Preventing Obesity in the Next Generation Today: An Epigenetic Approach

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Abstract: Researchers previously believed that genes were the primary source of inheritance of traits. However, new research has shown that many traits have low heritability. Specifically, obesity, a disorder affecting nearly a third of the global population, has little genetic heritability. Furthermore, researchers now believe that epigenetics (heritable changes in gene expression that do not involve changing the DNA sequence) is the missing link between the inheritance of obesity and our environmental stimuli. Research has shown that obese prenatal conditions and poor dietary choices are strongly correlated with differentiated epigenetic markers that, when inherited, can increase the child's chances of developing obesity later in life and lowering their well-being. Furthermore, potential parents ought to conserve a healthy epigenome by pursuing a healthy BMI so that their children are not restricted by their parents' lifestyles. This normative claim is justified using intergenerational equity principles, which suggests that the current generation must conserve the environment, specifically the epigenetic environment, so that the decisions previous generations make do not hinder future generations. Finally, preliminary research has shown that potential parents can practically conserve a healthy epigenome for the next generation by adopting a variety of behaviors.

Obesity is a heritable pandemic that affects around 650 million people worldwide.[1] It can augment the risk of other life-threatening diseases, lower life expectancy, and reduce quality of life. New research has been published to suggest that parents' lifestyle choices can be linked to the likelihood that their children will develop obesity later in life through epigenetic inheritance. Thus, there seems to be a moral responsibility on potential parents to lower their offspring's risk of developing obesity. In this paper, I argue that potential parents ought to pursue a lifestyle that conserves a healthy epigenome so that the next generation is not hindered by the behaviors of the previous generation. My strategy is as follows: first, I discuss how obesity has a low heritability and how epigenetics has been cast as the missing link to inheritance of obesity. Second, I explore research indicating that pre-natal conditions and parental diets alter epigenetic markers that can be inherited by offspring. Furthermore, these epigenetic markers have been significantly associated with higher birthweight and increased risk of obesity in the offspring's adulthood. Third, I justify my normative claim using intergenerational equity principles and criteria. Finally, I discuss practical applications of this claim and how recent experiments demonstrate that

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[1] "WHO | Obesity and Overweight." *WHO*. Last modified February, 2018, http://www.who.int/mediacentre/factsheets/fs311/en/.

these applications can reduce children's risk of developing obesity.[2]

To begin, research has shown that obesity has a low heritability. Heritability can be defined as the fraction of visible, phenotypic variation in a certain trait within a population due to genetic variation between individuals.[3] Therefore, traits with high heritability tend to show little phenotypic variation from genetic differences, and traits with low heritability tend to show large variation. Current literature suggests that approximately twenty percent of our BMI variation can be associated with genetic differences, leaving a large gap in the explanation of why certain individuals are at a larger risk of developing obesity than others.[4]

Recently, epigenetics has been described as the missing link between our environmental factors and the heritability of obesity. As a whole, epigenetics is a broad field of study that can be defined as "the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states".[5] Thus, epigenetics alters phenotypic properties by altering transcriptional and translational abilities of genes, not the genetic code itself. There are many epigenetic inheritance systems known to impact transcription and translation: self-sustaining loops, chromatin silencing, RNA interference (RNAi), and structural templating.[6] These mechanisms are extremely sensitive to environmental changes (i.e. lifestyle choices) and can be inherited by our offspring.

The most extensively studied epigenetic mechanism is DNA methylation, which falls under chromatin silencing.[7] Here, a methyl group is added to the CG dinucleotide (CpG site) of DNA.[8] When a gene is densely methylated, its propensity to be transcribed drops, effectively silences the gene and altering the phenotype of an individual. Recent research has shown that obese children possess significantly different methylation patterns to non-obese children. [9] While the causation between these methylation pattern differs and obesity has not yet been well established, the strong correlation can still be used as a biomarker to assess obesity risk in offspring. Due to this strong correlation, the remainder of this paper will draw from research on DNA methylation patterns to show associations between parental behaviors and the probability that their offspring will develop obesity.

