

DePauw University Scholarly and Creative Work from DePauw University

Student research

Student Work

4-2019

Evolution, Health, Medicine, and the Gap in Between

Mi Jedar

DePauw University

Follow this and additional works at: <https://scholarship.depauw.edu/studentresearch>

 Part of the [Public Health Commons](#)

Recommended Citation

Jedar, Mi, "Evolution, Health, Medicine, and the Gap in Between" (2019). *Student research*. 117.
<https://scholarship.depauw.edu/studentresearch/117>

This Thesis is brought to you for free and open access by the Student Work at Scholarly and Creative Work from DePauw University. It has been accepted for inclusion in Student research by an authorized administrator of Scholarly and Creative Work from DePauw University. For more information, please contact bcox@depauw.edu.

Evolution, Health, Medicine, and the Gap in Between

Author: Mi Jedar

DePauw University Honor Scholar Program, Class of 2019, Sponsor: Kevin

Moore, Committee members: Beth Benedix and David Harsha

Introduction

The founder of the Global Medical Forum, Dr. Raphael “Ray” Levey, at an annual summit meeting of leaders from every constituency in the health system once said that, “ a relatively small percentage of the population consumes the vast majority of the health-care budget for diseases that are very well known and by and large behavioral. That is, they’re sick because of how they *choose* to live their lives, not because of environmental or genetic factors beyond their control.” (Levey, 2005) Namely, Levey was speaking of the “too much” syndrome, too much smoking, drinking, eating, stress, and too little exercise.

Meanwhile, the CEO of the hospital at Johns Hopkins University at another annual summit instead talks about bypass surgery, a medical procedure averaging in cost around \$30 billion a year in the United States alone. While I am not here to explain the complexities of bypass surgery, instead I want to reveal the very real problem with bypass surgery, what people do not often realize is that the procedure provides temporary relief and is unlikely to prevent heart attacks or prolong lives. Simply put, is a temporary measure, rather than an exhaustive measure. Dr. Edward Miller describes that about half of the time, the bypass grafts clog up in a few years and the angioplasties clog up in a few month. There are many explanations regarding the inefficiency of the treatment but the problem does not lie in whether the treatment worked or not, nor in the surgery at all. In fact, what is most surprising is that many patients could avoid the return of pain and the need to repeat surgery by switching to healthier lifestyles. Unfortunately, very few do. Miller cites that, “if you look at people after coronary-artery bypass grafting two years later, 90% of them have not changed their lifestyle.” (Levey, 2005) So society, you and I, must ask ourselves, “what is the missing link here?”

The missing link in a nerve racking one, resulting in an eruption of pathology, significant increase of morbidity, decrease in quality of life, and adding to the national heap of debt. For that reason, my plea is simple. Eat *real* food. Exercise *more*. Sleep *right*. Be active. Eat a variety of food. Your nature does not define your experience, nurture yourself. Being healthy is more than taking supplements and prescribed medication, it is about proactively, consistently, and actively wanting to be healthy. A state of “good” health isn’t a fixated target in which once you achieve it you are “good to go.” This is far from the truth. A state of health is one in which is always moving, changing, growing, and adapting. Change doesn’t take place overnight. What you do in your youth determines your health when you’re older, so take care of your body, mind, and wellbeing. Straighten your posture, yes *you* hunching over reading this paper. Think twice before thrashing your feet on to cement for cardio everyday. Wonder why it hurts to run? Maybe check your shoes and look to your ancestors for answers. Eating right and taking your medication is not sufficient in catering and maintaining a healthy lifestyle.

Not too long ago The Atlantic posted an article titled: “ Less than 3 Percent of Americans Live a Healthy Lifestyle,” a study that illustrated rather dismal statistics of the American people. For instance, the study quoted that “in the 2013 ranking of affluent countries’ health, the United States came in last.” (Beck, 2016) Moreover, according to recent findings published by *Mayo Clinic Proceedings*, “less than 3 percent of Americans meet the basic qualifications for healthy lifestyle.” (Beck, 2016) The million dollar question now is: what constitutes a healthy lifestyle?

According to the author in the *Mayo Clinic Proceedings*, a “healthy lifestyle” is defined as one that met four qualifications:

1. Moderate or vigorous exercise for at least 150 minutes a week
2. A diet score in the top 40 percent on the Healthy Eating Index
3. A body fat percentage under 20 percent for men and 30 percent for women
4. Not smoking

These four qualifications may sound simple enough. Notice that there is no emphasis on taking x medication, or y treatments. Simply put these four qualifications are reasonable and hence should be manageable, to a certain degree.

How often do you need to be reminded that two-thirds of adults in countries like the United States are overweight or obese, that one-third of their children are too heavy, and that the percentage of obese people has doubled since that 1970s” (Lieberman, 2013). What if I tell you that the top ten health issues can be solved through untypical “non health” standards, i.e. lowering stress, modifying everyday activities? What if I also told you that the solution to a number of our prevailing health concerns does not require advanced technical wonders of the future, but a look into our past, yes, the past. In fact, is increasingly become more recognized that certain fundamental changes in diet and lifestyle that occurred after the Neolithic Revolution, and especially post Agricultural and Industrial Revolution, are too rapid, on the basis of an evolutionary time scale, for the human genome to catch up and subsequently adapt to. This phenomena, of how our stone age bodies struggle to stay healthy in modern times, says Daniel Lieberman, is aptly referred to as mismatch diseases.

Lieberman defines mismatch diseases as diseases that occur because our bodies are poorly, or inadequately, adapted to environments in which we have created and now live in. Relative to how fast paced environmental changes have emerged; the human genome has stayed relatively the same compared to our ancestors (Eaton et al, 1994). This mismatch between our historic physiology and current western diet and lifestyle underlies many prevalent diseases of today's era that was virtually nonexistent in in hunter-gatherer populations. The most obvious result of this discordance is evident by poor health, especially with regard to chronic and degenerative diseases and disorders such as type 2 diabetes, cardiovascular disease, cancers, and hypertension. Moreover, the creation of biochemicals that are in our diet, water, material goods, and the environment that we live in further widen the disparities of mismatches for which our bodies have not evolved adaptations for.

Specifically, in this work I want to present and expand the concept of mismatch diseases, unveiling the mysterious fog that surrounds it; further, I want to address the double layered cake, the health care problem that stems from inadequate health care teaching, ultimately advocating structural changes in medical schools to envelop practices of evolutionary medicine. Finally, I want to look at the state of health care as it stands today. America is a wonder, simultaneously a nation with the best health care and the worse health care in the world. How do we justify a system in which the rich have quality access to medicine and health care professionals, while the poor suffer? How do we justify a system in which healthcare and access to health care is so heavily capitalized on that health care has become a luxury in itself. I end with the argument that change starts from within. Change starts with an individual fully committing, wanting it rather than supplementing to a regime of pills, if you'd rather take a "one size fits all" health pill, rather

than going through the actual motions of actively pursuing and sustaining healthy habits, this work isn't for you. This work will touch on revolutionary phenomenons that will make you think twice on what you thought you knew about health and what you thought you knew about answers to health difficulties. This work will also ask you to look inward and ask yourself hard questions about your commitment to your own health, health of others, and universal health at that. The literature at hand is by no means an exhaustive approach to all mismatch diseases and the resulting reasons why it exist. Instead, my aim is to scratch the surface and whet the appetite, so that you, the reader, the most significant person in charge of your health, can either take this work and build off of it, or leave the words to exists only on these white pages.

Childhood Food Allergies

To ease into this analysis, let's start with something familiar, allergies anyone? Social rhetoric on childhood food allergies isn't commonly presented as a mismatch disease. However, Turke in *Childhood Food Allergies* presents both anthropological and immunological evidence and ultimately identifies a mismatch in dietary antigen exposure that has increased over the years in which food allergies have also increased. As a result, he proposes that the degree to which this mismatch is present is a key determinant of whether a childhood food allergy will or will not manifest.

Fundamentally, childhood food allergies are a rapidly growing public health concern in developed nations, including the USA. Their prevalence in the USA increased by 50% between 1997 and 2011, and peanut allergies, which have been a main scare, has more than tripled in number between 1997 and 2017 (Turke, 2017). Other developed countries have also experienced

similar upward trends, and as less developed countries expand their economies, they have also are seeing likewise increases in trends. Allergic conditions are among the most common medical conditions affecting children in the United States (CDC, 2013). Overall, 220-250 million people worldwide currently have allergies to one or more foods, and children comprise the majority of cases. According to the CDC, an allergic condition, is a hypersensitivity disorder in which the immune system reacts to substances in the environment that are otherwise considered harmless. Unlike skin allergies and respiratory allergies that increase in prevalence with increased age, food allergy prevalence was similar among all ages. Although it is common to think of allergic reactions as immune system mistakes, according to Turke, some almost are not because many of the exogenous compounds that humans come into close contact are harmful and provoke a response that may be adaptive. However, there are also allergic reactions that are clearly overpowering and can lead to fatal health concerns. Before engaging with Turkes argument in full, it is important to distinguish what foods elicit an allergic response and what defines a significant source of allergy. According to Anvari et al 2016, in the USA, eight foods are responsible for around 90% of childhood food allergies: peanuts, tree nuts, cow's milk, chicken eggs, wheat, soy, fish and shellfish. Also according to the ASCIA, *Australasian Society of Clinical Immunology and Allergy*, the same eight "culprit" foods from the USA, including the addition of sesame are responsible for roughly 90% of food allergies in Australia. In terms of what distinguishes a significant source of allergy to a more mild variant, Breiteneder and Mills 2005, states that "to be a significant source of allergy, a food must be widely consumed, and it must possess molecular properties that are intrinsically allergenic, such as thermal stability and resistance to proteolysis, the breakdown of proteins or peptides into amino acids by enzymes. To

understand what causes allergies and what comprises an allergic reaction, one must first understand how the body is designed to protect against threats. At the most fundamental level, the human immune system becomes “armed and potentially dangerous beginning in utero, and by necessity tolerance mechanisms develop in unison to control the growing powerful potential of a young naive immune system. There is growing evidence that suggests that the mechanisms responsible for building and guiding tolerance develop not only early but function is at its peak earliest in the lifespan, specifically during fetal development, and during infancy while being breastfed and introduced to first foods. If you want to learn about immunology in depth, I suggest you take a immunology course, pick up a book or two, and be prepared to be blown away by the beauty, intricacy, and expansiveness of immunology. However, what I can do is provide you a quick summary, just enough to catch the gist of Turke’s argument. T cells are the coaches of immune system functions, they direct and coordinate most but not all functions, including the production of different antibodies like IgE, which is the antibody the mediates most food allergies. However, before T cells are fully functional, they migrate to the thymus where they are presented with a range of antigens by cells called antigen presenting cells, APCs for short. Similar to Goldilock and her grueling dilemma, T cell selection is a rather complicated process that is a series of T cells binding to APCs in a fashion that is “just right” to advance to T cell maturation. Negative selection, as it sounds, is when T cells are eliminated because they “bind too tight” which are mostly T cells that are prone to attacking self antigens and other substances that should not be attacked. Submerging evidence has shown that infiltration into the thymus poses threats, specifically that microbes are known to infiltrate and manipulate negative selection in their favor so that T cells are unable to recognize and destroy them (Nunes-Alves et

al, 2013). Therefore, to understand what went wrong in our evolution, it is logical to compare Paleolithic diets to current diets to close the gap on how today's food antigen exposure over lifetimes differ from those that evolving hominin immune systems counted on for million of years (Eaton et al, 1988).

Turke identifies three inferences that a handful of specific sociocultural changes have broken these rules, at first slowly and then rapidly, resulting in the surge in childhood food allergies that developed countries like the USA and others experience. Turke states that paleolithic diets usually if not always were comprised of a great variety, contrary to the average American diet now (Eaton et al, 2005). Because of this change in behavior, something called evolution discordance is experienced. A quick refresher on evolution for anyone who might be rusty on it, evolution acting through natural selection represents an ongoing interaction between a species' genome and the environment it is in over the course of many many lifetimes. Genes are either positively or negatively selected for relative to their concordance or discordance with environmental selective pressures. This is important, now read these next few lines slowly and carefully: when the environment remains relatively constant, stabilizing selection tends to maintain genetic traits that represent the optimal average for the population. *However*, and a big *however*: if the environment permanently changes, evolution discordance arises between a species' genome and its environment and here the stabilizing selection is replaced by something called directional selection, moving the average population genome to a new set point. In the affected genotype, this evolutionary discordance manifest itself phenotypically as disease, increased morbidity and mortality, and reduced reproductive success (Eaton et al, 2005). Sounds familiar? The problem, with respect to childhood food allergies, is that the that mixing of dietary

traditions is at a crossroads. In conflict with popular opinion, a child who was not exposed to peanut or fish proteins during gestation, has a greater chance of being exposed to these proteins downstream in their life, via school, etc. According to [1], the central prediction of the mismatch hypothesis is that childhood food allergies arise from breaking 3 rules:

Rule 1: Paleolithic diets usually were comprised of great variety

Rule 2: Although our ancestors ate many different foods, it was almost always the same different foods year after year and lifetime after lifetime

Rule 3: Given Rule 2, throughout the Paleolithic era food antigen exposures encountered by fetal, infant and toddler immune systems would have closely matched subsequent exposures

Therefore, according to this logic, children alive in our hunter gatherer societies by age 1 would have been exposed to most or even all of the different types of food antigens they would ever be exposed to in their entire lifetime. This is in sharp contrast to children today who live in developed nations. Think about it, children in developed nations are surrounded by a diversity of different food antigens due to globalization and cultural diversity. While I am not speaking ill on cultural diversity and the inclusion of multiple food cultures, evolutionarily speaking, this does pose a risk of an unparalleled degree of mismatch between early and late food antigen exposures. What happened and how did we get here? Strictly speaking, farming, social stratification, trade, mobility and the internet are to blame for the mismatch at present. Here it becomes *really* easy to blame the *other*, *other's food*, *other's culture*, and *others immigration into one's nation*, and I

can't emphasize enough that that is not the point. There are things that can mitigate the mismatch and a lot of these motivations are heavily underappreciated and misunderstood.

