ON THE ORIGIN OF OBESITY

ON THE ORIGIN OF OBESITY: A CRITICAL REVIEW OF BIOLOGICAL, ENVIRONMENTAL, AND CULTURAL DRIVERS OF GENETIC RISK AMONG HUMAN POPULATIONS

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ABSTRACT

Genetic predisposition to obesity presents a paradox: how do genetic variants with such a detrimental impact on human health persist through evolutionary time? Numerous hypotheses, for instance the thrifty genotype hypothesis, attempt to explain this phenomenon, yet fail to provide a satisfying answer to the modern obesity epidemic. In this critical review, I appraise existing theories explaining the evolutionary origins of obesity and explore novel biological and sociocultural agents of evolutionary change that may help explain the distribution of obesity and leanness predisposing variants in modern human populations.

Gene pleiotropy and adaptations to diverse environmental niches may explain the rise and subsequent selection of obesity risk alleles. The regulation of gene expression by epigenetic mechanisms may serve as a stochastic factor affecting the manifestation of obesity phenotypes. Finally, exposure to malnutrition and disease epidemics in the wake of colonialism, culturally mediated notions of attractiveness and desirability, and diverse mating systems – including forced copulation, consanguinity and polygamy – may play a role in shaping the human genome. In short, I posit that in order to explain ethnic variation in obesity susceptibility, we must examine the origin of physiological adaptations and understand the sociocultural experiences of individuals and populations.

As an imperative first step towards the identification of important drivers of obesity gene evolution, this review will inform empirical research focused on testing evolutionary theories by way of population genetics and mathematical modelling. Ultimately, these data will promote a better understanding of the aetiology of obesity and are expected to guide the development of targeted management, treatment, and prevention strategies.

Keywords: evolution, obesity, natural selection, thrifty genotype hypothesis, pleiotropy

PREFACE

"…*Obesity must first be understood as a phenomenon with strong historical and sociocultural dimensions. In this case, genetic and epigenetic theorisation might be considered incomplete without the incorporation of social histories. Epigenetics is embedded in local social processes through the management of pregnancy and lactation, while the genetics of obesity is related to processes by which genes are transmitted, such as migration, settlement, kinship structures, marriages and procreation."*

– McLennan and Ulijaszek (2015). Public Health Nutr. Jun;18(8):1499-505.

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They say it takes a village to raise a child. I think a similar amount of communal effort is involved in the maturation of a Masters' dissertation.

Prefaced with a casual, "if my memory's good," my supervisor, Dr. David Meyre, somehow manages to recite full (and accurate) citations of papers, remembering the most minute of details. I thought encyclopaedic memories were fiction. Two years, however, have proven otherwise. I have yet to meet someone as dedicated and passionate about genetic epidemiology. Thank you for your mentorship and propelling me to do things I would have never imagined accomplishing. I would also like to extend a hearty thank you to my committee members, Drs. Russell de Souza and Andrew Mente, and my external reviewer, Dr. Constantine Samaan, for their guidance in development of this thesis.

If I have made it out of this Masters alive, it is through the unwavering support, encouragement and love of my family, friends, and colleagues. Without the endless prayers of my parents, Muhammad and Nusrat Qasim, the 6am Uber services provided by my brother Waqaas and the wisdom and impeccable listening skills of my roommate/sister Atika, what follows this preamble would be naught.

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Last but not least, a big thank you to Yamna Rizwan for being courageous enough to read this beast of a thesis on such a tight timeline. (And, though I tried to put up a fight, for forcing me to adopt the Oxford comma.) I owe you one. Big time.

It seems that somehow, with His help, I made it…

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LIST OF ALL ABBREVIATIONS AND SYMBOLS

%DFI	DNA fragmentation index
ADRB3[1]	β-3 adrenergic receptor
AMY1	human salivary amylase
ARA	arachidonic acid; 20:4n-6
BAT	brown adipose tissue
BDNF	brain-derived neurotrophic factor
BMD	bone mineral density
BMI	body mass index
CART	cocaine- and amphetamine-regulated transcript
CCR5	chemokine receptor 5
CLOCK	circadian locomotor output cycles kaput
CNVs	copy number variations
DHA	docosahexaenoic acid; 22:6n-3
DLK1	delta-like 1 homologue
DNA	deoxyribonucleic acid
E2	17-β-oestradiol
FTO	fat mass and obesity-associated
GWAS	genome-wide association studies
KCKN9	potassium channel subfamily K member 9
LCT	lactase
LEP	leptin
LEPR	leptin receptor
MATP	membrane-associated transporter protein
MC4R	melanocortin-4 receptor
mtDNA	mitochondrial DNA
OCA2	oculocutaneous albinism II
PC-1	prohormone convertase-1
PLCD4	phospholipase C delta 4
POMC	pro-opiomelanocortin
PRKCH	protein kinase C eta gene
PWS	Prader-Willi syndrome
SH2B1	SH2B adaptor protein 1
SLC6A14	solute carrier family 6 (neurotransmitter transporter) member 14
SLC16A11	solute carrier family 16 member 11
SLC24A5	solute carrier family 24 member 5
SNP	single nucleotide polymorphisms
TAL1	T-cell acute lymphocytic leukemia 1
TNKS	tankyrase
UVR	ultraviolet radiation

[1] Italics refer to gene name, while non-italics represent gene product. e.g., *AMY1* is the human salivary amylase gene, while AMY1 is the human salivary amylase protein.

VNTRs	variable numbers of tandem repeats
WAT	white adipose tissue
WHR	waist-to-hip ratio

GLOSSARY OF GENETICS TERMS

admixture	mating of individuals from two or more previously isolated populations
allele	different versions of a gene
assortative mating	non-random mating based on phenotype — positive assortative mating or homogamy occurs when mates are more similar — negative assortative mating or heterogamy occurs when mates are dissimilar
consanguineous union	mating of individuals who are genetically related (i.e., second cousins or closer)
DNA methylation	epigenetic modifier; affects gene expression; addition of a methyl group (CH_3) to DNA, inhibiting transcription of DNA — hypomethylation refers to a decrease in the methylation of DNA — hypermethylation refers to an increase in the methylation in DNA
epigenetic modifications	heritable changes in phenotype that does not result from changes in the DNA sequence; rather, refers to addition of chemical marks to chromatin proteins or DNA that lead to phenotypic changes
evolution	change in genetic makeup of a population, apparent in the variance or average value of a phenotype
fitness	ability to survive and reproduce in a given environment
founder effect	when a group of individuals from a parent population inhabit a new environment
gene flow	evolutionary force; changes in allele frequencies due to transfer of alleles from one population to another, e.g., through migration
gene pleiotropy	occurs when one gene/genetic variant affects more than one trait — antagonistic pleiotropy occurs when a gene/genetic variant affects traits with competing effects on organismal fitness — synergistic pleiotropy occurs when a gene/genetic variant affects traits that improve organismal fitness

genetic drift	evolutionary force; refers to random fluctuations in allele frequencies
genetic variants	— mutation refers to genetic defect that is rare (i.e., present in <5% of the population) — single nucleotide polymorphism (SNP) refers to common genetic defects, i.e., those that are present in >5% of the population
haploinsufficiency	when a diploid organism (i.e., has two copies of a chromosome) has only one functional copy of a gene, which is insufficient for normal function
heterozygous advantage	when the heterozygous genotype is associated with greater fitness than the homozygous genotype E.g., sickle-cell polymorphisms at the β-globin locus – Heterozygosity confers resistance to malaria while homozygosity leads to anaemia or vulnerability to malaria
monogenic obesity	early-onset morbid obesity caused by a *mutation* in a single gene
natural selection	evolutionary force; non-random differences in average reproductive success and survival of individuals, based on inherited characters — positive or directional selection occurs when an allele is favoured for the effect it has on the trait — sexual selection is similar to *directional selection* in that traits deemed more desirable to a mate are positively selected for — balancing selection occurs when multiple alleles are maintained in a population, favouring genetic diversity — disruptive selection occurs when extreme phenotypes are favoured (e.g., Finches on Galapagagos Island – beaks either small so small seeds could be eaten or large so that large seeds could be eaten. Medium sized beaks were selected against because were unable to retrieve small seeds and not strong enough to retrieve big seeds) — purifying or negative selection occurs when alleles are purged from a gene pool
overdominance	when a *heterozygote* exhibits a phenotype that is more extreme than that of either parent

	— polar overdominance occurs when a mutated allele must be inherited from one parent in order for the phenotype to manifest. To date, phenomenon only observed when mutated allele inherited from father
polygenic obesity	common obesity; results from modest genetic contributions from many genes/single nucleotide polymorphisms
population bottleneck	or survivorship effect; occurs upon marked reduction in size of a population occuring as a result of natural causes (e.g., floods) or human activities (e.g., genocide)
reproductive isolation	inability of individuals to mate successfully, whether due to geographic, biological or behavioural factors (i.e., mate is "off-limits" for socio-political or geographic reasons)
zygosity	refers to similarity between alleles — an individual is considered homozygous when they carry two copies of the same allele — an individual is considered heterozygous when they carry two different alleles

DECLARATION OF ACADEMIC ACHIEVEMENT

A. Qasim and D. Meyre developed the components of this thesis, with feedback from supervisory committee members R. de Souza and A. Mente. A. Qasim wrote and researched the critical review.

CHAPTER 1: Introduction

The worldwide prevalence of overweight (body mass index, BMI $\geq$ 25 kg/m^2) and obesity (BMI $\geq$ 30 kg/m^2) has risen by over 27% in the last three decades, bringing the number of affected individuals to a staggering 2.1 billion (Ng et al., 2014). Though obesity rates have slowed in developed nations, estimates indicate that 50% of the population in Tonga and in many countries in the Persian Gulf is obese (Ng et al., 2014). As an established risk factor for numerous comorbidities including osteoarthritis, type 2 diabetes, hypertension, cardiovascular disease and cancer (Haslam & James, 2005), obesity is a growing concern for the medical community. In extreme cases, obesity may lead to a reduction in life expectancy by 6-14 years (Kitahara et al., 2014). Behavioural and pharmacological interventions to manage obesity exist (Dietz et al., 2015). However, these interventions show little promise in tackling the epidemic. Invasive surgery, though effective at reducing body weight and related comorbidities and improving quality of life, is not without complications (Piche, Auclair, Harvey, Marceau, & Poirier, 2015). Without elucidating the biological, environmental, and social phenomena that underpin or exacerbate the disorder, we will remain ill-equipped to manage, treat, and prevent obesity.

Though rare in the animal kingdom (Pond, 1998; Wells, 2006), excess adiposity is “a normal response to an abnormal environment” (Egger & Swinburn, 1997, p. 477). All organisms, from prokaryotes to mammals, have developed lipid

storage mechanisms to overcome imbalance in nutrient availability (Birsoy, Festuccia, & Laplante, 2013). Naturally fat animals are more common at high altitudes or deserts – environments characterised by severe conditions and unpredictability of food supply (Pond, 1998). Fat deposits may serve different functions. Blubber, for instance, acts as an insulator and energy reserve among marine mammals. 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 (Pond, 1998). Capacity for energy storage among animals may have a strong genetic basis. Mexican cavefish, for example, are highly adapted to nutrient-poor environments and consequently harbour melanocortin-4 receptor (*MC4R*) mutations linked to increased appetite and resistance to starvation (Aspiras, Rohner, Martineau, Borowsky, & Tabin, 2015). Surprisingly, as the authors note, the same gene defect in humans has been implicated in monogenic obesity due to *MC4R* deficiency.

Obesity among animals, however, is in stark contrast to human obesity: animals exhibit a “healthy obese” phenotype, free of the metabolic complications typically seen among morbidly obese humans (Pond, 1998). Even among animals bred to store maximum energy – for example, cows and pigs – obesity exists without hyperglycaemia (Gerstein & Waltman, 2006). Conversely, when animals adapted to environments with nutritional stress are displaced from their native habitat, symptoms of metabolic disease are obvious. When placed in environments with low energy expenditure and high-fat diets, wild pigs from Ossabaw Island

exhibit characteristics of pre-diabetes and heart disease (Whitfield, 2003). Likewise, invasive lionfish living amid food over-abundance in the Atlantic Ocean have markedly increased interstitial fat deposits and comorbid liver damage (Wilcox, 2013). 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 believed to be largely affected by environment, with excess energy intake and physical inactivity pinned as the main culprits. However, even in shared environments, only a subset of individuals develops obesity (Valera, Sohani, Rana, Poirier, & Anand, 2015). 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 (Dhurandhar & Keith, 2014; Valera et al., 2015). Obesity rates also differ among ethnic groups living in similar environmental conditions (Valera et al., 2015). Though lifestyle choices may explain some of this variability, admixture studies demonstrate that specific genes also contribute to ethnic-dependent obesity risk (Cheng et al., 2010). Heritability estimates of obesity from twin and family studies range from 0.46 to 0.75 (Elks et al., 2012), suggesting a large portion of obesity risk may be due to inherited factors. To date, genetic association studies have identified 12 genes and 141 loci involved in monogenic and polygenic forms of obesity, respectively (Pigeyre, Yazdi, Kaur, & Meyre, 2016).

Over the past 50 years, numerous hypotheses have emerged to explain human propensity to obesity (Genne-Bacon, 2014). The thrifty genotype hypothesis, for

instance, posits that extra adipose tissue enabled our ancestors to survive in the face of feast-famine cycles (Neel, 1962). Neel's hypothesis, however, oversimplifies the matter: if obesity susceptibility variants were advantageous for survival, such variants would be fixed in humans. This, however, is not the case. In fact, "leanness genes," genes protective against obesity, have been identified in certain populations (Geller et al., 2004; Stutzmann et al., 2007). Additionally, some groups, for instance Pacific Islanders, may be enriched for obesity predisposing variants, whereas others, like East Asians, may be protected from obesity because of redundantly lower frequency of risk alleles (Li A, in preparation). This indicates that the modern obesity phenomenon is more complex than the thrifty genotype hypothesis contends.

Theories succeeding the thrifty genotype hypothesis attempt to capture these complexities. 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 hyperglycemia (Hales & Barker, 1992). 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 (Stoger, 2008). Though many "thrifty" theories exist that frame 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 (Speakman, 2007).

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, admixture events, and diverse ecological challenges. Jointly, these stresses 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, I highlight mechanisms that may explain the observed diversity in obesity and leanness predisposing genetic variants among human populations.

CHAPTER 2: Methodological approach and a primer in population genetics

2.1 Motivation behind a critical review

"Thrift remains a very useful concept in evolutionary approaches to human adiposity and metabolism; however, it is essential to emphasize from the outset that there is much more to thrift than fat, and much more to fat than thrift." (Wells, 2012, p. 596)

Curiosity about the evolutionary origins of obesity has persisted for decades, since Neel first put forth the thrifty genotype hypothesis, which posits that natural selection has enabled humans to develop efficient energy storage and utilisation mechanisms (Neel, 1962). In subsequent years, much of the literature on obesity evolution has rested on concepts of metabolic thrift and fitness advantages of adipose tissue. Pleiotropic effects of obesity risk alleles, however, have scarce been incorporated into an evolutionary framework for obesity. Though the demographic history of human populations is embedded within some evolutionary theories (Sellayah, Cagampang, & Cox, 2014), the impact of human agency and culture on the genetic landscape has been largely absent from explanations as to why obesity risk alleles persist in the current day and age (Laland, Odling-Smee, & Myles, 2010). For these reasons, a critical review methodology (Grant & Booth, 2009) was adopted:

(i) to summarise and critically evaluate the merit of existing theories about the evolutionary origins of obesity; and

(ii) 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.

Although a systematic search strategy was not employed, comprehensive searches were conducted using PubMed and Google 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/slavery on human health. A list of search terms used is listed in Appendix A.

With the exception of Speakman and Westerterp (Speakman & Westerterp, 2013), few researchers have tested evolutionary theories *via* mathematical models. Ultimately, this critical review will inform future research that focuses on empirically testing hypotheses explaining the evolutionary underpinnings of obesity.

2.2 Evolution and the "bases" of human genetic diversity

2.2.1 What is evolution?

Evolution is a change in the genetic makeup of a population that is manifest in the variance or the average value of a phenotype (Futuyama, 2010). *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 (Futuyama, 2010; Meier & Raff, 2010). Natural selection is the opposite of chance, referring instead to non-random differences in average reproductive success and survival of individuals on the basis of inherited characteristics (Futuyama, 2010). The ability to survive and reproduce in a given environment, and thereby transmit genes to the next generation, is termed *fitness* (Orr, 2009). Fitness can be thought of in terms of viability, mating success, and fecundity – factors which affect the number of offspring an individual is able to produce. Traits that confer fitness are not universal over time or place. That is, phenotypes that confer reproductive success and survival in one environment may reduce fitness in another environment as result of biological and physical environmental changes (Orr, 2009).

2.2.2 From where does genetic variation arise?

Natural selection, gene flow, and genetic drift act upon variation that arises from recombination or mutation (Futuyama, 2010). Recombination occurs during meiosis, as a result of crossing over of homologous chromosomes (pair of

chromosomes, one inherited from each parent) (Meier & Raff, 2010). A *de novo* mutation can be expected at a rate of $1x10^{-4}$ to $1x10^{-6}$ mutations per gamete for a particular gene, as a result of errors in the process of deoxyribonucleic acid (DNA) replication during cell division (Clancy, 2008). Mutations may also result from environmental exposures such as excessive ultraviolet radiation (Clancy, 2008). 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 (Arnheim & Calabrese, 2009). A type 2 diabetes risk haplotype in Mexican and Latin Americans in solute carrier family 16 member 11 (*SLC16A11*) has been traced back to Neanderthals (A. L. Williams et al., 2014). 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 (Futuyama, 2010; Nakamura, 2009). 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 and 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 encoded amino acid residues (i.e., synonymous) or occurs in pseudogenes or other non-functional regions (Futuyama, 2010). Not all missense mutations have negative consequences: among rare missense mutations, ~70% show only mildly deleterious effects (Kryukov, Pennacchio, & Sunyaev, 2007). However, not all synonymous mutations are neutral in terms of their impact on disease phenotypes (Sauna & Kimchi-Sarfaty, 2011). Genetic information may also be duplicated or deleted, taking the form of variable numbers of tandem repeats (VNTRs; variations in the number of repeats of short DNA segments) (El-Sayed Moustafa et al., 2012) or copy number variations (CNVs; regions of genome that vary in number of replicates) (Zarrei, MacDonald, Merico, & Scherer, 2015).

