A review of lifestyle factors that contribute to important pathways associated with major depression: Diet, sleep and exercise

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Abstract

Research on major depression has confirmed that it is caused by an array of biopsychosocial and lifestyle factors. Diet, exercise and sleep are three such influences that play a significant mediating role in the development, progression and treatment of this condition. This review summarises animal and human-based studies on the relationship between these three lifestyle factors and major depressive disorder, and their influence on dysregulated pathways associated with depression, namely neurotransmitter processes, immuno-inflammatory pathways, hypothalamic-pituitary-adrenal (HPA) axis disturbances, oxidative stress and antioxidant defence systems, neuroprogression, and mitochondrial disturbances. Increased attention in future clinical studies on the influence of diet, sleep and exercise on major depressive disorder and investigations of their effect on physiological processes will help to expand our understanding and treatment of major depressive disorder. Mental health interventions, taking into account the bidirectional relationship between these lifestyle factors and major depression are also likely to enhance the efficacy of interventions associated with this disorder.

Keywords: depression; diet; exercise; sleep; physical activity

1. Introduction

Technological advances have changed how we communicate, the activities we engage in, our occupational and recreational pursuits, and even the foods that we eat. While sport and leisure activity levels have remained stable or increased slightly over time, physical activity associated with work, home, and transportation has declined significantly (Brownson et al., 2005, Juneau and Potvin, 2010). In the United States it was estimated that over the past 50 years occupation-related energy expenditure decreased by more than 100 calories/day (Church et al., 2011). Driving to work increased from 67% of the working north American population in 1960 to 88% in 2000 (Brownson et al., 2005) and, in U.S. schoolchildren, walking or riding bikes to school decreased from 40% in 1969 to 13% in 2001 (McDonald, 2007). Dietary changes are also significant as worldwide sugar consumption has increased by 74-kcal/day per person from 1962 to 2000. Of this increase, 80% was derived from sugared beverages with additional contributions from restaurant and fast food sources (Popkin and Nielsen, 2003). Alarmingly, sugar consumption has increased most in children aged 6-11 years with an approximate 20% increase from 1988 to 2004 (Wang et al., 2008).

These and other changes of modernity over the past few decades have coincided with a reported increase in the prevalence of many psychiatric problems, including major depression. Between 1991-92 to 2001-2, one-year prevalence rates of major depression increased from 3.33% to 7.06% in a community population of American adults (Compton et al., 2006). Increases have also been observed in Australian communities with prevalence rates rising from 6.8% to 10.3% between 1998 and 2008 (Goldney et al., 2010). While these increased rates of depression may be due, in part, to improvements in diagnostic recognition, changes in diagnostic criteria and increased community acceptance of this condition, contemporary lifestyles might also explain why depression is on the rise. However, underlying mechanisms are not well understood. This review provides a summary of three major lifestyle mediators - diet, exercise and sleep - associated with major depression and their impact on a range of relevant biological and physiological pathways.

2. Methods

2.1. Search strategy

The PubMed, Google Scholar, and PsycInfo databases were searched from all years of record until August 2012. Most references were obtained from combinations of the following key terms: "depression", "diet", "nutrients", "sleep", "exercise", "inflammation", "oxidative stress", "mitochondria", "neurogenesis", "BDNF", "HPA", "cortisol", "serotonin" and "monoamines". The reference lists of relevant papers were also examined to locate additional studies that were not identified by the database searches.

2.2. Eligibility criteria

Studies were included in this review if they were published in English, comprised animal or human investigations and examined areas of exercise, sleep or diet and their impact either on inflammation, hypothalamic–pituitary–adrenal (HPA) axis, neurotransmitters, neuroprogression and oxidative/nitrosative stress.

3. Dysregulated pathways in major depression

Major depression has a multifactorial etiology arising from environmental, psychological, genetic and biological factors. As outlined in figure 1, research over the past decade has clarified that depression is associated with neurotransmitter imbalances, HPA disturbances, dysregulated inflammatory pathways, increased oxidative and nitrosative damage, neuroprogression, and mitochondrial disturbances (Leonard and Maes, 2012, Lopresti et al., 2012, Maes et al., 2009c, Manji et al., 2001, Raison and Miller, 2011). While these disturbances will each be discussed briefly they are not mutually exclusive.