Looking at the literature, Fraizer et al 2014, motivated to understand the etiology of the increasing frequency of childhood peanut or tree nut allergy, led a cohort study with the objective to examine the association between peripregnancy consumption of peanuts and tree nut P/TN by mothers and the risk of P/ TN allergy in their offspring. In the prospective cohort study, the 10,907 participants in the Growing Up Today Study 2, between January 1990 and December 31 1994, are the offspring of women who were part of the ongoing Nurses' Health Study II. In 2006, offspring reported whether or not they had a physician-diagnosed food allergy. To further authenticate the presence of a food allergy, mothers were then asked to confirm the diagnosis and provided subsequent medical records and allergy test records to confirm diagnosis. Two-board certified pediatricians independently reviewed each case and assigned a confirmation code, i.e, likely food allergy, to each case. Per the results, among the 8205 children, there were 308 identified cases of food allergy of any food, including 140 cases of P/ TN allergy. The probability of P/TN allergy was significantly lower among children of nonallergic mothers who consumed more P/TN in their diet during pregnancy (≥ 5 times vs < 1 time per month: odds ratio = 0.31; 95% CI, 0.13-0.75; $P_{\text{trend}} = .004$). However, there was a nonsignificant positive association between maternal pregnancy p/TN consumption and risk of P/TN allergy in the offspring of 146 P/TN allergic mothers, ($P_{\text{trend}} = .12$). Interestingly, the interaction between maternal P/TN consumption and maternal P/TN allergy status was statistically significant ($P_{\text{interaction}} = .004$). What does this mean? In short, this study supports the hypothesis that early allergen exposure increases tolerance and lowers risk of childhood food allergy. Given that

childhood peanut allergy has more than tripled from 1997 to 2010, and because of frequent overlap between peanut allergy and tree nut allergy, with 80% to 90% persistence of the food allergy into adulthood, there is much significance in looking at literature of P/TN allergies in diets, especially for pregnant mothers. Should mothers include P/TN in their diet, if it will likely aid the offspring in not developing P/TN allergy (Fraizer et al, 2014).

Aside from P/TN allergies, egg allergy also has become a mainstream topic in society, bearing that it is the most common IgE mediated food allergy in infants and young children. Although egg allergy itself can be outgrown, children with egg allergy are at an increased risk of acquiring other conditions such as, asthma and allergic rhinitis 13, 14, 15 and have comorbid food allergies such as peanut and tree nut allergy. According to infant feeding guidelines that long dominated infant care education have recommended delaying the introduction of solids and allergenic foods to prevent allergy in high-risk infants. Specifically, infants with a family history of allergy are typically recommended delaying introduction of allergenic foods, (including avoiding eggs until 2 years of age and nuts until 2 years of age), as well as delaying solid foods until after 6 months and breastfeeding for at least 12 months. Conversely, historically speaking, in the 1960s, most infants had been exposed to solid by 4 months and it wasn't until the 1990s that experts recommended delaying solids until after 6 months of age. Researchers, JJ et al, draw on data from HealthNuts, a cross sectional study of food allergy in 12 month old infants using food challenges to confirm allergy presence. Here, the motive of the research lie in the determination of whether egg allergy in 12-month-old infants is in fact associated with duration of breast-feeding and ages of introducing egg and solids. Per the results, of the 2589 infants who participated, 231 infants were classified as having an egg allergy. In terms of introduction of egg

and egg allergy, infants introduced to egg at 4 to 6 months had a lower risk of egg allergy than those introduced to egg at a later time, specifically introduction to egg at 10 to 12 months of age and after 12 months of age, even after adjusting for variables such as family history of allergy and infant allergy symptoms (JJ et al., 2010). Interestingly, the lowest risk of egg allergy was found among infants whose first exposure to egg occurred at 4 to 6 months in the form of cooked egg. Taken together, to echo Fraizer et al, 2016, the results from this population based study strengthen the idea that a relationship exists between delayed introduction of other foods and subsequent food allergies. This conclusion challenges the fundamentals of infant feeding principles, providing clear evidence that contradicts delaying egg introduction for protection against food allergy.

While we are talking about maternal diet and influences on fetal life, Willers et al, 2008, look at the role of maternal diet and risk of developing childhood asthma or allergy. Something worth noting with asthma is that the chance of developing asthma is influenced by many things, one being maternal diet and lifestyle, that can ultimately influence the development of the airways and immune system of the child in utero. Per the fetal programming theory, otherwise known as the Barker hypothesis, events during pregnancy, such as undernutrition, smoking, and infections can have long-term physiologic and metabolic effects in the fetus. As of recent, it has been shown that maternal intake of allergenic foods during pregnancy increase the risk of sensitization in the fetus and hence allergic disease. In this present study by Willers et al., 2008, Willers and colleagues investigated the influence of maternal food consumption during pregnancy on childhood asthma outcomes from 1 to 8 years of age. Taking data from a birth cohort study of 4,146 pregnant women, which asked women about their frequency of

consumption of fruit, vegetables, fish, egg, milk, milk products, nuts, and nut products, their offspring were then followed until 8 years of age and longitudinal analyses were conducted to assess associations between maternal diet during pregnancy and childhood asthma outcomes over the duration of 8 years. Per the methods, data was obtained from 2,832 children. Per the results, daily consumption versus rare consumption of nut products during pregnancy was associated with childhood wheeze, dyspnea, steroid use, and asthma symptoms. However, the odds ratio of daily versus rare consumption was minute, odds ratio [OR] daily versus rare consumption, 1.42; 95% confidence interval [95% CI], 1.06–1.89), dyspnea (OR, 1.58; 95% CI, 1.16–2.15), steroid use (OR, 1.62; 95% CI, 1.06–2.46), and asthma symptoms (OR, 1.47; 95% CI, 1.08–1.99) (JJ et al., 2008).

Energy Imbalance

While evolution discordance manifest itself phenotypically as a disease to the affected genotype, plural, mismatch diseases have been shown to strongly impact women's health and reproduction quite significantly in terms of cancer and reproduction. For example, in the beginning Lieberman reminded us again, "how often do you need to be reminded that two-thirds of adults in the United States are overweight or obese?" (Lieberman, 2013). We know for fact that obesity is linked to a wide array of health consequences, so much in fact that I have devoted a whole section on metabolic syndrome and energy imbalance. However, for women in particular, obesity is associated with increased risk of type II diabetes, cardiovascular disease, cancers including postmenopausal breast cancer, increased risk of hypertension, insulin resistance, metabolic syndrome, polycystic ovarian syndrome, and systemic inflammation just to

name a few (Ryan, 2007). Interestingly, obesity affects women's health differently in different stages of life. For instance, young women en route to becoming mothers experience obesity that impacts their reproductive health. During pregnancy obesity imposes health risks that affect both the mother and her fetus. Finally, as women age, obesity is associated with a number of chronic diseases, one being Dementia and Alzheimer's disease (Ryan, 2007). As women reading this, and as a woman writing this, it is distressing to swallow the words of what seems to be no win-no win situation. However, there is an intricate evolutionary explanation for everything, including this. Lieberman notes that there is an indisputable predisposition favoring more stored up fat in women because extra fat stores correlates to increased offspring survival. Therefore, natural selection favors 5 to 10 percent more body fat in women than men (Lieberman, 2013).

From a previous work of mine, I focus exclusively on evolutionary mismatches and women's health. For reference, I touch on how obesity is linked to a wide array of health consequences but disproportionately for women. For women in particular, obesity is associated with increased risk of type II diabetes, cardiovascular disease, numerous cancer including postmenopausal breast cancer, increased risk of hypertension, insulin resistance, metabolic syndrome, polycystic ovarian syndrome, and systemic inflammation to name a few (Ryan, 2007). Data from the Nurses' Health study suggests that weight gain alone accounts for 16% of postmenopausal breast cancer (Eliassen et al, 2007). Moreover, obesity has health impacts at each stage of a woman's life cycle. For instance, as women become parents, obesity impacts reproductive health. Concurrently, obesity also imposes serious risks during pregnancy which affects both mother and fetus. Finally, in older women, obesity is associated with a number of chronic diseases and there is increasing evidence that obesity is an independent risk factor for

Dementia and Alzheimer's disease (Ryan, 2007). The evidence for the adverse effects of obesity on women's health is overwhelming and indisputable. Granted, evolutionarily speaking, there is a predisposition favoring more stored up fat in women with regards to reproductive success in that extra fat stores correlates to more surviving offspring. However, the mismatch that is referenced in this review results from the fact that current body fat far surpass what the genome is familiar with.

Excess body fat is not only implicated in postmenopausal cancer, but also endometrial cancer. Unfortunately, it has been widely recognized that excess body fat is a main determinant of endometrial cancer (EC). Specifically, obese women experience at least a 3-fold increased risk of EC compared to women with average weight. Moreover, there is a distinction between lower body fat and upper body fat, with the latter fat distribution costlier to women's health. In this study, Austin, Austin Jr, Patridge, Hatch and Shingleton (1991) investigated the role of obesity and body fat distribution in endometrial cancer. Austin et al found that the trend between EC risk and increasing obesity is highly statistically significant however, excess risk is confined to very obese women. In terms of WHR, an index of upper versus lower body fat distribution, the researchers found a strong positive correlation between the BMI and the WHR. In contrast to these findings, they also found a positive independent association between the STR, an index of central versus peripheral obesity and EC. Moreover, there is a strong positive correlation between the BMI and the logarithm of serum estradiol and of serum estrone. In sum, there is strong evidence shown in support that overall obesity is a strong risk factor for EC.

Further, to add to the discussion on body fat distribution and mismatch diseases posed for women, literature has shown evidence of the correlation between obesity and established risk

factor for non-insulin-dependent mellitus (NIDDM). . Previously, a case control study on US women found that after adjustment for BMI, age, and education, women with NIDDM were 4.6 times as likely to be in the highest rather than the lowest category of WHR. The Gothenburg Study also found various measures of central fat distribution and BMI to be independently and simultaneously correlated with NIDDM risk. In the Nurses' Health Study, nurses aged 30-55 years and living in the US returned a mail questionnaire. The women of sample size of 42, 492 were asked every 2 years on risk factors and health outcomes, anthropometric measurements and diagnosis of diabetes and mellitus. Carey et al revealed that for age-adjusted relative risks of NIDDM for BMI, waist circumference, and WHR present a strong positive association between all of the obesity measures and NIDDM risk, specifically with waist circumference yielding the highest risk gradient. Moreover, the BMI-NIDDM risk relation remained strong after adjustment for age, family history of diabetes, exercise, smoking, intakes of saturated fat, calcium, potassium, and magnesium, the estimated relative risk function increase monotonically with increasing BMI and more strikingly, levels of BMI not considered to indicate obesity were associated with notably elevated NIDDM risk. By the same token, there was a consistent increase in NIDDM risk as waist size increased within each BMI category.

In this previous study I touch on the association between low birth weight and increased risk of hypertension and high birth weight and increased risk of adult BMI, menstrual cycle-related exacerbation of disease, menstrual cycle influence on cognitive function and emotion processing, salivary progesterone levels and rate of ovulation are significantly lower in poorer than in better off urban dwelling bolivian women, obesity in older women, and effects of age and estrogen status on serum parathyroid hormone levels and biochemical markers of bone turnover

in women. The review from beforehand does not provide the full picture of the health implications that women face due to mismatches that have become the norm in our environment but not well adapted to our genome. To briefly summarize, the major mismatch that I touch on results from obesity and estrogen, considering that our diet has substantial effects on our health and subsequently our menstrual cycles has been impacted by our environment. Coupled with lack of physical activity, changes in social norms, menstrual cycle frequency, reproductive hormones and subsequent reproductive health costs, mental and emotional health, it is plausible to see the inner workings of the negative associations of estrogen and fat deposits and its association with reproductive cancers, obesity related diseases, osteoporosis and diseases that results as women age, ovarian function, ovarian and menstrual cycle influence on women mental and emotional health and reproductive developmental resources.

