

Eating Your Way To Happiness

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In this thesis, I will argue that diet is a lifestyle measure that is sufficiently effective as to merit prescription for the treatment of depression. It is the author's opinion that many people do not tend to think of what they eat as being capable of truly affecting their mental health and mind in deep and profound ways. As an example of this, this year (2017/2018), Yale University recorded its largest enrollment in one course in the university's 300+ year history, at around 1200 students. This course is called Psychology and the Good Life, and focuses on helping students live a happier, better life. Yet there is no mention of dietary habits and how they might impact mental health in the entire semester. And so, in this paper, I will try to bring to light what many people might not know can help them.

Diet for depression is so advantageous and promising because it is useful as both a preventative and treatment option for depression. Moreover, it does not come with the toxicity that other treatments for depression might, not to mention the cost.

I'll start the essay by giving the reader some sense as to how big of a problem depression really is. Then, various forms of treatment for depression will be discussed, with a special emphasis on antidepressant drugs. After this, I'll discuss at length how diet might exert a protective effect – or a detrimental effect, depending on what is being eaten – on depression. It could be inflammation, antioxidants, folate (vitamin B9), arachidonic acid, the macronutrient breakdown of foods (i.e. carbohydrates versus fats), polyphenols, monoamine oxidase inhibitors, probiotics, or, and what seems most likely to the author, a cumulative, synergistic effect of all of

the compounds within an entire food. Importantly, this paper will explicitly state what constitutes a healthy diet and what constitutes an unhealthy diet.

Just How Big of a Problem is Depression?

It is important to first put the issue of depression in to context. This section examines the prevalence of depression not just in the United States but also globally. The burden of depression, both in terms of economics and in terms of health, will be discussed. It will also be examined as to whether or not depression is on the rise.

Although the prevalence of major depressive disorder (MDD) is unclear (Kessler et al., 2003), one study that conducted face-to-face household surveys with 9090 individuals over the age of 18 in the contiguous United States found a lifetime prevalence of, using the World Health Organization's (WHO) Composite International Diagnostic Interview (CIDI), 16.2%, which, at the time that this study was conducted, would have amounted to 32.6-35.1 million US adults (Kessler et al., 2003). This same study also found a 12-month prevalence of depression of 6.6%, which would have amounted to 13.1-14.2 million US adults (Kessler et al., 2003), with mean episode duration being 16 weeks (Kessler et al., 2003). Within these 12-month cases, in terms of severity, 10.4% were considered mild, 38.6% were moderate, 38.0% were severe, and 12.9% were very severe (Kessler et al., 2003).

This same study, using the Sheehan Disability Scale (SDS), reported a role impairment of those 12-month cases that were either severe or very severe of 59.3% (Kessler et al., 2003). Both lifetime and 12-month cases of depression

presented with comorbidity of other CIDI/DSM-IV disorders most of the time (72.1% and 78.5%, respectively) (Kessler et al., 2003). Crucially, of the 51.6% of 12-month cases that received treatment for MDD, the treatment was adequate in only 41.9% of these cases, which means that only 21.7% of these 12-month MDD patients were treated adequately (Kessler et al., 2003). This lead these authors to conclude that inadequate treatment for such a common, widely distributed disorder as depression, is of serious concern, not only in terms of screening and expansion of the treatment but also in terms of the needed improvement in treatment quality (Kessler et al., 2003).

More recently, the Centers for Disease Control examined depression in the United States from 2006 to 2008 using the Behavioral Risk Factor Surveillance System (BRFSS) survey data for these years (Centers for Disease Control, 2010). This analysis was not only more recent but also contained a much larger sample size than the previously covered study. This CDC analysis contained 235,067 adults in 45 states, Washington DC, Puerto Rico, and the U.S. Virgin Islands (Centers for Disease Control, 2010). It found a higher rate of depression than the above study at 9.0% (Centers for Disease Control, 2010). Interestingly, the rates of depression varied starkly between different states, with rates ranging from 4.8% (North Dakota) to 14.8% (Mississippi) (Centers for Disease Control, 2010).

The more recent and larger study conducted by the CDC between the years of 2006 and 2008 found a higher rate of depression than the study that was conducted in between 2001 and 2002. But is the rate of depression actually on the rise? The World Health Organization says that, globally, the burden of depression (as well as

other mental health problems) is on the rise (World Health Organization, 2017). In the last decade before the turn of the millennium, a study was conducted that examined data from 42,000 face-to-face interviews of United States residents at two different times – once from 1991-1992 and once from 2001-2002 (Compton, Conway, Stinson, & Grant, 2006). In 1991-1992, the rate of depression was 3.33%, while the rate from 2001-2002 was more than double at 7.06% (Compton et al., 2006). There was a statistically significant increase in depression for all age groups and for whites, blacks, and Hispanics (Compton et al., 2006).

