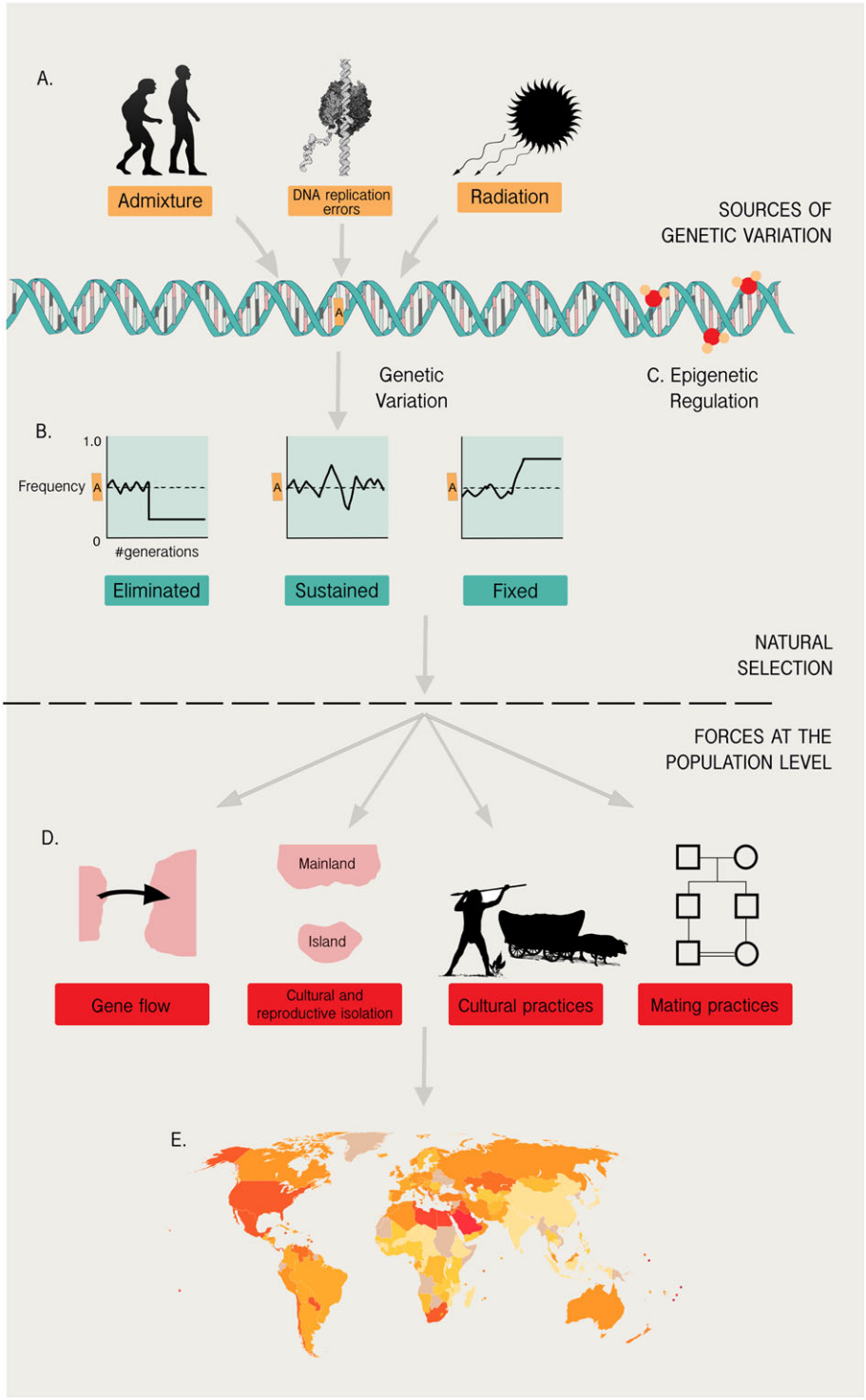

Figure 1 A theoretical framework explaining the evolution and persistence of obesity risk alleles. Global diversity in obesity risk allele frequency (E) may result from *de novo* mutations (A) and be variously affected by natural selection (B), epigenetic regulation (C), population expansion and unique cultural practices, ideologies and mating systems (D). [Colour figure can be viewed at wileyonlinelibrary.com]

encoded amino acid residues (i.e. synonymous) or occurs in pseudogenes or other non-functional regions (36). Not all missense mutations have negative consequences: among rare missense mutations, ~70% show only mildly deleterious effects (43). However, not all synonymous mutations are neutral in terms of their impact on disease phenotypes

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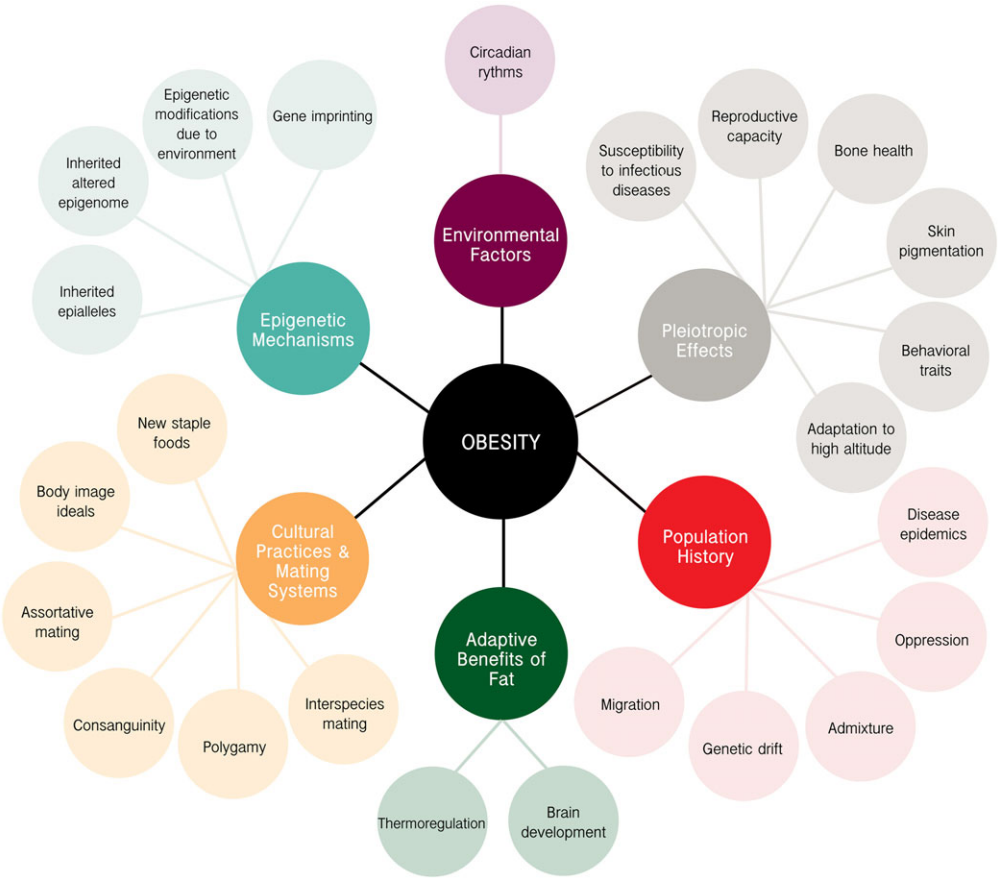

Figure 2 A thematic map outlining the biological, environmental and cultural forces that may explain the modern distribution of genetic variants predisposing to obesity and leanness in human populations. [Colour figure can be viewed at wileyonlinelibrary.com]

(44). Genetic information may also be duplicated or deleted, taking the form of variable numbers of tandem repeats (variations in the number of repeats of short DNA segments) (45) or copy number variations (regions of genome that vary in number of replicates) (46). Other types of genetic variations include chromosomal translocations, inversions and fusions (47).

What affects the frequency of a mutation?

Natural selection can affect frequencies of a given allele in different ways. When an allele is favoured for its phenotypic effect, positive selection (or directional selection if trait is quantitative) occurs (48,49). Sexual selection, the selection of traits deemed more attractive to a potential mate, may also be considered a form of positive selection (49). As opposed to increasing the frequency of an advantageous allele, balancing selection sustains genetic diversity at a locus greater than that expected under a neutral model (i.e. if natural selection were not acting on the population), as in cases of heterozygous advantage (37,48). Selection for extreme phenotypes that confer increased fitness to an individual is deemed disruptive selection (48). Purging of deleterious mutations – i.e. purifying or negative selection – may also occur (49).

Random genetic drift leads to unpredictable shifts in the frequency of an allele in a population in lieu of changing allele frequencies on the basis of trait fitness (37). Over time, one allele may be fixed in a population while another may be lost, with the time to fixation dependent on the size of the population and the effects of other evolutionary forces. Founder effects occur when a group of individuals from a parent population inhabit a new environment. Over time, a small founding population may experience drift such that the genetic diversity is markedly reduced in comparison with the parent population. Survivorship effects or population bottlenecks work in a similar fashion: catastrophic events greatly impact the size of a population and genetic drift randomly yet drastically alters allele frequencies (37).

Variation in human populations may be introduced via gene flow or admixture, for instance, through migration of populations from one region to another (37). It is important to note that migration does not imply gene flow. Isolation from potential mates (because of geographic isolation or reproductive isolation, i.e. the mate is 'off limits' for geographic or socio-political reasons) (37), use of contraception

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or debilitation from a disease may prevent transmission of genes. Thus, the mere presence of genetic variation in a population, even if favourable to fitness, may not lead to evolutionary change.

Yet more layers of complexity

Although selection may act on a single variant, selection for or against one allele may affect the frequency of other alleles in the gene pool via linkage disequilibrium (non-random association of two variants at more than one locus in a population) (36,49). A hitchhiking effect is observed when a positively selected allele increases along with linked alleles, independent of whether the linked alleles have a positive, negative or neutral effect on organismal fitness (49).