Another recent implication of a mismatch is how oral contraceptives cause increases in hormone exposure and actually acts as a risk factor for breast cancer. In the evolutionary past, women spent most of their reproductive lives either pregnant or in lactational amenorrhea, and thus rarely menstruated. The current pattern of frequent menses and the associated increase in endogenous hormonal exposure has been noted in the current breast cancer epidemic. While the association between menses and hormone exposure has been cited in previous works, it is not known whether oral contraceptives further increase or actually decrease hormonal exposure over one menstrual cycle. Lovett et al examined variation in hormonal exposure across seven oral contraceptive formulations, (OC), and found that after adjusting for relative binding affinity, (RBA), which was used to estimate the binding affinity of a ligand for a receptor and is thus a measure of the concentration of ligand that competes for half the total specific binding, it was

found that median ethinyl estradiol (EE), the synthetic form of estrogen that's mainly used in various hormonal contraceptives, across 28 days in the OCs was 11.4 nmol/l, similar to median E2 exposure. One formulation of OC was 40% higher in EE relative to median EE. Median exposure from progestins in OCs (1496 nmol/l) was 4-fold higher than the median endogenous exposure from progestins from P4 (364 nmol/l). Given that breast cancer risk increase with hormonal exposure, these findings suggest that four widely used formulations more than *quadruple* progestin exposure and this is definitely a cause for concern. These findings shed light on the importance of consumer choice but also the gap in knowledge within the field.

While we are on the topic of excessive energy and increased risk of pathology, let's turn our attention to men's health in relation to prostate cancer. It is clear that prostate cancer is the most commonly diagnosed cancer in men in the United States (Jemal et al, 2002), and its incidence is increasing around the world. Despite epidemiologic advances and years of research, only three factors are known with certainty to be associated with an increased risk of prostate cancer: age, being black, and positive family history, all three factors which are not under the control of men themselves. Recently it has been shown that there are a few modifiable risks factors that can lead to prostate cancer, including: high intake of red meat or saturated fat, dairy products and calcium, low physical activity, cigarette smoking, and higher central adiposity. Previous literature has shown that these suspected risk factors are associated with more advanced disease but not with early disease suggests that these risk factors may act on progression rather than on initiation or promotion (Platz, 2002). Risk factors such as red meat and saturated fat intake, low physical activity and larger body size fall under the umbrella of energy intake and this relationship lead Platz to question if excessive intake of energy relative to energy

expenditure adversely affect risk of clinically important prostate cancer? Energy imbalance is the concept that when an individual consumes more energy than is needed for maintenance of body size, and the effect of energy imbalance, as indicated by obesity influences on metabolic sequelae has been presented at sequelae in regards to women's health.

How does excess energy fit in the model of carcinogenesis? The effect of excess energy intake has been implicated in mouse and rat models. One of the most consistent findings suggest that diets with restricted total energy that are nutrient replete reduce tumor burden relative to free access feeding (Kritchevsky, 1999). Remarkably, compared with animals given free access to food, animals fed energy-restricted diets are smaller in size, have reduced fat mass, lower body temperature, enhanced insulin sensitivity, fewer mutations, and hence live longer (Thompson et al, 1999). Specifically, energy restriction impacts a broad spectrum of cellular and tissue activities, and many of its effects plausibly alleviate carcinogenesis. Namely, two of the effects of energy restriction, enhancement of apoptosis relative to proliferation and antiangiogenesis, are hypothesized to affect the promotion and progression phases of carcinogenesis. Tumor development is thought to be an imbalance between cell growth and cell death, as known as apoptosis. In tumor development, the rates of cell proliferation and cell apoptosis are higher than those in normal tissue, a tumor is able to grow if the rate of proliferation outcompetes the rate of apoptosis. Evidence that energy imbalance influences prostate carcinogenesis is beginning to surface. Sources of evidence include migrant studies, ecological or correlation studies, experimental studies in animal models and analytic epidemiologic studies. Per migrant studies, it has been show that when adult men move from countries with low prostate cancer incidence and mortality rates to countries with substantially higher rates, like the United States, their risk of

prostate cancer increase (Haenszel and Kurihara, 1968). The reasonings for this includes that immigration is followed by a host of changes in an individual's life, including the balance of food consumer and its energy density relative to the amount of physical activity, sounds familiar? Thus through indirect observation, migrant studies show that energy imbalance may be a possible contributor in prostate cancer risk. Per ecological studies, or correlation studies, disease rates for several countries or regions were plotted against per capita exposure. Three studies, 44-46, which used country specific supply data by the United Nations to estimate per capita energy intake, show a positive correlation between per capita energy intake and prostate cancer incidence or mortality. In a study led by Armstrong and Doll (Armstrong and Doll, 1975), the correlation coefficients were 0.3 for 23 countries, 0.6 for 32 countries for prostate cancer and incidence and mortality, respectively. Overall ecological studies indirectly show that energy intake is in fact related to prostate cancer incidence and mortality. Per mouse studies, two transplantable prostate tumor models were used: the Dunning R3327-H rat adenocarcinoma, which was transplanted into rats, and the LNCaP human adenocarcinoma, which was transplanted into SCID mice. Dunning R3327-H is an androgen-sensitive prostate cancer cell lines that is moderately differentiated. LNCaP human adenocarcinoma is an androgen sensitive but poorly differentiated. These rodents were then fed diets with energy restriction ranging from 80% to 60% of normal energy intake. Per the results, in general, the transplanted tumors were smaller, has increased stroma and smaller glands, had reduced expression of VEGF and had reduced microvessel density. The energy restricted rodents also had lower circulating concentrations of IGF-1 and these effects were observed irrespective of whether energy reduction came from fat, carbohydrate, or total diet. Moreover, because these models consist of

tumor-forming prostate cancer cell lines, these experiments directly address the effect of energy restriction on later phases in tumorigenesis. In sum, through three different approaches of research, the derived conclusion remains to be the same. However, there are many more questions that stem directly off of this review.

For instance:

- 1) Specifically when in prostate carcinogenesis pathway does energy imbalance act
- 2) What times in life are critical for the adverse effect of energy imbalance, is it early life, adolescence and puberty or later in life?
- 3) What is exactly the optimal energy balance for minimizing risk of clinically important prostate cancer?

In short, there is still so much research potential in the field of prostate cancer research. Regardless if this study looked exclusively at the outcomes of male health, the main message of energy imbalance touches on the global epidemic of obesity. If, as the results here indicate, energy imbalance does influence prostate carcinogenesis, coupled with an environment enriched in excess energy, prostate cancer rates can substantially rise.

Lower Back Pain

Here is a twist, didn't think you would see this as a component of the review, did you? However, something as "normal" and low priority as lower back pain is itself a disguised mismatch disease. In fact, lower back pain (LBP) is one of the most common and costly medical problems today (Hoy et al., 2010). Lower back pain manifest itself from intervertebral discs, bones, ligaments and muscles of the spine (Lieberman et al, 2015). A few risk factors LBP include both aspects of nature and nurture, i.e., what you came into the world with and how you

were raised, and also psychosocial and newly created biomechanical influences. However, data shows that although 85% of LBP cases have no clear etiology, estimates state that 97% may be due to musculoskeletal issues (Deyo and Weinstein, 2001). According to Lieberman, mechanically induced LBP is often thought to be a consequence of trade-offs in the spine. According to Lieberman's hypothesis, the costs of increased Fshear from lordosis were offset by the benefits of positioning the upper body's center of mass over the hips, which stabilizes the trunk and decreases the costs of upright posture. An alternative hypothesis that Liberman suggests, and that I focus on, is that some cases of LBP are the result of a recent mismatch in which the modern human spine is poorly adapted to recent environmental conditions. Since our ancestors led very different lives prior to the industrial era, one in which was very active, resulted in increased back muscle strength and endurance strongly correlate with LBP. Fast forward to the current day era, our species tend to be less active, resulting in weak and unstable back tissues and increased risk of pain and injury. Furthermore, the invent of soft mattresses and longer sit time in chairs, decreases loading and is correlated to increased LBP rates (Adams et al, 2012). While the conversation on lower back pain and its emergence as a mismatch disease is relatively new, and research is few and far, what is known is that some cases of LBP show strongly that it is a result of recent mismatches and that rates of LBP is likely to be on the rise if sedentary, low activity behavior increases. What that means for you and I, and our generation is that trunk strengthening and exercises in general, but also exercises involving endurance can help treat and prevent some cases of LBP that arises from the mismatch.

Eating Behavior, Metabolic Syndrome and Associated Problems

I. Human Eating Behavior and the Microbiome

Many of our health problem in the modern era arises from: not eating enough, eating too much, not eating enough of x, or eating too much of y. The phenomenon of eating too much paves the way to the pathology of obesity, what current researched classify as a chronic state of inflammation, which inevitably results in increased risks of high blood pressure, strokes, high cholesterol, high blood sugar, and heart disease. Why is human eating behavior seemingly so disadvantageous? What is eating human behavior? And, is it even human? Krebs observation of human feeding habits boil down to 4 things: the remarkable variety in food habits within and between populations, many populations derive food from farming methods rather than hunter gatherer methods, the importance of cultural traditions and ritual in relation to food, and the alarming fact that food is often processed- by cooking and other modes of alteration before it is consumed (Krebs, 2009). The last element of his observation is uniquely human he says, meaning that cooking or manufacturing food is a deviation that isn't shared by other species. Krebs acknowledges that the main rhetoric of human food preferences are shaped entirely by culture and individual choice, i.e., I like chocolate and thus I eat chocolate, or my culture eats a lot of rice and I've come to eat a lot of rice. However, Krebs points out that human food preferences interact with genetics, ecology, and evolution, and in particular how this might give rise to variation within and between populations. The framework of evolution food heritage is underscored by our anatomy and physiology. According to anthropologists, we have the teeth and digestive system of an omnivore, which we've inherited from our ancestors. Specifically,

fossil analysis of *Australopithecus africanus*, show that the diet comprised of 75% fruit and leaves and 25% meat (Krebs, 2007). Consequently, our 5 senses of taste- sweet, salty, unami, bitter, and sour prepared our species for the consumption for survival--- energy, salt, and protein, while steering us away from food items that were potentially dangerous for us. So, thus far, Krebs has underscored the interplay between genetics, the environment, and our ancestors as plausible theories of human food behavior, sounds simple enough, right? However, it gets much more complicated. Emerging studies have shown that human eating behavior is manipulated by gastrointestinal microbiota. Particularly, microbes in the gastrointestinal tract (GI tract) are under selective pressure to manipulate host eating behavior to increase their fitness, at the cost of the host fitness. Ever heard of the saying “survival of the fittest,” well that doesn’t only apply to humans. Microbes can either do this through two identified strategies: (1) generating cravings for foods that they specialize on or foods that suppress their competitors, or (2) inducing dysphoria until we eat foods that enhance their fitness (Alcock et al, 2014). If you are currently bewildered by this, I refer you to *I Contain Multitudes* by Ed Yong, Yong does a much better job explaining gut microbiome and their influence on human health and eating. So to answer the above question, eating behavior is not uniquely and solely human. Subsequently, unhealthy eating behavior is a major source of health problems including but not limited to obesity, sleep apnea, diabetes, heart disease, and various forms of cancer. However, because of the suggested multiple “selves” exist, and competition over resource is intense, eating behavior and unhealthy eating is more complicated than what it appears on the surface level. Furthermore, when we get down to the numbers, the evidence is daunting, microbial genes outnumber human genes by 100 to 1 in the intestinal microbiome. Because of the diversity of the gut microbes, fitness interests are not

universal, thus members of the microbiota compete with one another over habitat and nutrients. Thus, a very diverse population of gut microbes expend more energy in resource acquisition than a less diverse population. However, a less diverse population is likely to have a species that outnumber the others, meaning it is likely that it has monopoly over resource acquisition. Kreb hypothesizes that the lower diversity in the gut microbiome is correlated with increased risk of unhealthy eating behavior and greater obesity and subsequently decreased host fitness (Krebs, 2007). Remember how I said I crave chocolate, thus I eat it? Well, Rezzi and colleagues show that there is circumstantial evidence for a connection between cravins and the composition of gut microbiota. Specifically, individuals who crave chocolate have different microbial metabolites in their urine than individuals who don't like chocolates, and get this, this connection occurs *despite* eating identical diets (Rezzi et al, 2007). Further than just affecting host cravings, microbes also can affect their hosts' mood and behavior. For example, a double-blind, randomized, placebo controlled trial found that mood was strongly improved by drinking probiotic *Lactobacillus casei* in participants whose mood was initially in the lowest tertile (Benton et al, 2007). Microbes can also induce dysphoria that can affect human behavior, one mechanism in which it can influence eating is with bacterial virulence gene expression and host pain perception. How does this work? This mechanism works by production of virulent toxins often is triggered by a low concentration of growth-limiting nutrients (Krebs, 2007). Another route of manipulation involves modulation of host receptor expression, changing host receptor expression to benefit the microbe. For instance, one study found that germ-free mice had altered taste receptors for fat on their tongues and in their intestines compared to mice with a normal microbiome (Swartz et al, 2012). In another experiment, germ-free mice had a preference of more sweets and was observed to have

higher numbers of sweet taste receptors in the GI tract as compared to control mice (Swartz et al, 2012). Microbes can also influence host through neural mechanisms by “hijacking” their host’s nervous systems. Evidence has shown that microbes can have profound effects on behavior through the microbiome-gut-brain axis (Rhee et al, 2014). One of the nerves of the above communication axis, the vagus nerve is a central nerve connection 100 million neurons of the enteric nervous system in the gut to the base of the brain at the medulla. Emerging evidence has also shown that the vagus nerve regulates eating behavior and body weight. In a profound study, (Camilleri et al, 2008) if the vagus nerve is blocked, there has been reported cases resulting in drastic weight loss. If by now, you don’t have a deep appreciation for microbes and their profound impact, you will when you discover that microbes can also influence host through hormones. In fact, microbes produce neurochemicals that are exact analogs matches to mammalian hormones involved in mood and behavior (Lyte, 2011). In fact, more than 50% of the dopamine and serotonin have an intestinal source (Eisenhofer et al, 1997)). Microbes have the ability to manipulate human eating behavior by directly through production satiety regulating hormones analogs or indirectly by stimulating production of auto-antibodies that interfere with appetite regulation. The good news is that changing the composition of gut microbiome can change eating behavior. Prebiotics, probiotics antibiotics, fecal transplant and diet changes are are potential mechanism to alter microbiota. Also, microbiota transplantation is in the horizon as a measure in changing food preferences. There are also things that can further harm us and put humans at a disadvantage. Specifically, excess energy delivered to the gut, beyond what is ideal for the host, can lead to providing energy for microbial growths, allowing a population to boom in numbers, reducing diversity, increased manipulation at the cost of host fitness. This positive

feedback loop can cause long-term changes in human eating behavior and drives risk of obesity (Krebs, 2007).