Despite the increasing rates of depression in the 1990s, the economic burden of depression remained relatively stable during this time, increasing by only 7% to \$83.1 billion in 2000 (Greenberg et al., 2003). This remained true regardless of the fact that the proportion of depressed people who received treatment went up by more than 50% (Greenberg et al., 2003). However, in the next decade, from just 2005 to 2010, the economic burden of depression increased by 21.5% (Greenberg, Fournier, Sisitsky, Pike, & Kessler, 2015). So the burden went from an estimated \$83.1 billion in 2000, to an estimated \$173.2 billion in 2005, and then to an estimated \$210.5 billion (in inflation-adjusted dollars) in 2010 (Greenberg et al., 2015).

According to the World Health Organization, depression affects 300 million people globally (World Health Organization, 2017). Moreover, depression is the world's leading cause of disability (World Health Organization, 2017). Of course, depression can also lead to death – with almost 800,000 suicides every year (World Health Organization, 2017), and an estimated 10-20 million suicide attempts each

year (Birt et al., 2003), with suicide being the second leading cause of death in 15-29 year olds (World Health Organization, 2017). Moreover, from 2011-2012, the age-adjusted death rates for 8 of the 10 leading causes of death in the United States fell significantly, stayed the same for one, and increased for only one – which was suicide (CDC, 2012).

The Need For Better Treatment Options

For some depressed people, treating depression with medication can be difficult. A study that examined 62 articles that represented 59,462 patients with “treatment-resistant depression” -- the designation “treatment resistant” is used to describe patients who do not respond to antidepressant therapy after one or more adequate trials (9–11) (duration of at least six weeks and use of appropriate dosages [12–15]) -- found that the mean number of different drugs that were unsuccessful that these patients had tried was 4.7 plus or minus 2.7 (standard deviations) with an average of 2.1 plus or minus 0.3 (standard deviations) different drug classes (Mrazek, Hornberger, Altar, & Degtiar, 2014). Patients with treatment-resistant depression responded to drugs 36% plus or minus 1% of the time, and a staggering 17% plus or minus 6% had prior suicide attempts (Mrazek et al., 2014). The mean illness duration of those with treatment-resistant depression was 4.4 plus or minus 3.3 years (Mrazek et al., 2014). Up to 20% of patients with depression are treatment-resistant (Mrazek et al., 2014). These authors conclude that research

needs to be conducted to, among other things, find new therapeutic targets as well as existing and new treatment combinations (Mrazek et al., 2014).

Unfortunately, it gets worse, in what might be the most shocking research I've come across. One meta-analysis has shown that the apparent clinical effectiveness of antidepressants can be explained by the placebo effect (Penn & Tracy, 2012). Drug companies have selectively published research that showed positive results from antidepressants (Turner et al., 2008), and when the unpublished data is combined with the published data, there is no clinically significant advantage for antidepressants over placebo (Kirsch, 2008; Kirsch, 2015). Of course, not publishing negative results can undermine evidence-based medicine, and, in this case, puts millions of people at risk for taking unsafe, ineffective drugs (Shimazawa & Ikeda, 2014).

To make matters even more troubling, the FDA knew that this whole antidepressant drug trial farce was going on (Kirsch, 2009), a fact which brings in the issue of conflicts of interest in what might be America's most politically powerful and profitable industry – the pharmaceutical industry (Shimazawa & Ikeda, 2014). And there might be no more financial conflict of interest found in any field of medicine than in psychiatry (Shimazawa & Ikeda, 2014), which might be due to mental illness being what one author called the pharmaceutical industry's "golden goose" (Spence, 2013), as mental illness can often be incurable, long-term, common, and requiring multiple medications.

It is important to mention that antidepressants can and do help millions of people (Kirsch, 2014), as the placebo effect is very much a real and powerful

phenomenon. But antidepressants have side effects that placebos do not – long-term weight gain, fatigue/lethargy, insomnia, withdrawal symptoms (in about 20% of people who try to quit them), sexual dysfunction (in 70-80% of people taking antidepressants), and perhaps even making people even more vulnerable to depression (Kirsch, 2014). All of this led one author to conclude that doctors should prescribe sugar pills to their patients as antidepressants (Blease, 2010). One important note to make is that antidepressants do beat placebo in cases of severe depression (Fournier et al., 2014).

It is not just antidepressant drug treatments that do not produce the desired effects, though. Psychotherapies, another form of treatment for depression, do not lead to improvements that remain at clinically meaningful follow-up analysis, according to one study (Westen & Morrison, 2001). Unfortunately, there is not much research on different treatments of depression (Duval, Lebowitz, & Macher, 2006). But different kinds of depression might involve different treatment selections (Wirz-Justice, 2006), although whether or not clinicians can select certain treatments for each special case has not been well studied (Schulz & Berney, 2004). As an example, bright light therapy is often used in seasonal affective disorder and in depression in pregnant patients, and it seems to be safe and well-tolerated (Wirz-Justice, 2006; Krzystanek et al., 2005). Other treatments for depression include – among a whole host of other types of drugs besides antidepressants (and different types of antidepressants; Duval, Lebowitz, & Macher, 2006) – electroconvulsive therapy, transcranial magnetic stimulation, vagus nerve stimulation, deep brain stimulation, and chronotherapeutics, but these are oftentimes only used when drugs do not

work (Duval, Lebowitz, & Macher, 2006). Although electroconvulsive therapy seems unlikely to work, these other approaches are promising (Duval, Lebowitz, & Macher, 2006).