Phenotypic variation may result from gene expression. Some genetic variants, for instance, those located in intron 1 of *FTO*, may affect the expression of other genes (50–52). Epigenetic modifications refer to those changes in gene expression that result from the addition of chemical marks to chromatin proteins or DNA as opposed to changes to the underlying DNA sequence (53). Epigenetic modifications like DNA methylation may weaken the strength of natural selection at the level of genetic variants, by masking or unmasking disease risk alleles in response to environmental cues (54).

Cultural practices also affect the human genome. Gene-culture co-evolutionary theory explores the interaction of genes and culture over time and examines how learned behaviours can affect genetic variants that confer a fitness advantage in a given cultural environment (34). Moreover, because mating practices (e.g. consanguinity) and mate selection may be culturally dictated, non-random mating practices based on phenotype may result in assortative mating and thus have a remarkable impact over generations.

In pursuit of thrift

Neel's thrifty genotype hypothesis hinges on the assumption that feast–famine cycles were experienced by our hunter-gatherer ancestors, which favoured genetic mechanisms of adipose deposition (27). Those with greater metabolic thrift would be more likely to transmit genes to the next generation. This premise, however, can be disputed: cross cultural examinations of food quantity, extent and frequency of food shortages suggests no differences exist among agriculturalists and hunter-gatherers (55), even when controlling for habitat quality (56). Opponents of the thrifty genotype hypothesis note several other flaws in the argument. For one, starvation rarely leads to morality during times of famine. Yet when famine leads to mortality, it primarily affects children and the elderly, as opposed to individuals in the reproductive age (28,57). Bioarchaeological evidence advances the notion that both the gradual adoption of and complete reliance on agriculture led to a decline in health. Proto-agriculturalists living in the Nile Valley appear to have experienced greater nutritional stress and poor health, compared with those living in times of agricultural intensification (58). Skeletal remains of agriculturalists show higher rates of growth retardation and iron deficiency anaemia compared with those of hunter-gatherers, suggesting nutritional inadequacies in the former (59).

At the molecular level, some data suggest that selection pressures may have acted on obesity-related loci in *FTO* (60). 'Thrifty variants' in *CREBRF* in Samoans (61) and variants in *LCT* are strongly associated with BMI (62,63). Although arguably 'thrifty variants' in *CREBRF* may be partly explained by population history, these data provide tentative support for the thrifty genotype hypothesis. Alternative theories, however, also exist. Based on observations of diabetes rates among domesticated mammals, Gerstein and Waltman (64) suggest that ethnogeographic heterogeneity in diabetes can be linked to recent adaptive events. They argue that diabetes predisposing alleles in European populations may have been negatively selected for and purged from the population, because of a relatively stable food supply and the long-standing availability of labour-saving devices. By extension, obesity risk alleles may have been selected against alleles in the European population as a result of food security.

Wang and Speakman (65) searched for signatures of natural selection among 115 BMI-related SNPs across diverse ethnic groups. Four 4 BMI-related SNPs and five obesity-protective SNPs showed evidence of positive selection. The latter observation, although apparently counter-intuitive, is in line with Gerstein and Waltman's (64) hypothesis. Recent genome-wide association study meta-analyses lend additional support to this theory: data suggest that selection on common genetic loci has simultaneously increased height and decreased BMI among Europeans (66,67). Accordingly, other studies have failed to provide support for the thrifty genotype hypothesis (68).

Genetic association studies have recently shifted their focus to signals of polygenic adaptation, small shifts in allele frequencies at many loci. Studying polygenic selection signals for 32 BMI-related SNPs in a multi-ethnic panel, Berg and Coop (69) failed to identify any signals of selection at the global level. However, mean genetic BMI score was significantly lower in East Asia, which may suggest the presence of locally-acting selective pressures. In a similar vein, Field and colleagues (70) detected signals of polygenic adaptation for decreased male BMI and increased female waist-to-hip (WHR) ratio. Because the signals of natural selection for polygenic adaptation may be weak or moderate at best (70), it is possible that few obesity-related SNPs have reached the threshold of natural selection because of an underlying polygenic architecture. Evidence of population dependent selection further complicates the matter and may

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further explain some data refuting the thrifty genotype hypothesis.

Although much of our discussion in the following two sections focuses on the evolution of obesity from an adaptive lens, it is important to note the potential role of a force equally as powerful as natural selection: genetic drift. Speakman (28,71) incorporates the concept of drift into an evolutionary model, arguing that human obesity may be explained as a result of relaxed selection pressures for predation. Drawing on data from wild animals, Speakman (28,71) maintains that human body weight is regulated by two 'interventions points' between which weight fluctuates. Selection for genes regulating the lower intervention point, set to minimize the risk of starvation, has remained unchanged. The upper intervention point, set to minimize the risk of predation, may be subject to drift. Selection pressures may be absent because of the discovery of fire, establishment of social systems or use weapons that would have enabled our ancestors to ward off predators. Variation in human obesity ensues because genes regulating the upper intervention point of some individuals has experienced drift, while others have not.

Models of the evolutionary origin of obesity cannot simply be categorized as adaptive or non-adaptive. Natural selection and genetic drift do not work in isolation; rather, it is likely that both forces have worked in tandem to shape the genetic architecture of obesity. Because obesity is largely polygenic in nature (72), it is possible that natural selection has increased the frequency of alleles advantageous to survival, while genetic drift, serving as a form of 'blind justice,' has randomly affected the frequencies of others. The joint effects of these forces in diverse contexts may help explain ethnogeographic variation in obesity prevalence.

When fat is fit

Fat and the developing brain

Brain metabolism of adult humans represents 20–25% of resting metabolic rate (74). Energy requirements of the newborn human brain are higher: roughly 50–60% of energy intake is allocated to brain function (75). To buffer disruptions in energy supply during stages of cerebral maturation, the foetus develops a subcutaneous layer of fat in the third trimester (74,76), endowing a neonate born at full term with 500–600 g of fat (73,74,76).

An infant's body is composed of 11–17% fat on average (reviewed in (77)). The fattiest mammals thereafter, the guinea pig and harp seal, are born with an estimated 10.8% and 10.4% fat at birth, respectively (76). Guinea pigs, who are weaned at birth, undergo a period of undernutrition in the first week of life (78). Harp seals experience an extended post-weaning fast, during which stored energy in the lean body mass and blubber layer is mobilized (12,13). The large amount of fat amassed by human infants may also be explained by nutritional stress during weaning (76). Fat deposits of human infants are reduced in the face of energy challenge, whereas fat deposits of the grey seal, which uses fat deposits as a means of insulation, are maintained even after extended periods of starvation (76). This depletion of energy reserves may be related to cerebral energy requirements. In starvation conditions, adaptive metabolism provides fuel for the human brain by shifting from glycogenolysis and gluconeogenesis, the brain's usual sources of energy, to fatty acid oxidation (76). Ketones (i.e. β-hydroxybutyrate, acetoacetate, and acetone), synthesized from adipose stores fuel the brain when glucose is not accessible (73,76,79).

At the molecular level, tentative evidence points to a link between body composition at birth and obesity phenotypes. Positive associations between risk-allele scores and change in body weight and BMI from birth, and fat mass and lean mass at 1, 2–3, and 4–5 years of age have been reported (80). Rapid fat mass gain, as opposed to rapid weight gain, was more strongly associated with obesity and overweight in mid-childhood (81). However, rapid weight gain among formula-fed infants seems to be driven by lean mass gains (82). Infants fed high-protein formula have an increased risk of obesity at 6 years compared with infants that were breastfed or given low-protein formula (83). Future longitudinal studies examining fat and lean mass gains and the aetiology of obesity will help evaluate whether conservation of fat mass accrual by infants, possibly as an energy source during cerebral development, may explain the persistence of obesity-risk alleles.

The difference in composition of adipose deposits in baby and adult humans is also intriguing. Baby fat contains almost 3–4 times more arachidonic acid (ARA; 20:4n-6) and docosahexaenoic acid (DHA; 22:6n-3) than adult fat deposits (84). DHA plays an essential role in retinal function (85) and the central nervous system (86). Because DHA biosynthesis *in vivo* is complex and the resultant amount of DHA synthesized insufficient, DHA is largely supplied to the infant pre-made via diet/breast milk or through fat deposits (73,86). In fact, gestational age has been linked to composition and concentration of fatty acids in blood. Preterm infants (≤ 34 weeks gestation) have significantly lower DHA and ARA composition and concentration in blood, with each additional week of gestation contributing to a 3.7% or 1.6% increase in DHA and ARA blood concentration, respectively (87). Biosynthesis of DHA and ARA from precursor fatty acids is also impaired in premature infants (87). Because low birth weight predicts global cognitive impairment of children under the age of 5 (88), these data suggest that inadequate fat stores, and by extension low, DHA reserves among preterm infants may contribute to risk of neurodevelopmental delay (73). Despite the fact that developmental delay in this demographic can stem from

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diverse causes (e.g. perinatal hypoxia (89) and intraventricular haemorrhage (90)), conservation of adipogenesis during foetal development may improve fitness. Although obesity-risk alleles in *FTO* have been associated with decreased brain volume (91,92) and 6-year cognitive decline (93), rare loss-of-function mutations have been associated with microcephaly, severe psychomotor delay and functional brain deficits, without apparent effects on body adiposity (94). In light of this, we cautiously suggest that genes regulating adipogenesis, particularly during the infantile period, may have been selected to ensure proper neurological function throughout the life course.

Adiposity and thermoregulation

Adipose tissue is of two kinds. White adipose tissue (WAT) is an endocrine tissue and is essential in the storage of energy, while brown adipose tissue (BAT) is responsible for thermogenesis via mitochondrial respiration (95). Within WAT deposits, 'beige' adipocytes also exist, exhibiting thermogenic properties similar to brown adipocytes upon stimulation (96). BAT has been traditionally viewed as a fat deposit present only in neonates and small mammals (97). However, recent evidence shows that BAT mass is present in adults and is inversely related to obesity phenotypes (97). Moreover, the characteristics of BAT deposits may be different among individuals of different body types. Magnetic resonance imaging studies show that BAT and WAT deposits containing beige adipocytes among obese children have more fat content and less mitochondria compared with those of normal weight children (98). Genetic variants in *ADRB3*, which participates in energy regulation through heat generation and lipolysis, have been associated with BMI (99). Among East Asians, carriers of the Arg64 allele showed a significant increase in BMI by 0.31 kg m^{-2} in contrast with Trp64 homozygotes, while no significant association was observed among Europeans (99).