It is clear that the human and gut brain interact in complex ways, and research is still ongoing on this association. However, there are interesting implications that arise from this association. It has been suggested that abnormal conditions in the gut may predispose individuals to neurodevelopmental disorders, such as Autism Spectrum Disorders (ASD). Previous work by Hallmayer et al., investigated 192 twin pairs and found that both genetic and environmental factors contribute to the etiology of ASD. Currently, the treatments for ASD include behavioral therapy, speech and social therapy and diet/nutrition medical treatments. A hallmark work by Hallmayer et al, 2011 investigated 192 twin pairs and found that both genetic and environmental factor exert an influence on symptoms, and literature suggest that children with ASD have distinctive microbiomes compared to neurotypical children. On top of this, previous literature has shown, through mouse studies, that microbiomes and their metabolites can impact behavior through the gut-brain axis, including for ASD. Throughout the years, the notion of a fecal microbiota transplant (FMT) has gained popularity as it is a vector to modulate the gut microbiome. In this procedure, a large diversity and number of commensal microbes from a healthy donor are used to transform a dysbiotic gut microbiome into a health microbiome. Previously, Kang et al performed a open-label modified FMT trial with an intensive combination called Microbial Transfer Therapy (MTT) which included two-week vancomycin treatment followed by a bowel cleanse and a high dose of FMT for 1-2 days and 7-8 weeks of daily maintenance doses along with a stomach acid suppressant, administered to children with ASD and chronic gastrointestinal problems. Following this 10-week MTT treatment and an eight-

week-follow-up observation period, Kang et al observed an 80% reduction in GI symptoms and a slow but steady improvement in core ASD symptoms. Also, when the researchers looked at the gut microbial diversity itself, it was found that diversity significantly increased after MTT. Interesting, right? Well it gets even better. Two years after this original clinical trial was completed, participants were re-evaluated to determine whether observed improvements in behavior and GI symptoms lingered, thus taking a dive into the long-term impact of MTT on the gut microbiome of the study participants. Per the results itself, two years post treatment, most participants reported GI symptoms improved as compared to baseline. The improvement was on average 58% reduction in Gastrointestinal Symptom Rating Scale (GSRS) and 26% reduction in % days of abnormal stools relative to baseline, and this result was comparable to what Kang et al saw at the end of the treatment, two years later. Specifically, the improvement in GI symptoms was observed for all sub-categories of GSRS: abdominal pain, indigestion, diarrhea, and constipation. This progress is notable because all 18 participants reported that they had chronic GI problems, hence, chronic constipation or diarrhea since infancy. Most notable of all, based on the Childhood Autism Rating Scale (CARS), as rated by a professional evaluator, the severity of ASD at the two year follow up was 47% lower than baseline, compared to 23% lower at the end of week 10 post MTT. At the start of the open trial, 83% of participants rated in the severe ASD diagnosis per the CARS guidelines, however, at the two year follow-up, only 17% were rated as severe, 39% in the mild to moderate rate, and 44% were below the ASD diagnostic cut-off scores (Kang et al, 2011). After confirming via statistical analyses to determine whether improvements in GI and ASD severity were correlated, it was shown that percentages in CARS, SRS, and ABC scores were positively correlated with percent changes in GSRS scores (Spearman correlation

test, 2-tailed, $p < 0.005$ and $r > 0.7$, which implies that GI relief provided by MTT may ameliorate behavioral severity in children with ASD (Kang et al, 2011). Taken together, these results demonstrate that intensive MTT therapy is a viable option for treating children with ASD who have GI problems. From a medical perspective, these results encourage the inclusion of gut microbiome vectors as ways to aid in disease management.

The pathology that arise from changes in the microbiome is not strictly related to just humans. Growing evidence has shown that depression and obesity are widespread, and they have a tight association. In fact, data suggests that microbiome fluxes affect many organisms, specifically in a paper by Sun et al, Sun and colleagues found that shift in gut microbiota in mice lead to the pathogenesis of depression. Specifically, mice lacking fat mass and obesity-associated gene (*Fto*) were generated and subjected to chronic unpredictable mild stress (CUMS) for 6 weeks. A sample of mice were treated with antibiotics via their drinking water for 6 weeks in order to deplete their normal gut microbiome. Mice were then subjected to behavioral tests to evaluate anxiety and depression like behavior and plasma levels of inflammatory cytokines and lipopolysaccharides (LPS) were compared and the researchers were able to show that deletion of *Fto* lead to lower body weight and decreased anxiety- and depression-like behaviors. *Fto* heterozygous mice (+/-) were also less susceptible to stress stimulation and with regard to the gut microbiome, *Fto* deficiency mice contained specific bacterial signature of suppressing inflammation. While mechanisms that explain the obesity-depression association are highly complex, the field of the microbiome is up and coming and I certainly believe that this area of medicine is nothing but untapped potential.

Now that we laid the groundwork that human diet and health is an interplay of the environment and genetics, we can then move on to the next question. Are humans getting adequate nutrients via their diet as compared to our hunter gatherer ancestors? How has nutrient acquisition changed over the course of evolutionary time? Sebastian et al, 2002 addresses these very questions in, “ Estimation of the net acid load of the diet of ancestral preagricultural Homosapiens and their hominid ancestors.” The researchers reveal that the nutritional requirements of Homosapiens were established by natural selection through the course millions of years, in which our ancestors largely consumed from a menu of wild animals and plants. However, the menu that our ancestors picked and chose from is not consistent with the current era menu that homosapiens currently gravitate towards. Specifically, the invent of agriculture and animal husbandry and most recently, industrial-scale food production and distribution has thrown a curve ball to natural selection, ultimately providing natural selection an enormous challenge to eliminate the maladaptations that has risen from this shift in diet. The design of the research was fairly straightforward, Sebastian et al used computation methods to compute NEAP, net endogenous acid production for a large number of ancestral preagricultural diets and compared them with quantitative data for the typical American diet. Need a refresher on the typical American diet? The diet of contemporary Homosapiens is rich in saturated fat, simple sugars, sodium and chloride, while it is poor in fiber, magnesium, and potassium. These and numerous other postagricultural dietary compositional changes have been implicated as risk factors in the pathogenesis of “diseases of civilization”. Hence, the results that the researchers came to aren't too surprising, in fact, you might think it is redundant at this point.

Per the results, the mean NEAP for 159 retrojected preagricultural diets was -88, 87% were net base producing. A computational model predicted NEAP for the average American diet 48. The historical shift from negative to positive NEAP was accounted for by the displacement of high bicarbonate yielding plant foods in the ancestral diet by cereal grains and energy dense, nutrient poor foods common in contemporary diet, neither of which are net base producing. Therefore, these findings point to the idea that diet induced metabolic acidosis and its sequelae in humans eating contemporary diet reflects a mismatch between the nutrient composition of the diet and the genetically determined nutritional requirements for optimal systemic acid- base status (Nutr, 2002).

In the interplay of nutrition, diet, and health outcomes, popular rhetoric perception on metabolic syndrome is tossed around loosely in conversation, literature, and media. However, what precisely is metabolic syndrome? In a nutshell, while the definition varies from agency to agency, the metabolic syndrome consists of a handful of health complications, including but not limited to: type 2 diabetes, non-alcoholic fatty liver disease, certain lines of cancer, cardiovascular disease and Alzheimer's disease. In the perspective of evolution, in efforts to explain for why metabolic syndrome is a socially and not just medically related term relates to what some may call the "lazy" and others may call a misguided adaptation to our environment. In an evolutionary context, human switched from their primal hunter-gatherer lifestyle to a sedentary lifestyle one in which involved a plethora, dare say overabundance of energy-dense foods, frequent stress and a dramatic lack of exercise unlike that of our ancestral past. As a result of this rapid, too rapid for our genome to process metamorphosis, humans continually and progressively present metabolic disorder.

The Biggest Challenge in Health Care

Recall when founder of the Global Medical Forum, Dr. Raphael “Ray” Levey, at an annual summit meeting of leaders from every constituency in the health system once said that, “a relatively small percentage of the population consumes the vast majority of the health-care budget for diseases that are very well known and by and large behavioral. That is, they’re sick because of how they choose to live their lives, not because of environmental or genetic factors beyond their control.” (Change or Die) Namely, Levey was speaking of the “too much”, too much smoking, drinking, eating, stress, and not enough exercise. Further, how CEO of the hospital at Johns Hopkins University shifts the spotlight on bypass surgery--- averaging around \$30 billion a year in the United States alone. The consensus that, in reality, many patients could avoid the return of pain and the need to repeat surgery by switching to healthier lifestyles. Unfortunately, very few do. Miller cites that, “if you look at people after coronary-artery bypass grafting two years later, 90% of them have not changed their lifestyle.” (CD) So we must then ourselves (society), what link are we missing here?

Healthcare is a business in itself

The biggest challenge in healthcare, as evident in other businesses, is changing the behavior of people. Harvard Business School professor says that, “the central issue is never strategy, structure, culture, or systems. The core of the matter is always about changing the behavior of people.” (CD) One would presume that being in a state of crisis would lead to individuals actively seeking and maintaining change, yet, even with something as large scale as cardiac disease, is not enough for 90% of patients. Kotter says that, “behavior change happens mostly by speaking to people’s feelings, in highly successful change efforts, people find ways to

help others see the problems or solutions in ways that influence emotions, not just thought.” (CD) Hence, like Kotter, Ornish echoes that “providing health information is important but not always sufficient. We also need to bring in the psychological, emotional, and spiritual dimensions that are so often ignored.” (CD) In fact, Ornish published studies showing that his holistic program, focused around a vegetarian diet, weekly group support sessions led by a psychologist, guided meditation, relaxation, yoga, and aerobic exercise. Ornish’s program lasted for only a year but after three years, the study found that 77% of the patients had stuck with their lifestyle changes and, more importantly, avoided the bypass or angioplasty surgeries. Ornish rewired motivating patients with the “fear of dying” to the “joy of living.” Dr. Ornish also provides a rather radical insight, claiming that sweeping comprehensive changes are often easier for people than small, incremental ones. So how does this relate to the state of healthcare you may ask?

Equity and Equality

Coming from a refugee background, not having the taste of western healthcare until arriving in the states at 10 years old, emaciated, and grossly undervaccinated, it is both a disservice and unjust for me to not bring in the topic of equity and equality in my plea for better understanding human health and pathology and improving current state of health and well being, holistically. Remember Dr. Ornish’s program that was widely successful and highly tactful? While the results from his program is just what I aim to highlight, lifestyle changes and tweaking the little things in one’s life to improve well being, how many people do you think can afford, in both a time context and financial context, to participate in this program. Bluntly, while America has one of the best healthcare systems in the world, i.e, one that the rest of the world gleams in

envy, however, America's great healthcare is great healthcare for those who can afford it and for those who can't, well, I think you can fill yourself in. In the summer of 2017 HuffPost submitted a rather striking article titled, "In Matters of Health Care and Poverty, The United States is Ill-informed And Heartless: The American health care and poverty debates are rife with elitist biases and falsehoods." The author, P.L. Thomas writes that "while the U.S. has a long and disgusting history of racism and demonizing people in poverty, the current failure to provide social safety nets for the struggling has roots in Ronald Reagan's politics of hatred anchored by the false but effective "welfare queen" narrative." Following Reagan's administration, Bill Clinton's administration led to the erosion of more social programs. P.L. Thomas echoes that "a robust welfare system and universal health care driven by a single-player system are not only morally imperative in the U.S., but also fiscally essential to provide the stability that would enhance the market and everyone's ability to prosper." This is key: everyone's ability to prosper. Currently, there is a health care war on the poor and according to ABC news, "Almost 20 percent of Americans, or more than 40 million adults, can't afford or access needed health care." In the 2007 report from the Centers for Disease Control and Prevention (CDC), it illustrated that one-fifth of Americans could not afford one or more of these services:

1. Medical care
2. Prescription medicines
3. Mental health care
4. Dental care
5. Eye care

The problem, or one of the problems, is that people equate access to health care as insurance, when in fact it is not. What people don't realize is that there are still disparities present with healthcare, the discussion of quantity and quality is also relevant here. There is broad evidence that Americans often do not get the care they need even though the United States spends more money per person on health care than any other nation in the world. Again the irony that I outlined before, reactive measures overutilized and proactive measures under-utilized is at the heart of this discussion. Preventive care is underutilized, resulting in higher spending on complex, advanced diseases. Patients with chronic diseases such as hypertension, heart disease, and diabetes all too often do not receive proven and effective treatments such as drug therapies or self management services to help them more effectively manage their conditions. This is true for insured, uninsured, and underinsured Americans. These problems are exacerbated by a lack of coordination of care for patients with chronic diseases. The underlying fragmentation of the healthcare system is not surprising given that health care providers do not have the payment support or other tools they need to communicate and work together effectively to improve patient care. While the majority of patients do not receive medically necessary care, others receive care that me unnecessary, or even harmful. Research has documented the incredible variation in hospital inpatient duration of stay, visits to different specialists, procedures, testsings, and cost variation from one hospital to another, even in the same town! The evident discrepancy in the healthcare system is something that will be addressed shortly, but the main point is that there is a gap in the quality and efficiency of care, which I discuss is related to physician education and lack thereof. Further, these issues are particularly relevant to lower-income Americans and to

members of diverse and demographic groups who often face great disparities in health and healthcare.