Another form of treatment for depression is called activity scheduling, which is a behavioral treatment of depression that involves monitoring mood and daily activities, increasing the number of pleasant activities, and increasing positive interactions with one's environment (Cuijpers, van Straten, & Warmerdam, 2007). And one meta-analysis found that it effective as well as uncomplicated, time-efficient, and easy (Cuijpers et al., 2007).

Depression seems to be characterized by major disturbances in the circadian rhythm (Duval et al., 2006), and disturbances in circadian rhythm can even induce depressive episodes (Wirz-Justice, 1995). And other forms of treatment for depression include drugs that resynchronize circadian rhythms, showing powerful antidepressant efficacy in MDD (Duval et al., 2006). There are a lot of other treatments of depression out there, such as internet-based/ computerized treatments of depression, that are beyond the scope of this thesis.

Diet Versus Depression

Inflammation

How might diet impact depression? One theory is concerned with inflammation. Three observations encompass the major forms of evidence that link depression and inflammation (Hashmi, Butt, & Umair, 2013). The first is that major depressive disorder (MDD) is associated with raised inflammatory markers, such as cytokines like tumor necrosis factor-alpha and Interleukins, even in the absence of medical illness (Hashmi et al., 2013; Dowlatti et al., 2010). Cytokines may play a role of their own in depression by influencing brain functioning in a variety of ways, and, perhaps, together with psychosocial factors, triggering/provoking MDD (Hashmi et al., 2013). In mice, they induce sickness behavior such as social withdrawal, reduced appetite, and lethargy (Anisman, Gibb, & Hayley, 2008; Capuron & Miller, 2011), although the melancholia of MDD is more difficult to model and may be at least partially independent of these cytokine-induced effects (Hashmi et al., 2013).

The second major observation that links inflammation and depression is that inflammatory illnesses, of both the peripheral and central nervous systems, are associated with greater rates of depression (Hashmi et al., 2013; Capuron & Miller, 2011). The illnesses include rheumatoid arthritis, cancer, autoimmune disorders, heart disease, and infectious disease (Evans et al., 2005). The third overall, broad observation that links inflammation and depression is that cytokine therapy can increase the odds of developing major depressive disorder (Hashmi et al., 2013;

Capuron & Miller, 2011). Cytokines are commonly used to treat cancer and viral infections like hepatitis C (Hashmi et al., 2013). An example being interferon-alpha, which was shown to induce depression in 45% of patients being treated by it for malignant melanoma (Musselman et al., 2001). One fascinating evolutionary theory of depression has to do with inflammation (Anders, Tanaka, & Kinney, 2013).

If inflammation and depression are linked, does diet affect inflammation levels? In 1996, the natural process of inflammation resolution that occurs in the human body was dubbed Resoleomics (Bosma-den Boer, van Wetten, & Pruijboom, 2012). It is suggested that, given the modern pandemic increase in illnesses (including mental illnesses) linked to chronic inflammation, resoleomics is being impaired in the modern day by lifestyle factors including modern dietary patterns (especially since the Industrial revolution) that are pro-inflammatory (Bosma-den Boer et al., 2012). One example of these dietary changes that interfere with resoleomics is the dramatically increased omega 6/ omega 3 fatty acids ratio, from an estimated 2-3:1 for hunter-gatherer diets to today's ratio of 10-20:1 (Bosma-den Boer et al., 2012). Mediterranean diets, which are rich in fruits, vegetables, legumes, and whole grains have been shown to have anti-inflammatory potential (Galland, 2010), and have been shown to be protective against depression (Sánchez-Villegas et al., 2009).

One randomized controlled trial put people in to one of three groups: the control, which was a whole grain cereal and low-saturated-fat dairy diet, a group on that same diet but that was also taking a statin, and a group that was eating a diet characterized by plant sterols, viscous fibers, soy foods, and almonds (the dietary

portfolio group; Jenkins et al., 2003). The control group had a 10.0% reduction in C-Reactive Proteins (a marker of inflammation), while the statin group and the dietary portfolio group saw reductions of 33.3% and 28.2%, respectively, which were not statistically significantly different (Jenkins et al., 2003). Many other studies have associated poor diet quality (high in red and processed meats, refined carbohydrates, and processed foods) with increased inflammatory markers, and good diet quality (rich in fruits and vegetables, whole grains, and legumes) has been associated with lower levels of inflammatory markers (Fung et al., 2001; Lopez-Garcia et al., 2004; Chrysohoou, Panagiotakos, Pitsavos, & Stefanadis, 2004).