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[2] An objection may be presented that some of the practical applications discussed may only be accessible by people of higher socioeconomic status. I will only be discussing the biology of these applications, and the in-depth concerns about socioeconomics and accessibility are not within the scope of this paper.

[3] Eva Jablonka, Marion J Lamb, and Anna Zeligowski, *Evolution in Four Dimensions: Genetic, Epigenetic, Behavioral, and Symbolic Variation in the History of Life*, 2nd ed. (Cambridge: MIT Press, 2014), 357.

[4] Adam E. Locke et al., "Genetic Studies of Body Mass Index Yield New Insights for Obesity Biology," *Nature* 518, no. 7538 (February 12, 2015): 197–206, https://doi.org/10.1038/nature14177.

[5] Bird, Adrian. "Perceptions of Epigenetics." *Nature* 447 (May 23, 2007): 396-398. https://doi.org/10.1038/nature05913.

[6] Jablonka, Lamb, and Zeligowski, *Evolution in Four Dimensions: Genetic, Epigenetic, Behavioral, and Symbolic Variation in the History of Life*, 111-153.

[7] Jablonka, Lamb, and Zeligowski, 126.

[8] Kara Wegermann and Cynthia A. Moylan, "Epigenetics of Childhood Obesity," *Current Pediatrics Reports* 5, no. 3 (September 1, 2017): 111–17, https://doi.org/10.1007/s40124-017-0133-8.

[9] Xu Ding et al., "Genome-Wide Screen of DNA Methylation Identifies Novel Markers in Childhood Obesity," *Gene* 566, no. 1 (July 15, 2015): 74–83, https://doi.org/10.1016/j.gene.2015.04.032.

The first major area of methylation inheritance associated with childhood obesity occurs in pre-natal conditions. There are already many known substances and behaviors mothers that must avoid, such as drinking, smoking, and stress, in order to ensure the healthy development of her child. Similarly, there are pre-natal conditions that can lead to the inheritance of methylated genes associated with increased risk of obesity. Certain activities that mothers partake in during pregnancy may methylate certain genes, and they can be passed down to the fetus through the umbilical cord. According to one study, "differential methylation of 23 genes in umbilical cord blood and placenta explained seventy to eighty percent of variation in birth weight, more than was explained by the corresponding gene expression profiles." [10] Consequently, high birth weights have also been linked to increased risk of obesity in adult life. [11] Again, while the causation of these methylation patterns has not been confirmed, this strong correlation can be used as a biomarker for the offspring developing obesity in adulthood.

Maternal obesity during pregnancy has been shown to affect methylation patterns. Methylation, as mentioned before, is extremely sensitive to its environment. Thus, maternal cells that have been exposed to an unhealthy environment due to an excess of surrounding adipose (fat) tissue may methylate certain genes to adjust to the metabolic change. These methylation patterns, if present during pregnancy, can be inherited by the developing fetus through cord blood. Recent research suggests that obese pre-natal environments have been linked with methylation changes in genes related to embryonic development, growth, and metabolic disease in the offspring.[12]

A specific example of obese pre-natal conditions affecting fetal growth can be seen when studying the Insulin Growth Factor 2 (IGF2) gene. IGF2 is an imprinted gene encoding for fetal growth factors. Thus, this gene is mostly active during fetal development. A recent study found significant IGF2 methylation reduction in cord blood in mothers with BMI's greater than 30, resulting in elevated IGF2 protein levels within the umbilical cord. Furthermore, these increased IGF2 protein concentrations were then associated with increased birth weight.[13] Based on this data, a clear link can be shown between maternal obesity during pregnancy and an overweight phenotype in offspring. This phenotype is created before any lifestyle choices are made by the child themselves.

The second major area of methylation inheritance can be derived from the germ line (cellular lineage that develop into sperm and egg cells) . Before, only maternal lifestyle choices were correlated with increased obesity risk in children, but now paternal lifestyle choices can also be linked to methylation changes. Because the father is not directly connected to his offspring during fetal development, the only way for his lifestyle choices to impact his offspring is through the epigenetic markers of his sperm. Methylation patterns are quite stable in somatic cells, but previous research has suggested that during sexual

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[10] Wegermann and Moylan. "Epigenetics of Childhood Obesity." 111–17.