In a nutshell, the high cost of healthcare is stealing years of life from poor Americans. According to studies in *The Lancet*, the United States risks a “21st century health-poverty trap” if it fails to address low-income Americans’ growing inability to access or afford quality health care. The studies highlight several alarming trends:

1. America’s richest 1 percent live more than a decade longer on average than the poorest Americans
2. 40 percent of poor Americans skip going to the doctor because they can’t afford to
3. The neediest 20 percent of Americans spend almost twice what the richest 20 percent Americans spend on private health insurance
4. 1 out of every 10 households facing high medical costs declares bankruptcy, even after Obamacare

Dr. Jacob Bor from the Boston University School of Public Health stresses that “we are witnessing a slow-moving disaster unfolding for the health of lower income Americans who have spent their working lives in a period of rising income inequalities.” Our healthcare system, driven by capitalism and maintained throughout history, has made healthcare a commodity rather than a necessity. Dr. Jacob Bor concludes that, “ the goal of a healthcare system should be to keep people well, not to make stockholders rich. The USA has the most expensive, bureaucratic, wasteful, and ineffective healthcare system in the world.”

How do we change?

The answer to changing our healthcare system and health respectively is not simple and is far from easy. I have a few recommendations of how we go about implementing change, from the grassroots up but mind you these are neither exhaustive measures nor is what I recommend the “answer” to all of our problems.

I am a firm believer in grassroot changes, top down changes, and from the grassroots, change starts with how individuals perceive health, assessing where the majority of individuals get their health information, and what outlets they choose. The answer to these questions are: (1) school/ socialization through media, (2) doctor and health care professionals, (3) big rig pharmaceutical enterprises. Therefore, to change, we must look inwardly towards these three tenets that convolute the truth behind human health and where we went wrong. Because I am a big believer in education and the wonders that education can bring to lives, I also know that the opposite is also true, education can mislead people and keep them separated from the truth. I approach this problem through two lenses, (1) we ourselves are not adeptly versed in health through evolutionary terms due to lack of an evolutionary approach in school systems and in the same vein (2) our doctors that we go to for assistance, too are deprived of this information and hence can't pass along a complete picture. How do we change that?

The Great Opportunity of Evolutionary Approach to Medicine and Public Health

Evolutionary biology is essential basic science for medicine, but few doctors and medical researchers are familiar with its most relevant and fundamental principles. Evolutionary biology is an essential basic science for medicine, but few doctors and fewer medical researchers understand the fundamental principles. While some in the field discredit the existence of a gap in

knowledge, the magnitude of the gap is frightening, studies of medical education found that most medical schools in the UK and the USA don't even have one evolutionary biologist on the faculty (Nesses and Schiffman 2003). Many medical students do not even accept the theory of evolution (Downie 2004). The typical medical student path consists of two years of basic science education, including but not limited to: biochemistry, anatomy, histology, physiology, embryology, anatomy, and genetics. Yet, it is very rare to find a medical school course that encapsulates evolutionary biology as a tenet of basic medical science. The reality of the problem is that if healthcare providers are ill informed on disorders and how to properly treat symptoms, this leads to misinformation and unwarranted pain and discomfort on behalf of the patient. At the core of evolutionary medicine is the recognition that diseases need both proximate explanations of bodily mechanisms and evolutionary explanations of why natural selection has left the body vulnerable to disease. Tinbergen's 1963 article outlined four questions that must be answered to provide a full explanation for any biological trait. Simply enough, the first two questions are about the body's proximate mechanisms, from DNA transcription and physiological regulation, to bones, muscles, and behavior. Finally, the third and fourth questions touch on the evolutionary questions about how the body got to be the way it is, present tense. The problem with current medical education is that while medical textbooks address question 1 and 2, question 3 and 4 are often omitted and from this angle, current medicine has only used half of biology to reason out medical problems.

An interesting example of this gap of knowledge and how evolutionary explanations are essential has to do with bilirubin and jaundice. Textbooks commonly describe bilirubin as a potentially toxic metabolite of hemoglobin that can be excreted in bile. This is the proximate

explanation of bilirubin, and as of yet, there is no evolutionary indication of how it got to be in the human body in the first place. What is common to think is that bilirubin is just a waste product, however, the intermediate step between heme and bilirubin is biliverdin, a chemical product more soluble than bilirubin. Here, the evolutionary train of thought asks the question: why does the body go through the trouble to make a difficult to excrete toxin? It is both imperative to medical practitioners and necessary for patient outcome to ask these evolutionary questions and dig deeper than just the textbook.

Remarkably, bilirubin is an effective antioxidant that can protect against the oxidative damage that contributes to aging (Nesse and Williams 1994). Specifically, bilirubin protects against heart attacks as oxidative damage is partially responsible for atherosclerosis, a disease of the arteries characterized by the deposition of plaques of fatty material on their inner walls. Literature has shown repeatedly that higher levels of bilirubin acts as a protective factor against heart attacks. Interestingly, levels of bilirubin are higher than normal are indicative of Gilbert's disease as a result, middle-aged people with this genetic condition have rates of heart disease sixfold lower than those with normal bilirubin levels (Vitek et al. 2002). Given these results, it would seem that there would be more of an emphasis on evolution or natural selection in studies of bilirubin protection against atherosclerosis. The untapped potential of evolutionary thought behind medical processes is something worth mentioning. If researchers and doctors alike were able to use the details of a proximate mechanism to test an evolutionary hypothesis, to gather information of a specific trait or pathology, imagine where modern medicine could be right now. Yet, many studies have yet to be performed. According to (Nesse and Stearns, 2007) there are many well established applications that could benefit from evolutionary reason. Namely, () cite

phylogenetic methods, population genetics and areas that have greatly profited from evolutionary thought are: evolutionary genetics, genetic conflicts, aging research, infectious disease. Much of the recent work in evolutionary medicine asks questions about why natural selection has left the body vulnerable to diseases (Williams and Nesse 1991). The main points of this argument can be summed up into six different points: mismatch with the modern environment, pathogens coevolving with hosts, constraints on what selection can do, unavoidable trade-offs, reproduction at the expense of health, and defenses such as pain and fever that are useful despite causing suffering and complications (Nesse, 2005). There is a fundamental difference between evolutionary explanations for why selection has not made the body more resistant to disease, which is fundamentally different from proximate explanations about how the body works. The key is while evolutionary reasoning doesn't explain everything, it needs to be on the list because it is often the source of misunderstandings.

Some items to consider from an evolutionary perspective:

Nutrition and Development

For example, when looking at nutrition and development, a physician must understand the “thrifty gene hypothesis,” the hypothesis that refers to the benefits of weight gain and associated mechanisms that conserve calories in environments characterized by poor nutrition (Neel et al., 1998). In essence, natural selection shape mechanisms that adjust metabolic systems to cope with different nutritional environments. Later in this paper you will come across a study that looks at differences in socioeconomic classes and caloric uptake outcomes. Namely, children from lower SES consume more calories than children from more affluent upbringings due to the reasonings that the thrifty gene hypothesis echo. Furthermore, natural selection may also have shaped mechanisms that adjust metabolic systems to cope with different nutritional environments.

Notably, in a longitudinal study of 13,517 men and women who were born in Helsinki University Hospital during 1924-1944, whose body sizes at birth and during childhood were recorded, and in whom deaths, hospital records, and medical history was documented, Barker et al found that the combination of small size at birth and during infancy, followed by accelerated weight gain from age 3- 11 years is positively correlated with incidence of coronary heart disease, type 2 diabetes, and hypertension (Barker et al, 2002). There are many different directions that can be taken with the outcome of the research however what is clear is that these studies call our attention to the importance of the physiological state of mother and infant for the prevalence of lifestyle diseases later in life. In a study by Costello et al., the authors examined the relationship between low birth weight can serve as a predictor of depression. To assess this

relationship, a representative population-based sample from an 11-county area in western North Carolina was assessed annually for psychiatric disorders between the ages of 9 and 16 years. Costello et al tested the prediction from LBW and depression in models that included LBW only, LBW plus other prenatal and perinatal adversities, LBW plus significant perinatal and childhood adversities, and LBW plus significant perinatal and childhood adversities and adolescent correlates. From the 1420 participants, 49% were female and the results show that the cumulative prevalence of depression among adolescent girls with LBW was 38.1%, compared with 8.4% among adolescent girls with normal birth weight. Interestingly, in adolescence, there was a significant interaction between sex and LBW. LBW predicted female adolescent depression after controlling for other perinatal, childhood, and adolescent adversities. Moreover, girls with LBW and normal birth weight with no adversities had no adolescent depression, but each additional adversity increased the risk of in girls with LBW more than in girls with normal birth weight. What does this tell us? In sum, this further supports fetal programming, and the evolutionary question is whether this “fetal programming” is a “predictive adaptive response” resulting from a mechanism shaped by selection to monitor fetal nutrition and adjust development in ways that facilitate coping with deprivation.

Hygiene Hypothesis

The what hypothesis? You may have never heard this coined as the hygiene hypothesis but I bet you that you may have practiced this yourself or you know someone who does. Briefly, the hygiene hypothesis stems from the idea that children must be kept in an environment as clean as possible, however, now research suggest that being exposed to pathogens, i.e, unclean conditions is actually good for a child’s immune system. Research has indicated that children

kept in clean environments have a higher rate of hay fever, asthma, and a wide range of other conditions (Alina Bradford, 2016), and this is what is hygiene hypothesis. Thanks to public health interventions, vaccinations, sanitation, huge decrease in human mortality in the past century developed countries have seen a huge decrease in human mortality in the past century. However, all of the invents have changed the environment in which humans live in and the environments within human beings themselves. How? To start off, one result is a decreased burden of parasites such as worms in the gut. During most of human evolution we lived with helminth parasites, (parasitic worms), and their absence in developed societies explain the increase rates of autoimmune disease, not just childhood allergies, but diabetes and childhood leukemias (Elliot et al, 2007). While no one is complaining about the loss of helminth parasites, their loss however, has unforeseen and significant consequences. While the epidemiological evidence for helminthic protection from Crohn's disease and MS is present, the strongest evidence against helminth parasites is actually for asthma. Moreover, immune mediated diseases arose in those populations where exposure to helminths declined (Elliot et al., 2000)

Epidemiology

By far, the greatest opportunities for evolutionary applications relevant to health may be in public health and epidemiology. For instance, ubiquitous lighting has transformed human's lives. Instead of settling down when the sun sets, we have artificial lighting that allows us to extend our past time habits, reading, studying, dancing, watching television. No pun intended but this is as day to night with what our hunter gatherer ancestors experienced. What we fail to acknowledge, as a society, that light itself is risky because melatonin levels increase in the dark, as it should, but when you disturb this cycle, "circadian disruption", there are health

consequences. In a study of visually impaired women - who tend to have higher than normal melatonin levels, found risks of breast cancer about half of the rates for other women (Kliukiene et al, 2001). Reduced melatonin may increase breast cancer risk through several mechanisms, including increased estrogen production and altered estrogen receptor function. In a study in 2005, Stevens observed that nurses that worked the night shift and was exposed to light had increased cancer rates. Although future research is needed to validate these results, one simple takeaway is to sleep with lights off.

Overall, these few insights shed light on a global consensus, significant research is taking place at the interface of evolution and medicine. While work in the area is growing rapidly, the structure of evolutionary medicine is still ill defined. Why? Well I postulate that the error lies within education, or lack thereof.