Cross-sectional data suggest an association between inflammation and social isolation, although it is not known in what direction this association goes (Eisenberger, Inagaki, Mashal, & Irwin, 2010a). And this is especially relevant because both social isolation (Heinrich & Gullone, 2006) and inflammation (Capuron & Miller, 2011; Musselman et al., 2001) might contribute or even lead to depression or symptoms of depression. In one randomized controlled study, 39 participants were sorted in to one of two groups: one that was injected with endotoxins (an inflammatory agent), and one that was injected with a placebo (Eisenberger et al., 2010a). At all measured time points, the participants that received endotoxin had a statistically significant increase in both feelings of social disconnection and depressed mood (Eisenberger et al., 2010a). Along with depressed mood, anhedonia forms the key diagnostic criteria of depression (American Psychiatric Association, 2000), and it, like depressed mood, can also be induced by endotoxin injection, which was found in a randomized controlled trial (Eisenberger et al., 2010b).

Endotoxin stimulants are found in high concentrations in meat and processed foods, but minimal or undetectable in fresh fruit and vegetables (Erridge, 2011). To make matters worse, endotoxins appear to have a strong affinity for chylomicrons -- saturated fat transporters -- and so endotoxins along with saturated fat causes a higher increase in endotoxin levels (Harte et al., 2012). Endotoxin plasma concentrations are raised only by saturated fat (in the form of cream, in this study), with glucose (in the form of orange juice) not causing a rise in endotoxins (or any of the other inflammatory markers) (Deopurkar et al., 2010).

So what might be causing this increased inflammation? Among other things, poor diet quality (Berk et al., 2013). Diet quality has reduced globally in recent decades, characterized by a shift from fibrous, nutrient-rich foods with omega-3 polyunsaturated fats to diets higher in saturated fats and refined sugars (Berk et al., 2013). Poor diet quality has been shown by a number of studies to be associated with common mental disorders, and even individual nutrients such as lycopene are linked with depression (Berk et al., 2013).

High glycemic diets are associated with higher levels of the inflammatory marker CRP (Liu et al., 2002; Levitan et al., 2008). A diet disproportionately high in omega 6 fatty acids (characteristic of processed foods) is pro-inflammatory (Simopoulos, 2002). Both trans fats and saturated fats are also pro-inflammatory (Clarke, Shipley, Armitage, Collins, & Harris, 2009; Iwata et al., 2011).

One study identified a dietary pattern that was positively correlated with all inflammatory markers and sought to determine the relationship between this dietary pattern and depression risk among 43,685 women who did not have

depression at baseline in 1996 and who were followed until 2008 (Lucas et al., 2014). The inflammatory diet pattern was characterized by refined grains, sugary drinks, red meat, diet soft drinks, and margarine (Lucas et al., 2014), with some of these foods, like red meat (Azadhbakht & Esmailzadeh, 2008), refined grains and sugar sweetened beverages (Bosma-den Boer et al., 2012), having already been shown to induce inflammation in previous studies. This study found that an inflammatory diet pattern was associated with a higher risk of depression, with the Relative Risk comparing extreme quintiles of the inflammatory diet pattern for the broader definition of depression (after adjusting for confounders such as BMI) being 1.29 and for the stricter definition of depression being 1.41 (Lucas et al., 2014).

Antioxidants

Another aspect of depression that seems to be related to diet has to do with antioxidants. People who are depressed have been found to have lower antioxidant levels as well as lower levels of antioxidant enzyme activity (Maes, Galecki, Chang, & Berk, 2011). These factors can cause reduced protection against reactive oxygen species, which in turn can damage proteins, fatty acids, and DNA by oxidative and nitrosative stress (Maes, Galecki, Chang, & Berk, 2011; Berk et al., 2013), and clinical depression can accompany these factors (Berk et al., 2013). This damage can turn inactive autoepitopes (which are ubiquitous molecules) to neoantigens, which are immunogenic and can trigger autoimmune responses (Maes, Galecki, Chang, & Berk, 2011). An example of the many problems that this can cause is that LDL cholesterol

now causes more issues, as when it is oxidized, more IgG antibodies will be formed (Maes, Galecki, Chang, & Berk, 2011). This paper concludes by stating that these oxidative and nitrosative stress pathways, along with, as was previously discussed, inflammation, are key components of depression (Maes, Galecki, Chang, & Berk, 2011).

And how we eat has marked effects on our antioxidant status. One study compared the antioxidant status, oxidative stress status, coronary heart disease risk status, and inflammation status of 30 omnivores and 30 vegetarians (Szeto, Kwok, & Benzie, 2004). It found that vegetarians had a better antioxidant status and a lower risk of coronary heart disease than apparently healthy omnivores (Szeto et al., 2004), and proposes ascorbic acid levels as a potential marker of overall health status (Szeto et al., 2004), which is consistent with other research that, among other things, shows ascorbic acid is associated with lower rates of all-cause mortality (Khaw et al., 2001).