Thermogenesis may help explain variability in obesity rates: cold adaptations may have inadvertently provided mechanisms to expend excess energy (33,100). Populations highly adapted to arctic climates such as the Canadian Inuit have a higher metabolic rate, which could theoretically be protective against obesity. In contrast, African Americans, well-adapted to tropical climates, have lower metabolic rates and thus may be highly susceptible to obesity (33). Variation in BAT levels – and as a result, differences in thermogenesis – may be driven by varying degrees of cold exposure or differences in cultural strategies protective against the cold, e.g. clothing and use of fire (100). Intriguingly, Sellayah and colleagues (33) note that migration history and changing climactic pressures can help explain why populations descending from a single ancestral group may be differentially susceptible to obesity. For example, obesity-prone Pima Indians in the hot climate of Arizona and Mexico and the obesity-resistant indigenous peoples residing in the extreme cold of Tierra del Fuego descend from a common Siberian ancestor well-adapted to the cold. These observations highlight the idea that environmental adaptations may play a key role in defining body adiposity.

Recently, Speakman and Heidari-Bakavoli (101) studied the association between ambient temperature and the county level prevalence of type 2 diabetes and obesity. Although a significant association between type 2 diabetes and ambient temperature was detected after adjustment for race and average county income, only 0.15% of the variation in obesity prevalence was explained by ambient temperature, and the association was only nominally significant. The authors note that the variation in type 2 diabetes prevalence explained by ambient temperature differed by month. It is possible that the association between obesity and ambient temperature may be masked by aggregate temperature data. Moreover, estimates of ancestry based on social constructs of race may be crude, as individuals identifying themselves as African Americans may carry different amounts of African genomes (102). Because explanations of modern day obesity rates based ambient temperature and thermogenesis are focused on genetic ancestry and population history, it is imperative that future studies use more precise estimates of ancestry to evaluate any association between obesity and temperature.

Gene pleiotropy, natural selection and obesity

As implied by the thrifty genotype hypothesis, obesity genes are typically involved in appetite regulation, food seeking behaviours and metabolic efficiency. However, many of these genes have additional pleiotropic effects that may also be under natural selection. Traits associated with a given genetic variant may be differentially selected. Some may be synergistically or antagonistically selected for, while others may experience different selective pressures based on time or geography. These complex patterns of selection for different phenotypic traits may explain the diversity of obesity risk allele frequencies in human populations (Fig. 2).

Fat and fertility

Darwinian selection is based on fitness. Thus, traits such as body fat, which play a role in defining reproductive capacity, may have been directly selected for. Generally, obesity among children can hasten pubertal development (103). A minimum amount of fat is essential in regulating menarche, menstruation and ovulation (104). Abnormally low body weight, for instance, among women with anorexia nervosa, has been associated with delayed puberty, amenorrhea or irregular menstruation (105,106). This demonstrates that a minimum amount of body fat is essential in reaching reproductive potential. Reproductive outcomes are also

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associated with body adiposity. Some reports of elevated rates of miscarriage and caesarean sections among anorexic women exist, as do reports of similar negative reproductive outcomes among obese women (106). Although tentative, Wang and colleagues (107) estimate optimal BMI among Caucasian women to be approximately 23, combining the effects of BMI on all-cause mortality and future potential fertility based on BMI at age 20. This estimate further supports epidemiological data, demonstrating that BMI extremes negatively impact fitness and fertility.

The impact of obesity on male fertility, however, is not as conclusive. Theoretically, any changes to mitochondrial function, motility, volume or morphology of spermatozoa may impact male reproductive fitness. Although routine sperm parameters (i.e. sperm concentration, morphology and ejaculate volume) are similar among obese and normal weight males, differences in the motility of sperm, percentage of damaged DNA (DNA fragmentation index; %DFI) and mitochondrial membrane potential of spermatozoa exist (108). From an evolutionary standpoint, the successful transmission of the paternal genome to offspring would increase fitness of the father. %DFI may discriminate between fertile and infertile males (109) and has been shown to better predict natural conception when compared with routine sperm parameters (110). Moreover, high BMI does not appear to compromise DNA integrity (111–113). Rather, overweight is associated with a reduced incidence of DNA fragmentation (111,113), pointing to a beneficial effect of adiposity. In summary, epidemiological data point to an optimal level of body fatness for both sexes, deviations from which may result in decreased reproductive function. This link between body fatness and fitness may serve as partial explanation for the persistence of obesity-risk alleles.

Genetic association studies suggest that common obesity predisposing variants are also associated with earlier pubertal development (114–116), pointing to synergistic pleiotropic effects. Cases of rare, monogenic obesity, however, render the situation more complex. Morbidly, obese patients with genetic defects in *LEPR* exhibit hypogonadotropic hypogonadism, which may lead to delayed sexual maturation (117,118). Women who achieve menstruation may experience irregularities in their cycles (117,118). Hypogonadism has also been reported among patients with monogenic obesity because of *LEP* (119), *PC-1* (120) and *MC4R* (121) mutations, although the effects of MC4R deficiency on reproductive function is controversial (122–124). Severe forms of obesity may reduce fertility, but obesity does not render one sterile. Despite menstrual irregularities and pubertal delays among homozygous *LEPR* mutation carriers, natural pregnancy has been reported (125).

Similar complexity in the relationship between obesity and fertility is seen among women with polycystic ovary syndrome (PCOS). PCOS is an endocrine disorder, typically characterized by androgen excess, ovulatory dysfunction and polycystic ovaries (126). Although the exact aetiology of the disorder has yet to be elucidated (126), women with PCOS tend to have significantly higher BMI (127). Although Joham and colleagues (127) noted a 15-fold increase in infertility among women with PCOS independent of BMI, genetic association studies have highlighted that genes related to obesity, insulin signalling, sexual hormone function and type 2 diabetes are associated with PCOS (128–130). In short, these results highlight the possibility of a common genetic architecture governing obesity and PCOS.

It is important to note that assisted reproductive technologies, medical interventions to mitigate the effects of adverse reproductive outcomes (e.g. delivery through caesarian section), and use of contraception may complicate patterns of natural selection. If fitness can be artificially improved, selection pressure for variants beneficial to reproduction may be relaxed. In short, these data highlight a highly complex relationship between adiposity and fertility.

Susceptibility to infectious disease

Infectious disease affects both energy intake and expenditure – whether through decreased caloric intake because of lack of appetite, inefficiency of nutrient absorption or gastrointestinal problems (131). Malnourished children are more likely to experience episodes of infection, leading to further malnutrition (132). Peak levels of adiposity in infants roughly correlate with the ages at which infants are more susceptible to infectious disease episodes (76). Because children with more weight for height have lower rates of mortality and morbidity driven by infectious diseases on average, it is possible that infant adipose reserves may mitigate the effects of nutritional stress caused by infection (76,131), and thus may have been directly selected for.

The survival of cells and organisms requires the development of mechanisms to meet energy supply and demand for daily functioning while simultaneously being able to respond to pathogens and other environmental threats (133). Close and ongoing crosstalk between the immune system and evolutionarily conserved metabolic pathways is apparent in the animal kingdom. For example, in *Drosophila melanogaster*, the liver, adipose tissue and the immune system are all centred in a single organ: the fat body (133). In humans, some evidence at the molecular level suggests that a common genetic architecture may govern body type and immunological response. This link may have an evolutionary origin, as a number of genes related to exhibit signatures of positive selection, including *LEPR* (134). Thus, selection for genes conferring immunity may inadvertently has contributed to genetic risk for obesity.

The link between obesity and immunity, however, is complex. Leptin, an adipocyte-derived hormone, indicates the level of energy stores in the human body (135). Ozata and

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colleagues (119) describe changes in immune function in morbidly obese patients homozygous for a missense *LEP* mutation. In a consanguineous Turkish pedigree, 7 of 11 obese individuals died in early childhood during an episode of infection. Although genetic information was unavailable, these patients exhibited phenotypic similarities with homozygous mutation carriers in the family. Thus, the authors propose that congenital LEP deficiency diminished the immunological function of affected individuals, making them more susceptible to disease. In line with these findings, Farooqi and colleagues (118) note altered immunological profiles of individuals homozygous for *LEPR* mutations and report an increased frequency of episodes of infection – in particular, upper respiratory tract infections – among affected individuals. Premature deaths of two obese children in families of homozygous *LEPR* mutation carriers were linked to an acute respiratory tract infection, although this susceptibility to infectious diseases was not observed among adult homozygotes (118).

This apparent age-dependent susceptibility to infectious diseases among morbidly obese patients with congenital LEPR and LEP deficiency renders the pattern of natural selection more complex than classic directional selection. Although homozygosity is associated with increased risk of mortality as a consequence of increased adiposity, heterozygous carriers of *LEP* and *LEPR* mutations are neither morbidly obese nor do they display serious metabolic or immunological complications (117,119). Furthermore, although congenital LEP deficiency may increase susceptibility to episodes of infectious disease, this state of immunological vulnerability may be mitigated: administration of leptin has been shown to improve immunological profiles among obese patients (135). Moreover, Ozata and colleagues (119) suggest that the negative impact of LEP deficiency on physiological function is diminished over the human lifespan. This ability for the body to regain functions lost because of LEP insufficiency, coupled with modern-day pharmacological interventions to mitigate the effects of leptin deficiency, may drastically affect patterns of selection patterns for *LEP* and *LEPR* mutations.

Bone formation and metabolism

The vertebrate skeleton plays multiple roles in organismal physiology – from protecting vital organs and blood cell production to storing minerals and facilitating motion (136). Skeletal health may be an indicator of many aspects of overall health. Low bone mineral density (BMD) has been associated with a 1.17-fold and 1.13-fold increase in total and cardiovascular mortality, respectively (137). Echoing these findings, a recent meta-analysis estimates the odds of atherosclerosis among individuals with low BMD to be 2.96, compared with those with high BMD after adjustment for age, sex, BMI and vascular factors (138). Relationships between male fertility and BMD have also been reported. Infertile Chinese men displayed significantly lower lumbar spine and total hip BMD compared with fertile males (139), while low BMD has been reported among subfertile, hypogonadal men (140,141). Testosterone levels may mediate this relationship: testosterone therapy among aging (142) and hypogonadal males (140) has been linked to increase BMD.