2.2.3 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 the effect that it has on a given phenotype, *positive selection* (or *directional selection* if the selected trait is a quantitative trait) occurs (Hurst, 2009; Mitchell-Olds, Willis, & Goldstein, 2007). *Sexual selection*, the selection of traits deemed more attractive to a potential mate, may also be considered a form of positive selection (Hurst, 2009). As opposed to increasing the frequency of an advantageous allele, *balancing selection* sustains genetic diversity at a locus greater than that would be expected under a neutral model (i.e., expected if natural selection were not acting on the population) for example, in cases of *heterozygous advantage* (Meier & Raff, 2010; Mitchell-Olds et al., 2007). Selection

for extreme phenotypes which confer increased fitness to an individual is deemed *disruptive selection* (Mitchell-Olds et al., 2007). Purging of deleterious mutations – that is, *purifying* or *negative selection* – may also occur (Hurst, 2009).

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 (Meier & Raff, 2010). Over time, one allele may be fixed in a population while another may be lost, with the time to fixation dependant 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 populate a new environment. Over time, a small founding population may experience drift such that the genetic diversity is markedly reduced in comparison to 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 (Meier & Raff, 2010).

Variation in human populations may be introduced *via* gene flow or admixture, for instance, through migration of populations from one region to another (Meier & Raff, 2010). It is important to note that migration does not imply gene flow, since a number of factors may affect an individual's ability to reproduce. Isolation from potential mates (due to geographic isolation or reproductive isolation, i.e., the mate is "off limits" for geographic or socio-political reasons) (Meier & Raff, 2010), use of contraception, 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.

2.2.4 Yet more layers of complexity

Though selection may act on a single variant, via *linkage disequilibrium* (non-random association of two variants at more than one locus in a population), selection for or against one allele will affect the frequency of other alleles in the gene pool (Futuyama, 2010; Hurst, 2009). A *hitchhiking* effect is observed when a positively selected allele increases along with linked alleles, independent of whether they have a positive, negative or neutral effect on organismal fitness (Hurst, 2009). Correlation between genetic variants also ensues in cases of *gene pleiotropy*, where one gene affects more than one phenotype (Futuyama, 2010).

Phenotypic variation may result from the way in which genes are expressed. Some genetic variants, for instance, those located in intron 1 of the fat mass and obesity-associated gene (*FTO*), may affect the expression of other genes (Rask-Andersen, Almen, & Schioth, 2015). *Epigenetic modifications* refer to those changes in gene expression that do not arise from changes to the underlying DNA sequence, but result from the addition of chemical marks to chromatin proteins or DNA (Suzuki & Bird, 2008). Such changes also contribute to phenotypic variation. 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.

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 (Laland et al., 2010). Moreover, since mating practices (e.g., consanguinity) and mate selection may be culturally dictated, non-random mating practices based on phenotype may result in *assortative mating* (when mates are more similar, i.e., *positive assortative mating* or *homogamy*, or when mates are more dissimilar, i.e., *negative assortative mating* or *heterogamy*) and thus have a remarkable impact over generations.

CHAPTER 3: The rise of metabolic thrift

3.1 When Fat is Fit

Neel's thrifty genotype hypothesis assumes that feast-famine cycles experienced by our hunter-gather ancestors favoured genetic mechanisms of adipose deposition (Neel, 1962). 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-gathers (Benyshek & Watson, 2006), even when controlling for habitat quality (Berbesque, Marlowe, Shaw, & Thompson, 2014). In contrast, 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, as compared to those living during times of agricultural intensification (Starling & Stock, 2007). Comparison of skeletal remains of agriculturalists with those of hunter-gatherers show higher rates of growth retardation and iron deficiency anemia, suggesting nutritional inadequacies (Larsen, 1995). Thus, though adipose deposition could have been favoured historically for its energy-buffering capabilities, it may not be the sole selective pressure driving selection for obesity risk alleles.

3.1.1 Fat and the developing brain

Compared to brains of non-human primates, the human brain is more cognitively developed and larger, in both absolute size and in proportion to the body (Cunnane & Crawford, 2014). Among primates of a similar size, brain metabolism represents anywhere from 20-25% of resting metabolic rate in adult humans compared to only 8-10% in non-human primates (Leonard, 2014). Energy requirements of the newborn human brain are notably higher, with roughly 50-60% of energy intake allocated to brain function (Holliday, 1986). The developmental process of the brain is highly complex and vulnerable: successful brain function in adulthood is contingent on brain development proceeding normally in different stages of cerebral maturation (Cunnane & Crawford, 2014). To provide sufficient energy during this critical developmental period, a subcutaneous layer of fat develops in the foetus during the third trimester (Kuzawa, 1998; Leonard, 2014), endowing a neonate born at full term with 500-600g of fat (Cunnane & Crawford, 2014). Adipose deposition accelerates in the human infant until about a year, slowing until about age 6, at the time of the childhood adiposity rebound (Rolland-Cachera et al., 2009).

Estimates of fat content among newborns suggest that, on average, an infant's body is composed of anywhere between 11-17% fat (reviewed in (Harrington et al., 2002)). The fattiest mammals thereafter, the guinea pig and harp seal, are born with only 10.8% and 10.4% fat at birth, respectively (Kuzawa, 1998). Both guinea pigs and harp seals experience remarkable energy stress in the postnatal period.

The large amount of fat amassed by human infants may also be explained by nutritional stress during weaning (Kuzawa, 1998). Composition of adipose deposits in baby and adult humans, however, vary. Baby fat is deposited more subcutaneously as opposed to viscerally (Harrington et al., 2002). In addition, baby fat generally contains almost 3 to 4 times more arachidonic acid (ARA; 20:4n-6) and docosahexaenoic acid (DHA; 22:6n-3) than adult fat deposits (Cunnane, 2010). DHA is important in retinal function (Jeffrey, Weisinger, Neuringer, & Mitchell, 2001) and plays an essential role in the function of the central nervous system (Weiser, Butt, & Mohajeri, 2016). Since DHA biosynthesis *in vivo* is complex and the resultant amount of DHA synthesised insufficient, DHA is largely supplied to the infant premade, *via* diet/breast milk or though fat deposits (Cunnane & Crawford, 2014; Weiser et al., 2016).

Gestational age has been linked to composition and concentration of fatty acids in blood. Baack and colleagues (Baack, Puumala, Messier, Pritchett, & Harris, 2015) recently showed that preterm infants (≤ 34 weeks gestation) had 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. Biosynthesis of DHA and ARA from precursor fatty acids was also impaired in infants born preterm (Baack et al., 2015). Coupled with the observation that low birth weight predicts global cognitive impairment of children under the age of 5 (Linsell, Malouf, Morris, Kurinczuk, & Marlow, 2015), these data support the idea that inadequate fat stores, and by extension low DHA

reserves, among preterm infants contribute to risk of neurodevelopmental delay (Cunnane & Crawford, 2014). Conservation of adipogenesis during fetal development thus confers fitness, by increasing likelihood of proper neurological function in adulthood.

Infantile adipose deposits may also have been evolutionarily conserved to sustain brain function in cases of energy stress. Fat deposits used for insulation among mammals like the grey seal are maintained even after extended periods of starvation, whereas human infants' fat deposits are reduced (Kuzawa, 1998). This depletion of energy reserves may be related to cerebral energy requirements. In starvation conditions, adaptive metabolism provides fuel for the brain by shifting from glycogenolysis and gluconeogenesis, the brain's usual sources of energy, to fatty acid oxidation (Kuzawa, 1998). Ketones (i.e., β-hydroxybutyrate, acetoacetate, acetone), synthesised from adipose stores fuel the brain (Cunnane & Crawford, 2014; Kuzawa, 1998, 2010). In short, genetic regulators of adipose deposition during the infantile period may have been the immediate targets of natural selection, so that mobilisation of resources from these adipose deposits would ensure proper neurological function in adulthood and ensure cerebral energy requirements are met in the event of nutritional stress.

3.1.2 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 implicated in thermogenesis via mitochondrial respiration (Gil, Olza, Gil-Campos, Gomez-Llorente, & Aguilera, 2011). Within WAT deposits, "beige" adipocytes also exist, which exhibit thermogenic properties similar to brown adipocytes upon stimulation (Wu et al., 2012). BAT has been traditionally viewed as a fat deposit present only in neonates and small mammals (Sidossis & Kajimura, 2015). Recent advances in the field, however, show that BAT mass is present in adults and inversely related to obesity phenotypes (Sidossis & Kajimura, 2015). Moreover, the characteristics of BAT deposits may be different among individuals of different body types. Magnetic resonance imaging studies, for instance, that BAT and WAT deposits containing beige adipocytes among obese children have more fat content and less mitochondria compared to those of normal weight children (Deng et al., 2015). Genetic variants in the β-3 adrenergic receptor gene (*ADRB3*), which participates in energy regulation through heat generation and lipolysis, have been associated with BMI (Kurokawa et al., 2008). 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 (Kurokawa et al., 2008).

Sellayah and colleagues (Sellayah et al., 2014) argue that thermogenesis may help explain why Europeans and East Asians have the lowest obesity rates in

the industrialised world: cold adaptation inadvertently provided a mechanism by which to expend excess energy. Populations highly adapted to arctic climates such as the Canadian Inuit have a higher metabolic rate which would be protective against obesity. In contrast, African Americans, well adapted to tropical climates, have lower metabolic rates and are thus highly susceptible to obesity (Sellayah et al., 2014). Sellayah *et al.* (Sellayah et al., 2014) 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, Pima Indians in the hot climate of Arizona and Mexico and indigenous peoples residing in the extreme cold of Tierra del Fuego have remarkably different obesity rates, though both groups descend from a common Siberian ancestor well adapted to the cold. In short, selection for BAT deposits to enable thermogenesis in cold climates may explain some ethno-geographic variation in obesity rates.

3.2 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.

3.2.1 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 hastens pubertal development (Wagner et al., 2012). A minimum amount of fat is essential in regulating menstruation and ovulation (Frisch & McArthur, 1974). Abnormally low body weight, for instance among women with anorexia nervosa, has been associated with delayed puberty and irregular or absent menstruation (Becker, Grinspoon, Klibanski, & Herzog, 1999; Seli, Babayev, Collins, Nemeth, & Horvath, 2014). This demonstrates that a minimum amount of body fat is essential in reaching reproductive potential. Reproductive outcomes are also 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 (Seli et al., 2014). The impact of obesity on male fertility, however, is inconclusive. Theoretically, any changes to mitochondrial function, motility, volume or morphology of spermatozoa may impact male reproductive fitness. Though routine sperm parameters (i.e., sperm concentration, morphology, 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 (Campbell, Lane, Owens, & Bakos, 2015). 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 (Saleh et al., 2002) and has been shown to better predict natural conception when compared to routine sperm parameters (Malic Voncina et al., 2016). Moreover, high BMI does not appear to compromise DNA integrity (Andersen et al., 2015; Bandel et al., 2015; Eisenberg et al., 2014). Rather, overweight is associated with a reduced incidence of DNA fragmentation (Bandel et al., 2015; Eisenberg et al., 2014), pointing to a beneficial effect of adiposity. In short, epidemiological data point to an optimal level of body fatness for both sexes, deviations from which may result in decreased reproductive function.

Genetic association studies suggest that common obesity predisposing variants are also associated with earlier pubertal development (Cousminer et al., 2014; Fernandez-Rhodes et al., 2013), pointing to synergistic pleiotropic effects. Cases of rare, monogenic obesity, however, render the situation more complex. Morbidly obese patients with genetic defects in the leptin receptor gene (*LEPR*) exhibit hypogonadotropic hypogonadism, which may lead to delayed sexual maturation (Clement et al., 1998; Farooqi et al., 2007). Women who achieve menstruation may experience irregularities in their cycles (Clement et al., 1998; Farooqi et al., 2007). Hypogonadism has also been reported among patients with monogenic obesity due to leptin (*LEP*) (Ozata, Ozdemir, & Licinio, 1999),

prohormone convertase-1 *(PC-1*) (Jackson et al., 1997), and *MC4R* (Aldhoon Hainerová, Zamrazilová, Sedláčková, & Hainer, 2011) deficiencies, though the effects of MC4R deficiency on reproductive function is controversial (Farooqi et al., 2003; I. S. Farooqi et al., 2000; Kobayashi et al., 2002). Though severe forms of obesity may reduce fertility, obesity does not render one sterile. Despite menstrual irregularities and pubertal delays among homozygous *LEPR* mutation carriers, natural pregnancy has been reported (Nizard, Dommergues, & Clement, 2012). The rarity of monogenic obesity, however, may diminish the impact of antagonistic pleiotropic effects on the evolution of populations. It is important to note that in modern times, 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 eased, such that those who successfully produce offspring may not be the ones with biologically beneficial genes. In short, these data highlight a highly complex relationship between adiposity and fertility.

3.2.2. Susceptibility to infectious disease

Infectious disease affects both energy intake and expenditure – whether through decreased caloric intake due to lack of appetite, inefficiency of nutrient absorption, or gastrointestinal problems (Prentice & Paul, 2000). Malnourished

children are more likely to experience episodes of infection, leading to further malnutrition (Scrimshaw, 1990). Drawing on epidemiological data, Kuzawa (Kuzawa, 1998) notes that peak levels of adiposity in infants roughly correlate with the ages at which infants are more susceptible to infectious disease episodes. Since children with more weight for height have lower rates of infectious disease mortality and morbidity on average, it is possible that infant adipose reserves may mitigate the effects of nutritional stress caused by infection (Kuzawa, 1998; Prentice & Paul, 2000), and thus may have been directly selected for. A number of genes relating to immunity exhibit signatures of positive selection, including *LEPR* (Barreiro & Quintana-Murci, 2010). Since both energy excess and insufficiency have been linked to risk of infection and mortality (Matarese, Moschos, & Mantzoros, 2005), a common genetic architecture may govern body type and immunological response.

Leptin, an adipocyte-derived hormone, signals the adequacy of energy stores in the human body (Matarese et al., 2005). Ozata and colleagues (Ozata et al., 1999) describe changes in immune function in morbidly obese patients homozygous for a missense *LEP* mutation. In this consanguineous Turkish pedigree, 7 of 11 obese individuals died in early childhood during an episode of infection. Though genetic information was unavailable, these patients exhibited phenotypic similarities with homozygous mutation carriers in the family. Thus, the authors propose that congenital leptin deficiency diminished the immunological

function of affected individuals, making them more susceptible to disease. In line with these findings, Farooqi *et al.* (Farooqi et al., 2007) 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 2 obese children in families of homozygous *LEPR* mutation carriers were linked to an acute respiratory tract infection, though this susceptibility to infectious disease was not observed among adult homozygotes (Farooqi et al., 2007).

This apparent age-dependent susceptibility to infectious disease among morbidly obese patients with congenital *LEPR* and *LEP* deficiency renders the pattern of natural selection more complex than classic directional selection. Though 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 (Clement et al., 1998; Ozata et al., 1999). Additionally, although congenital leptin deficiencies may increase susceptibility to episodes of infectious diseases, this state of immunological vulnerability may be mitigated: administration of leptin has been shown to improve immunological profiles among obese patients (Matarese et al., 2005). Moreover, Ozata and colleagues (Ozata et al., 1999) 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 due to *LEP* insufficiency, coupled with modern-day

pharmacological interventions to mitigate the effects of leptin deficiencies, may drastically affect patterns of selection patterns for *LEP* and *LEPR* mutations.

3.2.3 Bone formation & metabolism

The vertebrate skeleton plays multiple roles in organismal physiology – from protecting vital organs and blood cells, storing minerals, to facilitating movement (Oldknow, MacRae, & Farquharson, 2015). 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 increase in total mortality and 1.13-fold increase in cardiovascular mortality (Qu et al., 2013). A recent meta-analysis echoes these findings, estimating the odds of atherosclerosis among individuals with low BMD compared to those with high BMD to be 2.96, even after adjustment for age, sex, BMI, and vascular factors (Ye et al., 2016). Relationships between male fertility and BMD have been also explored in the literature. Infertile Chinese men displayed significantly lower lumbar spine and total hip BMD compared to fertile males (B. Yang et al., 2012). Likewise, low BMD has been reported among subfertile, hypogoandal men (Bobjer et al., 2016; Kacker, Conners, Zade, & Morgentaler, 2014).

Intriguingly, increases in BMD with increasing BMI have been observed (Ishii et al., 2014). This relationship between body and bone mass may have a genetic basis. Farooqi and colleagues (I. Sadaf Farooqi et al., 2000) report

elevated BMD among *MC4R* deficient patients with severe early-onset obesity, adjusted for age and gender. Similarly, Loos *et al.* (Loos et al., 2008) 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. Accordingly, studies in *Mc4r* deficient mice deficiency suggest that increased BMD results from a decrease in bone resorption, mediated by increased signalling of the cocaine- and amphetamine-regulated transcript (CART), in line with observations among humans with *MC4R* insufficiency (Ahn, Dubern, Lubrano-Berthelier, Clement, & Karsenty, 2006; Elefteriou et al., 2005). 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.

3.2.4 Skin pigmentation

As humans dispersed out of Africa, encountering diverse ecological niches, strong selective pressures related to climate and latitude likely drove local adaptation. Skin pigmentation, for example, is associated with ultraviolet radiation (UVR) (Parra, 2007) and the minimal erythemal dose, the amount of ultraviolet

radiation sufficient to cause sunburns (Nina G. Jablonski, 2012). 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 (Nina G. Jablonski, 2012). Geographic variability in pigmentation may also be driven by selection for protection against folate metabolism and infections, sexual selection, or to serve as camouflage for early humans (N. G. Jablonski, 2004; Nina G. Jablonski, 2012; Parra, 2007). Allelic variants in genes contributing to pigmentary phenotypes, for instance solute carrier family 24 member 5 (*SLC24A5*) and membrane-associated transporter protein (*MATP*), show signatures of positive selection among European and East Asian populations (Norton et al., 2007; Sabeti et al., 2007).