Since the physicians and researchers of the future will be employing more applications of evolutionary science in their practical work, it is crucial that we engage today's medical students and tomorrow leaders around these concepts. In reality, evolution of education in the US lags behind that of other nations and misconceptions concerning the core principles of evolutionary science are widespread among the American public (Scott, 2008). One recent study surveyed curriculum deans of North American medical schools allowing them to rate their curriculum for coverage of 12 core concepts in evolution. Of those surveyed, 60 schools, 39% responded to the survey. Of the evolutionary principle that deans rated most significant, antibiotic resistance, environmental mismatch and somatic selection in cancer. However, despite this, coverage of evolutionary principles lagged behind the perceived importance of them on average 21% (Hidaka et al, 2014). While importance and coverage of principles were correlated ($r= 0.76$, $P <$

0.01), moderate coverage lagged behind importance by an average of 21%. Compared to 2003, a range of evolutionary principles were covered by 4 to 74% more schools. Not surprisingly, nearly half, 48% of responders anticipated igniting controversy at their medical school if they added evolution to their curriculum. However, despite calls from the AAMC and others for a strong undergraduate and medical school education in evolutionary biology for future health professionals, the researchers found that less than half (44%) of schools reported valuing or recommending an undergraduate course in evolutionary biology for admission. However, there have been strides in the right direction in education, especially in the Medical College Admission Test (MCAT), which is administered by the American Association of Medical Colleges (AAMC), as AAMC has been incorporating more questions on evolutionary biology in 2015. But why did 48% of responders anticipate controversy as the aftermath of the incorporation of evolution thoughts into medicine, well this is likely due to the fact that medical school curricula is already overflowed with content. Moreover, deans report that there is little to no interest in these new courses. This is not surprising as a 2013 poll found that 1 in 3 American adults reject evolution as an explanation for human origin. A survey of medical students in the U.K. found that religious beliefs were the most commonly cited reason for rejecting evolution. This paper is not about religious beliefs and I don't aim to convert anyone's ideologies. However, the evidence is here and this is but the tip of the glacier of evidence supporting the inclusion of evolution in medicine.

In sum, we live in a rapidly changing world with emerging infectious diseases, evasive cancer cells and environments that we never thought possible. The teaching of medical students about our evolutionary predispositions is not a suggestion, but a necessity.

Health is not just physical, it is also mental: How does evolution explain mental health?

1. Importance of Lifestyle

So far this work has touched on evolution, medicine, and physiological well being. However, I want to turn the page and shine the spotlight on something just as well deserving, mental health. Unfortunately, the stigma attached to mental illness is infuriatingly still alive and well. Not only is the stigma alive and well, a Health Affairs article published in 2016 verified that care management processes was used less often for depression than for any other chronic condition in US primary care practices (Bishop et al, 2016). Bishop et al., used national survey data for the period 2006-2013 and found that care management processes for depression was significantly less use for depression than for asthma, congestive heart failure, or diabetes in 2012-13. Bishop et al., show that on average practices used fewer than one management process for depression and this level has not changed since 2006-2007. However, in stark contrast to this, the use of diabetes care management processes has increased significantly among larger practices. In sum, the findings are unsettling as this indicate that US primary care services are incompetent with the tools and mindset necessary to manage depression as a chronic illness, despite the increases in depression that the U.S. alone has encountered (Bishop et al, 2016).

Depression and suicide are significant public health concerns, with over 40,000 Americans dying by suicide each year (Centers for Disease Control [CDC], 2017). Aside from lives lost to suicide, death by suicide cost America \$44.6 billion a year in combined medical and work loss costs in the US alone (CDC, 2017). Hence, suicide and the factors that may increase risk for suicide, including depression, is a serious public health concern that warrants public

concern and extensive research. Over the recent years, clinicians heading university counseling centers have reported markedly increased caseloads, with many more students seeking help for mental health issues in the year after 2010 compared to a few years prior (Twenge et al, 2017). While the numbers vary, analyses indicate an average of 30% increase in caseloads between 2009-2010 and 2014-2015 at 93 university counseling centers, especially in mood and anxiety disorders and suicidal ideation (Center for Collegiate Mental Health, 2015). This trend is not exclusively observed in college students alone, but also amongst high school students, as reports of increases in counseling use among high school students have also been noted (Anderssen, 2013). Put together, the conclusion from the literature notes that more young people are suffering from mental health issues than ever before, putting them at a higher risk for negative outcomes, including suicide. While there are many possible reasons for the observation of this trend, as many things occurred during the years indicated, there is one reason that has gained most popularity, electronics and social media.

Psychology Today, explains the six physiological mechanisms that explains electronics' tendency to produce mood disturbance:

1. Screen time disrupts sleep and desynchronizes the body clock. Why? Because light from screen devices mimics daytime, it suppresses melatonin, and disturbs the body clock which influences hormone imbalance and brain inflammation.
2. Screen time desensitizes the brain's reward system. Why? Electronics release dopamine and when this reward pathway is overused, it is less sensitive, and more stimulation and more frequent stimulation is needed to experience pleasure.

Dopamine also contributes to focus and motivation, thus it influences a child in more ways than one.

3. Screen times produces light at night. Researchers in Japan found suicidal feelings and self-injurious behavior in adolescents were associated with cell phone use after lights out. Light-at-night increased depressive symptoms, such as high cortisol levels and reduced pleasure-seeking and lethargy.
4. Screen time induces stress reactions. Both acute stress and chronic stress produce changes in brain chemistry and hormones that increase irritability. Moreover, hyperarousal and addiction pathways suppress the brain's frontal lobe, the area where mood regulation takes place.
5. Screen time overloads the sensory system, fractures attention, and depletes mental reserves (Dunckley, 2015)

Twenge and colleagues also point to electronic communication but specifically social media. Social media is a recent addition to mainstream society, the first recognizable social media platform was created in 1997, Six Degrees and mimics present day MySpace which was launched in 2003 and became the largest social media site in the world. Thus, the transition to a social network, through electronic interfaces, is a newer phenomena and we are now barely scratching the surface in understanding the complications and side effects of it. To add an additional layer on top of this, it is becoming an even more pressing issue to examine screen time and adolescents as iGen adolescents in the 2010s spend more time on electronic communication and less time on in-person interaction than their Millennial and Generation X predecessors at the same age (Twenge et al, 2017). Where does the evolutionary relevance fit in, you may ask? Well,

when looking back to our hunter-gatherer ancestors and their social environment, it worth noting that humans' neural foundation evolved under conditions of close, mostly continuous face-to-face contact with others (Lieberman, 2013) and that a decrease in the removal of a system's key inputs may risk destabilization of the system. In-person social interactions promotes emotional closeness while electronic communication can result in increased feelings of loneliness (Song et al, 2014). The interpersonal theory of suicide proposes that the desire for suicide results from the combination of two interpersonal risk factors: thwarted belongingness and perceived burdensome (Joiner, 2005). While this is only a mere proposal of suicide, literature does in fact support the theory. In a meta-analyzed work by Chu et al, the researchers findings support the interpersonal theory of suicide's hypotheses. Specifically, univariate analyses revealed significant weak-to-moderate positive relationships between (1) greater thwarted belongingness and more severe suicidal ideation ($r = .37$), greater suicide risk ($r = 0.33$), and continuous suicide attempt history ($r = 0.11$) (Chu et al, 2018). Twenge et al., first examined which activities were linked with depressive symptoms and suicide related outcomes. Second, Twenge et al determined whether the temporal trends in adolescents' screen and non-screen activities and group-level economic factors paralleled the trends in depressive symptoms, suicide related outcomes, and suicide rates. Twenge et al used the MtF, a nationally representative survey of 8th, 10th, and 12th graders with $n = 388, 275$. Further, the researchers used YRBSS a nationally representative sample of high school students administered by the CDC every other year, $n = 118, 545$ here. Suicide deaths per 100,000 population for the age group corresponding to the MtF and YRBSS respondents (age 13 to 18) were calculated from the online version of the CDC Fatal Injury Reports, a site that reports custom age ranges and breakdowns by sex, race/ ethnicity, and religion for suicide rates

in each year. The results from this meta-analysis revealed that depressive symptoms, suicide-related outcomes, and suicide deaths among adolescents all rose during the 2010s although these increases follow a period when mental health issues were declining or stable. Between 2009-2010 and 2015, 33% more adolescents exhibited high levels of depressive symptoms, 12% increase of reports of at least one suicide-related outcome and an increase in 31% more adolescents dying by suicide. What is even more shocking is that this trend, the increase in depressive symptoms and suicide related outcomes was driven almost exclusively by females.

Looking exclusively at females alone, between 2009-2010 and 2015, 58% more females scored high in depressive symptoms and 14% more reported at least one suicide related outcome. While the trend is evident for males, the increase in suicide rates are larger among females, rising 65% between 2010 and 2015 and more than doubling between the late 1990s and 2015. The trend was observed to be fairly similar among Hispanics, Blacks, and Whites with more variation in suicide rate trends by race or ethnicity. Looking at social economic class, the increases in depressive symptoms and suicide-related outcomes were similar among those of lower and higher socioeconomic class. Taken together, although depressive symptoms, suicide-related outcomes, and suicide deaths were on the decline or stable for several decades, American adolescents between 2010 and 2015, especially for females, depressive symptoms, suicide related outcomes, and suicide deaths became more prevalent (Twenge et al, 2018).

Paradoxically, since 2010, while adolescents spent more time on social media and electronic devices, activities positively correlated with depressive symptoms and suicide-related outcomes, adolescents also spent less time on non-screen activities such as in-person social interaction, sports/exercise, and attending religious services, activities negatively correlated with depressive

symptoms. Therefore, the rise in caseloads at high school and university counseling centers may be caused by the increased number of iGen adolescents experiencing mental health issues, due to how they spend their free time.

Coupled with Twenge et al., Chu et al 2017 findings support the interpersonal theory of suicide's hypotheses. Univariate analyses revealed significant weak-to-moderate positive relationships between (1) greater thwarted belongingness and more severe suicidal ideation ($r = 0.37$), greater suicide risk ($r = 0.33$), and (continuous) suicide attempt history ($r = 0.11$), and (2) greater perceived burdensomeness and more severe suicidal ideation ($r = 0.48$), greater suicide risk ($r = 0.42$), and (continuous) suicide attempt history ($r = 0.25$). While this theory in itself requires further empirical investigation, it does reveal several gaps in the literature pertaining to the theory of suicide. If numerous studies testing the interpersonal theory consistently yielded comparable results, research that targets the shortcomings of the present data will greatly contribute to the understanding of the practicality of the interpersonal theory of suicide for the prevention, management, and treatment of suicidal thoughts and behaviors (Chu et al, 2017).

Coincidentally, Roger Walsh from the University of California, Irvine College of Medicine, wrote an article that centered around a very simple thesis: Health professionals have significantly underestimated the importance of lifestyle on mental health. Put simply, there is untapped potential in treatment of multiple psychopathologies in regards to implementation of lifestyle changes. The importance of healthy lifestyle changes for fostering and maintaining social well being and psychological well being, remains to be an overlooked strategy in the field. Walsh offers eight major therapeutic lifestyle changes (TLCs) and the principles, the advantages, and the challenges

of implementing them. The fact that for modern affluent societies, the diseases exacting the greatest mortality and morbidity, such as cardiovascular disease, obesity, diabetes, and cancer are now found predominantly influenced by lifestyle factors is enough of a hunch to now take the same careful set of lenses into mental health and related psychological pathologies. While TLCs can be potent, in some cases they can ameliorate prostate cancer, reverse coronary arteriosclerosis, and be as effective as psychotherapy or medication for treating some depressive disorders (Frattaroli et al., 2008), yet, TLCs are underappreciated, taught, or even utilized. The sad irony of reality is that while there is growing awareness that contemporary medicine needs to restructure its foundation, such as focusing on lifestyle changes for primary and secondary intervention and to empower patients to manage their own health, economic and institutional pressures and socialization has pushed therapist towards less patient concentrated and more stylized interventions. Apart from other health care specialists that also face a similar issues, psychiatrists in particular are being pressured to offer less psychotherapy, prescribe more drugs, and focus on 15-minute medical checks (Mojatabai & Olfson, 2008).

Khaw et al, 2008 examined the prospective relationship between lifestyle and mortality in a prospective population study of 20,244 men and women aged 45-49 yrs with no known cardiovascular disease or cancer at baseline survey in 1993-1997, in the UK and followed up with said participants in 2006. During the 1993-1997 baseline survey, participants completed a detailed health and lifestyle questionnaire including questions that touched on health conditions such as heart attack, stroke, cancer, smoking, alcohol consumption, and physical activity. The four key behavior underscored in this study was: (1) smoking habit, (2) fruit and vegetable intake, (3) alcohol intake, and finally (4) physical activity. Khaw et al constructed a health

behavior score and participants scored one point for each of the following health behaviors: currently not smoking, not physically inactive, moderate alcohol consumption (1-14 units a week), and plasma vitamin C level > 50 mmol/l, which was indicative of fruit and vegetable intake of at least five servings a day. Further, pragmatic health behavior score were chosen based on preceding evidence on the relationship between these lifestyle factors and health endpoints. Therefore, with a total score ranging from zero to four, after an average 11 yr follow-up, the age-, sex-, body mass-, and social class- adjusted relative risks with 95% confidence intervals for all-cause mortality, approximately 1,987 deaths for men and women who had three, two, one, and zero compared to four health behaviors were respectively, 1.39, 1.95, 2.52, and 4.04, $p < 0.001$ trend. When crossed check with subgroups arranged by sex, age, body mass index, and social class the relationship remained consistent. Therefore, in essence, those individuals with a health behavior score of 0 were four times as likely to die than those with a score of 4, particularly from cardiovascular disease. By extension, people with a score of 2 were twice as likely to have died. These findings support Walsh's intuition on using lifestyle changes as a vector to ameliorate various pathologies. Collectively these results show that the combination of four health behaviors predicts a 4-fold difference in the risk of dying over an average period of 11 years for middle-aged and older people. The results suggest that changing health effects on large populations can be made possible through modest and achievable lifestyle changes. While this research does not focus on mental health, the principles remains the same by virtue that simple lifestyle changes can prove as effective, if not more effective, than current mainstream treatments.