Intriguingly, increases in BMD with increasing BMI have also been observed (143). This relationship between body and bone mass may have a genetic basis. Farooqi and colleagues (144) report elevated BMD among MC4R deficient patients with severe early-onset obesity, adjusted for age and gender. Similarly, Loos and colleagues (145) report association of rs17782313 near *MC4R* with elevated adiposity and bone mineral density, with each additional copy of the C-allele contributing to a 0.13 and 0.06 increase in Z-score for BMI and BMD, respectively. These findings suggest that increased bone mass is not simply a consequence of overall larger bone size among obese individuals. Rather, studies in Mc4r deficient mice suggest that increased BMD results from a decrease in bone resorption, mediated by increased signalling of *CART*, in line with observations among humans with *MC4R* insufficiency (i.e. among individuals carrying at least one mutated allele) (146,147). Given the observed epidemiological associations between low BMD and mortality risk and the association of low BMD with subfertility, it is possible that some variation in obesity risk may be explained by synergistic pleiotropic effects. That is, increased adiposity among some individuals may be explained by selection for alleles increasing BMD, which may be driven by fertility and survival advantages.

Altered skin pigmentation

As humans dispersed out of Africa, strong selective pressures related to climate and latitude likely drove local adaptation. Skin pigmentation, for example, is associated with UVR (148) and the minimal erythemal dose, the amount of UVR sufficient to cause sunburns (149). As such, human pigmentation is believed to have evolved as a means of photo-protection from UVR, while sufficiently enabling absorption of vitamin D to maintain bodily functions (149). Alternatively, geographic variability in pigmentation may have arisen to protect against folate deficiency and infections, as a means of camouflage for early humans or as a result of sexual selection (148–150). Allelic variants in genes contributing to pigmentary phenotypes, for instance, those in *SLC24A5* and *MATP*, show signatures of positive selection among European and East Asian populations (151,152).

Some obesity syndromes, although classically associated with hyperphagia, are also accompanied by altered

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pigmentation. This highlights shared biological pathways contributing to adiposity and variation in skin, hair and eye colour, driven by the common ectodermal origin of neuronal tissue and skin. Prader-Willi syndrome (PWS), for example, is associated with loss of function of the paternal genomic imprinting region at 15q11.2-q13, (e.g. because of deletion, two copies of maternal chromosome 15/maternal uniparental disomy 15 or gene imprinting centre defects), leading to a constellation of abnormalities including obesity, developmental delay and hypogonadism (153). Hypopigmentation, reported in up to 48% of individuals with PWS (154), is associated with hemizygosity of the oculocutaneous albinism II gene (155), while albinism may arise from homozygous loss of oculocutaneous albinism II (153,156). PWS phenotypes vary based on the molecular aetiology of the syndrome (i.e. deletion vs. uniparental disomy) and the length of deletion (153). Individuals with PWS resulting from chromosomal deletions display significantly lighter hair and skin complexions and increased sun sensitivity than those with PWS linked to other causes (154).

Severe, early-onset obesity caused by POMC deficiency, characterized by impairment of adrenal steroidogenesis, pale skin and red hair, is also associated with altered pigmentary phenotypes (157). Pigmentation in POMC-deficient children of Turkish (158), North African (159) and Indian descent (160) is different from the first cases described by Krude and colleagues (161) in the lack of distinctive red hair. Despite having brown hair, some affected patients of non-European origin may have reddish roots (158). Elevated levels of pheomelanin (contributes to red/yellow coloration) and eumelanin (contributes to dark coloration) have been observed in hair via microscopy, despite no observable differences in skin reflectance relative to unaffected relatives (159). Individuals with POMC deficiency administered setmelanotide to treat obesity and hyperphagia report darkening of hair and skin colour over the course of treatment (162). Pigmentary phenotypes may have been selected to improve fitness in diverse latitudinal clines while inadvertently conferring susceptibility to obesity. However, these ethnic-specific and pharmacologically induced changes in the classic pigmentary phenotype of POMC-deficient patients suggests a complex interaction between forces governing adaption to different environments in ancient times and those that counter-select for morbid obesity in the modern day.

Although tentative, some data do suggest that common genetic architecture underlie pigmentation and obesity phenotypes. A novel study by Li and colleagues (163) reports nominally significant associations between obesity-related SNPs and hair pigmentation. A higher gene score was associated with darker hair, independent of the effects of BMI. Better powered studies in the future will help to further evaluate these hypotheses.

Adaptation to altitude

Woolcott and colleagues (164) report an inverse association between median obesity prevalence and altitude among adults in the United States. Provincial altitude is also inversely related to the prevalence of obesity and overweight among Peruvians living near the Andes (165). Sherpa and colleagues (166) estimated that each kilometre increase in altitude reduced adult BMI by 1.31 kg m^{-2}, after accounting for physical activity, calories consumed, age and sex. The authors were unable to determine whether increased energy expenditure could mitigate the effects of increased caloric intake, as observed at higher altitudes. Intriguingly, differences in genetic ancestry and altitude may jointly explain variation in body mass. Bianba and colleagues (167) compared anthropometric measures of native Tibetan and Han Chinese children aged 9–10 living in Lhasa (3700 m above sea level) and Tingri (4300 m above sea level). Among native Tibetan children, those living at lower altitudes were significantly heavier and exhibited higher BMI, in contrast with those children living in Tingri, who were more often underweight. Native Tibetan children living in Lhasa were heavier and taller than their Han Chinese counterparts, who were more often normal weight and less likely to suffer from severely stunted growth.

The aforementioned studies are limited in their generalizability, owing to their lack of careful adjustment and characterization of numerous confounding factors that may affect body weight at high altitudes (e.g. physical activity, energy intake, changes in appetite and leptin levels). Selection for genes enabling survival at hypoxic conditions is well established (168). Although currently common target of selection cannot be identified, mouse models have highlighted mechanisms by which energy balance is regulated jointly by *HIF* and *POMC* (169–171). Studies in the near future will help evaluate the relationship between body phenotypes and altitude.

Behavioural traits

Alongside adaptations to survive in the geophysical environment, it is likely that genes coding adaptive behavioural traits were selected for human survival and reproductive success, after all, requires successful interpersonal interactions. Psychological traits that undermine social cohesion may also confer a fitness advantage in certain contexts. Aggression may prevent resources like property, food or a mate from being co-opted by others (172). Impulsivity (e.g. sensation seeking), particularly in adolescence, may be a means to increase reproductive success (173). Moreover, individuals with antisocial behaviours may be considered more inclined towards mating as opposed to parenting thus conferring them evolutionary success in hostile or unstable environments (173). Intriguingly, pleiotropic effects between

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obesity genes and social behaviours have been reported in the literature. Social isolation and aggression have been reported among obese individuals carrying loss-of-function mutations in *SH2B1* (174), while impulsivity and stubbornness have been noted among obese patients homozygous for *LEPR* mutations (117). Patients with LEP and LEPR deficiency may also resort to confrontation in order to access food (117,175).

Genes impacting both body adiposity and advantageous behavioural traits, however, may be subjected to more complex patterns of selection than classic directional selection. To illustrate, although some argue that depression is an adaptive trait (176,177), data show increased risk of mortality among depressive patients (178) and reduced fertility among women experiencing postnatal depression (179). The link between obesity and depression is also controversial (180–183). Samaan and colleagues (180) report an inverse relationship between the obesity predisposing A variant of the *FTO* rs9939609 and major depression, with each additional copy of the A variant associated with an 8% reduction in risk of major depression. This same genetic variant has also been inversely associated with completed suicide, independent of the effect of *FTO* rs9939609 and alcohol addiction (184). Contrastingly, the obesity risk allele at rs2984618 in *TAL1* has been associated with an increased risk for major depressive disorder, although a gene risk score composed of 21 obesity-risk alleles was not associated with depression (183). Adding to this complexity, the effect of rs1401635 in *BDNF* varied among Europeans and non-Europeans, conferring Europeans protection from depression while increasing risk of depression among non-Europeans (183). This shows that the survival benefits of behavioural traits are context-dependent. In some social settings, a trait may be advantageous in certain social settings but detrimental in others. Such diverse patterns of local, context-specific selection for behavioural traits may help explain some of the variation in obesity risk.

Bulging waistlines: a consequence of creating and inhabiting new environments?

Circadian rhythmicity and obesity

Physiological and behavioural processes in organisms as diverse as bacteria and humans are regulated by the circadian clock (185). The circadian clock is an intricate molecular network that enables the body to predict and react to changes in the environment (e.g. light, temperature, exercise, and food availability). This enables organisms to cope with fluctuations in energy requirements and availability efficiently, thereby improving fitness (185). The master clock, the suprachiasmatic nucleus of the hypothalamus, synchronizes the activities of peripheral molecular clocks that are localized in most tissues of the body such as BAT, WAT, the liver and the skeletal muscle (186). In the natural environment, the photoperiod (time during which an organism is exposed to light) is the main regulator of homeostatic rhythm in the body. Cycles of light and dark periods regulate sleeping and waking, the autonomous nervous system, melatonin secretion and core body temperature (186). Peripheral molecular clocks, entrained by cycles of feasting and starvation, regulate glucose and lipid levels, hormone secretion, digestion, immune response and detoxification (186). As Scheer and colleagues (187) illustrate, appetite and feelings of hunger may also be regulated by the circadian clock. Their data show that a peak in hunger is observed in the evening (~7:50 PM), while a trough is observed in the morning (~7:10–8:30 AM), possibly corresponding to energy storage before the overnight fast.