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3.1. Neurotransmitter imbalances

Imbalances in the production and transmission of neurotransmitters such as serotonin, dopamine, noradrenaline and glutamate are commonly observed in the central nervous system in major depression (Maletic et al., 2007). Deficiencies in serotonin availability, the most extensively studied neurotransmitter in depression, is supported by studies using tryptophan depletion models (which reduces central serotonin synthesis) (Hood et al., 2005, Toker et al., 2010) and findings of serotonin receptor abnormalities in depressed patients (Carr and Lucki, 2011). Depression is also associated with an increased availability of monoamine oxidase, an enzyme that metabolises serotonin and other monoamines in the brain (Meyer et al., 2006), and abnormalities in the expression of the enzyme tryptophan hydroxylase, which is involved in serotonin synthesis (Matthes et al., 2010). However, the strongest evidence of neurotransmitter imbalances in depression comes from the popular use and efficacy of pharmaceutical antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), which are thought to alleviate depression by increasing the availability of monoamines such as serotonin, noradrenaline (i.e., norepinephrine) and, possibly, dopamine (Connolly and Thase, 2012).

3.2. HPA disturbances

Dysfunction in the HPA axis is common in patients with major depression (Pariante and Lightman, 2008). This is characterised by heightened cortisol secretion in patients presenting with melancholic depression, and reduced levels in atypical depression (Gold and Chrousos, 2002). Depression is also associated with hypersecretion of corticotropin-releasing hormone (CRH) and impairment in responsiveness to glucocorticoids (Pariante and Lightman, 2008). An increased size and activity of the pituitary and adrenal glands are also found in major depression (Nemeroff et al., 1992). Successful treatment with antidepressants is associated with a normalisation of HPA axis activity and restoration in glucocorticoid receptor function (Anacker et al., 2011a, Anacker et al., 2011b).

3.3. Oxidative & nitrosative stress

Decreased antioxidant status and elevated oxidative and nitrosative stress are found in patients with major depression (Maes et al., 2011a). This is evidenced by reduced plasma concentrations of important antioxidants such as vitamin C (Khanzode et al., 2003), vitamin E (Maes et al., 2000, Owen et al., 2005), and coenzyme Q_{10} (Maes et al., 2009b), and by reduced antioxidant enzyme activity such as glutathione peroxidase (Maes et al., 2011d). These deficiencies in antioxidant defences impair protection against reactive oxygen species (ROS), leading to damage to fatty acids, proteins and DNA (Maes et al., 2011a).

Depression is also associated with increased levels of lipid peroxidation, comprising elevations in malondialdehyde (Ozcan et al., 2004, Sarandol et al., 2007, Wei et al., 2009), and increased oxidative damage to DNA, characterised by increased levels of 8-hydroxy-2-deoxyguanosine (Forlenza and Miller, 2006, Maes et al., 2009a). Depression is also associated with increased plasma levels of peroxides and xanthine oxidase (Herken et al., 2007, Maes et al., 2010). The efficacy of antioxidant therapies for depression is unknown, although N-acetylcysteine, a powerful antioxidant, was found to be useful for depressive episodes in bipolar disorder (Berk et al., 2008, Magalhaes et al., 2011) and zinc, which serves as a strong antioxidant, also has antidepressant activity (Szewczyk et al., 2011).

3.4. Neuroprogression

Neurogenesis and neuronal plasticity are compromised in major depression, with subsequent neurodegeneration (Lee and Kim, 2010). This results in stress-induced alterations to the number and shape of neurons and glia in brain regions of depressed patients (Duman, 2009) and decreased proliferation of neural stem cells (Eyre and Baune, 2012).

Brain-derived neurotrophic factor (BDNF) is the most abundant and widely distributed neurotrophin in the central nervous system, involved in neuronal survival, growth and proliferation (Martinowich and Lu, 2008). BDNF levels are low in people with major depression (Duman, 2009, Lee and Kim, 2010). However, BDNF levels increase with chronic administration of several classes of antidepressants, including monoamine oxidase inhibitors, SSRIs, tricyclic agents, and SNRIs (Duman and Monteggia, 2006, Sen et al., 2008). Early life and chronic stress, which is often typical in patients with major depression, also has detrimental effects on BDNF (Martinowich et al., 2007, Nagahara and Tuszynski, 2011).

3.5. Mitochondrial disturbances

Mitochondria are intracellular organelles that generate most of the cell's supply of adenosine triphosphate (ATP) and are also involved in a range of other processes such as signalling, cellular differentiation, cell death, and the control of the cell cycle and cell growth (McBride et al., 2006). High concentrations of mitochondria are found in the brain which increases its vulnerability to reductions in aerobic metabolism (Pieczenik and Neustadt, 2007).