Oxidative free radicals damage lipids, proteins, and DNA, and this can cause abnormal neural growth and differentiation (Pandya, Howell, & Pillai, 2013). Thus, therapeutic approaches involving taking supplements of antioxidants can be helpful in managing neuropsychiatric illnesses in the long run (Pandya et al., 2013) – however, some research conflicts with this, as will be discussed later. However, there is a sweet spot for supplementation with antioxidants, as too many/much can cause unwanted problems stemming from interfering with some of the helpful functions of reactive oxygen species (Pandya et al., 2013).

So, might eating antioxidant rich foods help with mental health problems like depression? This study analyzed data from the Canadian Community Health Survey of 296,121 Canadians that were at least 12 years old over a period from 2000 to 2009, controlling for a number of potentially confounding factors like exercise and smoking habits (McMartin, Jacka, & Colman, 2013). The aim of the study was to see if fruit and vegetable intake was associated with a major depressive disorder in the previous 12 months but also looked at other mental health markers (McMartin et al., 2013). The study found that higher fruit and vegetable intake was associated with lower odds of depression, psychological distress, self-reported mood and anxiety disorders, and poor perceived mental health (McMartin et al., 2013). The authors conclude that a diet high in fruits in vegetables, which are rich in antioxidants, might combat the negative effects of oxidative stress on mental health (McMartin et al., 2013). Another study of 1,609 Taiwanese people aged 65 and older found that only three or more servings per week of vegetables cut their risk of developing depression four years later by 60% (Tsai, Chang, & Chi, 2012).

Rather than simply asking people how many fruits and vegetables they eat, the blood of people could actually be measured for antioxidants. One study analyzed data from the National Health and Nutrition Examination Survey from 2005 to 2006 for nearly 1,798 US adults (Beydoun, Beydoun, Boueiz, Shroff, & Zonderman, 2013). The levels of various antioxidants, carotenoids, retinol, Vitamin C, and Vitamin E, in the blood were measured, and it was found that higher levels of carotenoids in the blood were associated with a lower risk of elevated depressive symptoms, with the odds decreasing overall by 37% (Beydoun et al., 2013). Moreover, a dose-response

relationship was observed, meaning the more carotenoids in the blood, the lower the risk of depression (Beydoun et al., 2013). However, no association was found for Vitamin C, Vitamin E, or retinol (Beydoun et al., 2013).

One study, more specifically, looked at lycopene, which it claims is the most powerful of all of the carotenoids (Niu et al., 2013). Lycopene is the red pigment found mostly in tomatoes (Niu et al., 2013), but also in guava, papaya, pink grapefruit, and watermelon. In a test tube, lycopene was 100 times more effective at singlet oxygen quenching action than Vitamin E (Niu et al., 2013). This study assessed the dietary intake of 986 Japanese individuals over the age of 70 and found that, even after adjusting for potentially confounding factors, those who ate the most tomato products had approximately half the odds of depression (Niu et al., 2013). This led the researchers to conclude that a diet high in tomato consumption may help in the prevention of depression (Niu et al., 2013).

One study examined the antioxidant, fruit, and vegetable intake of 278 people over the age of 60 between 1999 and 2007, and found that Vitamin C, lutein, and beta cryptoxanthin levels were lower in clinically depressed patients than those who were not, with fruit and vegetable intake, which is a primary determinant of antioxidant intake, lower in those with depression (Payne, Steck, George, & Steffens, 2012). Moreover, contrary to the Pandya et al. article cited above, this study found no association between antioxidant intake from dietary supplements and depression (Payne et al., 2012). Interestingly, the lack of antioxidants in depressed people might explain depression's association with cardiovascular disease (Payne et al., 2012). The authors of this study mention that perhaps the association between

fruits and vegetables and depression is not because of antioxidants but because of folate (Payne et al., 2012).

Folate

One study examined the dietary habits of 3,486 middle-aged, Finnish office workers and identified two different dietary patterns: a whole food dietary pattern and a processed food dietary pattern (Akbaraly et al., 2009). The whole food dietary pattern was high in fruits, vegetables, and fish, while the processed food dietary pattern was high in fried food, sweetened desserts, processed meat, refined grains, and high-fat dairy products (Akbaraly et al., 2009). Those who were in the highest third of the whole food dietary pattern had lower odds of depression five years later than those in the lowest third, and those who ate more of a processed dietary pattern had higher odds of depression five years later (Akbaraly et al., 2009). The higher antioxidant content in the whole foods could be a plausible mechanism for this, but it could also be the high folate content found in large amounts in whole plant foods like some cruciferous vegetables, leafy vegetables, other green vegetables, and legumes (Akbaraly et al., 2009). Folate might be important because when it is low, that might also mean low levels of S-adenosylmethionine, which is a universal methyl donor that is needed for the formation of myelin, neurotransmitters, and membrane phospholipids (Akbaraly et al., 2009). It is difficult to establish causality, as it might be that depression causes low folate (i.e. when one is depressed, one is less likely to want to eat vegetables), and so a