Some obesity syndromes, though classically associated with hyperphagia, are also accompanied by altered pigmentation. This highlights common biological pathways contributing to adiposity and variation in skin, hair, and eye colour. Prader-Willi syndrome (PWS), for example, is associated with absence of paternal genes at 15q11.2-q13 (e.g., due to deletion, two copies of maternal chromosome 15/maternal uniparental disomy 15, gene imprinting defects), leading to a constellation of abnormalities including obesity, developmental delay and hypogonadism (Cassidy, Schwartz, Miller, & Driscoll, 2012). Hypopigmentation, reported in up to 48% of individuals with PWS (Butler, 1989), is associated with hemizygosity of the oculocutaneous albinism II gene (*OCA2*) (Spritz et al., 1997). Albinism has also been reported among PWS patients (Lee et al., 1994), arising

from homozygous loss of *OCA2* (Cassidy et al., 2012). The phenotype of individuals with PWS varies based on the molecular aetiology of the syndrome (i.e., deletion versus uniparental disomy) and the length of deletion (Cassidy et al., 2012). 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 (Butler, 1989).

Altered pigmentary phenotypes are also associated with severe, early-onset obesity caused by pro-opiomelanocortin (POMC) deficiency, characterised by impairment of adrenal steroidogenesis, along with pale skin and red hair (Oswal & Yeo, 2007). However, pigmentary phenotypes in POMC deficient children of Turkish (Farooqi et al., 2006), North African (Clement et al., 2008), and Indian descent (C. N. Hung, Poon, Lee, Law, & Chan, 2012) are different from the first cases described by Krude and colleagues (Krude et al., 1998) in their lack of distinctive red hair. Closer examination of affected persons of non-European origin has shown that despite brown hair, some patients' hair may have reddish roots (Farooqi et al., 2006). Elevated levels of pheomelanin (contributes to red/yellow colouration) and eumelanin (contributes to dark colouration) have been observed in hair *via* microscopy, despite no observable differences in skin reflectance relative to unaffected relatives (Clement et al., 2008). These ethnic-specific changes in the classic pigmentary phenotype of POMC deficient patients highlights a complex interaction between forces governing adaption to latitudinal clines in ancient times and those that counter-select for morbid obesity in the modern day.

3.2.5 Behavioural traits

Alongside adaptations to survive in the geophysical environment, it is likely that genes coding for adaptive behavioural traits were selected for: human survival and reproductive success, after all, requires successful inter-personal interactions. Psychological traits that undermine social cohesion may also confer a fitness advantage in certain contexts. Aggression may prevent resources like property or a mate from being co-opted by others (Buss & Shackelford, 1997). Impulsivity (e.g., sensation seeking), particularly in adolescence, may be a means to increase reproductive success (Ball, 2011). 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 (Ball, 2011). Intriguingly, pleiotropic effects between obesity genes and social behaviours have been reported in the literature. Social isolation and aggression has been reported among obese individuals carrying loss-of-function mutations in SH2B adaptor protein 1 (*SH2B1*) (Doche et al., 2012), while impulsivity and stubbornness has been noted among obese patients homozygous for *LEPR* mutations (Clement et al., 1998). Patients with leptin and leptin receptor deficiency may also resort to confrontation in order to access food (Clement et al., 1998; Montagne et al., 2014)(Clement et al., 1998; Montagne et al., 2014)(Clement et al., 1998; Montagne et al., 2014).

Genes impacting both body adiposity and evolutionarily advantageous behavioural traits, however, may be subjected to more complex patterns of

selection than classic directional selection. To illustrate, though some have framed depression as an adaptive trait (Anders, Tanaka, & Kinney, 2013; Andrews & Thomson, 2009), data also show increased risk of mortality among depressive patients (Cuijpers & Smit, 2002) and reduced fertility among women experiencing postnatal depression (Myers, Burger, & Johns, 2016). The link between obesity and depression is also controversial (C. F. Hung et al., 2014; Lawlor et al., 2011; Samaan et al., 2013; Samaan et al., 2015). Samaan and colleagues (Samaan et al., 2013) 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 (Chojnicka et al., 2014). Contrastingly, the obesity risk allele at rs2984618 in the T-cell acute lymphocytic leukemia 1 (*TAL1*) gene has been associated with an increased risk for major depressive disorder, though a gene risk score composed of 21 obesity-risk alleles was not associated with depression (Samaan et al., 2015). Adding to this complexity, the effect of rs1401635 in brain-derived neurotrophic factor gene (*BDNF*) varied among Europeans and non-Europeans, conferring Europeans protection from depression while increasing risk of depression among non-Europeans (Samaan et al., 2015). Thus, some behavioural traits may confer survival advantages in certain social contexts and may be detrimental to survival

in others. Such diverse patterns of local selection for behavioural traits may help explain some of the variation in obesity risk.

3.3 Bulging waistlines: A consequence of creating and inhabiting new environments?

3.3.1 Circadian rhythmicity and obesity

Physiological and behavioural processes in organisms as diverse as bacteria and humans are regulated by the circadian clock (Gerhart-Hines & Lazar, 2015). 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, food availability). This enables organisms to cope with fluctuations in energy requirements and availability efficiently, thereby improving fitness (Gerhart-Hines & Lazar, 2015). The master clock, the suprachiasmatic nucleus of the hypothalamus, synchronises the activities of peripheral molecular clocks that are localised in most tissues of the body such as BAT, WAT, the liver, and skeletal muscle (Oike, Oishi, & Kobori, 2014). 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 (Oike et al., 2014). Peripheral molecular clocks, entrained by cycles of feasting and starvation, regulate glucose and lipid levels, hormone secretion, digestion, immune response, and detoxification (Oike et al., 2014). As Scheer and colleagues (Scheer, Morris, & Shea, 2013) 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 (~7:50pm), while a trough is observed in the morning (~7:10am-8:30am), 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 Circadian Locomotor Output Cycles Kaput (*CLOCK*) (Galbete et al., 2012) or nuclear receptor *REV-ERBα* (Ruano, Canivell, & Vieira, 2014). Alternatively, "circadian desynchrony," when environmental stimuli and biological processes are no longer harmonised, may affect body adiposity (Wyse, 2012). Since circadian clock mechanisms are highly evolutionarily conserved, changes in the environmental cues to which the circadian clock is tuned (e.g., light, temperature, food availability) may affect energy metabolism (Gerhart-Hines & Lazar, 2015). Studies have linked nighttime light exposure with increased odds of obesity as measured by BMI, waist-to-hip ratio (WHR), waist-to-height ratio, and waist circumference (McFadden, Jones, Schoemaker, Ashworth, & Swerdlow, 2014). Unfavourable sleep habits – habitual long and short sleep duration, and poor sleep quality – have also been linked with obesity risk (Theorell-Haglow, Berglund, Berne, & Lindberg, 2014; Westerlund et al., 2014). Age- and sex- specific differences in nutrient intake have been associated with sleep duration, with nutrient intake possibly moderated by variants in *CLOCK* (Dashti et al., 2015). Coupled with studies reporting elevated

BMI among shift-workers, for instance nurses and midwives working at least 8 or more night shifts per month (Peplonska, Bukowska, & Sobala, 2015), it is apparent that certain aspects of Western lifestyles – for instance, artificial light, shift-work, disturbed sleeping patterns, constant ambient temperature, frequent travel through time-zones, continuous access to calorie-dense foods – may have important implications for metabolic health (Gerhart-Hines & Lazar, 2015; Wyse, 2012).

Tau, the length of the circadian period (length of the daily cycle), may also explain some ethnic variation in obesity predisposition. As compared to African Americans, Caucasians have longer taus (Smith, Burgess, Fogg, & Eastman, 2009). This may enable individuals to better track and adapt to changes in photoperiods. 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 (Wyse, 2012). 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 (Wyse, 2012). Genetic variation in circadian clock genes among different ethnic groups have been observed, although evolutionary drivers of these genetic differences are unclear. Ciarleglio and colleagues (Ciarleglio et al., 2008), for example, propose that differences in allele frequencies are driven by random genetic drift, while Cruciani *et al.* (Cruciani et al., 2008) suggest the role of positive selection, driven by factors other than latitude.

3.3.2 Novel foods and natural selection

The transition from a hunting and gathering to more sedentary lifestyle has often been cited as a contributing factor to the obesity epidemic. Indeed, cases of forced settlement of semi-nomadic foragers on the Andaman Islands by colonialists (Sahani, 2013) and departures from the traditional food procurement strategies of Pacific Islanders (McLennan & Ulijaszek, 2015) and Pima Indians (Ravussin, Valencia, Esparza, Bennett, & Schulz, 1994) 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 (Enattah et al., 2008; Tishkoff et al., 2007). Various SNPs in the lactase gene (*LCT*) have recently undergone strong positive selection (Bersaglieri et al., 2004), supporting the notion that these polymorphisms represent a survival advantage. Lactase persistence genes arose independently in European and African populations (Tishkoff et al., 2007), with lactase non-persistence alleles decreasing in frequency from South to North and from East to West in Britain (G. D. Smith et al., 2009). Genetic adaptation to changes in food procurement strategies may explain some of the predisposition to obesity, as carriers of the lactase persistence *LCT* variant exhibit elevated BMI (Kettunen et al., 2010), especially among those with high consumption of dairy products (Lamri et al., 2013). Adaptations to optimise starch digestion *via* the positive selection of the human salivary amylase

gene (*AMY1*) (Perry et al., 2007) is an example of the opposite effect of genetic adaptations to cultural advancement: increased copy numbers of *AMY1* may be protective against obesity (Falchi et al., 2014; Mejia-Benitez et al., 2015). Perry and colleagues (Perry et al., 2007) 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 point to the impact of a cultural pressures in driving evolutionary change.

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

The epigenome, the collective epigenetic information carried by an individual (Suzuki & Bird, 2008), represents both heritable and transient changes induced by environmental cues such as diet (Gillberg, Jacobsen, Ronn, Brons, & Vaag, 2014) and exercise (Rönn et al., 2013). Epigenetic modifiers are chemical marks added to chromatin proteins or DNA that regulate gene expression (Suzuki & Bird, 2008), leading to activation or silencing of genes and regulation of transcriptional activity (Bierne, Hamon, & Cossart, 2012; Desai, Jellyman, & Ross, 2015). DNA methylation, one of many epigenetic modifications, involves the differential addition of methyl groups to cytosine residues along the genetic sequence (Suzuki & Bird, 2008). Typically, methylation is associated with gene silencing, particularly when modifications are made at promoters or enhancers (Bierne et al., 2012; Desai et al., 2015).

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 (M. K. Skinner, 2011). In line with this, methylation patterns of spermatozoa differ among obese and lean males (Donkin et al., 2016) while offspring of obese parents exhibit altered DNA methylation at imprinted genes (Soubry et al., 2015). Alternatively, some genetic variants, for example the *FTO* obesity risk alleles rs9939609 and rs8050136, modify their own methylation patterns in addition to the those of other genes (Almen et al., 2012; Bell et al., 2010). Grundberg and colleagues (Grundberg et al., 2013) analysed the methylome in adipose tissue, comparing methylation profiles of monozygotic and dizygotic twins with those of unrelated individuals. They estimate heritability of DNA methylation to be 0.34. That is, 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” (Suzuki & Bird, 2008). Among mammals, since most of the genome is methylated, transposable elements may be passively methylated (Suzuki & Bird, 2008). *Alu* element mediated hypermethylation at the intron2-exon3 boundary of *POMC*, implicated in energy homeostasis, has been associated with an increased

risk of obesity (Kuehnen et al., 2012). This indicates that methylation 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 (Peters, 2014). At minimum, genetic variants in 12 different imprinted genes are implicated in leanness and obesity phenotypes (Peters, 2014), for instance delta-like 1 homologue gene (*DLK1*) and rs2471083 near the *KCNK9* whose paternal alleles are associated with adiposity (Hoggart et al., 2014; Wermter et al., 2008). Gene imprinting is postulated to have evolved as a mechanism of conferring fitness to the mother or father by limiting or maximising use of maternal resources respectively, or to maximise offspring fitness by favouring selection of genes making the child more phenotypically similar to the mother or father (Haig, 2014; Peters, 2014). It is plausible that regulation of body weight *via* gene imprinting may represent pleiotropic effects, with the metabolic impact being secondary to growth retardation (Peters, 2014). 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 the tubby gene (*TUB*) (Rönn et al., 2013). 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 as a result 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.

Though famines may have occurred infrequently over our species' history (Benyshek & Watson, 2006; Berbesque et al., 2014), 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 *et al.* (Tobi et al., 2014) observed differentially methylated regions associated with prenatal malnutrition, mapping to genes associated with growth and development. As the authors note, some differently 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 (Tobi et al., 2014). As postulated by Neel (Neel, 1962), famine may have directly favoured the selection of metabolically thrifty alleles, but may also induce physiologically relevant change at the level of the epigenome (Tobi et al., 2014), rendering the natural selection process for adiposity-related variants more complex.

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

Feinberg and Irizarry (Feinberg & Irizarry, 2010) hypothesise 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 1000 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 (Feinberg & Irizarry, 2010). In changing environments, where selection for or against a trait varies from generation to generation, the most variable genotype dominates. Moreover, though the average value of the trait hovers around a central point, variation in the trait increases consistently.

Since *FTO* contributes to obesity (Meyre et al., 2009), is associated with phenotypic variation in BMI (J. Yang et al., 2012) and is also highly sensitive to environmental factors such as diet (Qi et al., 2014) and physical activity (Reddon et al., 2016), *FTO* may regulate variation in body type as per Feinbery and Irizarry's (Feinberg & Irizarry, 2010) model. 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 (Liu et al., 2015) to argue that *FTO* was historically under positive selection. Recent research, however, provides evidence against the applicability of Feinberg and Irizarry's (Feinberg & Irizarry, 2010) model to obesity.

Haploinsufficiency of *Trim28* in mouse models triggers a bi-modal distribution of bodyweight (Dalgaard et al., 2016). Mutant mice exhibit either a normal or obese phenotype, with few exhibiting intermediate body weights (Dalgaard et al., 2016). If variability in body adiposity were favoured, variation in body weight would be normally distributed, with increased variance at the tails of the distribution. Absence of a low body weight mode among *Trim28* mutant mice brings into question whether stochastic epigenetic variation can help explain the evolution of obesity.

CHAPTER 4: Unnatural selection: Human agency, obesity and the genome

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

The Nauru, with their exceptionally high obesity rates, may exemplify selection for "thrifty genes." Diamond (Diamond, 2003) 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, sometimes led to periods of starvation (Diamond, 2003). Anecdotal evidence suggests that Nauruans were themselves portly and found large bodied individuals attractive. Upon discovery of high-quality phosphate reserves on the island by European colonialists, the Nauru markedly increased their sugar consumption and began to lead more sedentary lives. During World War II, the Nauruan genome was further enriched for thrifty genes: 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 (Diamond, 2003).

4.1.1 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 (Prevention, 2016a, 2016b). The conditions 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. Mortality rates of African slaves travelling across the Atlantic are U-shaped: 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 (Miller, 1981). Longer trips, those lasting upwards of 50 days, led to a gradual influx in the mortality rate, likely driven by hardships endured by spending additional time at sea with dwindling food rations (Miller, 1981). 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 genotype. Indeed, overcrowding and unsanitary conditions faced on the slave ships, coupled with mistreatment by slavers, disease outbreaks and nutritional deficits experienced by slaves is understood to have provided a sufficiently strong selective pressure (Miller, 1981).

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 (Foster, 2011; Getman, 1984). 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, since the offspring of slaves were born into bondage and thus of economic benefit to slave owners (Foster, 2011; Getman, 1984). Fertile, “large, able-bodied” women were selected as breeders (Douglass, 1845, p. 62), while slave masters prevented some male slaves from copulation, such that no “runts” would be born from these unions (Foster, 2011, p. 456). Thus, encouraging mating among slaves with particular body types may have contributed to the current prevalence of obesity among African Americans.

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 (Foster, 2011; Getman, 1984). Some slave women were sold as concubines, while the sexual services of others were offered to white men by their masters (Getman, 1984). Inevitably, this led to widespread admixture of metabolically thrifty African genomes and those of the European slave owners. Though proportions of European ancestry have been associated with lower BMI among African Americans (Cheng et al., 2010), specific genomic regions, for instance Xq25 and Xq13.1 on the X chromosome are strongly associated with high BMI (Cheng et al., 2009). Bryc and colleagues (Bryc et al., 2010) 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 (Bryc et al., 2010). 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 the delta-like 1 homologue gene (*DLK1*) are preferentially transmitted to obese offspring (Wermter et al., 2008). A similar phenomenon may partly explain the higher prevalence of obesity among females of African American descent. Though speculative, the solute carrier family 6 neurotransmitter transporter, member 14 (*SLC6A14*), a candidate gene that has been associated with X-linked obesity in Finnish, Swedish (Suviolahti et al., 2003) and French populations (Durand et al., 2004), is located in the chromosomal region identified by Cheng and colleagues to be associated with elevated BMI in Africans. Since associations between rs2071877 and obesity show sex-specific effects (Durand et al., 2004), sex linkage may possibly drive elevated obesity risk among African American women.

4.1.2 Historical admixture and obesity among Aboriginal Canadians

Aboriginal Canadians 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 ("2015 Report on Diabetes: Driving Change," 2015) while a recent meta-analysis estimates 36.6% of Aboriginal Canadians have

a BMI ≥ 30 kg/m^2 (Kolahdooz, Sadeghirad, Corriveau, & Sharma, 2015). Historical selection pressures may have affected the Aboriginal genome similar to the way that the slave trade may have made the African American genome more vulnerable to obesity. Northcott and Wilson (Northcott & Wilson, 2001) advance the idea that Aboriginal Peoples, even prior to contact with Europeans, experienced bouts of starvation juxtaposed with times of ample food supply. Thus, the Aboriginal genome may have been enriched for metabolically thrifty genes *via* food shortages. The harsh Canadian landscape may have presented sufficient challenges to food procurement, especially in the alteration of seasons. Indeed, some indication for the Aboriginal genome being more susceptible to metabolic disease exists. Oster and Toth (Oster & Toth, 2009), for instance, demonstrate that obesity and diabetes prevalence is higher among individuals identifying as Aboriginal Canadians, in contrast to non-Aboriginals. Similarly, studies in Pima Indians show that non-diabetic individuals had almost twice the European ancestry that diabetic individuals demonstrated. Moreover, a strong negative relationship exists between BMI and European admixture in North American Aboriginal populations (R. C. Williams, Long, Hanson, Sievers, & Knowler, 2000).