Depression is associated with mitochondrial dysfunction or disease with evidence of deletions of mitochondrial DNA (Gardner and Boles, 2008a, Shao et al., 2008), and lower activities of respiratory chain enzymes and ATP production (Gardner et al., 2003). Depressed patients presenting with somatic complaints also have low ATP production rates in biopsied muscles (Gardner and Boles, 2008a, Gardner and Boles, 2008b). In addition, rates of depression are increased in patients with mitochondrial disorders (Fattal et al., 2007, Koene et al., 2009).

3.6. Immuno-inflammation

Increased inflammation in major depression has been confirmed in three recent meta-analyses. Elevated levels of C-reactive protein (CRP), interleukin-1 (IL-1), and interleukin-6 (IL-6) were reported in a meta-analysis on depression in clinic and community samples (Howren et al., 2009), levels of tumour necrosis factor-α (TNF-α) and IL-6 were significantly higher in depressed patients than controls (Dowlati et al., 2010), and blood levels of soluble interleukin-2 receptors, TNF-α and IL-6 were higher in a meta-analysis on patients with major depressive disorder than controls (Liu et al., 2012b). Major depression is also characterised by a Th-1-like cell-mediated response, with evidence of increased production of interferon-γ (IFN-γ), increased IFN-γ/IL-4 ratios and increased neopterin levels (Maes et al., 1994, Myint et al., 2005). In addition, anti-depressant medications have anti-inflammatory effects (Hannestad et al., 2011).

An elevated immuno-inflammatory response in major depression is further supported by investigations into kynurenine pathway metabolites or TRYCATS (tryptophan catabolites along the IDO pathway) (Dantzer et al., 2011, Maes et al., 2011c). As shown in Figure 2, TRYCATS are produced by the breakdown of tryptophan, involving the enzyme indoleamine 2,3-dioxygenase (IDO). IDO is expressed in multiple cell types including macrophages, dendritic cells, astrocytes and microglia and is strongly activated by the pro-inflammatory cytokine IFN-γ and to a lesser extent TNF-α, IL-1, and IL-6. These TRYCATS have both neurotoxic and neuroprotective qualities. Preliminary research has demonstrated a relationship between depression and low levels of the neuroprotective TRYCAT, kynurenic acid (KYNA) (Maes et al., 2011b, Myint et al., 2007, Wichers et al., 2005), and high levels of the excitotoxic TRYCAT, quinolinic acid (QUIN) (Raison et al., 2010a, Steiner et al., 2011). However, further research is warranted as Hughes et al., (2012) found no differences in IDO expression or plasma levels of TRYCATS between depressed patients and controls.

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4. Lifestyle factors associated with major depression

Dysregulation in the pathways reviewed above can be influenced by environmental, social, psychological, lifestyle, genetic and physiological factors (Hidaka, 2012, Leonard and Maes, 2012). Diet, sleep and exercise are three such influences that play an important role in the

etiology, progression and treatment of depression. A bidirectional relationship likely exists between depression and these mediators.

4.1. The relationship between diet and depression

An association between diet and depression has now been confirmed in prospective and epidemiological studies. For example, in elderly men and women, the consumption of fish, vegetables, olive oil, and cereal correlated negatively with the severity of depressive symptoms (Mamplekou et al., 2010). The benefits from fish and olive oil intake remained significant even when adjusted for confounders such as age, sex, education status, BMI and physical activity status, as well as the presence of a number of medical conditions. In a prospective study, and after adjusting for sex, age, smoking status, BMI, physical activity levels and employment status, adherence to a Mediterranean diet comprising high levels of vegetables, fruit, nuts, cereal, legumes, and fish, a moderate alcohol intake, and a low consumption of meat or meat products and whole-fat dairy, was protective against the development of depression (Sanchez-Villegas et al., 2009). In a study by Jacka et al. (2010b), consuming a 'traditional' diet comprising vegetables, fruit, meat, fish, and whole grains was also associated with a 35% reduced risk of depression or dysthymia. Research into the diet of adolescents (Jacka et al., 2010a) and of low socio-economic, community dwelling, elderly people (German et al., 2011) has also provided evidence for an association between diet quality and depression. Depressive symptoms are also positively associated with the consumption of sweets (Jeffery et al., 2009). Similarly, high intake of fast food (hamburgers, sausages, pizza) and processed pastries (muffins, doughnuts, croissants) are associated with an increased risk of depression up to 6 years later (Sanchez-Villegas et al., 2012).

High-quality treatment studies investigating the impact of diet on depression are scarce, although in a randomised-controlled trial, meat-eating adults placed on a two-week vegetarian diet reported significantly greater improvements in mood compared to participants who continued to eat meat, fish or poultry (Beezhold and Johnston, 2012). In another randomised-controlled trial, six days on a low protein diet significantly decreased depressive symptoms in type 2 diabetics (Ciarambino et al., 2011), and in a randomised study on overweight and obese individuals, those placed on an energy-restricted, low-fat diet for one year experienced greater improvements in mood compared to participants on an energy-restricted, low-carbohydrate diet (Brinkworth et al., 2009). These changes were independent of weight loss.