Genetic association studies have shown the importance of the circadian clock in energy balance. As such, the circadian clock may contribute to obesity directly, by way of genetic variants in circadian clock genes like *CLOCK* (188) or *REV-ERBα* (189). Alternatively, 'circadian desynchrony,' when environmental stimuli and biological processes are no longer harmonized, may affect body adiposity (190). Because circadian clock mechanisms are highly evolutionarily conserved, changes in the environmental cues to which the circadian clock is tuned (e.g. light, temperature and food availability) may affect energy metabolism (185). Studies have linked night time light exposure with increased odds of obesity as measured by BMI, WHR, waist-to-height ratio and waist circumference (191). Unfavourable sleep habits – habitual long and short sleep duration and poor sleep quality – have also been linked with obesity risk (192,193). Age-specific and sex-specific differences in nutrient intake have been associated with sleep duration, with nutrient intake possibly moderated by variants in *CLOCK* (194). Coupled with studies reporting elevated BMI among shift-workers, for instance, nurses and midwives working at least 8 or more night shifts per month (195), it is apparent that certain aspects of modern lifestyles – for instance, artificial light, shift-work, disturbed sleeping patterns, constant ambient temperature, frequent travel through time-zones and continuous access to calorie-dense foods – may have important implications for metabolic health (185,190).

Tau, the length of the circadian period (length of the daily cycle), may also explain some ethnic variation in obesity predisposition. Ethnic variation in tau length has been observed: Caucasians have longer taus compared with African Americans. (196). A longer tau may enable better adaptability to changes in photoperiod. Biological processes of those native to equatorial regions are reliant on more rigid circadian rhythms, which increases the likelihood of circadian desynchrony in northern latitudes, where

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photoperiod fluctuates more throughout the year (190). By extension, those native to northern latitudes have circadian rhythms that are more resilient to variation in photoperiod, thereby having a protective effect against obesity (190). Genetic variation in circadian clock genes among different ethnic groups has been observed, although evolutionary drivers of these genetic differences are unclear. Ciarleglio and colleagues (197), for example, propose that differences in allele frequencies are driven by random genetic drift, while Cruciani and colleagues (198) suggest the role of positive selection driven by factors other than latitude.

Novel foods and natural selection

The transition from a hunting and gathering to more sedentary lifestyles often cited as a contributing factor to the obesity epidemic. Indeed, cases of forced settlement of seminomadic foragers on the Andaman Islands by colonialists (199) and departures from the traditional food procurement strategies of Pacific Islanders (200) and Pima Indians (201) have been associated with increased rates of overweight and obesity. The adoption of new staple foods has directly impacted the human genome with implications for obesity risk. With the advent of dairy farming, populations reliant on cattle, for instance European, African and Middle Eastern peoples, have adapted the ability to digest milk late into adulthood (202,203). Various SNPs in *LCT* have undergone strong positive selection in the last 5,000–10,000 years (204), supporting the notion that these polymorphisms represent a survival advantage. Lactase persistence genes arose independently in European and African populations (202), with lactase non-persistence alleles decreasing in frequency from South to North and from East to West in Britain (205). Genetic adaptation to changes in food procurement strategies may explain some predisposition to obesity, as carriers of the lactase persistence *LCT* variant exhibit elevated BMI (62), especially among those with high consumption of dairy products (63). Adaptations to optimize starch digestion via positive selection of *AMY1* (206) are examples of the opposite effect of genetic adaptations to cultural advancement: increased copy numbers of *AMY1* may be protective against obesity (207,208). This relationship, however, was recently shown to be modified by starch intake. Rukh and colleagues (209) observed decreased BMI with increasing copies of *AMY1* and low starch intake but elevated BMI with increasing copies of *AMY1* among those with high starch intake. Perry and colleagues (206) show that populations that consume more starch rich diets have more *AMY1* copies, while copy number variation among populations consuming lower amounts of starch results from genetic drift. These data highlight the role of cultural pressures in driving evolutionary change.

To be thrifty or not to be thrifty? Obesity and the epigenome

The epigenome, the collective epigenetic information carried by an individual (53), represents both heritable and transient changes induced by environmental cues such as diet (210) and exercise (211). Epigenetic modifiers are chemical marks added to chromatin proteins or DNA that regulate gene expression (53), leading to activation or silencing of genes and regulation of transcriptional activity (212,213). DNA methylation, one of many epigenetic modifications, involves the differential addition of methyl groups to cytosine residues along the genetic sequence (53). Typically, methylation is associated with gene silencing, particularly when modifications are made at promoters or enhancers (212,213). Methylation patterns are tissue specific. Expression of different genes in blood and subcutaneous, omental/visceral adipose tissue has been associated with obesity phenotypes (e.g. *HIF3A*, *SSPN* and, *CCDC125*) (214,215). Methylation profiles in subcutaneous and visceral fat depots are also known to change before and after bariatric surgery and significant weight loss (216,217). Despite these associations between altered methylation and obesity, causality may be difficult to ascertain. Wahl and colleagues (218) suggest altered methylation may be a consequence of adiposity, as opposed to its cause.

Heritability of epigenetic marks may occur in one of two ways. Environmental exposures that induce epigenetic changes may affect the germline of an individual, such that the somatic cells of subsequent generations inherit an altered epigenome (219). In line with this, methylation patterns of spermatozoa differ among obese and lean males (220), while offspring of obese parents exhibit altered DNA methylation at imprinted genes (221). Alternatively, some genetic variants, e.g. *FTO* obesity risk alleles rs9939609 and rs8050136, modify their own methylation patterns in addition to those of other genes (222,223). Grundberg and colleagues (224) analysed the methylome in adipose tissue, comparing methylation profiles of monozygotic and dizygotic twins with those of unrelated individuals. They estimated that approximately 34% of the variability in the methylome can be attributed to genetic variants. Thus, selection pressures favouring these regulatory genetic variants – whether for their direct or pleiotropic effects on human physiology – may contribute to obesity risk.

Among plants and fungi, DNA methylation appears to be a mechanism of genome defence, where methylation targets transposable elements or 'jumping genes' (53). Among mammals, because most of the genome is methylated, transposable elements may be passively methylated (53). *Alu* element mediated hypermethylation at the intron2-exon3 boundary of *POMC*, implicated in energy homeostasis,

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has been associated with an increased risk of obesity (225). Further research by Kühnen and colleagues (228) suggest that this *Alu* element mediated hypermethylation of *POMC* may be a cause, as opposed to consequence, of obesity. Not only are methylation patterns stable throughout the life course, methylation at these regions is consistently correlated with BMI in different tissues. This indicates that methylation, in the context of genome defence, may be a random process with important consequences for energy metabolism.

Gene imprinting, the monoallelic expression of genes based on parental origin, is also impacted by epigenetic mechanisms: differential methylation of imprinted genes results in differences of gene dosage (227). At minimum, genetic variants in 12 different imprinted genes are implicated in leanness and obesity phenotypes (227). For instance, the paternal alleles in *DLK1* and rs2471083 near *KCKN9* are associated with adiposity (228,229), while the maternal A allele of rs3736485 in *DMXL-2* has been positively associated with weight Z-score in children from birth to 5 years of age (230). Gene imprinting is postulated to have evolved as a mechanism of conferring fitness to the mother or father by limiting or maximizing use of maternal resources, respectively. Alternatively, offspring fitness can be maximized by favouring selection of genes making the child more phenotypically similar to the mother or father (227,231). It is plausible that regulation of body weight via gene imprinting may represent pleiotropic effects, with the metabolic impact being secondary to growth retardation (227). Evolutionary conservation of methylation may indirectly affect obesity phenotypes.

On the other hand, temporal differences in exposure to epigenome-altering environment cues, such as exercise and famine, may explain the recent influx in obesity prevalence and persistence of obesity risk alleles across generations. Physical activity affects the methylation pattern of obesity-related genes in adipose tissue, for instance, *FTO* and *TUB* (211). Differential methylation may mask or unmask alleles associated with obesity phenotypes and may thereby render patterns of selection for obesity and leanness variants more elaborate. Whether obesity risk alleles arose historically through natural selection or because of *de novo* mutations, methylation may have silenced alleles via increased physical activity among our ancestors, nullifying the impact of adiposity-related variants. As humans have become more sedentary, altered methylation profiles may amplify or mitigate the effects of these thrifty genes, contributing to variability in obesity.

Although famines may have occurred infrequently over our species' history (55,56), bouts of severe nutritional deficiency may also have driven evolution by inducing change at the genetic and epigenetic levels. In a recent investigation of methylation patterns among individuals exposed to famine during the Dutch Hunger Winter, Tobi and colleagues (232) observed differentially methylated regions associated with prenatal malnutrition, mapping to genes associated with growth and development. As the authors note, some differentially methylated regions associated with prenatal malnutrition are linked to birth weight and serum low-density lipoprotein cholesterol levels, pointing to a potential role in metabolic syndrome in adulthood (232). As postulated by Neel (27), famine may have directly favoured the selection of metabolically thrifty alleles; however, famine may also induce physiologically relevant change at the level of the epigenome (232), rendering the natural selection process for adiposity-related variants more complex.

Can the selection of variation in obesity be adaptive instead of obesity *per se*?

Feinberg and Irizarry (233) hypothesize that increased variability in a phenotypic trait regulated by epigenetic mechanisms may confer greater fitness than the selection of a trait in and of itself. Simulating fluctuations in a phenotype over 1,000 generations using mathematical models, they show that a phenotype with the smallest variance is selected for in a fixed environment that favours positive values of a given trait (233). In changing environments, where selection for or against a trait varies from generation to generation, the most variable genotype dominates (233). Moreover, although the average value of the trait hovers around a central point, variation in the trait increases consistently.

Because *FTO* contributes to obesity (234), is associated with phenotypic variability of BMI (235) and is also highly sensitive to environmental factors such as diet (236) and physical activity (237), *FTO* may regulate variation in body type as per Feinberg and Irizarry's model (233). Comparing genomes of humans and vertebrates, a recent paper demonstrates that most coding sites in *FTO* show signals of strong purifying selection and neutral mutation, leading Liu and colleagues (60) to argue that *FTO* was historically under positive selection. Recent research, however, provides evidence against the applicability of Feinberg and Irizarry's model to obesity (233). Haploinsufficiency of *Trim28* in mouse models triggers a bimodal distribution of body weight (238). Mutant mice exhibit either a normal or obese phenotype, with few exhibiting intermediate body weights (238). This demonstrates that a subset of SNPs may modulate variability in BMI. Future studies may evaluate the applicability of Feinberg and Irizarry's model (233) to the context of obesity, by determining whether variants favouring variability in BMI have been under selection.