Despite this, estimates of obesity prevalence among different groups of Aboriginal Peoples – First Nations, Inuit, and Métis – highlight the complex aetiology of obesity in this demographic. Statistics Canada and Kolahdooz *et al*. report that of First Nations, Inuit, and Métis, the latter tend to be more obese (Kolahdooz et al., 2015; "Obesity in Canada,"). Though the number of studies

pooled in Kolahdooz and colleagues' (Kolahdooz et al., 2015) subgroup analyses necessitates interpretation with caution, 41.7% of Métis were predicted to be obese. Since the Métis historically arose out of unions between European fur traders and Indigenous women dating back to the early 1600s (Brown, 2009), it is interesting that Aboriginal groups with European genetic ancestry have elevated rates of obesity: European admixture among non-diabetic Pima Indians has been associated with lower BMI (R. C. Williams et al., 2000). Differential expression of Aboriginal obesity predisposing alleles transmitted by the mother by way of polar overdominance may help explain this counter-intuitive observation of elevated obesity rates among the admixed Métis. In a similar vein, though overall proportions of European ancestry have been associated with lower BMI (Cheng et al., 2010) in admixed populations, specific genomic regions characterised by increased European ancestry, for instance 5q13.3, have also been associated with increased BMI among African Americans (Cheng et al., 2009). 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 due to overdominance of Indigenous obesity predisposing genes must be interpreted with caution. For one, Aboriginals of mixed ancestry have been difficult to identify historically. At times, offspring of Aboriginal-European unions were integrated into the Aboriginal mothers' tribes or baptized and thereby identified as French (Brown, 2009). Moreover, varying proportions of European ancestry has been detected in

diverse First Nations groups, including the Cree, Ojibwa, and Chipewyan (Hunley & Healy, 2011). One would predict that the Métis, by virtue of being the most admixed of Aboriginal groups, would display obesity prevalence intermediate between non-admixed Aboriginal Canadians and Europeans. Data, however, does not conclusively support this. Studies exploring risk of metabolic disease lack genetic determination of First Nation, Métis, and Inuit status. To evaluate the degree to which the Aboriginal genome in and of itself contributes to obesity risk, future research will benefit from accurately quantifying percentage admixture between Aboriginals and Europeans.

4.1.3 The Holocaust and obesity

Holocaust survivors arriving at concentration camps such as Auschwitz vividly narrate moments of being “subjected to selection – for life or death” upon arrival, where the fit men were gathered separately from the weak men, women and children (Unger, 1986, p. 280). Prisoners were provided extremely limited food rations. For those few individuals that survived starvation, lack of disinfection, compounded by overcrowding in barracks, and infestations by rodents and pests led to frequent outbreaks of typhus epidemics (Karay, 1994). Those not debilitated by illness suffered the consequences of hard labour. Those incapacitated were selected weekly, murdered and replaced by new inductees to the death camp (Karay, 1994).

Exhaustive systematic reviews have catalogued the diverse psychological and physiological impacts of the Holocaust (Barel, Van, Sagi-Schwartz, & Bakermans-Kranenburg, 2010). However, no reports of elevated BMI among survivors exists. Some researchers have commented on elevated obesity rates among children born during the Holocaust (Bercovich, Keinan-Boker, & Shasha, 2014; Keinan-Boker, Shasha-Lavsky, Eilat-Zanani, Edri-Shur, & Shasha, 2015), though previous studies have failed to report a significant association between maternal or paternal exposure to the Holocaust and obesity (Flory, Bierer, & Yehuda, 2011). The evidence, thus, suggests that epigenetic changes impacting fetal plasticity may have been enacted by the severe trauma and food deprivation of the Holocaust. Changes at the level of the epigenome, however, would relax selection pressure for genes conferring metabolic thrift. Alternatively, we may imagine that the survivors of the Holocaust were the healthier, more metabolically thrifty. The children of survivors, thus may be more genetically susceptible to obesity by virtue of carrying the thriftier, more fit genotypes.

The argument that the human genome and epigenome may be shaped by a “traumatic memory” is provocative. However, as is apparent in the case of Holocaust survivors, measuring, verifying and quantifying the severity or perception of historical trauma is not without its challenges. Among minority groups continually experiencing social injustice, it may prove difficult to disentangle proximal underpinnings of physiological consequences from historical trauma and equally challenging to accurately measure the effect of historical experiences on

long term human biology (Green & Darity, 2010). Nevertheless, the repercussions of historical injustice on human health are undeniable; its impact on underlying genetic architecture is an area warranting further research.

4.2 Disease epidemics and obesity

Increased rates of obesity among African Americans and Aboriginal Canadians 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 (Curtin, 1968). 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 (Curtin, 1968). Over time, a persistent pathogenic stress will eliminate the weakest of its population, making the collective genome of the survivors "healthier." Thus, a historical pressure may lead to selection for certain genotypes. For example, it has been postulated that human immunodeficiency virus resistance alleles in the chemokine receptor 5 gene (*CCR5*), which shows a geographical distribution across Europe, has been selected for as a result of recurrent episodes of smallpox (Galvani & Slatkin, 2003). Thus, it is possible that inherited immunities to malaria and smallpox may have repercussions for weight gain among African Americans and Aboriginals, respectively.

Historical data support this hypothesis. Analysing logs of surgeons aboard slave ships between 1792 and 1796, Steckel and Jensen (Steckel & Jensen, 1986) estimate 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). In a similar vein, contact of Aboriginal 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 Aboriginal groups, while others like the Beothuk were affected by tuberculosis (Northcott & Wilson, 2001). Since infectious diseases affect energy balance (Prentice & Paul, 2000), individuals with adequate energy stores and efficient energy utilisation will likely be the ones to survive severe and/or recurrent episodes of infection.

4.3 Body image ideals, mating choices and genetic predisposition to obesity

4.3.1 Beauty and the body

Evidence for assortative mating on the basis of 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 (Di Castelnuovo, Quacquaruccio, Donati, de Gaetano, & Iacoviello, 2009). In an analysis of spousal concordance in BMI using current BMI and recalled BMI at 20 and 30 years old, Hebebrand and colleagues (Hebebrand et al., 2000) note increased symmetry of body type among

parents of obese children, particularly in subjects in the upper extremes of body mass. Jacobson *et al.* (Jacobson, Torgerson, Sjostrom, & Bouchard, 2007) 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 (Speakman, Djafarian, Stewart, & Jackson, 2007), and when assessing body weight correlations between partners prior to marriage and cohabitation (Allison et al., 1996).

Obesity prevalence in the United States over the last decade appears to have reached a standstill (Ogden, Carroll, Kit, & Flegal, 2014). Despite this apparent plateau, significant increases in all classes of obesity, ranging from BMI ≥30 to BMI ≥40 have been observed among American children (A. C. Skinner, Perrin, & Skelton, 2016). Since spousal concordance in body type, based on BMI in early childhood, has increased in parallel with the growing prevalence of obesity (Ajslev et al., 2012), it is possible that the increased prevalence of extreme obesity may be driven in part by mate choice. Assortative mating by BMI leads to an increase in the mean BMI and prevalence of obesity among offspring (Dawson, Dhurandhar, Vazquez, Peng, & Allison, 2013), 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 (Fisher et al., 2014) 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.

Historically, segregation of obesity and leanness predisposing variants in pedigrees would have occurred randomly. Alternatively, 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 idealisations of our ancestors, deities, representations of fertility or symbolic responses to increased risk of mortality during childbirth and pregnancy (Colman, 1998; Józsa, 2011; Shewan, 2006). The exaggerated breasts and genitalia, along with red ochre traces often interpreted to represent menstrual blood, give weight to the latter conjecture (Seshadri, 2012). Evolutionarily speaking, the 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 (Bovet & Raymond, 2015; Singh, 2002; Sugiyama, 2004; Wetsman & Marlowe, 1999; Yu & Shepard, 1998). Singh (Singh, 2002) 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 (E2) and progesterone, possibly leading to increased probability of conception (Jasienska, Ziomkiewicz, Ellison, Lipson, & Thune, 2004). Data suggests that narrow waists were consistently considered beautiful in Western and non-Western populations alike (Singh, Renn, & Singh, 2007), with ideal WHR in Western females centering around the normal fertile range over the last 2, 500 years (Bovet & Raymond, 2015). However, variation in preference of WHR among non-industrialised populations, such as the Matsigenka peoples of Peru (Yu & Shepard, 1998), the Shiwiar of the Ecuadorian Amazon (Sugiyama, 2004) and Hadza of Tanzania (Wetsman & Marlowe, 1999) has also been observed.

It is important to note that overall adiposity and WHR represent different, albeit related, phenomena. Though some overlap between genetic variants related to BMI and WHR exist, GWAS have revealed genetic loci that are associated with WHR independent of BMI (Shungin et al., 2015). 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 (Sugiyama, 2004). 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 (Sugiyama, 2004). Similarly, the range in observed WHR among women with idealised bodies has increased markedly over time (Bovet & Raymond, 2015). 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 (Rubinstein & Caballero, 2000). In short, 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, resulting in complex patterns of selection for obesity and leanness predisposing alleles.

4.3.1 Mating rituals and predisposition to obesity

Cultural dictates of who may mate with whom 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 (Saeed et al., 2015). Intriguingly, the *LEP* frameshift mutation G133_VfsX14 appears to segregate within a specific, close knit caste which has practiced consanguinity for generations, likely reflecting a founder effect (Saeed et al., 2015). 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 (Bittles & Black, 2010). Typically, such marriages are believed to strengthen familial ties and are encouraged for their perceived economic and fertility benefits (Hussain, 1999).

Comparing the geographic distribution of consanguinity with recent obesity prevalence rates does not reveal a generalizable trend. Though 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% (Ng et al., 2014). The prevalence of consanguinity in this population is believed to be as high as 55.7% (Al-Awadi et al., 1985), though some variation may exist due to socioeconomic factors and association with Bedouin culture (Radovanovic, Shah, & Behbehani, 1999). 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 (Bittles & Black, 2010).

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 (Bittles & Black, 2010). 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.

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 (Scannell Bryan et al., 2014), 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 (Corry, 2014).

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 (Reich, Thangaraj, Patterson, Price, & Singh, 2009). Reproductively isolated groups, such as the Hutterite (Boycott et al., 2008) and Amish (Francomano, McKusick, & Biesecker, 2003), or geographically isolated populations such as French Canadians inhabiting the Saguenay-Lac St. Jean region in Québec (Daigneault, Aubin, Simard, & De Braekeleer, 1991), 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, low genetic risk of obesity or both. However, in a study of hypertension among lean and obese families in Saguenay-Lac St. Jean, increased homogeneity among obese hypertensive families was noted (Pausova et al., 2002). 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 around the world that lead to an increase in the number of matings by a single individual or a group of related individuals may also impact genetic architecture over time. Polygyny, the mating of a single male with multiple females has been practiced historically and is still prevalent in Africa (Eaton et al., 2014; Lawson et al., 2015). Royalty may practice polygyny on grander scale: King Abumi II of Bafut, Cameroon is reported to have 100 wives (Methu, Hancock, & Anyangwe, 2015). Polygamy also encompasses polyandry, females that mate with multiple male partners. Historically, Tibetans have practiced polyandry (Johnson & Zhang, 1991) and evidence of fraternal polyandry, the mating of a single female with multiple brothers, still exists in rural areas of Punjab, India (Garg, 2005; Sidner, 2008). Where a single individual or group of related individuals take multiple mates, genetic similarity between individuals in the population may ensue, since 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 (Zerjal et al., 2003). 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 (Balaresque et al., 2015). 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 been able to support multiple wives, allowing them to contribute to the genetic makeup of a greater number of offspring. Should they be carriers of thrifty genes, the probability of obesity risk alleles being transmitted increases as the number of mating events increase.

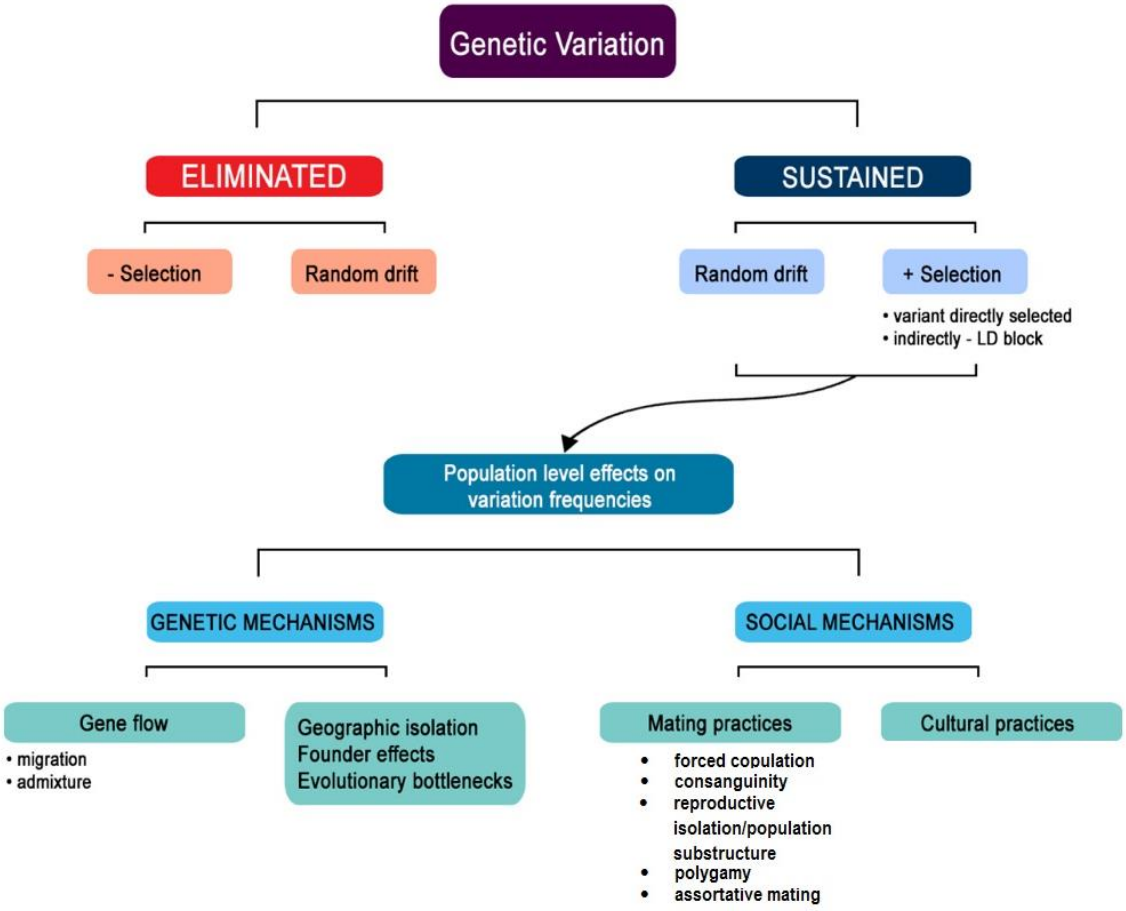
It should be noted that though mating systems may have a profound effect on the genetic landscape, social mores regarding mating are inconsistent through time and space. Thus, the impact of mating systems on obesity and leanness risk alleles across the globe may be variable.

CHAPTER 5: Conclusions and future directions

Diverse forces have worked in tandem to shape the human genetic landscape. Though 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, I expand on Neel's concepts of thrift and outline novel biological mechanisms that may have given rise to obesity predisposing variants. Additionally, I describe social phenomena and epigenetic mechanisms by which the human genome may be shaped and reshaped (Figure 1). In large part, 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. Drawing on data from human genetics, archaeobiology, palaeonutrition, and history, these novel theories of obesity evolution may be empirically tested. Though mathematical models are oversimplifications of reality and methodological tools to account for complex models are limited, the ability to simulate geographic and time-dependant pressures of selections 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. Though speculative, estimations of Neandertal body size based on skeletal measurements have suggested that BMI of some individuals ranged from 26.9 to 28.2 kg/m^2 (Helmuth, 1998). It cannot be elucidated

whether this reflects the muscularity or corpulence of Neandertals. Intriguingly, however, Simonti and colleagues (Simonti et al., 2016) recently reported nominally significant associations between Neandertal variants and risk of obesity and overweight in modern Europeans. Modern human populations carry varying proportions of genetic material from archaic humans, including Denisovans (Sankararaman, Mallick, Patterson, & Reich, 2016). Thus, if ancient DNA contributes to obesity or leanness phenotypes in the modern day, some variation in obesity risk may be attributable to historic admixture. Ultimately, in-depth comparisons of ancient and modern human DNA will allow us to formulate conjectures about the forces that drove these changes in mutation frequency.

Figure 1: A summary of potential biological, environmental, and social drivers of evolutionary change that may explain global distributions of obesity and leanness predisposing variants.



When genetic variation enters the human gene pool, arising from mutation, gene flow or genomic introgression, natural selection may eliminate or sustain the variant, based on associated fitness advantages. The variant may be directly selected for or may increase in frequency as result of linkage disequilibrium. Alternatively, random genetic drift may lead to an increase or decrease in allele frequency randomly. Fixation may occur – whether due to strong selection pressure, or due to genetic drift – decreasing genetic variation in the population. When a genetic variant is sustained in a gene pool, genetic and social mechanisms may affect the frequency of the variant further. Gene flow resulting from migration or admixture will increase genetic variation within a population, but decrease variation between populations. Geographic isolation and founder effects may

severely skew allele frequencies, by virtue of genetic drift. Culturally dictated mating practices may increase the frequency of a variant sustained the gene pool, if the variant contributes to fitness in the sociocultural context. Consanguinity, reproductive isolation and assortative mating will lead to increased genetic similarity between individuals. Forced copulation, sometimes observed in master-slave relationships, may also lead to increased genetic similarity between individuals, enriching populations for certain traits. Ultimately, epigenetic mechanisms will regulate the expression of variants. Thus, although demographic and social factors may affect the frequency of variants in a population, the impact of the variant on phenotypic variation is dependent on whether or not the genotype is expressed.