Polyunsaturated fatty acids (PUFAs) and particularly omega-3 essential fatty acids (ω-3 EFA) have received significant attention in relation to depression. In a meta-analysis of 14 studies comparing the levels of PUFAs between depressed patients and control subjects, the levels of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and total ω-3 EFA were significantly lower in depressed patients than controls (corresponding to effect sizes of -0.18, -0.35 and -0.51, respectively). There was no significant change in arachidonic acid (AA) or total ω-6 PUFAs (Lin et al., 2010). A meta-analysis of the effects of EPA supplementation in 15 clinical trials in depressed populations revealed beneficial effects from fish oil containing high levels of EPA (effect size = 0.53) (Sublette et al., 2011).

Other investigations on the relationship between nutrients and depression have demonstrated a role of folate (Farah, 2009, Gilbody et al., 2007, Morris et al., 2008), tryptophan (Cowen et al., 1989, DeMyer et al., 1981, Maes et al., 1987), zinc (Cope and Levenson, 2010, Lai et al., 2012, Szewczyk et al., 2011), iron (Maes et al., 1996, Stewart and Hirani, 2012, Vahdat Shariatpanaahi et al., 2007, Yi et al., 2011), CoQ10 (Maes et al., 2009b), vitamin B6 (Merete et al., 2008, Moorthy et al., 2012, Skarupski et al., 2010, Williams et al., 2005), vitamin B12 (Hintikka et al., 2003, Moorthy et al.,

2012), and selenium (Gao et al., 2012, Mokhber et al., 2011, Pasco et al., 2012). However, findings on most of these nutrients require further investigation before definitive conclusions about their relationship with depression can be made.

4.1.1. Diet and its effect on inflammation

There is now strong evidence in human studies that adherence to a Mediterranean diet is associated with reduced inflammatory markers (Camargo et al., 2012, Richard et al., 2012, Urpi-Sarda et al., 2012). In a study on people with metabolic syndrome, five weeks on a Mediterranean diet corresponded with lowered plasma CRP and an arbitrary inflammatory score that included CRP, IL-6, IL-18, and TNF-α. These changes were independent of any weight loss (Richard et al., 2012). Compared to participants placed on a low-fat diet, one year on a Mediterranean diet was associated with lowered plasma concentrations of IL-6, and two TNF receptors (Urpi-Sarda et al., 2012). In contrast, intercellular adhesion molecule-1 and TNF receptor concentrations were increased in people consuming a low-fat diet. In another intervention study, postprandial inflammatory gene expression in mononuclear cells decreased after three weeks on either a Mediterranean diet enriched with olive oil, a diet rich in saturated fatty acids, or a low-fat/high-carbohydrate diet enriched with ω-3 PUFU compared to the other diets (Camargo et al., 2012, Yubero-Serrano et al., 2012)). Luciano and colleagues (2012) also found that CRP levels were lower in an elderly population on a Mediterranean diet compared to a standard 'healthy diet' comprising a high intake of fruits and low consumption of eggs, spirits or liqueurs, and meats such as bacon, pork, lamb, and sausages .

In relation to the anti-inflammatory effect of PUFAs, in a recent review of twenty-six randomised clinical trials, dietary ω-3 EFAs were found to be associated with lower plasma biomarker levels, reflecting lower levels of inflammation and endothelial activation (e.g., IL-6, CRP, TNF- α, sICAM-1 and GM-CSF) in cardiovascular disease and other chronic and acute diseases. Calder (2012) recently concluded that fatty acids were able to partly inhibit a number of aspects of inflammation including leukocyte chemotaxis, adhesion molecule expression and leukocyte-endothelial adhesive interactions, production of eicosanoids from arachidonic acid, production of inflammatory cytokines, and T cell reactivity.

4.1.2. Diet and its effect on neurotransmitters

Diet quality is important in the production of monoamines such as serotonin and dopamine and can influence receptor sensitivity and neurotransmitter transporters. In animal studies, semi-starvation on a high carbohydrate or protein diet affected serotonin turnover in the brain (Schweiger et al., 1989). In addition, the consumption of sugar as part of a meal (Inam et al., 2006) or eating a high-carbohydrate diet (Buwalda et al., 2001) influenced 5-HT_{1A} receptor sensitivity; and one week on a high fat, low carbohydrate diet decreased serotonin release in the hypothalamus (Banas et al., 2009). In contrast, the acute intake of a carbohydrate-rich food increased brain tryptophan and consequent brain serotonin levels (Fernstrom and Wurtman, 1971). This was likely due to carbohydrates acutely increasing brain tryptophan availability compared to other large neutral amino acids (Wurtman and Wurtman, 1995).