randomized controlled or cohort study is required (Gilbody, Lightfoot, & Sheldon, 2007), which is what the Tolmunen et al. study covered next is. Although some studies did not find the same association (Kamphuis, Geerlings, Grobbee, & Kromhout, 2008), one study of 2,313 Finnish men did find that those below the energy-adjusted median for folate levels had a three times higher risk of getting a discharge diagnosis of depression than those above this median (Tolmunen et al., 2004). However, consistent with the Payne et al. study but contrasting with the Pandya et al. study, folic acid (the dietary supplement version of folate) was found to have no protective effect against mood disorders as compared to placebo (Sharpley, Hockney, McPeake, Geddes, & Cowen, 2014), which may be due to the fact that folate is a general term for a group of water soluble B vitamins known as B9, which are found in large amounts in green leafy vegetables, while folic acid is an oxidized, synthetic compound (Sharpley et al., 2014). Fish is another possible mechanism via its high content of long-chain omega-3 polyunsaturated fatty acids, but it might be incorrect to try and pin this association down to simply one component of whole foods (i.e. folate), as it might be a cumulative, synergistic effect of all of the components of the whole foods that explain the protective effect of diet on depression (Akbaraly et al., 2009), which could also explain the lack of protection that folic acid supplementation seems to give.

Brief Supplementation Sidenote

Of note, to make the waters in regard to supplementation even more murky, one randomized, double-blind, placebo-controlled trial of 14 days for 81 healthy young adults found that those taking high dose Vitamin C (Ascorbic Acid) supplements had a decrease in Beck depression scores (Brody, 2002).

Arachidonic Acid, Fish

As we have already seen, it is not just what one eats that can help with mental health, but also what one does not eat. One compound that might be to blame for this is called arachidonic acid. It has been found to promote brain changes like neuroinflammation that can disturb one's mood (Farooqui, Horrocks, & Farooqui, 2007), and it is consumed more in omnivorous diets than vegetarian diets (Beezhold, Johnston, & Daigle, 2012; Beezhold & Johnston, 2012), being found primarily in chicken, eggs, beef, and other animal products (National Cancer Institute, 2016). One study of 234 pregnant women found that those eating more arachidonic acid had a higher risk for suicide and major depressive episodes (Vaz, Kac, Nardi, & Hibbeln, 2014). However, omega 3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid), which are higher in omnivorous diets due to increased fish intake, counteract the negative effects of arachidonic acid (Farooqui, Horrocks, & Farooqui, 2007; Beezhold & Johnston, 2012), yet, despite this, one study of 138 Seventh Day Adventists found that vegetarians reported significantly less negative emotion than omnivores (Beezhold, Johnston, & Daigle, 2012). One later randomized control trail put 39 people in one of three groups: the omnivorous

group that served as the control, which continued eating meat, fish, and poultry daily, the fish group that stopped eating meat and poultry but that ate fish three or four times per week, or the vegetarian group that avoided meat, fish, and poultry (Beezhold & Johnston, 2012). The vegetarian group showed improvement in various aspects of mood states, such as confusion, stress, and tension, in just two weeks, while the omnivorous control group and fish group showed no improvement (Beezhold & Johnston, 2012). This is in contrast to other studies that show mood benefits from eating large amounts of fish in nonvegetarian populations (Assisi et al., 2006), perhaps because nonvegetarian diets benefit from the extra omega-3 in order to combat their higher intakes of arachidonic acid.

Polyphenols

Polyphenols, found in plants, can combat oxidative stress and stimulate the signaling pathway of molecules that are involved in synaptic plasticity, which is a brain process that underlies cognitive functioning, and can also influence cellular energy metabolism (Gomez-Pinilla & Nguyen, 2012). Polyphenols have the added advantage (over other treatments) of affecting a lot of different mechanisms in the brain that are helpful in maintaining healthy cognition and mental health (Gomez-Pinilla & Nguyen, 2012) – and even assist processes that are helpful in the prevention of neurodegenerative disorders (Gomez-Pinilla & Nguyen, 2012). The authors of this study examining the molecular factors, like polyphenols, that can

make diet an effective means for treating cognitive and psychiatric disorders conclude that diets high in polyphenols might serve as a cheap and non-invasive strategy to supporting a healthy brain (Gomez-Pinilla & Nguyen, 2012).