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 (mtDNA), which reflects maternal lineage (Quintana-Murci et al., 1999), has been hypothesised to contribute to obesity phenotypes (Dunham-Snary & Ballinger, 2013; Flaquer et al., 2014; Knoll et al., 2014). Shifts in abundances of microbial organisms living in and around the human body have also been associated with increased adiposity (Cani, 2013). Recent studies in mouse models suggest that though microbiota may be modelled by the environment, the host genome also affects the composition of the microbiome (Goodrich et al., 2014; Ussar et al., 2015). Thus, the effects of evolutionary forces on shaping the human genome may inadvertently exert a pleiotropic effect that modulates the microbiome, which may have ramifications for human metabolic phenotypes.

Drivers of evolutionary change do not work in isolation. Rather, each agent – be it biological or social – affects the genomic landscape independent 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 recognised as a multifactorial condition, but theories explaining the evolutionary origins of obesity rarely draw on different fields to explain the aetiology of the disease. As such, I 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 pointed prevention, management and treatment strategies in the future.

REFERENCES

2015 Report on Diabetes: Driving Change. (2015). Toronto: Canadian Diabetes Association.

Ahn, J. D., Dubern, B., Lubrano-Berthelier, C., Clement, K., & Karsenty, G. (2006). Cart overexpression is the only identifiable cause of high bone mass in melanocortin 4 receptor deficiency. *Endocrinology, 147*(7), 3196-3202. doi: 10.1210/en.2006-0281

Ajslev, T. A., Angquist, L., Silventoinen, K., Gamborg, M., Allison, D. B., Baker, J. L., & Sorensen, T. I. (2012). Assortative marriages by body mass index have increased simultaneously with the obesity epidemic. *Front Genet, 3*, 125. doi: 10.3389/fgene.2012.00125

Al-Awadi, S. A., Moussa, M. A., Naguib, K. K., Farag, T. I., Teebi, A. S., el-Khalifa, M., & el-Dossary, L. (1985). Consanguinity among the Kuwaiti population. *Clin Genet, 27*(5), 483-486.

Aldhoon Hainerová, I., Zamrazilová, H., Sedláčková, D., & Hainer, V. (2011). Hypogonadotropic Hypogonadism in a Homozygous MC4R Mutation Carrier and the Effect of Sibutramine Treatment on Body Weight and Obesity-Related Health Risks. *Obesity Facts, 4*(4), 324-328.

Allison, D. B., Neale, M. C., Kezis, M. I., Alfonso, V. C., Heshka, S., & Heymsfield, S. B. (1996). Assortative mating for relative weight: genetic implications. *Behav Genet, 26*(2), 103-111.

Almen, M. S., Jacobsson, J. A., Moschonis, G., Benedict, C., Chrousos, G. P., Fredriksson, R., & Schioth, H. B. (2012). Genome wide analysis reveals association of a FTO gene variant with epigenetic changes. *Genomics, 99*(3), 132-137. doi: 10.1016/j.ygeno.2011.12.007

Anders, S., Tanaka, M., & Kinney, D. K. (2013). Depression as an evolutionary strategy for defense against infection. *Brain Behav Immun, 31*, 9-22. doi: 10.1016/j.bbi.2012.12.002

Andersen, J. M., Herning, H., Aschim, E. L., Hjelmesaeth, J., Mala, T., Hanevik, H. I., . . . Witczak, O. (2015). Body Mass Index Is Associated with Impaired Semen Characteristics and Reduced Levels of Anti-Mullerian Hormone across a Wide Weight Range. *PLoS One, 10*(6), e0130210. doi: 10.1371/journal.pone.0130210

Andrews, P. W., & Thomson, J. A., Jr. (2009). The bright side of being blue: depression as an adaptation for analyzing complex problems. *Psychol Rev, 116*(3), 620-654. doi: 10.1037/a0016242

Arnheim, N., & Calabrese, P. (2009). Understanding what determines the frequency and pattern of human germline mutations. *Nat Rev Genet, 10*(7), 478-488. doi: 10.1038/nrg2529

Aspiras, A. C., Rohner, N., Martineau, B., Borowsky, R. L., & Tabin, C. J. (2015). Melanocortin 4 receptor mutations contribute to the adaptation of cavefish to nutrient-poor conditions. *Proc Natl Acad Sci U S A, 112*(31), 9668-9673. doi: 10.1073/pnas.1510802112

Baack, M. L., Puumala, S. E., Messier, S. E., Pritchett, D. K., & Harris, W. S. (2015). What is the relationship between gestational age and docosahexaenoic acid (DHA) and arachidonic acid (ARA) levels? *Prostaglandins, Leukotrienes and Essential Fatty Acids (PLEFA), 100*, 5-11. doi: 10.1016/j.plefa.2015.05.003

Balaresque, P., Poulet, N., Cussat-Blanc, S., Gerard, P., Quintana-Murci, L., Heyer, E., & Jobling, M. A. (2015). Y-chromosome descent clusters and male differential reproductive success: young lineage expansions dominate Asian pastoral nomadic populations. *Eur J Hum Genet, 23*(10), 1413-1422. doi: 10.1038/ejhg.2014.285

Ball, R. A. (2011). Biological and biosocial theory. In C. D. Bryant (Ed.), *Routledge Handbook of Deviant Behavior* (pp. 157-163). New York, NY: Routledge

Bandel, I., Bungum, M., Richtoff, J., Malm, J., Axelsson, J., Pedersen, H. S., . . . Giwercman, A. (2015). No association between body mass index and sperm DNA integrity. *Hum Reprod, 30*(7), 1704-1713. doi: 10.1093/humrep/dev111

Barel, E., Van, I. M. H., Sagi-Schwartz, A., & Bakermans-Kranenburg, M. J. (2010). Surviving the Holocaust: a meta-analysis of the long-term sequelae of a genocide. *Psychol Bull, 136*(5), 677-698. doi: 10.1037/a0020339

Barreiro, L. B., & Quintana-Murci, L. (2010). From evolutionary genetics to human immunology: how selection shapes host defence genes. *Nat Rev Genet, 11*(1), 17-30. doi: 10.1038/nrg2698

Becker, A. E., Grinspoon, S. K., Klibanski, A., & Herzog, D. B. (1999). Eating Disorders. *New England Journal of Medicine, 340*(14), 1092-1098. doi: 10.1056/NEJM199904083401407

Bell, C. G., Finer, S., Lindgren, C. M., Wilson, G. A., Rakyan, V. K., Teschendorff, A. E., . . . Hitman, G. A. (2010). Integrated genetic and epigenetic analysis identifies haplotype-specific methylation in the FTO type 2 diabetes and obesity susceptibility locus. *PLoS One, 5*(11), e14040. doi: 10.1371/journal.pone.0014040

Benyshek, D. C., & Watson, J. T. (2006). Exploring the thrifty genotype's food-shortage assumptions: a cross-cultural comparison of ethnographic accounts of food security among foraging and agricultural societies. *Am J Phys Anthropol, 131*(1), 120-126. doi: 10.1002/ajpa.20334

Berbesque, J. C., Marlowe, F. W., Shaw, P., & Thompson, P. (2014). Hunter-gatherers have less famine than agriculturalists. *Biol Lett, 10*(1), 20130853. doi: 10.1098/rsbl.2013.0853

Bercovich, E., Keinan-Boker, L., & Shasha, S. M. (2014). Long-term health effects in adults born during the Holocaust. *Isr Med Assoc J, 16*(4), 203-207.

Bersaglieri, T., Sabeti, P. C., Patterson, N., Vanderploeg, T., Schaffner, S. F., Drake, J. A., . . . Hirschhorn, J. N. (2004). Genetic signatures of strong recent positive selection at the lactase gene. *Am J Hum Genet, 74*(6), 1111-1120. doi: 10.1086/421051

Bierne, H., Hamon, M., & Cossart, P. (2012). Epigenetics and bacterial infections. *Cold Spring Harb Perspect Med, 2*(12), a010272. doi: 10.1101/cshperspect.a010272

Birsoy, K., Festuccia, W. T., & Laplante, M. (2013). A comparative perspective on lipid storage in animals. *J Cell Sci, 126*(Pt 7), 1541-1552. doi: 10.1242/jcs.104992

Bittles, A. H., & Black, M. L. (2010). Evolution in health and medicine Sackler colloquium: Consanguinity, human evolution, and complex diseases. *Proc Natl Acad Sci U S A, 107 Suppl 1*, 1779-1786. doi: 10.1073/pnas.0906079106

Bobjer, J., Bogefors, K., Isaksson, S., Leijonhufvud, I., Akesson, K., Giwercman, Y. L., & Giwercman, A. (2016). High prevalence of hypogonadism and associated impaired metabolic and bone mineral status in subfertile men. *Clin Endocrinol (Oxf), 85*(2), 189-195. doi: 10.1111/cen.13038

Bovet, J., & Raymond, M. (2015). Preferred women's waist-to-hip ratio variation over the last 2,500 years. *PLoS One, 10*(4), e0123284. doi: 10.1371/journal.pone.0123284

Boycott, K. M., Parboosingh, J. S., Chodirker, B. N., Lowry, R. B., McLeod, D. R., Morris, J., . . . Innes, A. M. (2008). Clinical genetics and the Hutterite population: a review of Mendelian disorders. *Am J Med Genet A, 146A*(8), 1088-1098. doi: 10.1002/ajmg.a.32245

Brown, J. S. H. (2009). Métis. Retrieved February 4, 2016, from Historica Canada http://www.thecanadianencyclopedia.ca/en/article/metis/

Bryc, K., Auton, A., Nelson, M. R., Oksenberg, J. R., Hauser, S. L., Williams, S., . . . Bustamante, C. D. (2010). Genome-wide patterns of population structure and admixture in West Africans and African Americans. *Proc Natl Acad Sci U S A, 107*(2), 786-791. doi: 10.1073/pnas.0909559107

Buss, D. M., & Shackelford, T. K. (1997). Human aggression in evolutionary psychological perspective. *Clin Psychol Rev, 17*(6), 605-619.

Butler, M. G. (1989). Hypopigmentation: a common feature of Prader-Labhart-Willi syndrome. *Am J Hum Genet, 45*(1), 140-146.

Campbell, J. M., Lane, M., Owens, J. A., & Bakos, H. W. (2015). Paternal obesity negatively affects male fertility and assisted reproduction outcomes: a systematic review and meta-analysis. *Reprod Biomed Online, 31*(5), 593-604. doi: 10.1016/j.rbmo.2015.07.012

Cani, P. D. (2013). Gut microbiota and obesity: lessons from the microbiome. *Brief Funct Genomics, 12*(4), 381-387. doi: 10.1093/bfgp/elt014

Cassidy, S. B., Schwartz, S., Miller, J. L., & Driscoll, D. J. (2012). Prader-Willi syndrome. *Genet Med, 14*(1), 10-26. doi: 10.1038/gim.0b013e31822bead0

Cheng, C. Y., Kao, W. H., Patterson, N., Tandon, A., Haiman, C. A., Harris, T. B., . . . Reich, D. (2009). Admixture mapping of 15,280 African Americans identifies obesity susceptibility loci on chromosomes 5 and X. *PLoS Genet, 5*(5), e1000490. doi: 10.1371/journal.pgen.1000490

Cheng, C. Y., Reich, D., Coresh, J., Boerwinkle, E., Patterson, N., Li, M., . . . Kao, W. H. (2010). Admixture mapping of obesity-related traits in African Americans: the Atherosclerosis Risk in Communities (ARIC) Study. *Obesity (Silver Spring), 18*(3), 563-572. doi: 10.1038/oby.2009.282

Chojnicka, I., Fudalej, S., Walczak, A., Wasilewska, K., Fudalej, M., Stawinski, P., . . . Ploski, R. (2014). Inverse association between obesity predisposing FTO genotype and completed suicide. *PLoS One, 9*(9), e108900. doi: 10.1371/journal.pone.0108900

Ciarleglio, C. M., Ryckman, K. K., Servick, S. V., Hida, A., Robbins, S., Wells, N., . . . Johnson, C. H. (2008). Genetic differences in human circadian clock genes among worldwide populations. *J Biol Rhythms, 23*(4), 330-340. doi: 10.1177/0748730408320284

Clancy, S. (2008). DNA damage & repair: mechanisms for maintaining DNA integrity. *Nature Education, 1*(1), 103.

Clement, K., Dubern, B., Mencarelli, M., Czernichow, P., Ito, S., Wakamatsu, K., . . . Leger, J. (2008). Unexpected endocrine features and normal pigmentation in a young adult patient carrying a novel homozygous mutation in the POMC gene. *J Clin Endocrinol Metab, 93*(12), 4955-4962. doi: 10.1210/jc.2008-1164

Clement, K., Vaisse, C., Lahlou, N., Cabrol, S., Pelloux, V., Cassuto, D., . . . Guy-Grand, B. (1998). A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature, 392*(6674), 398-401. doi: 10.1038/32911

Colman, E. (1998). Obesity in the Paleolithic Era? The Venus of Willendorf. *Endocrine Practice, 4*(1), 58-59.

Corry, P. C. (2014). Consanguinity and prevalence patterns of inherited disease in the UK Pakistani community. *Hum Hered, 77*(1-4), 207-216. doi: 10.1159/000362598

Cousminer, D. L., Stergiakouli, E., Berry, D. J., Ang, W., Groen-Blokhuis, M. M., Korner, A., . . . Widen, E. (2014). Genome-wide association study of sexual maturation in males and females highlights a role for body mass and menarche loci in male puberty. *Hum Mol Genet, 23*(16), 4452-4464. doi: 10.1093/hmg/ddu150

Cruciani, F., Trombetta, B., Labuda, D., Modiano, D., Torroni, A., Costa, R., & Scozzari, R. (2008). Genetic diversity patterns at the human clock gene period 2 are suggestive of population-specific positive selection. *Eur J Hum Genet, 16*(12), 1526-1534. doi: 10.1038/ejhg.2008.105

Cuijpers, P., & Smit, F. (2002). Excess mortality in depression: a meta-analysis of community studies. *J Affect Disord, 72*(3), 227-236.

Cunnane, S. C. (2010). Human brain evolution: A question of solving key nutritional and metabolic contraints on mammalian brain development. In S. C. Cunnane & K. M. Stewart (Eds.), *Human Brain Evolution: The Influence of Freshwater and Marine Food Resources* (pp. 33-64). Hoboken, N. J.: Wiley-Blackwell.

Cunnane, S. C., & Crawford, M. A. (2014). Energetic and nutritional constraints on infant brain development: implications for brain expansion during human evolution. *J Hum Evol, 77*, 88-98. doi: 10.1016/j.jhevol.2014.05.001

Curtin, P. D. (1968). Epidemiology and the slave trade. *Polit Sci Q, 83*, 190-216.

Daigneault, J., Aubin, G., Simard, F., & De Braekeleer, M. (1991). Genetic epidemiology of cystic fibrosis in Saguenay-Lac-St-Jean (Quebec, Canada). *Clin Genet, 40*(4), 298-303.

Dalgaard, K., Landgraf, K., Heyne, S., Lempradl, A., Longinotto, J., Gossens, K., . . . Pospisilik, J. A. (2016). Trim28 Haploinsufficiency Triggers Bi-stable Epigenetic Obesity. *Cell, 164*(3), 353-364. doi: 10.1016/j.cell.2015.12.025

Dashti, H. S., Follis, J. L., Smith, C. E., Tanaka, T., Cade, B. E., Gottlieb, D. J., . . . Ordovas, J. M. (2015). Habitual sleep duration is associated with BMI and macronutrient intake and may be modified by CLOCK genetic variants. *Am J Clin Nutr, 101*(1), 135-143. doi: 10.3945/ajcn.114.095026

Dawson, J. A., Dhurandhar, E. J., Vazquez, A. I., Peng, B., & Allison, D. B. (2013). Propagation of obesity across generations: the roles of differential realized fertility and assortative mating by body mass index. *Hum Hered, 75*(2-4), 204-212. doi: 10.1159/000352007

Deng, J., Schoeneman, S. E., Zhang, H., Kwon, S., Rigsby, C. K., Shore, R. M., & Josefson, J. L. (2015). MRI characterization of brown adipose tissue in obese and normal-weight children. *Pediatr Radiol, 45*(11), 1682-1689. doi: 10.1007/s00247-015-3391-z

Desai, M., Jellyman, J. K., & Ross, M. G. (2015). Epigenomics, gestational programming and risk of metabolic syndrome. *Int J Obes (Lond), 39*(4), 633-641. doi: 10.1038/ijo.2015.13

Dhurandhar, E. J., & Keith, S. W. (2014). The aetiology of obesity beyond eating more and exercising less. *Best Pract Res Clin Gastroenterol, 28*(4), 533-544. doi: 10.1016/j.bpg.2014.07.001

Di Castelnuovo, A., Quacquaruccio, G., Donati, M. B., de Gaetano, G., & Iacoviello, L. (2009). Spousal concordance for major coronary risk factors: a systematic review and meta-analysis. *Am J Epidemiol, 169*(1), 1-8. doi: 10.1093/aje/kwn234

Diamond, J. (2003). The double puzzle of diabetes. *Nature, 423*(6940), 599-602. doi: 10.1038/423599a

Dietz, W. H., Baur, L. A., Hall, K., Puhl, R. M., Taveras, E. M., Uauy, R., & Kopelman, P. (2015). Management of obesity: improvement of health-care training and systems for prevention and care. *The Lancet, 385*(9986), 2521-2533. doi: 10.1016/s0140-6736(14)61748-7

Doche, M. E., Bochukova, E. G., Su, H. W., Pearce, L. R., Keogh, J. M., Henning, E., . . . Farooqi, I. S. (2012). Human SH2B1 mutations are associated with maladaptive behaviors and obesity. *J Clin Invest, 122*(12), 4732-4736. doi: 10.1172/JCI62696

Donkin, I., Versteyhe, S., Ingerslev, L. R., Qian, K., Mechta, M., Nordkap, L., . . . Barres, R. (2016). Obesity and Bariatric Surgery Drive Epigenetic Variation of Spermatozoa in Humans. *Cell Metab, 23*(2), 369-378. doi: 10.1016/j.cmet.2015.11.004

Douglass, F. (1845). *Narrative of the Life of Frederick Douglass, an American Slave. Written by Himself*. Boston: Anti-Slavery Office.