Dopaminergic systems are also influenced by diet as the consumption of combinations of dietary fat and sugar reduced D_2 receptor signalling (Pritchett and Hajnal, 2011), the intake of a high fat diet altered dopamine-related gene expression (Lee et al., 2010, Vucetic et al., 2012), a high-fat diet during early life altered biochemical markers of dopamine signalling in the nucleus accumbens (Teegarden et al., 2009), and the long-term consumption of a low protein-high

carbohydrate diet decreased D_2 dopamine receptor density (Hamdi et al., 1992). Striatal dopamine levels were also increased in rats supplemented with strawberry, spinach, or vitamin E (Martin et al., 2000).

Other nutrients which are altered in patients with major depression and that can influence neurotransmitter production include tryptophan (and other large neutral amino acids: valine, leucine, isoleucine, phenylalanine and tyrosine) (Maes et al., 2011c, Markus, 2008, Toker et al., 2010), folic acid (Miller, 2008, Stahl, 2008), zinc (Cichy et al., 2009, Szewczyk et al., 2011, Szewczyk et al., 2009), vitamin B12 (Bottiglieri, 1996, Deana et al., 1977), vitamin B6 (Calderon-Guzman et al., 2004, Demisch and Kaczmarczyk, 1991, Hartvig et al., 1995) and iron (Baumgartner et al., 2012, Burhans et al., 2005, Coe et al., 2009). Omega-3 EFAs are also able to modify monoaminergic neurotransmission (Chalon, 2006, Su, 2009).

4.1.3. Diet and its effect on oxidative stress

Given the crucial role that diet plays in antioxidant intake, it comes as no surprise that diet quality influences levels of oxidative stress. In animal studies, rats fed a high-sugar/high-fat diet had increased lipid peroxidation in the brain (Ribeiro et al., 2009, Stranahan et al., 2011), elevated plasma malondialdehyde (MDA) concentrations (a marker of lipid peroxidation) (Panchal et al., 2011) and increased mRNA expression levels of genes involved in ROS production in both the liver and adipose tissue (Matsuzawa-Nagata et al., 2008). In obese adults with metabolic syndrome, reducing energy intake by 2000kJ, mainly via carbohydrate restriction, was associated with decreased oxidative stress and increased levels of antioxidant markers, alpha-tocopherol and ceruloplasmin (Skalicky et al., 2009). However, placing adults with metabolic syndrome on a 12-week high-fat diet or low-fat, high complex-carbohydrate diet had no effect on markers of oxidative stress and inflammation (Petersson et al., 2010).

The Mediterranean diet is associated with increased circulating plasma antioxidant levels and decreased oxidative stress (Azzini et al., 2011, Esposito et al., 2011, Yubero-Serrano et al., 2011). The protective properties of this diet may be derived not only from its increased antioxidant concentration but also through its high raw food intake, lower production of cooking-related oxidants and consequent decreased use of nutritional and endogenous antioxidants, and increased fibre intake (Ghiselli et al., 1997). Olive oil, the main source of fat in the Mediterranean diet, is also effective in lowering lipid peroxidation and oxidative stress (Alarcon de la Lastra et al., 2001, Fito et al., 2007)

4.1.4. Diet and its effect on neuroprogression

Diet quality is important for the brain given its capacity both to enhance neurogenic factors and to influence rates of neurodegeneration. In animal studies, brain levels of BDNF decreased in rats maintained on a high carbohydrate diet (Maioli et al., 2012) and high fat diet (Yamada-Goto et al., 2012). Human trials have also demonstrated a relationship between diet and BDNF. Compared to a low-fat diet, adherence to a Mediterranean diet was associated with an improvement in plasma BDNF concentration in individuals with depression (Sanchez-Villegas et al., 2011). In healthy adults, a high-fat meal decreased plasma BDNF by almost 30% (Karczewska-Kupczewska et al., 2011). The importance of diet on neuroprogression is further confirmed by a study on insulin-resistant, overweight and obese subjects where serum BDNF levels increased after three months on a reduced calorie diet (Araya et al., 2008).