Monoamine Oxidase

Monoamine oxidase A is an enzyme that helps to maintain the right amount of monoamines in the brain by reducing amounts to normal levels, which are a type of neurotransmitters that include serotonin, dopamine, and norepinephrine, and imbalances in these neurotransmitters, especially in that these monoamines tend to be lower in people who are depressed (Meyer et al., 2006), are what essentially constitute the monoamine theory of depression (Mulinari, 2012). One study measured the monoamine oxidase A levels in the brains of 17 depressed people and 17 non-depressed people and found that it was significantly elevated in all of the ten different brain regions analyzed for depressed people (Meyer et al., 2006), levels that were on average 34% higher than non-depressed people, which represents two standard deviations (Meyer et al., 2006). Thus, elevated levels of monoamine oxidase A in the brains of depressed people might explain the lower levels of serotonin, norepinephrine, and dopamine in the brains of depressed people (Meyer et al., 2006). Many common antidepressants work by acting on any one or more of the various monoamines themselves (Bourin, David, Jolliet, & Gardier et al., 2002; Feighner, 1999), yet, since the monoamine imbalance stems from levels of monoamine oxidase A that are too high, drugs that work directly on this enzyme

also exist (Feighner, 1999). However, these drugs can cause serious side effects, such as the so-called Cheese effect, which can result in death (Malozowski & Chiesa, 2010), and comes from interactions with foods and beverages that contain amines (i.e. tyramine), with the name coming from the fact that some cheeses have relatively high amounts of amines (Anderson, Hasan, McCrodden, & Tipton, 1993).

It appears we can get monoamine oxidase A inhibitors through our diet, though, and without all of the side effects that come from drugs. While various plant foods have monoamine oxidase inhibitors, many of these food sources have amounts that are too small to significantly impact the levels of monoamine oxidase in our brains (Clarke & Ramsay, 2010). For example, spices such as cloves, oregano, cinnamon, and nutmeg, have eugenol, a monoamine oxidase inhibitor, but in amounts too small to reach consistently significant levels of neuronal monoamine oxidase (Clarke & Ramsay, 2010). Tobacco has large amounts of monoamine oxidase that reach the brain, which might help explain why smoking can make someone feel so good (van Amsterdam, Talhout, Vleeming, & Opperhuizen, 2006), although alcoholics get the same monoamine oxidase inhibition as tobacco users, but this might be attributable to concomitant tobacco use in alcoholics (van Amsterdam et al., 2006). Of course, the pros of the monoamine oxidase inhibition in tobacco do not outweigh the cons. Fortunately, quercetin, which is found in a variety of plant foods including apples, berries, kale, onions, grapes, and green tea (Harnly et al., 2006), was found to significantly increase monoamine oxidase inhibitors in the brain (Clarke & Ramsay, 2010).

Carbohydrates

The macronutrient makeup of plant-based foods might also be favorable for depression. One study of 28 subjects, 19 of which suffered from severe premenstrual syndrome and nine of which served as controls, found that a meal high in carbohydrates and low in protein during the luteal phase of the menstrual cycle (but not the follicular phase) improved depression, tension, confusion, sadness, fatigue, anger, calmness, and alertness scores in those with premenstrual syndrome ($p < 0.01$) (Wurtman, Brzezinski, Wurtman, & Laferrere, 1989). The authors note that this effect might be due to the fact that brain serotonin increases after intake of carbohydrates, and serotonin is involved in mood and appetite (Wurtman et al., 1989).

Further support for this comes from a randomized controlled study of 106 overweight or obese participants who were assigned to one of three groups for one year: a calorie restricted group, a low-carbohydrate, high-fat group, or a high-fat, low-carbohydrate group (Brinkworth, Buckley, & Noakes, 2009). Weight loss was not significantly different between the groups, yet the low-fat, high-carbohydrate group experienced much more favorable psychological outcomes than the high-fat, low-carbohydrate group, with less mood disturbance, anger-hostility, confusion-bewilderment, and depression-dejection ($p < 0.05$) (Brinkworth et al., 2009). Thus, one should avoid low-carbohydrate diets for weight loss, as they offer no significant improvements in weight loss but do cause worse psychological outcomes, with high-carbohydrate diets potentially inferring benefits.

The Microbiome and Probiotics

The microbiome and its connection to our mental health is becoming an increasingly hot topic, with the field being dubbed enteric neuroscience (Mayer, 2011). But even over a century ago, melancholia was successfully treated with dietary interventions that involved starting patients on a vegetarian diet and a probiotic (Phillips, 1910). The gut has about as many neurons as the spinal cord, at about 200-600 million (Furness, 2006), and intestinal bacteria might directly communicate with the central nervous system via the vagal sensory nerve fibers and the peripheral immune system (Mayer, 2011). Approximately 2/3 of the body's immune system cells are located in the gut, which makes sense given the fact that our intestines are our body's largest area of contact with the outside world, having 100 times the surface area of our skin (Mayer, 2011). Our intestines have approximately 100 trillion microorganisms from 40,000 different species with a staggering 100 times the number of genes as are in the human genome (Kurokawa et al., 2007).

Our minds can affect our gut microbiome (Knowles, Nelson, & Palombo, 2008). This study actually scraped feces from the toilet paper of undergraduates either during exam week or at the beginning of the semester, and found that around exam time (the day before the exam, the day of the exam, and then for five days after the exam), fecal lactic acid bacteria levels were lower than at the baseline condition of the first week of the semester (Knowles et al., 2008).