Dunham-Snary, K. J., & Ballinger, S. W. (2013). Mitochondrial genetics and obesity: evolutionary adaptation and contemporary disease susceptibility. *Free Radic Biol Med, 65*, 1229-1237. doi: 10.1016/j.freeradbiomed.2013.09.007

Durand, E., Boutin, P., Meyre, D., Charles, M. A., Clement, K., Dina, C., & Froguel, P. (2004). Polymorphisms in the amino acid transporter solute carrier family 6 (neurotransmitter transporter) member 14 gene contribute to polygenic obesity in French Caucasians. *Diabetes, 53*(9), 2483-2486.

Eaton, J. W., Takavarasha, F. R., Schumacher, C. M., Mugurungi, O., Garnett, G. P., Nyamukapa, C., & Gregson, S. (2014). Trends in concurrency, polygyny, and multiple sex partnerships during a decade of declining HIV prevalence in eastern Zimbabwe. *J Infect Dis, 210 Suppl 2*, S562-568. doi: 10.1093/infdis/jiu415

Egger, G., & Swinburn, B. (1997). An "ecological" approach to the obesity pandemic. *BMJ, 315*(7106), 477-480.

Eisenberg, M. L., Kim, S., Chen, Z., Sundaram, R., Schisterman, E. F., & Buck Louis, G. M. (2014). The relationship between male BMI and waist circumference on semen quality: data from the LIFE study. *Hum Reprod, 29*(2), 193-200. doi: 10.1093/humrep/det428

El-Sayed Moustafa, J. S., Eleftherohorinou, H., de Smith, A. J., Andersson-Assarsson, J. C., Alves, A. C., Hadjigeorgiou, E., . . . Coin, L. J. (2012). Novel association approach for variable number tandem repeats (VNTRs) identifies DOCK5 as a susceptibility gene for severe obesity. *Hum Mol Genet, 21*(16), 3727-3738. doi: 10.1093/hmg/dds187

Elefteriou, F., Ahn, J. D., Takeda, S., Starbuck, M., Yang, X., Liu, X., . . . Karsenty, G. (2005). Leptin regulation of bone resorption by the sympathetic nervous system and CART. *Nature, 434*(7032), 514-520. doi: 10.1038/nature03398

Elks, C. E., den Hoed, M., Zhao, J. H., Sharp, S. J., Wareham, N. J., Loos, R. J., & Ong, K. K. (2012). Variability in the heritability of body mass index: a systematic review

and meta-regression. *Front Endocrinol (Lausanne), 3*, 29. doi: 10.3389/fendo.2012.00029

Enattah, N. S., Jensen, T. G., Nielsen, M., Lewinski, R., Kuokkanen, M., Rasinpera, H., . . . Peltonen, L. (2008). Independent introduction of two lactase-persistence alleles into human populations reflects different history of adaptation to milk culture. *Am J Hum Genet, 82*(1), 57-72. doi: 10.1016/j.ajhg.2007.09.012

Falchi, M., El-Sayed Moustafa, J. S., Takousis, P., Pesce, F., Bonnefond, A., Andersson-Assarsson, J. C., . . . Froguel, P. (2014). Low copy number of the salivary amylase gene predisposes to obesity. *Nat Genet, 46*(5), 492-497. doi: 10.1038/ng.2939

Farooqi, I. S., Drop, S., Clements, A., Keogh, J. M., Biernacka, J., Lowenbein, S., . . . O'Rahilly, S. (2006). Heterozygosity for a POMC-null mutation and increased obesity risk in humans. *Diabetes, 55*(9), 2549-2553. doi: 10.2337/db06-0214

Farooqi, I. S., Keogh, J. M., Yeo, G. S., Lank, E. J., Cheetham, T., & O'Rahilly, S. (2003). Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. *N Engl J Med, 348*(12), 1085-1095. doi: 10.1056/NEJMoa022050

Farooqi, I. S., Wangensteen, T., Collins, S., Kimber, W., Matarese, G., Keogh, J. M., . . . O'Rahilly, S. (2007). Clinical and Molecular Genetic Spectrum of Congenital Deficiency of the Leptin Receptor. *New England Journal of Medicine, 356*(3), 237-247. doi: 10.1056/NEJMoa063988

Farooqi, I. S., Yeo, G. S., Keogh, J. M., Aminian, S., Jebb, S. A., Butler, G., . . . O'Rahilly, S. (2000). Dominant and recessive inheritance of morbid obesity associated with melanocortin 4 receptor deficiency. *J Clin Invest, 106*(2), 271-279. doi: 10.1172/jci9397

Farooqi, I. S., Yeo, G. S. H., Keogh, J. M., Aminian, S., Jebb, S. A., Butler, G., . . . O'Rahilly, S. (2000). Dominant and recessive inheritance of morbid obesity associated with melanocortin 4 receptor deficiency. *Journal of Clinical Investigation, 106*(2), 271-279.

Feinberg, A. P., & Irizarry, R. A. (2010). Evolution in health and medicine Sackler colloquium: Stochastic epigenetic variation as a driving force of development, evolutionary adaptation, and disease. *Proc Natl Acad Sci U S A, 107 Suppl 1*, 1757-1764. doi: 10.1073/pnas.0906183107

Fernandez-Rhodes, L., Demerath, E. W., Cousminer, D. L., Tao, R., Dreyfus, J. G., Esko, T., . . . Franceschini, N. (2013). Association of adiposity genetic variants with menarche timing in 92,105 women of European descent. *Am J Epidemiol, 178*(3), 451-460. doi: 10.1093/aje/kws473

Fisher, C. I., Fincher, C. L., Hahn, A. C., Little, A. C., DeBruine, L. M., & Jones, B. C. (2014). Do assortative preferences contribute to assortative mating for adiposity? *Br J Psychol, 105*(4), 474-485. doi: 10.1111/bjop.12055

Flaquer, A., Baumbach, C., Kriebel, J., Meitinger, T., Peters, A., Waldenberger, M., . . . Strauch, K. (2014). Mitochondrial genetic variants identified to be associated with BMI in adults. *PLoS One, 9*(8), e105116. doi: 10.1371/journal.pone.0105116

Flory, J. D., Bierer, L. M., & Yehuda, R. (2011). Maternal exposure to the holocaust and health complaints in offspring. *Dis Markers, 30*(2-3), 133-139. doi: 10.3233/DMA-2011-0748

Foster, T. A. (2011). The Sexual Abuse of Black Men under American Slavery. *Journal of the History of Sexuality, 20*(3), 445-464. doi: 10.1353/sex.2011.0059

Francomano, C. A., McKusick, V. A., & Biesecker, L. G. (2003). Medical genetic studies in the Amish: historical perspective. *Am J Med Genet C Semin Med Genet, 121C*(1), 1-4. doi: 10.1002/ajmg.c.20001

Frisch, R. E., & McArthur, J. W. (1974). Menstrual cycles: fatness as a determinant of minimum weight for height necessary for their maintenance or onset. *Science, 185*(4155), 949-951.

Futuyama, D. J. (2010). Evolutionary Theory. In M. P. Muehlenbein (Ed.), *Human Evolutionary Biology* (pp. 3-16). New York, NY: Cambridge University Press.

Galbete, C., Contreras, R., Martinez, J. A., Martinez-Gonzalez, M. A., Guillen-Grima, F., & Marti, A. (2012). Physical activity and sex modulate obesity risk linked to 3111T/C gene variant of the CLOCK gene in an elderly population: the SUN Project. *Chronobiol Int, 29*(10), 1397-1404. doi: 10.3109/07420528.2012.728657

Galvani, A. P., & Slatkin, M. (2003). Evaluating plague and smallpox as historical selective pressures for the CCR5-Delta 32 HIV-resistance allele. *Proc Natl Acad Sci U S A, 100*(25), 15276-15279. doi: 10.1073/pnas.2435085100

Garg, B. (2005). Draupadis bloom in rural Punjab. *The Times of India*. http://timesofindia.indiatimes.com/india/Draupadis-bloom-in-rural-Punjab/articleshow/1172638.cms

Geller, F., Reichwald, K., Dempfle, A., Illig, T., Vollmert, C., Herpertz, S., . . . Hebebrand, J. (2004). Melanocortin-4 receptor gene variant I103 is negatively associated with obesity. *Am J Hum Genet, 74*(3), 572-581. doi: 10.1086/382490

Genne-Bacon, E. A. (2014). Thinking evolutionarily about obesity. *Yale J Biol Med, 87*(2), 99-112.

Gerhart-Hines, Z., & Lazar, M. A. (2015). Circadian metabolism in the light of evolution. *Endocr Rev, 36*(3), 289-304. doi: 10.1210/er.2015-1007

Gerstein, H. C., & Waltman, L. (2006). Why don't pigs get diabetes? Explanations for variations in diabetes susceptibility in human populations living in a diabetogenic environment. *Cmaj, 174*(1), 25-26. doi: 10.1503/cmaj.050649

Getman, K. A. (1984). Sexual Control in the Slaveholding South: The Implementation and Maintenance of a Racial Caste System. *Harvard Women's Law Journal 7*, 115-152.

Gil, A., Olza, J., Gil-Campos, M., Gomez-Llorente, C., & Aguilera, C. M. (2011). Is adipose tissue metabolically different at different sites? *Int J Pediatr Obes, 6 Suppl 1*, 13-20. doi: 10.3109/17477166.2011.604326

Gillberg, L., Jacobsen, S. C., Ronn, T., Brons, C., & Vaag, A. (2014). PPARGC1A DNA methylation in subcutaneous adipose tissue in low birth weight subjects--impact of 5 days of high-fat overfeeding. *Metabolism, 63*(2), 263-271. doi: 10.1016/j.metabol.2013.10.003

Goodrich, J. K., Waters, J. L., Poole, A. C., Sutter, J. L., Koren, O., Blekhman, R., . . . Ley, R. E. (2014). Human genetics shape the gut microbiome. *Cell, 159*(4), 789-799. doi: 10.1016/j.cell.2014.09.053

Grant, M. J., & Booth, A. (2009). A typology of reviews: an analysis of 14 review types and associated methodologies. *Health Info Libr J, 26*(2), 91-108. doi: 10.1111/j.1471-1842.2009.00848.x

Green, T. L., & Darity, W. A., Jr. (2010). Under the skin: using theories from biology and the social sciences to explore the mechanisms behind the black-white health gap. *Am J Public Health, 100 Suppl 1*, S36-40. doi: 10.2105/ajph.2009.171140

Grundberg, E., Meduri, E., Sandling, J. K., Hedman, A. K., Keildson, S., Buil, A., . . . Deloukas, P. (2013). Global analysis of DNA methylation variation in adipose tissue from twins reveals links to disease-associated variants in distal regulatory elements. *Am J Hum Genet, 93*(5), 876-890. doi: 10.1016/j.ajhg.2013.10.004

Haig, D. (2014). Coadaptation and conflict, misconception and muddle, in the evolution of genomic imprinting. *Heredity (Edinb), 113*(2), 96-103. doi: 10.1038/hdy.2013.97

Hales, C. N., & Barker, D. J. (1992). Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia, 35*(7), 595-601.

Harrington, T. A., Thomas, E. L., Modi, N., Frost, G., Coutts, G. A., & Bell, J. D. (2002). Fast and reproducible method for the direct quantitation of adipose tissue in newborn infants. *Lipids, 37*(1), 95-100.

Haslam, D. W., & James, W. P. T. (2005). Obesity. *The Lancet, 366*(9492), 1197-1209. doi: 10.1016/s0140-6736(05)67483-1

Hebebrand, J., Wulftange, H., Goerg, T., Ziegler, A., Hinney, A., Barth, N., . . . Remschmidt, H. (2000). Epidemic obesity: are genetic factors involved via increased rates of assortative mating? *Int J Obes Relat Metab Disord, 24*(3), 345-353.

Helmuth, H. (1998). Body height, body mass and surface area of the Neanderthals. *Z Morphol Anthropol, 82*(1), 1-12.

Hoggart, C. J., Venturini, G., Mangino, M., Gomez, F., Ascari, G., Zhao, J. H., . . . Kutalik, Z. (2014). Novel approach identifies SNPs in SLC2A10 and KCNK9 with evidence for parent-of-origin effect on body mass index. *PLoS Genet, 10*(7), e1004508. doi: 10.1371/journal.pgen.1004508

Holliday, M. (1986). Body composition and energy needs

during growth. In F. Falkner & J. Tanner (Eds.), *Human Growth: AComprehensive Treatise* (pp. 117-139). New York: Plenum Press.

Hung, C. F., Rivera, M., Craddock, N., Owen, M. J., Gill, M., Korszun, A., . . . McGuffin, P. (2014). Relationship between obesity and the risk of clinically significant depression: Mendelian randomisation study. *Br J Psychiatry, 205*(1), 24-28. doi: 10.1192/bjp.bp.113.130419

Hung, C. N., Poon, W. T., Lee, C. Y., Law, C. Y., & Chan, A. Y. (2012). A case of early-onset obesity, hypocortisolism, and skin pigmentation problem due to a novel homozygous mutation in the proopiomelanocortin (POMC) gene in an Indian boy. *J Pediatr Endocrinol Metab, 25*(1-2), 175-179. doi: 10.1515/jpem-2011-0437

Hunley, K., & Healy, M. (2011). The impact of founder effects, gene flow, and European admixture on native American genetic diversity. *Am J Phys Anthropol, 146*(4), 530-538. doi: 10.1002/ajpa.21506

Hurst, L. D. (2009). Fundamental concepts in genetics: genetics and the understanding of selection. *Nat Rev Genet, 10*(2), 83-93. doi: 10.1038/nrg2506

Hussain, R. (1999). Community perceptions of reasons for preference for consanguineous marriages in Pakistan. *J Biosoc Sci, 31*(4), 449-461.

Ishii, S., Cauley, J. A., Greendale, G. A., Nielsen, C., Karvonen-Gutierrez, C., Ruppert, K., & Karlamangla, A. S. (2014). Pleiotropic effects of obesity on fracture risk: the Study of Women's Health Across the Nation. *J Bone Miner Res, 29*(12), 2561-2570. doi: 10.1002/jbmr.2303

Jablonski, N. G. (2004). The Evolution of Human Skin and Skin Color. *Annual Review of Anthropology, 33*(1), 585-623. doi: 10.1146/annurev.anthro.33.070203.143955

Jablonski, N. G. (2012). The evolution of human skin colouration and its relevance to health in the modern world. *J R Coll Physicians Edinb, 42*(1), 58-63. doi: 10.4997/JRCPE.2012.114

Jackson, R. S., Creemers, J. W., Ohagi, S., Raffin-Sanson, M. L., Sanders, L., Montague, C. T., . . . O'Rahilly, S. (1997). Obesity and impaired prohormone processing associated with mutations in the human prohormone convertase 1 gene. *Nat Genet, 16*(3), 303-306. doi: 10.1038/ng0797-303

Jacobson, P., Torgerson, J. S., Sjostrom, L., & Bouchard, C. (2007). Spouse resemblance in body mass index: effects on adult obesity prevalence in the offspring generation. *Am J Epidemiol, 165*(1), 101-108. doi: 10.1093/aje/kwj342

Jasienska, G., Ziomkiewicz, A., Ellison, P. T., Lipson, S. F., & Thune, I. (2004). Large breasts and narrow waists indicate high reproductive potential in women. *Proc Biol Sci, 271*(1545), 1213-1217. doi: 10.1098/rspb.2004.2712

Jeffrey, B. G., Weisinger, H. S., Neuringer, M., & Mitchell, D. C. (2001). The role of docosahexaenoic acid in retinal function. *Lipids, 36*(9), 859-871.

Johnson, N. E., & Zhang, K. T. (1991). Matriarchy, polyandry, and fertility amongst the Mosuos in China. *J Biosoc Sci, 23*(4), 499-505.

Józsa, L. G. (2011). Obesity in the paleolithic era. *Hormones, 10*(3), 241-244.

Kacker, R., Conners, W., Zade, J., & Morgentaler, A. (2014). Bone mineral density and response to treatment in men younger than 50 years with testosterone deficiency and sexual dysfunction or infertility. *J Urol, 191*(4), 1072-1076. doi: 10.1016/j.juro.2013.10.070

Karay, F. (1994). The social and cultural life of the prisoners in the Jewish forced labor camp at Skarzysko-Kamienna. *Holocaust Genocide Stud, 8*(1), 1-27.

Keinan-Boker, L., Shasha-Lavsky, H., Eilat-Zanani, S., Edri-Shur, A., & Shasha, S. M. (2015). Chronic health conditions in Jewish Holocaust survivors born during World War II. *Isr Med Assoc J, 17*(4), 206-212.

Kettunen, J., Silander, K., Saarela, O., Amin, N., Muller, M., Timpson, N., . . . Peltonen, L. (2010). European lactase persistence genotype shows evidence of association with increase in body mass index. *Hum Mol Genet, 19*(6), 1129-1136. doi: 10.1093/hmg/ddp561

Kitahara, C. M., Flint, A. J., Berrington de Gonzalez, A., Bernstein, L., Brotzman, M., MacInnis, R. J., . . . Hartge, P. (2014). Association between class III obesity (BMI of 40-59 kg/m2) and mortality: a pooled analysis of 20 prospective studies. *PLoS Med, 11*(7), e1001673. doi: 10.1371/journal.pmed.1001673

Knoll, N., Jarick, I., Volckmar, A. L., Klingenspor, M., Illig, T., Grallert, H., . . . Hinney, A. (2014). Mitochondrial DNA variants in obesity. *PLoS One, 9*(5), e94882. doi: 10.1371/journal.pone.0094882

Kobayashi, H., Ogawa, Y., Shintani, M., Ebihara, K., Shimodahira, M., Iwakura, T., . . . Nakao, K. (2002). A Novel homozygous missense mutation of melanocortin-4 receptor (MC4R) in a Japanese woman with severe obesity. *Diabetes, 51*(1), 243-246.