Lifestyle changes can provide many therapeutic pros for not only patients but therapists, and to a degree, society at large. For starters, TLCs are more accessible and affordable to alternative options, hence TLCs are both effective and cost effective, for instance as exercise is to depression, the use of fish oil is to prevent psychosis in high risk youth, may be as effective as pharmacotherapy or psychotherapy (Amminger et al, 2010). Also for those who choose not to pursue help because of the stigma associated with depression, TLCs are free of stigma and have fewer side effects and complications than medications (Amminger et al, 2010). Moreover, TLCs such as medication, relaxation, recreation and time in nature are enjoyable and may therefore can become healthy self-sustaining habits (Di-donna, 2009). In terms of the lifestyle changes that warrant consideration, significant research and clinical evidence support the following eight TLCs: exercise, nutrition and diet, time in nature, relationships, recreation, relaxation and stress management, religious and spiritual involvement, and contribution and service to others (Walsh, 2011).

1. Exercise

It is no surprise that exercise offers wide spread physical benefits for the whole body. First, it reduces risk of multiple disorders, such as metabolic syndrome, cancer, cardiovascular diseases, etc (Khaw et al, 2008). Moreover, exercise is also, as the *Harvard Mental Health Letter* describes is a “healthful, inexpensive, and insufficiently used treatment for a variety of psychiatric disorders” (“Therapeutic Effects,” 2000, p. 5). Exercise offers both physical and therapeutic psychological benefits as well as proactive and reactive measures. For example, in terms of proactive measures, both cross sectional and prospective studies show that exercise can reduce the risk of depression as well as neurodegenerative disorders such as age-related

cognitive decline, Alzheimer's disease, and Parkinson's disease (Hamer & Chida, 2009). On the other hand, in terms of therapeutic benefits, disorders including depression, anxiety, eating, addictive, and body dysmorphic disorders can greatly be benefited by exercise. In terms of the data itself, the most studied disorder in relation to exercise is mild to moderate depression. Cross sectional, prospective, and meta analytic studies have shown that exercise again is both preventive and therapeutic. So what kind of exercise are we talking about here? Both aerobic and non-aerobic weight training are effective for both short-term measures and long-term maintenance, and similar to taking antidepressants and targeted drugs, exercise appears to be a dose response relationship, meaning, higher intensity workouts are more effective than low or moderate intensity workouts (Hamer & Chida, 2008). So how does exercise mediate factors of depression? There are many proposed physiological mediators including changes in serotonin metabolism, improved sleep, as well as endorphin release and the "runner's high" that is so often tossed around (Deslandes et al., 2009). Moreover exercise enhances self-efficacy and self-esteem and research even suggest that exercise leads to the breakdown of muscular armor, which is the chronic psychosomatic muscle tension patterns that express emotional conflicts and are a focus of somatic therapies (Smith, 2000). When looking at the effects of exercise neurally, research shows that exercise increases brain volume (both gray and white matter), vascularization, blood flow, and functional measures (Hamer & Chida, 2009). In mouse studies, data shows that exercise induced changes in the hippocampus leading to increased neuronogenesis, synaptogenesis, neuronal preservation, interneuronal connections, and brain derived neurotrophic factors (BDNF), BDNF is the neurotrophic factors that antidepressants act to upregulate (Cotman & Berchtold, 2002). Altogether, given the range of neural effects, it is not

shocking that exercise can confer significant cognitive benefits, ranging from improved academic performance in youth, to reducing age-related memory loss and the risk of both Alzheimer's and non-Alzheimer's dementia in the elderly (Hammer and Chida, 2009). Finally, meta-analyses reveal the specific elements of exercise that benefit cognition. For short programs, one to three months long, exercise confers significant benefits, but longer programs of six months or longer, are more beneficial. In terms of the duration of the session itself, benefits are seen with sessions longer than 30 minutes, and cognitive benefits are enhanced with combined strength training with aerobics (Colcombe & Kramer, 2003). However, despite the advantages of exercise, relatively few health professionals recommend it. For reference, only some 10% of health professional counsel and motivate patients to exercise (Long et al., 1996).

2. Nutrition and Diet

Ah yes, the infamous section on nutrition and diet. Is anyone else getting tired of hearing the phrases "fix your diet," "you're not getting proper nutrition," etc. For a while, researchers and scholars alike were not bridging the relation between food and mental health. However, now, there is considerable and undeniable evidence of the importance of nutrition for mental health, and an extensive review of over 160 studies show that dietary factors are so important that the mental health of nations may be linked to them (Gomez-Pinillia, 2008). Walsh deduces the principle of nutrition and diet down to two major components: food selection and supplements. Walsh highlights that food selection should

1. Consists majorly of a color spectrum of fruits and vegetables, i.e., a rainbow diet
2. Contains some fish, as fish (i.e., salmon), are high in omega-3 fish oils, while avoiding fish that are high in mercury (shark, swordfish, king mackerel, and tilefish)

3. Reduction of excessive calories, this revisits the epidemic of obesity and it is seen that on the national level, and the individual level, a reduction of excessive calories offers economic and public health benefits on a societal scale, and neuroprotection on the individual scale

Similar to the benefits witnessed with exercise, multiple human and animal studies suggest that pescovegetarian diets may prevent or ameliorate psychopathologies across the life span (Gomez-Pinilla, 2008). Pescovegetarian diets can enhance cognitive and academic performance in children and for adults can ameliorate affective and schizophrenic disorders. In a meta-analysis of the Mediterranean diet, including 12 prospective studies with over 1.5 million subjects-- found reductions in the incidence of both Alzheimer's, and Parkinson's disease (Gomez-Pinilla, 2008). Specifically, dietary elements that appear to confer neuroprotection include fish, vegetables, fruit, and lower intake of animal fats (Gomez-Pinilla, 2008). While society often underplays the importance of diets and health, it is critical to understand that owing to epigenetic factors, "the effects of diet on mental health can be transmitted across generations" (Gomez-Pinilla, 2008).

Apart from the diet itself, growing evidence reveals that food supplements offer valuable prophylactic and therapeutic benefits for mental health. Research highlights the benefits directly to Vitamin D, folic acid, S-adenosyl-methionine, and most of all- fish oil (Sarris, Schodendorfer & Kavanagh, 2009). Fish and fish oil are important for mental health. Fish oil is essential for supplying omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), which are necessary to neural function. How does this happen? Literature shows that systemically, omega-3s are anti-inflammatory and counteract pro-inflammatory effects of

omega-6 fatty acids are provide full body protection. Ironically enough, the modern diet is high in omega-6 fatty acids and deficient in omega-3 fatty acids (Freeman et al., 2006). Looking at the data itself, lower omega-3s in tissue are correlated with greater symptoms severity in both affective and schizophrenic disorders, which hint that inflammation may play a role in these disorders (Amminger et al., 2006). Several meta-analyses suggest that supplementation may be effective for unipolar, bipolar, and perinatal depressive disorders as an add on or even a stand alone treatment. In terms of the effective dosage of DHA and EPA, it is recommended that a dose of 1,000 mg of EPA daily yields maximum benefits (Freeman et al., 2006). Despite the therapeutic effects of supplements, there are also cognitive benefits of supplementation. In infants, both maternal intake and feeding formula supplementation enhance children's subsequent cognitive performance, while in adults, fish and fish oil supplements appear to reduce cognitive decline (Freeman et al., 2006). In a randomized, double-blind, placebo-controlled study conducted of 81 youths between 13 and 25 years of age with subthreshold psychosis, administering fish oil with 1.2 g of omega-3s once per day for 12 weeks reduced both positive and negative symptoms as well as the risk of progression to full psychosis. The calculated risk was 27.5% for controls but the risk decline to 4.9% in treated subjects. Moreover, these benefits persisted during the nine months of follow-up after treatment ended, this is specifically interesting because long term effects aren't observed with antipsychotic medications, which comprise more side effects. However, with any treatment, there are risks. One highlighted risk of fish oil supplementation is that patients on anticoagulants or with bleeding disorders should consult a physician before use, as fish oils can slow blood clotting. In sum, supplementation and pescovegetarian diets have multiple benefits and fairly few side effects. Supplementation and

diet can ameliorate certain disorders and can work in tandem with mental illnesses and medications. Here, the major takeaway is that mind health equates to bodyhealth.

3. Nature

Natural settings can enhance both physical and mental health. In normal populations, these enhancements include greater cognitive, attentional, emotional, spiritual, and subjective well being (Ho et al., 2006). As of now, studies of specific psychotherapeutic benefits are limited, and the benefits are sometimes muddled with other lifestyle factors. However, the limited research that is available indicates that nature does appear to reduce symptoms of stress, depression, and ADHD and to foster community benefits (Taylor & Kuo, 2009). Hospital outcomes are greatly impacted by whether or not there are views of a natural setting. In hospital rooms that offer views of a natural setting, patients experience less pain and stress, have better mood and postsurgical outcomes, are able to leave the hospital sooner (Devlin & Arneill, 2003). In a time when there is a rush towards urbanization and technology, the need for mental health professionals to advocate for increased time in natural settings is becoming even more pressing.

4. Relationships

It is no surprise that good relationships are critical to psychotherapy. Multiple meta-analyses show that they account for approximately one third of outcome variance, significantly more than does the specific type of therapy (Duncan et al., 2009). To some extent, therapeutic relationship is the cornerstone of effective therapy and the “paramount task is to build a relationship together that will itself become the agent of change” (Duncan et al., 2009). Compared to our hunter gatherer ancestors, Americans today spend less time with family and friends, have fewer intimate friends and confidants, and are less socially involved in

communities (McPherson et al., 2006). In sum, relationships are important to individual and collective well-being, yet the number of intimate relationships are declining and “the great majority of individuals seeking therapy have fundamental problems in their relationships” (Yalom, 2002). Therefore, focusing on enhancing the number and quality of clients’ relationship clearly warrants a central place in mental health care.

5. Recreation and Enjoyable Activities

This one might not be a stretch to the imagination either. At the root of it, through experiences of positive emotions people transform themselves, becoming more creative, knowledgeable, resilient, socially integrated, and healthy individuals (Fredrickson, 2002). In behavioral terms, many people in psychological distress suffer from low reinforcement rates, and recreation increases reinforcement. Recreation can be coupled with other TLCs such as exercise, social interaction, time in nature, to confer maximum benefits. In a nutshell, “the bottom line message is that we should work to cultivate positive emotions in ourselves and in those around us not just as end states in themselves, but also as a means of achieving psychological growth and improved psychological and physical health over time” (Fredrickson, 2002).

6. Relaxation and Stress Management

Chronic stressors can exact a major toll across multiple organ systems and levels. This toll extends from psychological to physiological to chemical to genomic expression (Dusek et al., 2008). Although stress is universal, very few people are trained or adept in managing it, hence many people respond poorly or even destructively to stressors. However, literature now points to many skillful strategies for stress management, from lifestyle changes to psychotherapy to self-management skills. Specific stress management skills include somatic, psychological, and

contemplative approaches. For instance, the Chinese mindful movement practices of tai chi are well popularized in the West, and research suggests they are associated with both physical and psychological benefits (Kuramoto, 2006). Contemplative skills such as meditation and yoga are also widely popular in the West and an explosion of meditation research has demonstrated a wider array of effects --- psychological, therapeutic, neural, physiological, biochemical, and genetic than associated with any other psychotherapy (Walsh, 2011). Considerable research suggests that meditation can ameliorate a wide array of psychological and psychosomatic disorders in both adults and children and studies including meta-analyses show that meditation can reduce stress measures in both clinical and normal populations (Chiesa & Seretti, 2009). Further, meditation may also enhance measures of psychological capacities, health, and maturity in both patients and non patients (Walsh & Shapiro, 2006). Meditation can enhance qualities such as empathy, sensitivity, emotional stability, and psychological maturity while reducing distress and burnout. On the cognitive side, studies suggest that meditation can enhance some measures of cognition and may reduce age-related cognitive losses and corresponding brain shrinkage. Therefore, the universality of stress, as well as the multiple benefits of both lifestyle changes and self-regulation skills for managing stress, suggests that these TLCs and self-regulation skills deserve to be central components of health professionals' training, personal and professional practice, and public outreach.