Investigations into the potential effects of ω-3 PUFAs have revealed that they may also play a role in neuroprogression. In animal studies, ω-3 PUFAs supplementation provided protection against reduced plasticity and normalised BDNF after traumatic brain injury (Wu et al., 2004). During pregnancy and lactation, supplementation with ω-3 PUFAs protected levels of BDNF and nerve growth factor (NGF) in female rats when they consumed a micronutrient-imbalanced diet (Sable et al., 2012), while brain levels of BDNF decreased during diets deficient in ω-3 PUFAs (Bhatia et al., 2011, Rao et al., 2007). In an human open-label trial, 3 months of ω-3 PUFAs supplementation increased serum BDNF levels and prevented posttraumatic distress after accidental injury in patients presenting at an intensive care unit (Matsuoka et al., 2011). However, in a randomised, double-blind, placebo-controlled study of diabetic patients with major depression, 12 weeks of ethyl-EPA supplementation or placebo, in addition to ongoing antidepressant therapy, failed to increase serum BDNF levels (Bot et al., 2011).

4.1.5. Diet and its effect on the HPA axis

Diet composition and timing have a significant influence on acute cortisol secretion due to the primary role of cortisol in gluconeogenesis. However, the long-term effect of diet on HPA activity is not well understood. In a study on women living in a Mediterranean area, a disturbed HPA axis was associated with a higher content of fat and saturated fatty acids in the diet. In contrast, adherence to a dietary pattern closer to the Mediterranean diet was linked with smaller HPA axis disturbances (Garcia-Prieto et al., 2007). Investigations into the effect of ω-3 PUFAs on HPA activity have also provided some evidence of their capacity to lower cortisol activity. For example, Delarue et al. (2003) showed that after 3 weeks on a diet supplemented with ω-3 PUFAs, levels of plasma noradrenaline and cortisol stimulated by mental stress were significantly blunted. In another study on patients with major depression, serum cortisol levels decreased after 8 weeks of treatment with EPA alone or in combination with fluoxetine (Jazayeri et al., 2010). Finally, intravenous lipopolysaccharide-induced adrenocorticotropic hormone (ACTH) and cortisol plasma levels decreased significantly in healthy subjects supplemented with one month of fish oil compared to placebo (Michaeli et al., 2007).

4.1.6. Diet and its effect on mitochondria

Mitochondrial dysfunction is influenced significantly by nutrition (Civitarese et al., 2007, Hepple, 2009, Page et al., 2010, Vitetta and Anton, 2007). Increased fatty acid exposure, resulting from high fat diets or overfeeding, is linked both with decreased mitochondrial number and markers of oxidative phosphorylation. Conversely, caloric restriction can stimulate mitochondrial biogenesis by elevating the transcriptional processes that regulate mitochondrial mass, improve mitochondrial efficiency, activate ROS scavenging mechanisms, and lower ROS production (Civitarese et al., 2007). Dietary antioxidants or caloric restriction, as well as chemical antioxidants, can lower mitochondrial ROS production (Vitetta and Anton, 2007). Nutrients such as CoQ10, vitamin B2 and l-carnitine also have a significant influence on mitochondrial metabolism (Gardner and Boles, 2011).

4.2. The relationship between sleep and depression

In the general population approximately 30% of people report symptoms of insomnia, 10 to 20% describe dissatisfaction with sleep, and approximately 6% have a formal diagnosis of insomnia (Leger et al., 2000, Ohayon, 2002). These rates are significantly increased in major depression, with as high as 90% of patients reporting sleep disturbances (Motivala et al., 2006, Riemann and

Voderholzer, 2003). Insomnia is also one of the most common prodromal features of depression with sleep symptoms preceding an episode of depression in 40% of cases. A history of persistent insomnia is also associated with a significantly increased risk of developing a new depressive episode (Taylor et al., 2005). In a recent meta-analysis, compared to people with no sleep difficulties, non-depressed people with insomnia were predicted to have a twofold increased risk of developing depression (Baglioni et al., 2011). Depressed patients suffering from insomnia also have a poorer response to treatment and are at increased risk of relapse (Dombrovski et al., 2008).

Further support for a relationship between sleep and depression is provided by studies documenting improvements in mood and depressive symptoms following insomnia-specific interventions. For example, in a randomised controlled study, Manber and colleagues (2008) found that augmenting antidepressant medication with a symptom-focused cognitive-behavioural therapy for insomnia (CBTI) enhanced treatment outcomes in participants with co-morbid major depression and insomnia. Compared to participants allocated to control treatment, people receiving CBTI experienced significantly greater remission rates in both depression (61.5% vs 33.3%) and insomnia (50% vs 7.7%). In women with insomnia and breast cancer, CBTI was also more effective in improving sleep, depression and anxiety symptoms than a control condition (Savard et al., 2005). Eight weeks of mindfulness-based cognitive therapy for treating insomnia symptoms also improved sleep, anxiety and depressive symptoms in patients with an anxiety disorder (Yook et al., 2008).