Kolahdooz, F., Sadeghirad, B., Corriveau, A., & Sharma, S. (2015). Prevalence of Overweight and Obesity among Aboriginal Populations in Canada: A Systematic Review and Meta-analysis. *Crit Rev Food Sci Nutr*, 0. doi: 10.1080/10408398.2014.913003

Krude, H., Biebermann, H., Luck, W., Horn, R., Brabant, G., & Gruters, A. (1998). Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. *Nat Genet, 19*(2), 155-157. doi: 10.1038/509

Kryukov, G. V., Pennacchio, L. A., & Sunyaev, S. R. (2007). Most rare missense alleles are deleterious in humans: implications for complex disease and association studies. *Am J Hum Genet, 80*(4), 727-739. doi: 10.1086/513473

Kuehnen, P., Mischke, M., Wiegand, S., Sers, C., Horsthemke, B., Lau, S., . . . Krude, H. (2012). An Alu element-associated hypermethylation variant of the POMC gene is associated with childhood obesity. *PLoS Genet, 8*(3), e1002543. doi: 10.1371/journal.pgen.1002543

Kurokawa, N., Young, E. H., Oka, Y., Satoh, H., Wareham, N. J., Sandhu, M. S., & Loos, R. J. (2008). The ADRB3 Trp64Arg variant and BMI: a meta-analysis of 44 833 individuals. *Int J Obes (Lond), 32*(8), 1240-1249. doi: 10.1038/ijo.2008.90

Kuzawa, C. W. (1998). Adipose tissue in human infancy and childhood: an evolutionary perspective. *Am J Phys Anthropol, Suppl 27*, 177-209.

Kuzawa, C. W. (2010). Beyond feast-famine: Brain evolution, human life history, and the metabolic syndrome. In M. P. Muehlenbein (Ed.), *Human Evolutionary Biology* (pp. 518). New York, NY: Cambridge University Press.

Laland, K. N., Odling-Smee, J., & Myles, S. (2010). How culture shaped the human genome: bringing genetics and the human sciences together. *Nat Rev Genet, 11*(2), 137-148. doi: 10.1038/nrg2734

Lamri, A., Poli, A., Emery, N., Bellili, N., Velho, G., Lantieri, O., . . . Fumeron, F. (2013). The lactase persistence genotype is associated with body mass index and dairy consumption in the D.E.S.I.R. study. *Metabolism, 62*(9), 1323-1329. doi: 10.1016/j.metabol.2013.04.006

Larsen, C. S. (1995). Biological Changes in Human Populations with Agriculture. *Annual Review of Anthropology, 24*(1), 185-213. doi: 10.1146/annurev.an.24.100195.001153

Lawlor, D. A., Harbord, R. M., Tybjaerg-Hansen, A., Palmer, T. M., Zacho, J., Benn, M., . . . Nordestgaard, B. G. (2011). Using genetic loci to understand the relationship between adiposity and psychological distress: a Mendelian Randomization study in the Copenhagen General Population Study of 53,221 adults. *J Intern Med, 269*(5), 525-537. doi: 10.1111/j.1365-2796.2011.02343.x

Lawson, D. W., James, S., Ngadaya, E., Ngowi, B., Mfinanga, S. G., & Borgerhoff Mulder, M. (2015). No evidence that polygynous marriage is a harmful cultural practice in northern Tanzania. *Proc Natl Acad Sci U S A, 112*(45), 13827-13832. doi: 10.1073/pnas.1507151112

Lee, S.-T., Nicholls, R. D., Bundey, S., Laxova, R., Musarella, M., & Spritz, R. A. (1994). Mutations of the P Gene in Oculocutaneous Albinism, Ocular Albinism, and Prader-Willi Syndrome Plus Albinism. *New England Journal of Medicine, 330*(8), 529-534. doi: doi:10.1056/NEJM199402243300803

Leonard, W. R. (2014). The global diversity of eating patterns: human nutritional health in comparative perspective. *Physiol Behav, 134*, 5-14. doi: 10.1016/j.physbeh.2014.02.050

Linsell, L., Malouf, R., Morris, J., Kurinczuk, J. J., & Marlow, N. (2015). Prognostic Factors for Poor Cognitive Development in Children Born Very Preterm or With Very Low Birth Weight: A Systematic Review. *JAMA Pediatr, 169*(12), 1162-1172. doi: 10.1001/jamapediatrics.2015.2175

Liu, X., Weidle, K., Schrock, K., Tonjes, A., Schleinitz, D., Breitfeld, J., . . . Kovacs, P. (2015). Signatures of natural selection at the FTO (fat mass and obesity associated) locus in human populations. *PLoS One, 10*(2), e0117093. doi: 10.1371/journal.pone.0117093

Loos, R. J., Lindgren, C. M., Li, S., Wheeler, E., Zhao, J. H., Prokopenko, I., . . . Mohlke, K. L. (2008). Common variants near MC4R are associated with fat mass, weight and risk of obesity. *Nat Genet, 40*(6), 768-775. doi: 10.1038/ng.140

Malic Voncina, S., Golob, B., Ihan, A., Kopitar, A. N., Kolbezen, M., & Zorn, B. (2016). Sperm DNA fragmentation and mitochondrial membrane potential combined are better for predicting natural conception than standard sperm parameters. *Fertil Steril, 105*(3), 637-644 e631. doi: 10.1016/j.fertnstert.2015.11.037

Matarese, G., Moschos, S., & Mantzoros, C. S. (2005). Leptin in Immunology. *The Journal of Immunology, 174*(6), 3137-3142. doi: 10.4049/jimmunol.174.6.3137

McFadden, E., Jones, M. E., Schoemaker, M. J., Ashworth, A., & Swerdlow, A. J. (2014). The relationship between obesity and exposure to light at night: cross-sectional analyses of over 100,000 women in the Breakthrough Generations Study. *Am J Epidemiol, 180*(3), 245-250. doi: 10.1093/aje/kwu117

McLennan, A. K., & Ulijaszek, S. J. (2015). Obesity emergence in the Pacific islands: why understanding colonial history and social change is important. *Public Health Nutr, 18*(8), 1499-1505. doi: 10.1017/S136898001400175X

Meier, R. J., & Raff, J. A. (2010). Genetics in Human Biology. In M. P. Muehlenbein (Ed.), *Human Evolutionary Biology* (pp. 48-73). New York, NY: Cambridge University Press.

Mejia-Benitez, M. A., Bonnefond, A., Yengo, L., Huyvaert, M., Dechaume, A., Peralta-Romero, J., . . . Froguel, P. (2015). Beneficial effect of a high number of copies of salivary amylase AMY1 gene on obesity risk in Mexican children. *Diabetologia, 58*(2), 290-294. doi: 10.1007/s00125-014-3441-3

Methu, S., Hancock, C., & Anyangwe, E. (2015). The king with 100 wives. *CNN*.

Meyre, D., Delplanque, J., Chevre, J. C., Lecoeur, C., Lobbens, S., Gallina, S., . . . Froguel, P. (2009). Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations. *Nat Genet, 41*(2), 157-159. doi: 10.1038/ng.301

Miller, J. C. (1981). Mortality in the Atlantic slave trade. *J Interdiscip Hist, 11*(3), 385-423.

Mitchell-Olds, T., Willis, J. H., & Goldstein, D. B. (2007). Which evolutionary processes influence natural genetic variation for phenotypic traits? *Nat Rev Genet, 8*(11), 845-856. doi: 10.1038/nrg2207

Montagne, L., Raimondo, A., Delobel, B., Duban-Bedu, B., Noblet, F. S., Dechaume, A., . . . Bonnefond, A. (2014). Identification of two novel loss-of-function SIM1 mutations in two overweight children with developmental delay. *Obesity (Silver Spring), 22*(12), 2621-2624. doi: 10.1002/oby.20886

Myers, S., Burger, O., & Johns, S. E. (2016). Postnatal depression and reproductive success in modern, low-fertility contexts. *Evol Med Public Health, 2016*(1), 71-84. doi: 10.1093/emph/eow003

Nakamura, Y. (2009). DNA variations in human and medical genetics: 25 years of my experience. *J Hum Genet, 54*(1), 1-8.

Neel, J. V. (1962). Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? *Am J Hum Genet, 14*, 353-362.

Ng, M., Fleming, T., Robinson, M., Thomson, B., Graetz, N., Margono, C., . . . Gakidou, E. (2014). Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet, 384*(9945), 766-781. doi: http://dx.doi.org/10.1016/S0140-6736(14)60460-8

Nizard, J., Dommergues, M., & Clement, K. (2012). Pregnancy in a woman with leptin-receptor mutation. *New England Journal of Medicine, 366*(11), 1064-1065.

Northcott, H. C., & Wilson, D. M. (2001). The History of Dying and Death in Canada *Dying and Death in Canada* (pp. 14-34). Aurora, ON: Garamond Press.

Norton, H. L., Kittles, R. A., Parra, E., McKeigue, P., Mao, X., Cheng, K., . . . Shriver, M. D. (2007). Genetic evidence for the convergent evolution of light skin in Europeans and East Asians. *Mol Biol Evol, 24*(3), 710-722. doi: 10.1093/molbev/msl203

Obesity in Canada. (2011-06-23). Retrieved February 4, 2016, from http://www.phac-aspc.gc.ca/hp-ps/hl-mvs/oic-oac/abo-aut-eng.php

Ogden, C. L., Carroll, M. D., Kit, B. K., & Flegal, K. M. (2014). Prevalence of childhood and adult obesity in the United States, 2011-2012. *Jama, 311*(8), 806-814. doi: 10.1001/jama.2014.732

Oike, H., Oishi, K., & Kobori, M. (2014). Nutrients, Clock Genes, and Chrononutrition. *Curr Nutr Rep, 3*, 204-212. doi: 10.1007/s13668-014-0082-6

Oldknow, K. J., MacRae, V. E., & Farquharson, C. (2015). Endocrine role of bone: recent and emerging perspectives beyond osteocalcin. *J Endocrinol, 225*(1), R1-19. doi: 10.1530/JOE-14-0584

Orr, H. A. (2009). Fitness and its role in evolutionary genetics. *Nat Rev Genet, 10*(8), 531-539. doi: 10.1038/nrg2603

Oster, R. T., & Toth, E. L. (2009). Differences in the prevalence of diabetes risk-factors among First Nation, Metis and non-Aboriginal adults attending screening clinics in rural Alberta, Canada. *Rural Remote Health, 9*(2), 1170.

Oswal, A., & Yeo, G. S. (2007). The leptin melanocortin pathway and the control of body weight: lessons from human and murine genetics. *Obes Rev, 8*(4), 293-306. doi: 10.1111/j.1467-789X.2007.00378.x

Ozata, M., Ozdemir, I. C., & Licinio, J. (1999). Human leptin deficiency caused by a missense mutation: multiple endocrine defects, decreased sympathetic tone, and immune system dysfunction indicate new targets for leptin action, greater central than peripheral resistance to the effects of leptin, and spontaneous correction of leptin-mediated defects. *J Clin Endocrinol Metab, 84*(10), 3686-3695. doi: 10.1210/jcem.84.10.5999

Parra, E. J. (2007). Human pigmentation variation: evolution, genetic basis, and implications for public health. *Am J Phys Anthropol, Suppl 45*, 85-105. doi: 10.1002/ajpa.20727

Pausova, Z., Jomphe, M., Houde, L., Vezina, H., Orlov, S. N., Gossard, F., . . . Hamet, P. (2002). A genealogical study of essential hypertension with and without obesity in French Canadians. *Obes Res, 10*(6), 463-470. doi: 10.1038/oby.2002.64

Peplonska, B., Bukowska, A., & Sobala, W. (2015). Association of Rotating Night Shift Work with BMI and Abdominal Obesity among Nurses and Midwives. *PLoS One, 10*(7), e0133761. doi: 10.1371/journal.pone.0133761

Perry, G. H., Dominy, N. J., Claw, K. G., Lee, A. S., Fiegler, H., Redon, R., . . . Stone, A. C. (2007). Diet and the evolution of human amylase gene copy number variation. *Nat Genet, 39*(10), 1256-1260. doi: 10.1038/ng2123

Peters, J. (2014). The role of genomic imprinting in biology and disease: an expanding view. *Nat Rev Genet, 15*(8), 517-530. doi: 10.1038/nrg3766

Piche, M. E., Auclair, A., Harvey, J., Marceau, S., & Poirier, P. (2015). How to choose and use bariatric surgery in 2015. *Can J Cardiol, 31*(2), 153-166. doi: 10.1016/j.cjca.2014.12.014

Pigeyre, M., Yazdi, F. T., Kaur, Y., & Meyre, D. (2016). Recent progress in genetics, epigenetics and metagenomics unveils the pathophysiology of human obesity. *Clin Sci (Lond), 130*(12), 943-986. doi: 10.1042/CS20160136

Pond, C. (1998). *The Fats of Life*. Cambridge: Cambridge University Press.

Prentice, A. M., & Paul, A. A. (2000). Fat and energy needs of children in developing countries. *Am J Clin Nutr, 72*(5 Suppl), 1253s-1265s.

Prevention, C. f. D. C. a. (2016a, February 10, 2016). Health of Black or African American non-Hispanic Population. Retrieved February, 28, 2016, from http://www.cdc.gov/nchs/fastats/black-health.htm

Prevention, C. f. D. C. a. (2016b, February 10, 2016). Health of White non-Hispanic Population. Retrieved February 28, 2016, from http://www.cdc.gov/nchs/fastats/white-health.htm

Qi, Q., Chu, A. Y., Kang, J. H., Huang, J., Rose, L. M., Jensen, M. K., . . . Qi, L. (2014). Fried food consumption, genetic risk, and body mass index: gene-diet interaction analysis in three US cohort studies. *BMJ, 348*, g1610. doi: 10.1136/bmj.g1610

Qu, X., Huang, X., Jin, F., Wang, H., Hao, Y., Tang, T., & Dai, K. (2013). Bone mineral density and all-cause, cardiovascular and stroke mortality: a meta-analysis of prospective cohort studies. *Int J Cardiol, 166*(2), 385-393. doi: 10.1016/j.ijcard.2011.10.114

Quintana-Murci, L., Semino, O., Bandelt, H. J., Passarino, G., McElreavey, K., & Santachiara-Benerecetti, A. S. (1999). Genetic evidence of an early exit of Homo sapiens sapiens from Africa through eastern Africa. *Nat Genet, 23*(4), 437-441. doi: 10.1038/70550

Radovanovic, Z., Shah, N., & Behbehani, J. (1999). Prevalence and social correlates to consanguinity in Kuwait. *Ann Saudi Med, 19*(3), 206-210.

Rask-Andersen, M., Almen, M. S., & Schioth, H. B. (2015). Scrutinizing the FTO locus: compelling evidence for a complex, long-range regulatory context. *Hum Genet, 134*(11-12), 1183-1193. doi: 10.1007/s00439-015-1599-5

Ravussin, E., Valencia, M. E., Esparza, J., Bennett, P. H., & Schulz, L. O. (1994). Effects of a traditional lifestyle on obesity in Pima Indians. *Diabetes Care, 17*(9), 1067-1074.

Reddon, H., Gerstein, H. C., Engert, J. C., Mohan, V., Bosch, J., Desai, D., . . . Meyre, D. (2016). Physical activity and genetic predisposition to obesity in a multiethnic longitudinal study. *Sci Rep, 6*, 18672. doi: 10.1038/srep18672

Reich, D., Thangaraj, K., Patterson, N., Price, A. L., & Singh, L. (2009). Reconstructing Indian population history. *Nature, 461*(7263), 489-494. doi: 10.1038/nature08365

Rolland-Cachera, M.-F., Deheeger, M., Guilloud-Bataille, M., Avons, P., Patois, E., & Sempé, M. (2009). Tracking the development of adiposity from one month of age to adulthood. *Annals of Human Biology, 14*(3), 219-229. doi: 10.1080/03014468700008991

Rönn, T., Volkov, P., Davegårdh, C., Dayeh, T., Hall, E., Olsson, A. H., . . . Ling, C. (2013). A Six Months Exercise Intervention Influences the Genome-wide DNA Methylation Pattern in Human Adipose Tissue. *PLoS Genet, 9*(6), e1003572. doi: 10.1371/journal.pgen.1003572

Ruano, E. G., Canivell, S., & Vieira, E. (2014). REV-ERB ALPHA polymorphism is associated with obesity in the Spanish obese male population. *PLoS One, 9*(8), e104065. doi: 10.1371/journal.pone.0104065

Rubinstein, S., & Caballero, B. (2000). Is Miss America an undernourished role model? *Jama, 283*(12), 1569.

Sabeti, P. C., Varilly, P., Fry, B., Lohmueller, J., Hostetter, E., Cotsapas, C., . . . Stewart, J. (2007). Genome-wide detection and characterization of positive selection in human populations. *Nature, 449*(7164), 913-918. doi: 10.1038/nature06250

Saeed, S., Bonnefond, A., Manzoor, J., Shabir, F., Ayesha, H., Philippe, J., . . . Froguel, P. (2015). Genetic variants in LEP, LEPR, and MC4R explain 30% of severe obesity in children from a consanguineous population. *Obesity (Silver Spring), 23*(8), 1687-1695. doi: 10.1002/oby.21142

Sahani, R. (2013). Foraging to settled life: a comparative study of anthropometry and nutrition of Onges of Little Andaman Island. *Homo, 64*(5), 391-397. doi: 10.1016/j.jchb.2013.07.003

Saleh, R. A., Agarwal, A., Nelson, D. R., Nada, E. A., El-Tonsy, M. H., Alvarez, J. G., . . . Sharma, R. K. (2002). Increased sperm nuclear DNA damage in normozoospermic infertile men: a prospective study. *Fertil Steril, 78*(2), 313-318.

Samaan, Z., Anand, S. S., Zhang, X., Desai, D., Rivera, M., Pare, G., . . . Meyre, D. (2013). The protective effect of the obesity-associated rs9939609 A variant in fat mass- and obesity-associated gene on depression. *Mol Psychiatry, 18*(12), 1281-1286. doi: 10.1038/mp.2012.160

Samaan, Z., Lee, Y. K., Gerstein, H. C., Engert, J. C., Bosch, J., Mohan, V., . . . Epi, D. G. I. (2015). Obesity genes and risk of major depressive disorder in a multiethnic population: a cross-sectional study. *J Clin Psychiatry, 76*(12), e1611-1618. doi: 10.4088/JCP.14m09720

Sankararaman, S., Mallick, S., Patterson, N., & Reich, D. (2016). The Combined Landscape of Denisovan and Neanderthal Ancestry in Present-Day Humans. *Curr Biol, 26*(9), 1241-1247. doi: 10.1016/j.cub.2016.03.037

Sauna, Z. E., & Kimchi-Sarfaty, C. (2011). Understanding the contribution of synonymous mutations to human disease. *Nat Rev Genet, 12*(10), 683-691. doi: 10.1038/nrg3051

Scannell Bryan, M., Argos, M., Pierce, B., Tong, L., Rakibuz-Zaman, M., Ahmed, A., . . . Ahsan, H. (2014). Genome-wide association studies and heritability estimates of body mass index related phenotypes in Bangladeshi adults. *PLoS One, 9*(8), e105062. doi: 10.1371/journal.pone.0105062

Scheer, F. A., Morris, C. J., & Shea, S. A. (2013). The internal circadian clock increases hunger and appetite in the evening independent of food intake and other behaviors. *Obesity (Silver Spring), 21*(3), 421-423. doi: 10.1002/oby.20351

Scrimshaw, N. S. (1990). Energy cost of communicable diseases in infancy and childhood. In B. Schurch & N. S. Scrimshaw (Eds.), Activity, Energy Expenditure and Energy Requirements of Infants and Children. Lausanne, Switzerland: IDECG. Retrieved from

http://archive.unu.edu/unupress/food2/UID09E/UID09E0T.HTM#energy%20cost%20of%20communicable%20diseases%20in%20infancy%20and%20childhood.