So can our microflora affect our minds? Chronic Fatigue syndrome is a complex illness that involves disturbances in the emotional realm (especially anxiety) as well as disturbances in the intestinal microbial flora (Rao et al., 2009). One randomized, double-blind, placebo-controlled trial of 39 Chronic Fatigue Syndrome patients put people on either a probiotic or a placebo pill for two months (Rao et al., 2009). It found that the patients in the probiotic group experienced a significant rise in the measured gut flora as well as a corresponding improvement in anxiety symptoms as compared with the control group ($p=0.01$) (Rao et al., 2009). And similar results were found in another clinical trial, except this one was in healthy people (who did not have Chronic Fatigue Syndrome), with a probiotic for one month significantly reducing anxiety, depression, anger, and hostility (Messaoudi et al., 2011). And the mechanism of action for probiotics is an exciting mode of inquiry, as it could influence how they are made in the future (Lyte, 2011). One theory is that probiotics might even produce neurochemicals, allowing them to be considered as delivery vehicles for neuroactive compounds (Lyte, 2011).

A More Broad, Holistic Perspective

Although the literature cited thus far included many studies that controlled for a wide variety of variables, the following studies should be emphasized for their scientific power, as randomized controlled trials (a few of which have already been cited) are the gold standard in science, given how they control for confounding variables. Moreover, meta-analyses also should be highlighted, as they pool a large

amount of studies on a given topic together to get a more broad, complete, and thorough answer to a question.

Regardless of the molecular mechanisms (i.e. monoamine oxidase inhibitors, inflammation, etc.), a healthy diet seems to help with depression. One 2014 systematic review and meta-analysis of literature moved away from looking at the inconsistent research on single nutrients and instead looked at studies that examined overall dietary pattern and its effects on depression (Lai et al., 2013). It identified 21 studies that were considered sufficiently methodologically rigorous (Lai et al., 2013). Consistent with aforementioned studies, it found that a healthy diet pattern (high in fruits, vegetables, whole grains, and fish) was significantly associated with a reduced odds of depression ($P < 0.001$) (Lai et al., 2013). However, a different finding of this review is inconsistent with some of the aforementioned research – it found no association with the Western diet pattern (which is the less healthy of the two identified dietary patterns) and depression, although the authors mention that there were not enough of these studies to make a precise estimate of the effect (Lai et al., 2013).

One 18- week, randomized controlled study of 292 participants of a variety of ethnicities (at multiple different sites) found that a plant-based, vegan diet, as compared to the control group, improved impairments because of health, overall work impairment because of health, non-work related activity impairment because of health, fatigue, anxiety, emotional well-being, daily functioning because of physical health, general health, and depression (Agarwal et al., 2015). These results are consistent with another randomized controlled trial (Katcher, Ferdowsian,

Hoover, Cohen, & Barnard, 2010). The authors discuss how lifestyle interventions for physical and mental health are being increasingly accepted (Lopresti, Hood, & Drummond, 2013), and that “among the most effective of these is the use of plant-based diets” (Agarwal et al., 2015).

Conclusion

The goal of this thesis was to empower the reader to take better control of their depression. It is important to note that, although the focus of this paper is depression, the “healthy” diet pattern discussed in this thesis seems to help with mental health in general (rather than just depression). In other words, dietary manipulations are a promising area for people with any mental illnesses. Moreover, the benefits of this lifestyle intervention go beyond mental health – unlike antidepressant medications, the “side effects” of using diet as a treatment for depression are benefits to physical health.

Future research should look at other lifestyle factors that might be able to influence depression and mental health, such as exercise and meditation. Moreover, further examination in to the link between depression and fish should be done, as this paper reports conflicting evidence. The link between aspartame and depression should also be further reported on. As there is conflicting evidence about whether or not unhealthy dietary patterns are linked to depression, this should be studied more.

There is a lot of clinical and policy work that needs to be done to advance the agenda. This paper addressed diet and health. But while we may know what diet one should eat for health and what diet one should avoid for health, we do not know exactly what the best ways are to actually get the public to eat healthy foods and to minimize consumption of unhealthy foods. The same problem applies for how healthcare providers can get their patients to eat healthier.

With all of that said, I want to conclude this paper by summarizing – in the form of practical takeaways – the most important lessons from this paper. First, people should be encouraged to eat more plant foods and fewer animal foods (and animals, in general). Second, people should eat more “whole” foods and less processed foods. Finally, it is critical that people know that it does not have to be an all or nothing effort, a little effort can go a long way.

Author Contributions

The topic and then subsequent idea for this thesis was discussed and decided upon by Brooks Butler and David Katz. The research and writing was done by Brooks Butler, and a draft was read and reviewed by David Katz, with comments, suggestions, and critiques coming from David Katz. General support throughout the process was given by David Katz.

Although he was not directly involved with this thesis, I would be remiss to not include an acknowledgement to Dr. Michael Greger, whose work was extremely helpful in the research process of this thesis.

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