4.2.1. Sleep and its effect on inflammation

Sleep difficulties increase inflammatory mediators; conversely elevated inflammatory molecules heighten the risk of sleep problems. In particular, IL-1, IL-6 and TNF-α may be directly involved in sleep regulation (Santos et al., 2007). Data derived from electrophysiological, biochemical and molecular genetic studies demonstrate that these cytokines are sleep regulatory, as they support the regulation of spontaneous sleep-wake behaviour (Opp, 2005). Other cytokines that may also be involved in the regulation of sleep include IL-2, IL-8, IL-15, IL-18, epidermal growth factor, acidic fibroblast growth factor, colony stimulating factor, and interferons (Krueger, 2008).

In patients with major depression, difficulty initiating sleep correlated with increased pre-sleep levels of IL-6 (Motivala et al., 2005). In a study on 210 healthy young men and women, difficulty falling asleep was related to higher morning levels of CRP and IL-6, but only in women (Suarez, 2008). Sleep disturbances also occur in up to 30% of patients with chronic hepatitis C undergoing IFN-α therapy (Sockalingam et al., 2010), and its administration reduces sleep continuity and depth and induces a sleep pattern consistent with insomnia and hyperarousal (Raison et al., 2010b). Studies on patients diagnosed with primary insomnia offer additional evidence for the relationship between sleep and inflammation, as circulating levels of IL-6 and TNF are higher than in healthy sleepers (Burgos et al., 2006, Vgontzas et al., 2002).

Sleep restriction studies in animals and humans provide further confirmation for the association between sleep and inflammation. Although the relationship is not necessarily linear, there is evidence that in humans, sleep restriction increases levels of IL-6, TNF-α, CRP and IL-1β (Motivala, 2011, van Leeuwen et al., 2009, Vgontzas et al., 1999, Vgontzas et al., 2004). Five days of sleep deprivation in healthy adults also modified a number of kynurenine pathway metabolites in healthy adults, including 5-hydroxyindoleacetic acid (5-HIAA), xanthurenic acid and anthranilic acid (Kuhn et al., 1968).

4.2.2. Sleep and its effect on neurotransmitters

Surprisingly little research on the influence of sleep on monoamines such as serotonin and dopamine has been conducted, although sleep restriction may disrupt systems associated with monoamine communication. In an animal study, desensitisation in serotonin receptors was detected after eight days of sleep restriction. Despite unlimited recovery sleep, this desensitisation persisted for at least seven days (Roman et al., 2005b), and was independent of adrenal hormones (Roman et al., 2006). In addition, Novati and colleagues (2008) demonstrated that exposure to a schedule of chronic, partial sleep deprivation reduced sensitivity of $5HT_{1A}$ receptors and/or receptors for CRH (Novati et al., 2008).

4.2.3. Sleep and its effect on oxidative stress

It has been proposed that cerebral free radicals accumulate during wakefulness and are removed during sleep (Reimund, 1994). This has been supported by animal studies where sleep loss caused oxidative damage in the brain (Ramanathan et al., 2002, Suer et al., 2011) and increased lipid peroxidation (Thamaraiselvi et al., 2012). However, some animal studies have found that one to two weeks of sleep deprivation had no effect on oxidative stress in any brain region, including protein oxidation and lipid peroxidation (D'Almeida et al., 1997, Gopalakrishnan et al., 2004). These inconsistent findings are likely a reflection of differing sleep restriction protocols, and different markers of oxidative stress measured across studies.

Most studies on oxidative stress in clinical sleep research have focused on obstructive sleep apnoea syndrome, which is known to increase oxidative stress produced by recurrent episodes of ischemia-reperfusion injury (Kent et al., 2011, McNicholas, 2009). However, several studies have also linked oxidative stress with insomnia. For example, levels of thiobarbituric acid reactive substances were elevated in postmenopausal women with insomnia, although blood concentrations of catalase, superoxide dismutase, and glutathione were found to be normal (Hachul de Campos et al., 2006). In an investigation on participants with primary insomnia, significantly lower GSH-Px (selenium-containing antioxidant enzyme) activity and higher MDA levels were found compared with controls (Gulec et al., 2012). Further evidence of a relationship between sleep and oxidative stress is provided by a study revealing increased levels of myeloperoxidase-modified low-density lipoprotein following five nights of sleep restriction in healthy males (Boudjeltia et al., 2011).