[11] I. W. Johnsson et al., "A High Birth Weight Is Associated with Increased Risk of Type 2 Diabetes and Obesity," *Pediatric Obesity* 10, no. 2 (April 1, 2015): 77–83, https://doi.org/10.1111/ijpo.230.

[12] Susan J. van Dijk et al., "Recent Developments on the Role of Epigenetics in Obesity and Metabolic Disease," *Clinical Epigenetics* 7 (July 11, 2015): 66, https://doi.org/10.1186/s13148-015-0101-5..

[13] Cathrine Hoyo et al., "Association of Cord Blood Methylation Fractions at Imprinted Insulin-like Growth Factor 2 (IGF2), Plasma IGF2, and Birth Weight," *Cancer Causes & Control* 23, no. 4 (April 2012): 635–45, https://doi.org/10.1007/s10552-012-9932-y.

reproduction there is a reprogramming of these epigenetic markers.[14]

Several mammalian studies have been conducted to show that diet changes can impact methylation patterns in the germ line and can be inherited by offspring. Compared to human studies, where there are many lifestyle choices that could impact these epigenetic markers, animal studies provide a more controlled environment to detect epigenetic changes.[15] In one experiment, high-fat diets in female mice were shown to alter methylation patterns of metabolic genes in their oocytes and even their offspring's oocytes and liver cells.[16] Other experiments showed unique methylation of sperm in certain developmental genes when paternal mice were fed a low-protein diet. Furthermore, an approximate twenty percent difference in methylation patterns were found in liver cells of offspring from these mice with low-protein diets compared to a control diet, suggesting that these methylation patterns may have been inherited from the germ line.[17] These experiments show that a poor parental diet can create heritable and harmful consequences for the metabolic rates of their offspring.

Due to the heritability of diet induced methylation changes, these epigenetic markers can increase risk of obesity in offspring. In an experiment conducted by Peter Huypens and his team, mice were fed either a high-fat diet, low-fat diet, or standard mouse diet for six weeks. Gametes were then extracted from these groups and then in vitro fertilized (IVF), meaning they were manually combined to form a zygote in a laboratory dish. These zygotes were then placed into a healthy surrogate mother. The IVF was done to eliminate the possibility of pre-natal conditions of the obese mothers impacting the offspring's susceptibility of developing obesity. Adult offspring were then fed high-fat diets, and the researchers found that offspring from two obese parents (both on high-fat diets) were prone to gaining more weight; while offspring from two lean parents gained the least weight on the high-fat diet.[18] Based on the results of this experiment and of the previously discussed germ line studies, methylation inheritance and other epigenetic mechanism have been shown to directly impact the metabolic rate of offspring.

Up until now, I have explored epigenetic research explaining the prevalence of obesity today. Because of the severe consequences of this disease, there is a need to prevent future generations from dealing with these burdens. People with obesity are at a significantly higher risk for several other diseases including heart disease, Type two diabetes, gallbladder disease, some types of cancer, and even mental health disorders significantly increas-

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[14] Suhua Feng, Steven E. Jacobsen, and Wolf Reik, "Epigenetic Reprogramming in Plant and Animal Development," *Science* 330, no. 6004 (2010): 622–27.

[15] Van Dijk, "Recent Developments on the Role of Epigenetics in Obesity and Metabolic Disease." 66.

[16] Zhao-Jia Ge et al., "DNA Methylation in Oocytes and Liver of Female Mice and Their Offspring: Effects of High-Fat-Diet–Induced Obesity," *Environmental Health Perspectives* 122, no. 2 (February 2014): 159–64, https://doi.org/10.1289/ehp.1307047.

[17] Benjamin R. Carone et al., "Paternally-Induced Transgenerational Environmental Reprogramming of Metabolic Gene Expression in Mammals," *Cell* 143, no. 7 (December 23, 2010): 1084–96, https://doi.org/10.1016/j.cell.2010.12.008.