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Colonialism, social injustice and the rise of the thrifty genome and epigenome

The Nauru

The Nauru, with their exceptionally high obesity rates, have often been cited as a population exemplifying selection for 'thrifty genotypes.' Diamond (239) proposes that the Nauruan genome has been enriched for genes conferring metabolic thrift. Similar to other Pacific Islanders, the Nauru traditionally relied on agriculture and fishing – the latter, which required long voyages between islands, allegedly led to periods of starvation (239). According to Diamond (239), World War II may have further enriched the Nauruan genome for thrifty genotypes: occupation of the island by the Japanese resulted in forced labour, reductions in food rations and eventual starvation after being forced off to Truk Island. The survivors, those with better metabolic thrift, were the ones to return to the island. Thereafter, affluence, overabundance of food and reductions in physical activity led Nauruan thrifty genes to be maladaptive (239). Gosling and colleagues (240), however, demonstrate a lack of anthropological and bioarchaeological evidence to support these claims. Instead, they suggest that other factors, for instance, founder effects, admixture, disease epidemics, and culturally-mediated selection for particular phenotypes may have played a major role in shaping the genomes in Oceanic populations.

The African slave trade and genetic predisposition to obesity

Obesity rates differ drastically between Black and White Americans, with Black Americans having an excess of 3.2% and 24.1% obese males and females, respectively (241,242). The conditions that slaves faced during the out-of-Africa exodus and maltreatment at the hands of their masters can be used as partial explanation for the ethnic disparity in obesity prevalence. Estimation of mortality rates aboard African slave ships show that a higher number of individuals died during the earlier stages of travel, while the rate declined closer to the time the ship docked in the New World (Fig. 3) (243). Longer trips, those lasting upwards of 50 days, led to a gradual increase in the mortality rate, likely driven by hardships endured by spending additional time at sea with dwindling food rations (243). This trajectory of mortality rate may reflect the purging of individuals with lower metabolic thrift and overall fitness. Presumably, slaves that survived the most arduous journeys across the Atlantic were those with the thrifty genotypes. Indeed, overcrowding and unsanitary conditions faced on the slave ships, coupled with mistreatment by slavers, disease outbreaks and nutritional deficits experienced by slaves are understood to have provided a sufficiently strong selective pressure to eliminate the weakest slaves from the population (243). In theory, this initial selection may have led to an increase in metabolically thrifty variants (Fig. 3).

The purging of the weakest slaves during the Middle Passage across the Atlantic has important consequences for understanding disease risk among descendants of these initial African populations. Mating between African slaves was both consensual and forced – rape by more powerful slaves on the plantation or copulation among slaves forced by owners was prevalent (244,245). Theoretically, these matings would have led to increased homozygosity, potentially enriching the collective genome of slaves for metabolic thrift and survivability in their new environment. Slave breeding was also a common practice, because the offspring of slaves were born into bondage and thus of economic benefit to slave owners (244,245). Fertile, 'large, able-bodied' women were selected as breeders (246), while slave masters prevented some male slaves from copulation, such that no 'runts' would be born from these unions (245). Thus, encouraging mating among slaves with particular body types may have contributed to the current prevalence of obesity among African Americans (Fig. 3).

The sexual control of African slaves may have also provided a means of increasing genetic variation among the second generation of slaves. Master–slave copulation is also well-documented in the historical record, with masters and mistresses forcing slaves to engage in sexual liaisons with them (244,245). Some slave women were sold as concubines, while the sexual services of others were offered to white men by their masters (244). Inevitably, this led to widespread admixture of potentially metabolically thrifty African genomes and those of the European slave owners. Higher overall proportions of European ancestry have been associated with lower BMI among African Americans (22). This relationship is also observed at specific genomic regions. Greater local European ancestry at Xq25 and Xq13.1 on the X chromosome has been associated with lower BMI (247). Bryc and colleagues (102) note an elevated proportion of West African ancestry in chromosome 6 and the X chromosome of African Americans, the former association reaching only nominal significance. This, as the researchers note, supports the notion that admixture between African slaves and their owners was gender biased, with female slaves being forced into more sexual liaisons (102). If regions of the X chromosome among African Americans confer greater susceptibility to obesity, the markedly elevated obesity rates among African American females may represent overdominance or X-linked obesity. Polar overdominance has been observed in cases of severe early-onset obesity, where paternally inherited risk alleles in *DLK1* are preferentially transmitted to obese offspring (228). A similar phenomenon may explain the higher prevalence of obesity among females of African American descent. Although speculative, *SLC6A14*, a candidate gene

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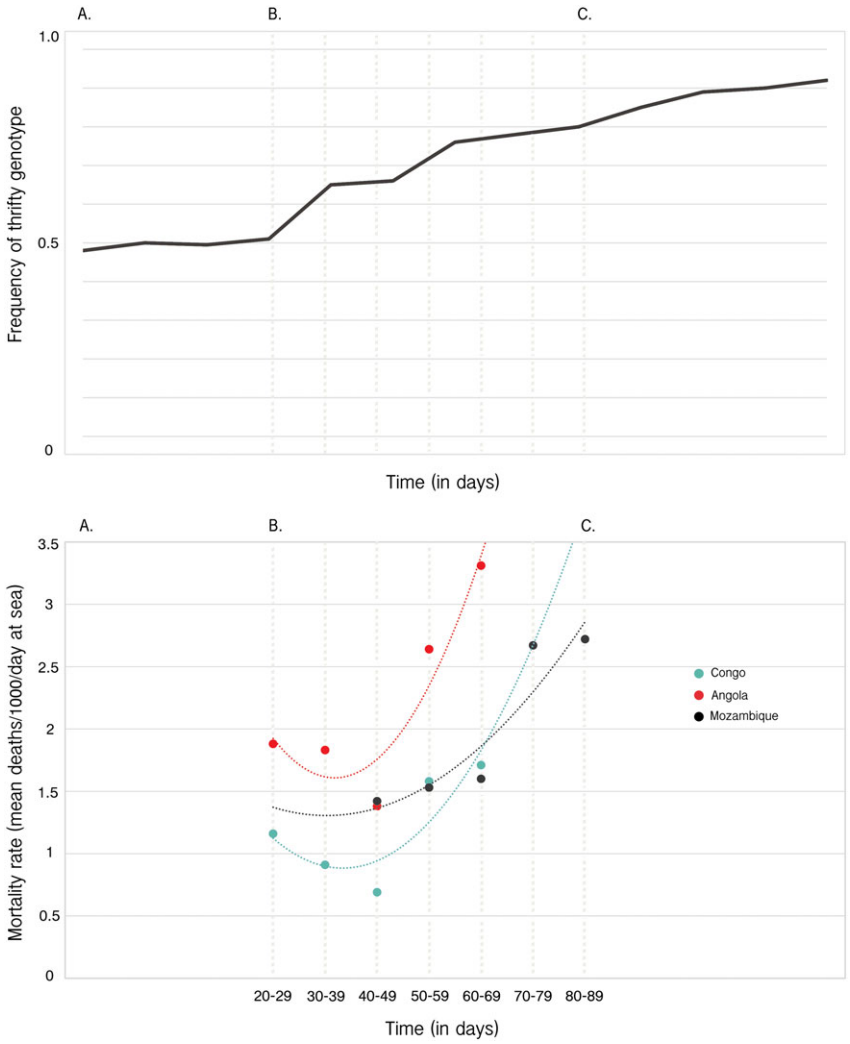

Figure 3 (Top) A theoretical representation of fluctuations in thrifty genotypes among African slaves prior to embarking on the trans-Atlantic voyage (A), during the journey (B) and subsequent to settlement in North America (C). (Bottom) Morality rates (mean deaths/1,000/day at sea) of African slaves captured from different sea ports prior to ship embarking on trans-Atlantic voyage (A), during the journey (B) and subsequent to settlement in North America (C). Data are from Miller (1981). [Colour figure can be viewed at wileyonlinelibrary.com]

that has been associated with X-linked obesity in Finnish, Swedish (248) and French populations (249), is located in the chromosomal region identified by Cheng and colleagues to be associated with elevated BMI in Africans. Because associations between *SLC6A14* rs2071877 and obesity show sex-specific effects (249), SNPs at this locus may possibly drive elevated obesity risk among African American women.

Historical admixture and obesity among indigenous peoples in Canada

Indigenous Peoples exhibit elevated rates of overweight and obesity in comparison with the general Canadian population. According to Statistics Canada, 20.2% of Canadian adults are obese (250). A recent meta-analysis estimates 36.6% of Indigenous Peoples have a BMI $\geq$ 30 kg m^{-2} (251). Historical selection pressures may have affected the Indigenous genome and made this population more vulnerable to obesity. Northcott and Wilson (252) advance the idea that Indigenous Peoples, even prior to contact with Europeans, experienced bouts of starvation juxtaposed with times of ample food supply. Thus, the Indigenous genome may have been enriched for metabolically thrifty genotypes via food shortages. The harsh Canadian landscape may have presented sufficient challenges to food procurement, especially in the alteration of seasons. Admittedly, flaws in the argument that food shortages may have led selection for obesity risk alleles exist (28,57). However, despite the exact nature of events shaping the genome, there is some indication that the Indigenous genome may be more susceptible to metabolic diseases. Oster and Toth (253), for

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instance, demonstrate that obesity and diabetes prevalence is higher among individuals identifying as Indigenous Peoples, in contrast to non-Indigenous Canadians. Similarly, studies in Pima Indians show that individuals without diabetes had almost twice more European ancestry when compared with those with diabetes. Moreover, a strong negative relationship exists between BMI and European admixture in North American Aboriginal populations (254).