Seli, E., Babayev, E., Collins, S. C., Nemeth, G., & Horvath, T. L. (2014). Minireview: Metabolism of female reproduction: regulatory mechanisms and clinical implications. *Mol Endocrinol, 28*(6), 790-804. doi: 10.1210/me.2013-1413

Sellayah, D., Cagampang, F. R., & Cox, R. D. (2014). On the evolutionary origins of obesity: a new hypothesis. *Endocrinology, 155*(5), 1573-1588. doi: 10.1210/en.2013-2103

Seshadri, K. G. (2012). Obesity: A Venusian story of Paleolithic proportions. *Indian J Endocrinol Metab, 16*(1), 134-135. doi: 10.4103/2230-8210.91208

Shewan, L. (2006). The Venus figurines. *Int J Cardiol, 113*(3), 439. doi: 10.1016/j.ijcard.2005.11.063

Shungin, D., Winkler, T. W., Croteau-Chonka, D. C., Ferreira, T., Locke, A. E., Magi, R., . . . Mohlke, K. L. (2015). New genetic loci link adipose and insulin biology to body fat distribution. *Nature, 518*(7538), 187-196. doi: 10.1038/nature14132

Sidner, S. (2008). Brothers share wife to secure family land. *CNN*. http://www.cnn.com/2008/WORLD/asiapcf/10/24/polygamy.investigation/index.html

Sidossis, L., & Kajimura, S. (2015). Brown and beige fat in humans: thermogenic adipocytes that control energy and glucose homeostasis. *J Clin Invest, 125*(2), 478-486. doi: 10.1172/JCI78362

Simonti, C. N., Vernot, B., Bastarache, L., Bottinger, E., Carrell, D. S., Chisholm, R. L., . . . Capra, J. A. (2016). The phenotypic legacy of admixture between modern humans and Neandertals. *Science, 351*(6274), 737-741. doi: 10.1126/science.aad2149

Singh, D. (2002). Female mate value at a glance: relationship of waist-to-hip ratio to health, fecundity and attractiveness. *Neuro Endocrinol Lett, 23 Suppl 4*, 81-91.

Singh, D., Renn, P., & Singh, A. (2007). Did the perils of abdominal obesity affect depiction of feminine beauty in the sixteenth to eighteenth century British literature? Exploring the health and beauty link. *Proc Biol Sci, 274*(1611), 891-894. doi: 10.1098/rspb.2006.0239

Skinner, A. C., Perrin, E. M., & Skelton, J. A. (2016). Prevalence of obesity and severe obesity in US children, 1999-2014. *Obesity (Silver Spring), 24*(5), 1116-1123. doi: 10.1002/oby.21497

Skinner, M. K. (2011). Environmental epigenetic transgenerational inheritance and somatic epigenetic mitotic stability. *Epigenetics, 6*(7), 838-842. doi: 10.4161/epi.6.7.16537

Smith, G. D., Lawlor, D. A., Timpson, N. J., Baban, J., Kiessling, M., Day, I. N., & Ebrahim, S. (2009). Lactase persistence-related genetic variant: population substructure and health outcomes. *Eur J Hum Genet, 17*(3), 357-367. doi: 10.1038/ejhg.2008.156

Smith, M. R., Burgess, H. J., Fogg, L. F., & Eastman, C. I. (2009). Racial differences in the human endogenous circadian period. *PLoS One, 4*(6), e6014. doi: 10.1371/journal.pone.0006014

Soubry, A., Murphy, S. K., Wang, F., Huang, Z., Vidal, A. C., Fuemmeler, B. F., . . . Hoyo, C. (2015). Newborns of obese parents have altered DNA methylation patterns at imprinted genes. *Int J Obes (Lond), 39*(4), 650-657. doi: 10.1038/ijo.2013.193

Speakman, J. R. (2007). A nonadaptive scenario explaining the genetic predisposition to obesity: the "predation release" hypothesis. *Cell Metab, 6*(1), 5-12. doi: 10.1016/j.cmet.2007.06.004

Speakman, J. R., Djafarian, K., Stewart, J., & Jackson, D. M. (2007). Assortative mating for obesity. *Am J Clin Nutr, 86*(2), 316-323.

Speakman, J. R., & Westerterp, K. R. (2013). A mathematical model of weight loss under total starvation: evidence against the thrifty-gene hypothesis. *Dis Model Mech, 6*(1), 236-251. doi: 10.1242/dmm.010009

Spritz, R. A., Bailin, T., Nicholls, R. D., Lee, S. T., Park, S. K., Mascari, M. J., & Butler, M. G. (1997). Hypopigmentation in the Prader-Willi syndrome correlates with P gene deletion but not with haplotype of the hemizygous P allele. *Am J Med Genet, 71*(1), 57-62.

Starling, A. P., & Stock, J. T. (2007). Dental indicators of health and stress in early Egyptian and Nubian agriculturalists: a difficult transition and gradual recovery. *Am J Phys Anthropol, 134*(4), 520-528. doi: 10.1002/ajpa.20700

Steckel, R. H., & Jensen, R. A. (1986). New evidence on the causes of slave and crew mortality in the Atlantic slave trade. *J Econ Hist, 46*(1), 57-77.

Stoger, R. (2008). The thrifty epigenotype: an acquired and heritable predisposition for obesity and diabetes? *Bioessays, 30*(2), 156-166. doi: 10.1002/bies.20700

Stutzmann, F., Vatin, V., Cauchi, S., Morandi, A., Jouret, B., Landt, O., . . . Meyre, D. (2007). Non-synonymous polymorphisms in melanocortin-4 receptor protect against obesity: the two facets of a Janus obesity gene. *Hum Mol Genet, 16*(15), 1837-1844. doi: 10.1093/hmg/ddm132

Sugiyama, L. S. (2004). Is beauty in the context-sensitive adaptations of the beholder? *Evolution and Human Behavior, 25*(1), 51-62. doi: 10.1016/s1090-5138(03)00083-7

Suviolahti, E., Oksanen, L. J., xD, hman, M., Cantor, R. M., Ridderstr, . . . ivi. (2003). The SLC6A14 gene shows evidence of association with obesity. *J Clin Invest, 112*(11), 1762-1772. doi: 10.1172/JCI17491

Suzuki, M. M., & Bird, A. (2008). DNA methylation landscapes: provocative insights from epigenomics. *Nat Rev Genet, 9*(6), 465-476. doi: 10.1038/nrg2341

Theorell-Haglow, J., Berglund, L., Berne, C., & Lindberg, E. (2014). Both habitual short sleepers and long sleepers are at greater risk of obesity: a population-based 10-year follow-up in women. *Sleep Med, 15*(10), 1204-1211. doi: 10.1016/j.sleep.2014.02.014

Tishkoff, S. A., Reed, F. A., Ranciaro, A., Voight, B. F., Babbitt, C. C., Silverman, J. S., . . . Deloukas, P. (2007). Convergent adaptation of human lactase persistence in Africa and Europe. *Nat Genet, 39*(1), 31-40. doi: 10.1038/ng1946

Tobi, E. W., Goeman, J. J., Monajemi, R., Gu, H., Putter, H., Zhang, Y., . . . Heijmans, B. T. (2014). DNA methylation signatures link prenatal famine exposure to growth and metabolism. *Nat Commun, 5*, 5592. doi: 10.1038/ncomms6592

Unger, M. (1986). The Prisoner's First Encounter With Auschwitz. *Holocaust and Genocide Studies, 1*(2), 279-295.

Ussar, S., Griffin, N. W., Bezy, O., Fujisaka, S., Vienberg, S., Softic, S., . . . Kahn, C. R. (2015). Interactions between Gut Microbiota, Host Genetics and Diet Modulate the Predisposition to Obesity and Metabolic Syndrome. *Cell Metab, 22*(3), 516-530. doi: 10.1016/j.cmet.2015.07.007

Valera, B., Sohani, Z., Rana, A., Poirier, P., & Anand, S. S. (2015). The ethnoepidemiology of obesity. *Can J Cardiol, 31*(2), 131-141. doi: 10.1016/j.cjca.2014.10.005

Wagner, I. V., Sabin, M. A., Pfaffle, R. W., Hiemisch, A., Sergeyev, E., Korner, A., & Kiess, W. (2012). Effects of obesity on human sexual development. *Nat Rev Endocrinol, 8*(4), 246-254. doi: 10.1038/nrendo.2011.241

Weiser, M. J., Butt, C. M., & Mohajeri, M. H. (2016). Docosahexaenoic Acid and Cognition throughout the Lifespan. *Nutrients, 8*(2), 99. doi: 10.3390/nu8020099

Wells, J. C. (2006). The evolution of human fatness and susceptibility to obesity: an ethological approach. *Biol Rev Camb Philos Soc, 81*(2), 183-205. doi: 10.1017/S1464793105006974

Wells, J. C. (2012). The evolution of human adiposity and obesity: where did it all go wrong? *Dis Model Mech, 5*(5), 595-607. doi: 10.1242/dmm.009613

Wermter, A. K., Scherag, A., Meyre, D., Reichwald, K., Durand, E., Nguyen, T. T., . . . Bronner, G. (2008). Preferential reciprocal transfer of paternal/maternal DLK1 alleles to obese children: first evidence of polar overdominance in humans. *Eur J Hum Genet, 16*(9), 1126-1134. doi: 10.1038/ejhg.2008.64

Westerlund, A., Bottai, M., Adami, H. O., Bellocco, R., Nyren, O., Akerstedt, T., & Lagerros, Y. T. (2014). Habitual sleep patterns and the distribution of body mass index: cross-sectional findings among Swedish men and women. *Sleep Med, 15*(10), 1196-1203. doi: 10.1016/j.sleep.2014.06.012

Wetsman, A., & Marlowe, F. (1999). How universal are preferences for female waist-to-hip ratio? Evidence from the Hadza of Tanzania. *Evolution and Human Behavior, 20*, 219-228.

Whitfield, J. (2003). Fat pigs ape obese humans. *Nature*. http://www.nature.com/news/2003/030806/full/news030804-5.html

Wilcox, C. (2013). The Worst Marine Invasion Ever. *Slate*. http://www.slate.com/articles/health_and_science/science/2013/07/lionfish_invasion_the_invasive_fish_are_eating_so_many_native_species_that.single.html

Williams, A. L., Jacobs, S. B., Moreno-Macias, H., Huerta-Chagoya, A., Churchhouse, C., Marquez-Luna, C., . . . Consortium, S. T. D. (2014). Sequence variants in SLC16A11 are a common risk factor for type 2 diabetes in Mexico. *Nature, 506*(7486), 97-101. doi: 10.1038/nature12828

Williams, R. C., Long, J. C., Hanson, R. L., Sievers, M. L., & Knowler, W. C. (2000). Individual estimates of European genetic admixture associated with lower body-mass index, plasma glucose, and prevalence of type 2 diabetes in Pima Indians. *Am J Hum Genet, 66*(2), 527-538. doi: 10.1086/302773

Wu, J., Bostrom, P., Sparks, L. M., Ye, L., Choi, J. H., Giang, A. H., . . . Spiegelman, B. M. (2012). Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. *Cell, 150*(2), 366-376. doi: 10.1016/j.cell.2012.05.016

Wyse, C. A. (2012). Does human evolution in different latitudes influence susceptibility to obesity via the circadian pacemaker?: migration and survival of the fittest in the modern age of lifestyle-induced circadian desynchrony. *Bioessays, 34*(11), 921-924. doi: 10.1002/bies.201200067

Yang, B., Sun, H., Wan, Y., Wang, H., Qin, W., Yang, L., . . . Yao, B. (2012). Associations between testosterone, bone mineral density, vitamin D and semen quality in fertile and infertile Chinese men. *Int J Androl, 35*(6), 783-792. doi: 10.1111/j.1365-2605.2012.01287.x

Yang, J., Loos, R. J., Powell, J. E., Medland, S. E., Speliotes, E. K., Chasman, D. I., . . . Visscher, P. M. (2012). FTO genotype is associated with phenotypic variability of body mass index. *Nature, 490*(7419), 267-272. doi: 10.1038/nature11401

Ye, C., Xu, M., Wang, S., Jiang, S., Chen, X., Zhou, X., & He, R. (2016). Decreased Bone Mineral Density Is an Independent Predictor for the Development of Atherosclerosis: A Systematic Review and Meta-Analysis. *PLoS One, 11*(5), e0154740. doi: 10.1371/journal.pone.0154740

Yu, D. W., & Shepard, G. H., Jr. (1998). Is beauty in the eye of the beholder? *Nature, 396*(6709), 321-322. doi: 10.1038/24512

Zarrei, M., MacDonald, J. R., Merico, D., & Scherer, S. W. (2015). A copy number variation map of the human genome. *Nat Rev Genet, 16*(3), 172-183. doi: 10.1038/nrg3871

Zerjal, T., Xue, Y., Bertorelle, G., Wells, R. S., Bao, W., Zhu, S., . . . Tyler-Smith, C. (2003). The genetic legacy of the Mongols. *Am J Hum Genet, 72*(3), 717-721. doi: 10.1086/367774

APPENDIX A: SEARCH KEYWORDS

The following is a non-exhaustive list of terms that were used to build hypotheses about the evolutionary origins of obesity. Searches were conducted in PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and supplanted with general Google searches (https://www.google.ca) where necessary.

evolution AND obesity
benefits AND (adipos* OR adipose tissue OR fat)
fat AND human survival
fat AND reproductive success
- leptin fertility human
- anorexia infertility
- anorexia sterility
- obesity male female negative
- males underweight infertility
- obesity male fertility

expensive tissue obesity
thrifty genotype hypothesis
in utero reprogramming
gene pleiotropy AND obesity
- obesity AND asthma
- FTO AND depression
- FTO AND pleiotropy
- obesity AND psych* disorders
- prostate cancer AND obesity
- obesity AND immunity
- POMC obesity hair skin colour
- obesity pleiotropy skin pigmentation
- obesity skin hair mutation
- hair pigmentation evolution
- pigmentation AND obesity pleiotropy
- leptin deficiency AND mood
- leptin obesity depression
- obesity AND infection
- obesity AND childhood infection
- leptin AND infection
- infection obesity climate
- bone AND obesity
- bone density AND obesity

- bone metabolism AND obesity
- bone mineral density AND obesity
- bone mineral density AND evolution
- bone mineral density AND comborbidity
- bone mineral density AND mortality
- brown adipose tissue AND obesity
- brown adipose tissue climate
- brown adipose tissue environment
- brown adipose tissue season variation
- brown adipose tissue latitude
- brown adipose tissue ethnic obesity
- brown adipose tissue cold adaptation human
- brown adipose tissue cold
- sleep obesity body mass index
- clock light obesity
- habit sleep duration body mass index
- tau circadian rhythm obesity
- period 2 obesity
- PER2 obesity
- night light weight gain
- ethnicty AND circadian clock
- shift work obesity
- race obesity shift work
- genetic differences human circadian clock
- circadian clock thermogenesis

fat storage animals

- pets obesity
- obesity fish
- obesity vertebrates
- obesity animals
- obesity flies
- obesity drosophilia
- MC4R polar bear

primates AND lean AND gene

- apes AND lean AND gene
- ASIP AND obesity
- primate obesity gene
- primate weight predation
- wild primates body weight
- non human primate AND obesity

evolutionary forces

- natural selection
- sexual selection human

alu elements obesity

copy number variation AND obesity
microsatellite AND obesity
sex chromosome AND obesity
Y chromosome AND obesity
obesity AND gene imprinting
gene imprinting AND metabolism
inherit* microbiome
epigenetics AND human obesity
    exercise epigeneitcs obesity
    epigenetic obesity diet
    DNA methylation AND body mass index
    epigenetic inheritance
    epigenome inheritance
    evolutionary function of epigenetics
    causes of methylation
    conception obesity epigenetics
    starvation obesity epigenetics
    famine obesity epigenetics
    retrosposon methylation human
neandertal AND obesity
    neandertal imbreeding
    homosapiens sexual selection
    hominin sexual selection
obesity AND palaeolithic
    venus obesity
hunter gatherer transition obesity
subsistence pattern obesity
urban lifestyle obesity
physical activity obesity
famine fertility
Jewish obesity
    Jewish metabolic disease
    obesity Holocaust survivors
    eating concentration camp
    eating war prisoner
    conditions concentration camp
    Holocaust survivor weight
    posttraumatic stress disorder epigenetic
slavery survivors metabolic syndrome
residential schools obesity
    residential schools survivors
    starvation aboriginal Canadians
    residential schools metabolic disease
    residential school survivors health

maltreatment Aboriginals obesity
Metis slavery colonialism
indigenous genes metis disease
Aboriginal genocide Canada
overweight obesity Aboriginal
European Aboriginal admixture
trans Atlantic slave
African slave trade rape
African American descendants of slaves
genome native Africans African Americans
gene native Africans African Americans
Nauru evolution
Nauru obesity
Nauru Japan obesity
Andaman island obesity
Pacific island obesity
Micronesia obesity
colonization obesity
colonialism obesity
Westernization obesity
obesity inbreeding
consanguinity obesity
Saguenay-Lac-St-Jean AND obesity
obesity rates Saguenay-Lac-St-Jean
migration consanguinty disease
Amish obesity diabetes
Hutterite disease
polygamy disease
polyandry disease
mate choice obesity
assortative mating primates
epidemics food access
Chinese famine obesity