[18] Peter Huypens et al., "Epigenetic Germline Inheritance of Diet-Induced Obesity and Insulin Resistance," *Nature Genetics* 48, no. 5 (May 2016): 497, https://doi.org/10.1038/ng.3527.

ing the chances of a lower quality of life.[19] While many may assume that obese individuals are fully responsible for their physical well-being, we have explored an overwhelming amount of research suggesting that one's susceptibility to developing obesity can be associated with parental lifestyle choices before their birth. Thus, a moral responsibility should be placed on parents to prevent their children from facing the consequences of obesity.

Parents ought to pursue a lifestyle that conserves a healthy epigenome for their children. This will be justified based on an intergenerational equity argument. Intergenerational equity deals with conflicting interests between the current generation and future generations. Typically, this philosophical approach pertains to environmental issues. For example, our current generation's desire to travel comfortably places a burden on future generations due to an increase in carbon dioxide emissions. In essence, intergenerational equity argues that, "each generation is considered a custodian of the planet for further generations".[20] Because intergenerational equity's focus on conflict between current generations and future ones, I will explore more deeply how its principles play a role in epigenetic inheritance.

To resolve these conflicting interests, intergenerational equity creates normative claims for the current, living generation to follow. Edith Brown Weiss, a leading theorist in intergenerational equity, claims that there are three normative principles for current generations. The first states that current generations ought to conserve natural and cultural resources for the next generation. This should be done so that future generations are not restricted to solving problems which arise from a lack of resources at their disposal due to previous generations' wastefulness. The second claim advocates that each generation should maintain the quality of the planet so that each new generation inherits the planet in no worse a condition than it was received. The third claim argues that the current generation ought to provide members of the next generation with equitable rights to legacy. These three normative principles are created based on four criteria: they must not restrict the current generation from using the necessary resources to meet their current needs; they must predict the desires and ambitions of future generations; they should be clear in their solutions to current problems, and they must be shared by different cultural traditions and accepted by different economic and political systems.[21] Overall, much of intergenerational equity's normative claims focus on the conservation of resources such that there is equity between generations to carry out their lives in ways that are sustainable yet not limiting.

The normative claims of intergenerational equity can be used to justify the current issue of epigenetic inheritance of increased risk of obesity by extension of the second claim. The claim deals with maintaining the quality of the planet for future generations, which includes the landscape and life. As the future generation will be part of the life on

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[19] "Health Risks of Being Overweight | NIDDK." National Institute of Diabetes and Digestive and Kidney Diseases. https://www.niddk.nih.gov/health-information/weight-management/health-risks-overweight.

[20] Mark A. Rothstein, Yu Cai, and Gary E. Marchant, "THE GHOST IN OUR GENES: LEGAL AND ETHICAL IMPLICATIONS OF EPIGENETICS," *Health Matrix* (Cleveland, Ohio : 1991) 19, no. 1 (2009): 1–62.

[21] Edith Brown Weiss, "In Fairness To Future Generations and Sustainable Development," American University International Law 8, no. 1 (1992): 19–26.

this planet, avoiding environmental harms that could impact their epigenome should be avoided. Mark Rothstein writes that "[i]f humankind has a responsibility to future generations to refrain from activities that cause environmental harms to the planet, including damaging current and future generations of wildlife, then it follows that the responsibility also extends to environmental harms that could damage the genomes and epigenomes of future generations of humans."[22] Thus, based on the research previously presented, parental diets and pre-natal conditions must be modified so that the epigenome is conserved for the following generation so that it does hinder their opportunities in life.

It is necessary to mention that the epigenome should be conserved, not improved, to avoid presenting a eugenic claim. Eugenics, known as the Original Sin of modern genetics, was first introduced by Sir Francis Galton. He declared that eugenics was a humane approach to improving humanity by selectively breeding mentally superior individuals with those of similar traits. He proposed this act with the main goal of increasing the genetically well-endowed and decreasing the genetically inferior.[23] These could easily be applied to epigenetics as well. If eugenic ideals were to be placed into this intergenerational conflict, parents should seek the healthiest diets and best pre-natal conditions to ensure the fittest methylation patterns for their children. This allows for the parents of children who are susceptible to congenital obesity to be easily discriminated against based on factors that are out of their control. Epigenetics markers can be altered and reversed to some extent, which we will explore later, but creating the healthiest possible generation will create a stigma against the parents who cannot foster these conditions during pregnancy. People would assume that those parents did not care about the well-being of their children instead of understanding that one of the parents may carry a genetic disorder related to carrying excess adipose tissue. Thus, parents should maintain a healthy, not superior, epigenome for their children.