Despite this, estimates of obesity prevalence among different groups of Indigenous Peoples – First Nations, Inuit and Métis – highlight the complex aetiology of obesity in this demographic. Statistics Canada and Kolahdooz and colleagues report that of First Nations, Inuit and Métis, the latter tend to be more obese (251,255). Because the Métis historically arose out of unions between European fur traders and Indigenous women dating back to the early 1600s (256), it is interesting that Indigenous Peoples with European genetic ancestry have elevated rates of obesity: European admixture among Pima Indians without diabetes has been associated with lower BMI (254). Overdominance of some obesity predisposing variants may help explain this counterintuitive observation of elevated obesity rates among the Métis. Thus, admixture with Europeans may also confer heightened susceptibility to obesity, depending on the ancestral origin of each locus in an individual's genome.

The proposition that elevated obesity risk among the Métis may be because of overdominance of Indigenous obesity predisposing variants must be interpreted with caution. Indigenous Peoples of mixed ancestry have been difficult to identify historically. Varying proportions of European ancestry have been detected in diverse First Nations groups, including the Cree, Ojibwa and Chipewyan (257). Likewise, offspring of Indigenous-European unions were sometimes integrated into the tribes of their Indigenous mother or baptized and thereby identified as French (256). Existing studies exploring the risk of metabolic disease lack genetic determination of First Nations, Métis and Inuit statuses. To evaluate the degree to which the Indigenous genome alone contributes to obesity risk, future research will benefit from genetic determination of First Nations, Métis, and Inuit statuses and accurately quantifying percentage admixture between Indigenous Peoples and Europeans.

Disease epidemics and obesity

Increased rates of obesity among African Americans and Indigenous Peoples in Canada may also be explained by a selective pressure imposed by epidemics. A disease environment is in constant flux, with the environment's range of diseases changing and affecting the immunities of the host population (258). The more isolation experienced by a population, the more unique its disease environment is likely to become. Immunities to pathogens can be inherited or acquired (258). Over time, a persistent pathogenic stress will eliminate the weakest of its population, making the collective genome of the survivors 'healthier.' Thus, an immunological pressure may lead to selection for certain genotypes over generations. For example, it has been postulated that human immunodeficiency virus resistance alleles in *CCR5*, which shows a geographical distribution across Europe, have undergone selection as a result of recurrent episodes of smallpox (259). Thus, it is possible that inherited immunities to malaria and smallpox may have repercussions for weight gain among African Americans and Indigenous peoples, respectively.

Historical data support this hypothesis. Analysing logs of surgeons aboard slave ships between 1792 and 1796, Steckel and Jensen (260) estimated that over 40% of slave mortality was attributed to gastrointestinal diseases (e.g. dysentery), while 8% of deaths attributed to fevers (likely including malaria and yellow fever). Although the nature of their interaction differed, contact of Indigenous Peoples with Europeans resulted in a marked reduction in the number of Indigenous Peoples living in Canada. Smallpox epidemics, for instance, have been associated with the decimation of many Indigenous groups, while others like the Beothuk were affected by tuberculosis (252). Because infectious diseases affect energy balance (131), and some epidemiological studies of infectious disease highlight the protective effects of adiposity (261), it is possible that individuals with adequate energy stores are likely the ones to survive severe and/or recurrent episodes of infection.

Body image ideals, mating choices and genetic predisposition to obesity

Beauty and the body

Evidence for assortative mating based on body type exists in the literature. Spousal correlations in BMI are estimated at 0.15, with the odds of spouses being obesity concordant 1.44 (262). In an analysis of spousal concordance in BMI using current BMI and recalled BMI at 20 and 30 years old, Hebebrand and colleagues (263) note increased symmetry of body type among parents of obese children, particularly in subjects in the upper extremes of body mass. Jacobson and colleagues (264) show that spousal correlations in BMI affect BMI in adult offspring, with the odds of offspring obesity increasing markedly when both parents are obese. Symmetry in spousal body type is apparent even when using dual-energy X-ray absorptiometry to analyse body composition in lieu of BMI (265) and when assessing body weight correlations between partners prior to marriage and cohabitation (266).

Obesity prevalence in the United States over the last decade appears to have reached a standstill (267). Despite this

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apparent plateau, significant increases in all classes of obesity have been observed among American children (2). Because spousal concordance in body type, based on BMI in early childhood, has increased in parallel with the growing prevalence of obesity (268), it is possible that the increased prevalence of extreme obesity may be driven partly by mate choice. Assortative mating by BMI leads to an increase in the mean BMI and prevalence of obesity among offspring (269), which may contribute to an increase in obesity rates. Assortative mating for body type may not be limited to the obese, however, Fisher and colleagues (270) provide evidence that individuals with low BMI may prefer mates with a similar body type. The global reach of the obesogenic environment may thus make the effects of assortative mating on body type distribution more pronounced. As the prevalence of obesity increases, preference for mates with similar body types becomes more obvious, possibly leading to positive directional selection for obesity and leanness predisposing alleles.

Mate selection may have been driven by using body proportions as an index of fertility and mate superiority, ultimately leading to the differential selection of genes contributing to adiposity. The palaeoarchaeological record shows evidence of increased adiposity among archaic humans. Upper Palaeolithic figurines found throughout Europe such as the Venus of Willendorf are interpreted to be idealizations of our ancestors, deities, representations of fertility or symbolic responses to increased risk of mortality during childbirth and pregnancy (271–273) (Fig. 4). The exaggerated breasts and genitalia, along with red ochre traces, often interpreted to represent menstrual blood, give weight to the latter conjecture (274). Evolutionarily speaking, the larger, more fertile woman would be the most desirable, as such a mate would improve the likelihood of successful genetic transmission to subsequent generations.

A preponderance of literature explores of the use of WHR as a trait for mate selection (275–279). Singh (275) argues that WHR is a reliable indicator of female attractiveness, health and reproductive capacity and is thus an adaptive explanation for mate preference. Indeed, studies have shown that women with lower WHR have different hormone profiles, i.e. higher levels of 17-β-oestradiol and progesterone, possibly leading to increased probability of conception (280). Data suggest that narrow waists were consistently considered beautiful in Western and non-Western populations alike (281), with ideal WHR in Western females centring around the normal fertile range over the last 2,500 years (277). However, variation in WHR preference among non-industrialized populations, such as the Matsigenka peoples of Peru (276), the Shiwiar of the Ecuadorian Amazon (278) and Hadza of Tanzania (279), has also been observed.

It is important to note that overall adiposity and WHR represent different, albeit related, phenomena. Although some overlap between genetic variants related to BMI and WHR exist, genome-wide association study have revealed

Figure 4 Representations of idealized body image in works of art. (Left) Palaeolithic Venus figurine. (Right) 'L'Homme qui marche' by Alberto Giacometti.

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genetic loci that are associated with WHR independent of BMI (282). References for WHR, and the relative importance of WHR as a measure of mate attractiveness, are context dependent and may thus vary across generations and environments (278). Among the Shiwiar, for instance, women with greater body weight may be preferred overall; however, where body weight is less variable, the women with the lowest WHR are preferred (278). Similarly, the range in observed WHR among women with idealized bodies has increased markedly over time (277). That is, there appears to be more subjectivity in what is culturally defined as attractive. Temporal trends in BMI have also been observed among Miss America pageant winners since the 1920s, with BMI decreasing over time, falling below the World Health Organization's BMI cut off for underweight in the 1980s (283). In summary, the variation in obesity rates among modern human populations may be due in part to the temporality of the natural selection process. In certain generations, preference for larger mates or mates with specific patterns of fat deposition may have been favoured because of biological and reproductive benefits, while in modern times, body image ideals may be influenced by the media (Fig. 4). These varied forces may contribute to complex patterns of selection for obesity and leanness predisposing alleles.

Mating rituals and predisposition to obesity

Cultural norms governing mating can drastically affect the genetic landscape and ultimately impact genetic risk of obesity. Increased prevalence of rare, early-onset obesity mutations in *LEP*, *LEPR* and *MC4R* have been detected in consanguineous Pakistani populations (284). Intriguingly, the *LEP* frameshift mutation G133_VfsX14 appears to segregate within a specific, close knit caste that has practiced consanguinity for generations, likely reflecting a founder effect (284). Approximately 10% of the global population is estimated to represent consanguineous couples (second cousins or closer) and their offspring, with the practice more common among north and south Sub-Saharan Africa, the Middle East and west, central and south Asia (285). Typically, such marriages are believed to strengthen familial ties and are encouraged for their perceived economic and fertility benefits (286). Comparing the geographic distribution of consanguinity with recent obesity prevalence rates does not reveal a generalizable trend. Although speculative, obesity and consanguinity prevalence estimates are of interest in some Middle Eastern countries. Obesity rates among Kuwaiti women, for instance, are estimated to be around 60% (1). The prevalence of consanguinity in this population is believed to be as high as 55.7% (287), although some variation may exist because of socioeconomic factors and association with Bedouin culture (288). For a complex disease-like obesity, consanguinity is expected to have a large impact on disease prevalence if rare autosomal recessive alleles – as in the case of monogenic obesity – are implicated in its genetic predisposition (285).

In populations favouring consanguinity, high genetic similarity may be observed between two individuals simply because of common ethnic or cultural background, although they may not be from the same pedigree (285). Emigration of a group of individuals identifying with a culture advocating consanguineous marriage may compound the effect of such unions greatly. Consider a population where consanguinity has been practiced for several hundred years. Emigration of a group of individuals into another region of the world (founder effect) may further increase the prevalence of disease risk alleles passively by genetic drift. If culturally-mediated mating practices still exist in the country of immigration, a limited number of suitable mates will lead to increased homozygosity in the immigrant population, drastically affecting disease risk (Fig. 5). Overall estimates of BMI heritability have been reported to drop markedly – from 0.619 to 0.466 – when individuals closer than 2nd or 3rd cousins are removed from estimates (289), suggesting that increased genetic similarity between individuals leads to increased heritability of body weight. This may explain the rates of rare diseases among migrant populations in the West. An increased prevalence of autosomal recessive disorders, for instance, has been noted among Pakistanis residing in the United Kingdom (290).