7. Religious and Spiritual Involvement

While this isn't exclusive, religious and spiritual concerns are vitally important to most people and most patients. It is approximated that some 90% of the world's population engages in religious or spiritual practices; these practices are a major means of coping with stress and

illness; and most patients say that they would welcome their health professional's inquiring about religious issues (Koenig, 2002). However, very few health professionals do, whether due to stigma or individual convictions is uncertain. Regardless, this lack of attention may be unfortunate given the prevalence and importance of religious and spiritual practices, their influences on lifestyle and health, their impact on therapeutic relationships and effectiveness, and the deep existential issues they open (Koenig, 2009). In general, regardless of which religion or spiritual involvement, the key is that when it centers on themes such as love and forgiveness, and is less helpful and even harmful to mental health when themes of punishment and guilt predominate. What do these benefits look like? Well, mental health benefits include enhanced psychological, relational, and marital well-being, as well as reduced rates of disorders such as anxiety, depression, substance abuse, and suicide. For physical benefits, religious involvements seems related to disorders such as hypertension and to nonspecific mortality rates (Koenig et al., 2001). A striking note is that for those who attend religious services at least weekly tend to live approximately seven years longer than those who do not, even when factors such as baseline health and health behaviors are statistically controlled (Koenig et al., 2001).

8. Contribution and Service

In our own time, both theory and research point to correlations between altruism and measures of psychological and physical health. Multiple studies, including those that control for prior health factors, suggest that people who volunteer more are psychologically happier and healthier, are physically healthier, and may even live longer. The so-called "paradox of happiness" is that spending one's time and resources on others can make one happier (Walsh, 1999). Alfred Adler emphasized the benefits of "social interest," and helping other group members contributes to the

effectiveness of group therapy and support groups such as Alcoholics Anonymous (Duncan et al., 2009). As the Dalai Lama put it, “If you’re going to be selfish, be wisely selfish --- which means to love and serve others, since love and service to others bring rewards to oneself that otherwise would be unachievable.”

In summary, given the many advantages of TLCs, why have mental health professions been so slow or resistant to adopt them? The answer is quite complex and involves patients, therapists, and society at large. For patients, TLCs require considerable and sustained effort, and many patients feel unable or unwilling to tackle them if there is an easier alternative available, i.e., medications. Patients also may not fully understand the significance of TLCs and therefore aren’t as motivated to pursue these lifestyle changes. Societally, whole industries are geared toward encouraging unhealthy choices. Individuals are overstimulated with advertisements encouraging the consumption of alcohol, nicotine, and fast food. Therapists also face challenges, one, they are also influenced by negative socialization and also they are unfamiliar with the large literature on TLCs, because they themselves weren’t trained in school to acknowledge the importance of TLCs, thus they can not practice what they weren’t taught, as a result, there is a very real bias toward pharmacological and formal psychotherapeutic interventions. Therefore, wide-scale inclusion of TLCs will likely require wide-scale interventions that encompass educational, mental health, and public health systems. In the 21st century, therapeutic lifestyles may need to be a central focus of mental, medical, and public health.

In sum, this thesis does not even scratch the surface on evolution, medicine, and the gap between. However, I hope I have at least whet the appetite of the literature and observations that exist for: mismatch diseases, our evolutionary past, and what can be done now to ameliorate said mismatches. What I hope you've gathered reading this is that there are significant misconceptions within the field of medicine, within the field of research, and within ideologies of evolution itself. Moreover, what I hope that I have underscored is that for us, as a society, to move forward, we must look back, move back into data on our ancestors, and ask ourselves questions that we've long omitted: why has selection and related processes left the human body vulnerable to disease? Homo sapiens have come a long way over the last 10,000 years, moving from hunter-gatherers to today's modern, high-tech society. Despite the many cultural changes our species has gone through, however, the human body and its immune and other systems remain comparable to those of our early ancestors, says Randolph Nesse, a physician and evolutionary biologist at the University of Michigan–Ann Arbor. “The great mystery of medicine is the presence, in a machine of exquisite design, of what seem to be flaws, frailties, and makeshift mechanisms that give rise to most disease. The question isn't just how do we get sick, it's why?” The answer, he says, lies in the emerging field of evolutionary medicine (Dybas, 2007). Evolutionary thought, and by extension, evolution is not a one dimensional precursory course to upper level biology related courses. Evolution is the groundwork, that frames the rest of medicine, in my opinion. What we built off the groundwork, is up to us. Not are the consequences up to us, but, we have to be conscious of the equity and equality that exists within medicine. Like I mentioned, you, yourself are the most influential person in your narrative of

health and wellness. After you equip yourself with this newfound knowledge, you, yourself, have the ability to spread this information in order to better someone else's outcomes. Thank you.

I leave you with a few quotes that inspired me to write this thesis:

It is health that is real wealth and not pieces of gold and silver- Mahatma Gandhi

Doctors won't make you healthy. Nutritionists won't make you slim. Teachers won't make you smart. Gurus won't make you calm. Mentors won't make you rich. Trainers won't make you fit. Ultimately, you have to take responsibility. Save yourself. -Naval Ravikan

In order to change we must be sick and tired of being sick and tired – Unknown

The doctor of the future will give no medicines, but will interest his patients in the care of the human frame, in diet, and in the causes and prevention of disease - Thomas Edison

Work Cited:

(PDF) Modern Diet and its Impact on Human Health. (n.d.). Retrieved from https://www.researchgate.net/publication/284167515_Modern_Diet_and_its_Impact_on_Human_Health. A., E. (2002, November 01).

Energy Imbalance and Prostate Cancer. Retrieved from <https://academic.oup.com/jn/article/132/11/3471S/4768323>. A., E. (2002, November 01). Energy Imbalance and Prostate Cancer. Retrieved from <https://doi.org/10.1093/jn/132.11.3471S> Armstrong, B., & Doll, R. (1975, April 15).

Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/1140864> Austin, H., Austin, J. M., Partridge, E. E., Hatch, K. D., & Shingleton, H. M. (1991, January 15).

Endometrial cancer, obesity, and body fat distribution. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/1985774> Barker, D. J., Eriksson, J. G., Forsén, T., & Osmond, C. (2002, December).

Fetal origins of adult disease: Strength of effects and biological basis. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/12540728>

Birth Weight and Adult Hypertension and Obesity in Women. (n.d.). Retrieved from <http://circ.ahajournals.org/content/94/6/1310.full#ref-12>Bishop, T. F., Ramsay, P. P., & Casalino, L. P. (2016, March).

Care Management Processes Used Less Often For Depression Than For Other Chronic Conditions In US Primary Care Practices. Retrieved from

<https://www.healthaffairs.org/doi/full/10.1377/hlthaff.2015.1068>

Care Management Processes Used Less Often For Depression Than For Other Chronic Conditions In US Primary Care Practices. (n.d.). Retrieved from

<https://www.healthaffairs.org/doi/full/10.1377/hlthaff.2015.1068>Carey, J., V., Walters, E., E., Colditz, Graham, . . . E., J. (1997, April 01).

Body Fat Distribution and Risk of Non-Insulin-dependent Diabetes Mellitus in Women: The Nurses' Health Study. Retrieved from

<https://academic.oup.com/aje/article/145/7/614/94653>Chu, C., Buchman-Schmitt, J. M., Stanley, I. H., Hom, M. A., Tucker, R. P., Hagan, C. R., . . . Joiner, T. E. (2017, December).

The interpersonal theory of suicide: A systematic review and meta-analysis of a decade of cross-national research. Retrieved from

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5730496/>Dunckley, V. L. (2015, August 18).

Screening Time Is Making Kids Moody, Crazy and Lazy. Retrieved from <https://www.psychologytoday.com/us/blog/mental-wealth/201508/screening-time-is-making-kids-moody-crazy-and-lazy> Eaton, S. B., Pike, M. C., Short, R. V., Lee, N. C., Trussell, J., Hatcher, R. A., . . . Konner, M. J. (1994, September).

Women's reproductive cancers in evolutionary context. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/7972680> Eaton, S. B., Pike, M. C., Short, R. V., Lee, N. C., Trussell, J., Hatcher, R. A., . . . Konner, M. J. (1994, September).

Women's reproductive cancers in evolutionary context. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/7972680> EJ, C., C, W., & A, A. (2007, March).

Prediction from low birth weight to female adolescent depression: A test of competing hypotheses. Retrieved from <https://scholars.duke.edu/display/pub757752> Elliot, D. E., Urban, J. F., Argo, C. K., & Weinstock, J. V. (2000, September 1).

Does the failure to acquire helminthic parasites predispose to Crohn's disease? Retrieved from <https://www.fasebj.org/doi/10.1096/fj.99-0885> Elliot, D. E., Summers, R. W., & Weinstock, J. V. (2006, December 28). Helminths as governors of immune-mediated inflammation. Retrieved from <https://www.sciencedirect.com/science/article/pii/S0020751906004462?via=ihub#bib19> Eriksson

, N., Benton, G. M., Do, C. B., Kiefer, A. K., Mountain, J. L., Hinds, D. A., . . . Tung, J. Y. (2012, June 30).

Genetic variants associated with breast size also influence breast cancer risk. Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3483246/>Eriksson, N., Benton, G. M., Do, C. B., Kiefer, A. K., Mountain, J. L., Hinds, D. A., . . . Tung, J. Y. (2012, June 30).

Genetic variants associated with breast size also influence breast cancer risk. Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3483246/>Frazier, A. L. (2014, February 01). Peanut or Tree Nut Allergy in Offspring. Retrieved from <https://jamanetwork.com/journals/jamapediatrics/fullarticle/1793699>Haenszel, W., & Kurihara, M. (1968, January).

Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/5635018>Holmes, L., & Holmes, L. (2016, March 09).

Not Even Doctors Treat Depression Like A Serious Illness. Retrieved from https://www.huffpost.com/entry/mental-illness-physical-illness_n_56def9a7e4b0ffe6f8eac4aaJemal, A., Thomas, A., Murray, T., & Thun, M. (2002).

Cancer statistics, 2002. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/11814064>Kang, D., Adams, J. B., Coleman, D. M.,

Pollard, E. L., Maldonado, J., McDonough-Means, S., . . . Krajmalnik-Brown, R. (2019, April 09)

. Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota. Retrieved from <https://www.nature.com/articles/s41598-019-42183-0>Khodarahmi, M., & Azadbakht, L. (2014, January).

The association between different kinds of fat intake and breast cancer risk in women. Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3915474/>Khosla, Sundeep, Atkinson, J., E., Melton, Joseph, L., . . . Lawrence, B. (1997, May 01).

Effects of Age and Estrogen Status on Serum Parathyroid Hormone Levels and Biochemical Markers of Bone Turnover in Women: A Population-Based Study *. Retrieved from <https://doi.org/10.1210/jcem.82.5.3946>Koplin, J. J., Osborne, N. J., Wake, M., Martin, P. E., Gurrin, L. C., Robinson, M. N., . . . Allen, K. J. (2010, October).

Can early introduction of egg prevent egg allergy in infants? A population-based study. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/20920771>Kritchevsky, D. (1999, December).

Caloric restriction and experimental carcinogenesis. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/10630585>L., J., Reiber, Chris, Anna, Hurtado, Magdalena, . . . Terry. (2016, October 15).

Evolutionary science as a method to facilitate higher level thinking and reasoning in medical training. Retrieved from <https://doi.org/10.1093/emph/eow029>Levey, R. (2001, May).

Change or Die. Retrieved from <https://www.brainhq.com/news/change-or-die/>Lieberman, D. (2014). *The story of the human body: Evolution, health, and disease*. New York: Vintage Books.Lovett, J. L., Chima, M. A., Wexler, J. K., Arslanian, K. J., Friedman, A. B., Yousif, C. B., & Strassmann, B. I. (2017, June 05).

Oral contraceptives cause evolutionarily novel increases in hormone exposure: A risk factor for breast cancer. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/28685096>Lyn, C. (2007, October 01).

Evolutionary Biology and Human Health. Retrieved from <https://academic.oup.com/bioscience/article/57/9/729/233568>Ryan, A. S., Pratt, W. F., Wysong, J. L., Lewandowski, G., McNally, J. W., & Krieger, F. W. (1991, August).

A comparison of breast-feeding data from the National Surveys of Family Growth and the Ross Laboratories Mothers Surveys. Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1405705/>Scott, B. G. (2008, July).

Overcoming Obstacles to Evolution Education: In the Beginning. Retrieved from <https://evolution-outreach.biomedcentral.com/track/pdf/10.1007/s12052-007-0012-9>Sundström Poromaa, I., & Gingnell, M. (2014, November 24).

Menstrual cycle influence on cognitive function and emotion processing-from a reproductive perspective. Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4241821/>Thompson, H. J., Jiang, W., & Zhu, Z. (1999).

Mechanisms by which energy restriction inhibits carcinogenesis. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/10709676>Vitzthum, Bentley, R., G., Spielvogel, Caceres, Thornburg, . . . Esperanza. (2002, July 01).

Salivary progesterone levels and rate of ovulation are significantly lower in poorer than in better-off urban-dwelling Bolivian women. Retrieved from <https://academic.oup.com/humrep/article/17/7/1906/576950#9277826W>, P. (2017, October 04).

Childhood food allergies: An evolutionary mismatch hypothesis. Retrieved from <https://doi.org/10.1093/emph/eox014W>, P. (2017, October 04).

Childhood food allergies: An evolutionary mismatch hypothesis. Retrieved from <https://doi.org/10.1093/emph/eox014W>Willers, S. M., Wijga, A. H., Brunekreef, B., Kerkhof, M., Gerritsen, J., Hoekstra, M. O., . . . Smit, H. A. (2008, July 15).

Maternal food consumption during pregnancy and the longitudinal development of childhood asthma. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/18403722>