In compliance with the criteria of principles of intergenerational equity, there should exist some practical application to this claim that parents should conserve a healthy epigenome for the next generation. Additionally, as stated before, this practical application should have the potential to exist in multiple cultural traditions under a variety of economic and political conditions. Much of the research presented focuses on how adipose tissue of parents impacts the methylation inheritance from both the womb and germ line. Thus, parents ought to pursue a healthy BMI (18.5-24.9) before and during the development of the child. There are many ways to fulfill this objective regardless of economic, cultural, or personal limitations/preferences. Some of these strategies include exercise, a low-calorie diet, or even bariatric surgery for those with the financial means to do so. Of course, the means of approaching a healthy BMI should be in a healthy manner and not done through starvation or other forms of disordered eating. Moreover, any dietary or exercise plan should be approved by a physician. Overall, this practical application of pursuing a healthy BMI can be obtained in a multitude of ways, ensuring that no restraints are placed on the current generation to fulfill this objective.

Also, new research shows that efforts to pursue a healthy BMI can alter methylation

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[22] Mark A. Rothstein, Yu Cai, and Gary E. Marchant, "THE GHOST IN OUR GENES: LEGAL AND ETHICAL IMPLICATIONS OF EPIGENETICS," Health Matrix (Cleveland, Ohio : 1991) 19, no. 1 (2009): 1–62.

[23] Dominique Aubert-Marson, "Sir Francis Galton: the father of eugenics," *Medicine Sciences* 25, no. 6–7 (July 2009): 641–45, https://doi.org/10.1051/medsci/2009256-7641.

patterns in somatic and germ line cells, positively influencing epigenetic inheritance for children. As methylation is highly sensitive to environmental changes, it is not unreasonable to believe that parents can adopt new, healthier lifestyle choices that could alter their epigenetic markers for the better. Researchers in Australia found that men who adopted an exercise routine for three months showed genome-wide methylation changes in their sperm cells.[24] Another group looked at how bariatric surgery changed methylation patterns in sperm. Here, researchers found that sperm methylation patterns in men were completely remodeled one year after bariatric surgery. Most notably, many of these methylation patterns were changed in genes associated with controlling appetite.[25] While there is still much more research that needs to be done to show the reversal of epigenetic markers, these initial experiments, in addition to existing methylation inheritance research, are promising that parents can reverse their unhealthy methylation patterns instead of passing healthy epigenetic markers onto their children.

In this paper, I have showcased scientific literature suggesting that unique DNA methylation patterns from parental lifestyle choices can be inherited and can increase the risk of the offspring developing obesity. Because the study of epigenetics is still in its preliminary stages, more research needs to be done to determine causality between these epigenetic markers and increased risk of obesity. Nevertheless, the strong correlation can be used as a biomarker for this risk. Furthermore, I have justified that potential parents must conserve a healthy epigenome for the next generation using the intergenerational equity rationale. Finally, I have shown how to practically apply this normative claim to everyday life across a multitude of cultural, economic, and personal limitations/preferences and how recent research supports that these applications can positively benefit heritable methylation patterns. The future generation should not be restrained by the actions of the previous generation. Therefore, parents should attempt to provide an equal opportunity of prosperity for their children with decisions they make today.

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[24] Joshua Denham et al., "Genome-Wide Sperm DNA Methylation Changes after 3 Months of Exercise Training in Humans," *Epigenomics* 7, no. 5 (April 13, 2015): 717–31, https://doi.org/10.2217/epi.15.29.

[25] Ida Donkin et al., "Obesity and Bariatric Surgery Drive Epigenetic Variation of Spermatozoa in Humans," *Cell Metabolism* 23, no. 2 (February 9, 2016): 369–78, https://doi.org/10.1016/j.cmet.2015.11.004.

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