Cultural beliefs that restrict mating to a limited pool of individuals – whether based on caste, language, religion or occupation – have a similar effect on decreasing genetic diversity within socially defined groups, as observed among castes and language groups within India (291). Reproductively isolated groups, such as the Hutterite (292) and Amish (293), or geographically isolated populations, such as French Canadians inhabiting the Saguenay-Lac St. Jean region in Québec (294), show an enrichment of recessive diseases, associated with increased genetic homogeneity and high rates of consanguinity in the population. To our knowledge, elevated obesity rates have not been reported in either of the Amish or Hutterite. It cannot be determined whether this reflects the adoption of a healthy lifestyle, epigenetic modifications, absence of monogenic obesity mutations in the ancestral gene pool or a combination of these and other factors. However, in a study of hypertension among lean and obese families in Saguenay-Lac St. Jean, increased genetic homogeneity among obese hypertensive families was noted (295). Thus, increased rates of obesity, linked to rare or common alleles, may be affected by increased rates of mating among more genetically similar individuals or from selecting a partner from a limited pool of mates.

Polygamous mating systems that increase the number of matings of a single individual or a group of related individuals may also impact genetic architecture over time. Polygyny, the mating of a male with multiple female partners, is not a

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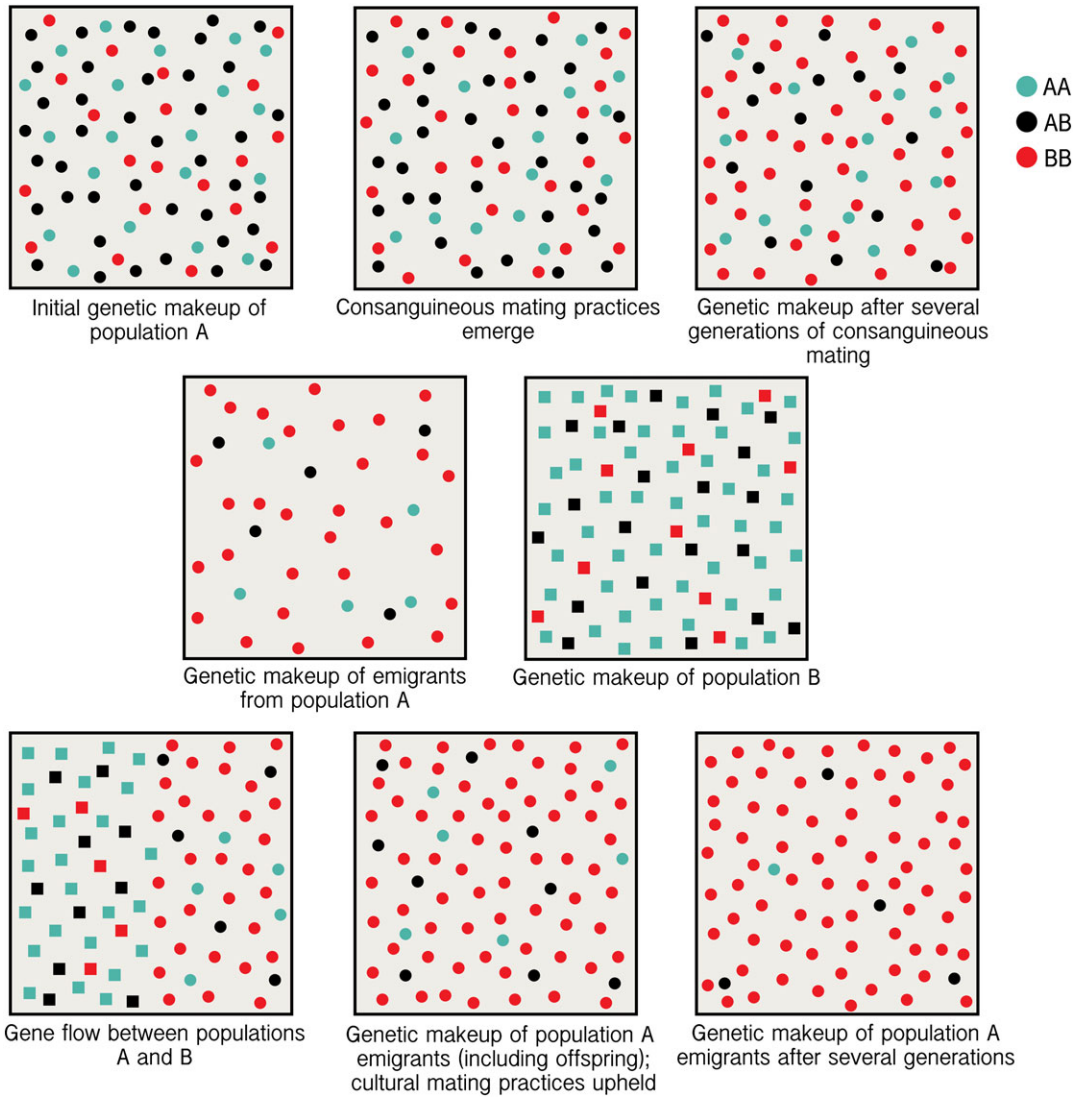

Figure 5 Theorized changes in genotype frequencies as a result of the joint effects of consanguinity and emigration. [Colour figure can be viewed at wileyonlinelibrary.com]

practice of the past. In Africa, polygynous unions persist (296–298) and may be practiced by royalty on a grander scale (298). Polygamy also encompasses polyandry, the mating of a female with multiple male partners. Historically, Tibetans have practiced polyandry (299). Fraternal polyandry, the mating of a single female with multiple brothers, may still occur in rural areas of Punjab, India (300,301). Where a single individual or group of related individuals take multiple mates, genetic similarity between individuals in the population may ensue, because disproportionately large genetic contributions are made by a small group of individuals. For instance, a single founding male, thought to be the Mongol emperor Genghis Khan, may have contributed to the Y-chromosomes of 0.5% of the world's male population (302). Likewise, indications of high reproductive success among certain male lineages has been noted, based on elevated frequencies of distinct Y-chromosome microsatellite haplotypes among certain Asian populations (303). Thus, individuals with high reproductive success, social prestige and multiple mates may transmit increased amounts of genetic information to genomes of certain populations. In theory, adoption of polygamy by the powerful elite could have impacted the transmission of thrifty genes. Wealthy males, for instance, may have supported multiple wives, which would have enabled them to contribute to the genetic makeup of a greater number of offspring. Should they be carriers of thrifty genotypes, the probability of obesity risk alleles being transmitted increases as the number of mating events increase.

Admittedly, although mating systems may have a profound effect on the genetic landscape, social customs regulating mating vary culturally and have changed through times. Thus, the impact of mating systems on obesity and

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leanness risk alleles may vary from population to population.

Inter-species mating

Modern human populations carry varying proportions of genetic material from archaic humans, including Neanderthals and Denisovans (304). Although speculative, estimations of Neanderthal body size based on skeletal measurements have suggested that BMI of some individuals ranged from 26.9 to 28.2 kg m^{-2} (305). It cannot be elucidated whether this reflects the muscularity or corpulence of Neanderthals. Intriguingly, Simonti and colleagues (306) recently reported nominally significant associations between Neanderthal genetic variants and risk of obesity and overweight in modern Europeans. Thus, if ancient DNA contributes to obesity phenotypes in the modern day, some variation in obesity risk may be attributable to historic matings between modern humans and their archaic counterparts.

Conclusions and future directions

Diverse forces have worked in tandem to shape the human genetic landscape. Although the thrifty genotype hypothesis fails to capture the complexity of genetic predisposition to obesity, Neel has been instrumental in informing evolutionary thought about metabolic disease. In this review, we expand on Neel's concepts of thrift and outline novel biological mechanisms that may have given rise to obesity predisposing variants. Additionally, we describe social phenomena and epigenetic mechanisms by which the human genome may be shaped and reshaped (Figs 1 and 2). Pleiotropic effects may explain why alleles apparently detrimental in the current obesogenic environment still remain in the human gene pool. Historical experiences of populations and cultural dictates of mating and mate preference may underlie ethnic-specific variability in the distribution of obesity risk alleles. Alternatively, genetic drift may have acted to randomly affect the frequency of obesity risk-alleles.

Drawing on data from human genetics, archaeobiology, palaeonutrition and history, these novel theories of obesity evolution may be empirically tested. Although mathematical models are oversimplifications of reality and methodological tools to account for complex models are limited, theoretical models have been successfully used to evaluate the merit of other evolutionary hypotheses (307–310). The ability to simulate geographic and time-dependent pressures of selection may be invaluable in understanding the evolutionary drivers of obesity risk. Alternatively, comparison of modern human genomes with those of archaic humans may reveal the origin of obesity and leanness predisposing variants (306). Only in-depth comparisons of ancient and modern human DNA will allow us to formulate conjectures about the forces that drove these changes in allele frequency.

This review highlights drivers of evolutionary change acting on the nuclear genome that may impact genetic predisposition to obesity. Beyond the nuclear genome, however, there are other genomes that may be important to consider. Recently, mitochondrial DNA, which reflects maternal lineage (311), has been hypothesized to contribute to obesity phenotypes (312–314). Shifts in abundances of microbial organisms living in and around the human body have also been associated with increased adiposity (315). Recent studies in mouse models suggest that although microbiota may be modelled by the environment, the host genome also affects the composition of the microbiome (316,317). Thus, the effects of evolutionary forces shaping the human genome may inadvertently exert a pleiotropic effect that modulates the microbiome, which may have ramifications for human metabolic phenotypes (318).

Drivers of evolutionary change do not work in isolation. Rather, each agent – be it biological or social – affects the genomic landscape independently and jointly with other forces. The persistence of alleles in *LEP*, *LEPR* and *MC4R* that confer obesity susceptibility in the modern day, for instance, may be understood through the cumulative effects of natural selection acting at different levels. Obesity is recognized as a multifactorial condition, but theories explaining the evolutionary origins of obesity rarely draw on different mechanisms to explain the aetiology of the disease. As such, we advocate a holistic, interdisciplinary approach to understanding the evolutionary underpinnings of obesity with the hope that such investigations of individual and population-level drivers of genetic risk will foster targeted prevention, management and treatment strategies in the future.

Conflict of interest statement

A. Q., M. T., R. J. S., M. C. S., D. C., J. D., J. R. S., and D. M. have no conflict of interest to declare.

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Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article. https://doi.org/10.1111/obr.12625

Supporting Information

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