4.2.4. Sleep and its effect on neuroprogression

Sleep problems may also contribute to depressive symptomatology via their effect on brain structure, neurogenesis and, in particular, hippocampal function (Lucassen et al., 2010, Meerlo et al., 2009, Novati et al., 2011). Experimental studies show that prolonged sleep restriction or disruption affects hippocampal integrity (Guzman-Marin et al., 2006, Kopp et al., 2006, McDermott et al., 2003, Roman et al., 2005a). For example, in young male rats, one month of chronic sleep restriction reduced dorsal hippocampal volume by 10% (Novati et al., 2011). Hippocampal cell proliferation was also affected by a single day of sleep deprivation in rats (Roman et al., 2005a). Clinical studies have also reported a reduction in hippocampal volume in primary insomnia and sleep apnoea (Morrell et al., 2003, Riemann et al., 2007). Insomnia severity in a sample of patients with post-traumatic stress disorder was also associated with decreased volume in the CA3/dentate hippocampal subfield (Neylan et al., 2010).

While sleep restriction itself may not be neurotoxic, it may enhance neuronal sensitivity to subsequent excitotoxic insults. Novati and colleagues (2012) found that after 30 days of sleep restriction in rats, there were no adverse effects on cholinergic cells in the nucleus basalis magnocellularis (NBM). However, an injection of a neurotoxic dose of N-methyl-d-aspartate into the NBM caused an accentuated loss of cholinergic NBM cells and cortical fibres in the sleep-restricted rats compared to controls. Thus, chronic sleep restriction may constitute a mild threat to the brain that does not lead to neurodegeneration by itself but increases vulnerability to subsequent neurotoxic challenges.

4.2.5. Sleep and its effect on the HPA axis

Insomnia appears to be associated with hyperarousal. In a study on patients with chronic insomnia, 24-hour urinary cortisol levels correlated positively with total wake time. Sleep quality also correlated negatively with urinary levels of catecholamine metabolites, thereby suggesting disturbances in both limbs of the stress system (i.e., the HPA axis and the sympathetic system) (Vgontzas et al., 1998). In another study, ACTH and cortisol secretions were significantly higher in insomniacs compared with normal controls, with greatest elevations in the evening and first half of the night. Cortisol levels were also positively correlated with the severity of reported sleep disturbance (Vgontzas et al., 2001). Increased evening and nocturnal plasma cortisol concentrations were also observed in patients with primary insomnia, with a strong positive correlation between evening cortisol secretion and the number of nocturnal awakenings both in insomniac patients and controls (Rodenbeck and Hajak, 2001).

Findings in sleep deprivation and restriction studies are less consistent, with several studies reporting mild elevations of cortisol (Leproult et al., 1997, Spiegel et al., 1999) while others have found no change or even slightly decreased levels (Follenius et al., 1992, Kant et al., 1984). In several animal studies, sleep deprivation led to mild activations of the HPA axis and elevated plasma levels of glucocorticoids (Meerlo et al., 2002, Suchecki et al., 1998), whereas others found little or no effect of acute sleep deprivation on glucocorticoid levels (Rechtschaffen et al., 1983). According to Meerlo et al. (2008) the available data from studies in laboratory animals suggest that sleep restriction may gradually change certain brain and neuroendocrine systems in a manner similar to that seen in stress-related disorders such as depression.

4.2.6. Sleep and its effect on mitochondria

Because of the important role of sleep on oxidative stress, it would seem logical to assume that mitochondria will be adversely affected by sleep deprivation. In support of this, sleep deprivation in mice reduced the activity of the complex I, II and III enzymes of the mitochondrial electron transport chain. Complex II and II-III activity was particularly decreased in the hypothalamus of mice during 24-hour recovery sleep (Andreazza et al., 2010). In a model developed by Andreazza et al. (2010), it was proposed that sleep restriction may lead to mitochondrial dysfunction which, in turn, increases the production of ROS, leading to increased oxidative damage to lipids, protein and DNA.

4.3. The relationship between exercise & depression

Depression is commonly associated with low levels of physical activity. While data derived from epidemiological and correlational studies do not necessarily confirm causation, a consistent relationship does exist across a number of populations. In adults, an active lifestyle was

associated with reduced depressive symptoms independent of education and physical health status. This relationship was stronger in women and those aged 40 years and older (Stephens, 1988). In overweight/obese adults, a reduced risk of depression was associated with increasing moderate-to-vigorous-intensity physical activity and decreasing sedentary time (Vallance et al., 2011). Another study on data from over 4,000 men and women aged 20 years or more confirmed that adults with depression spent significantly less time both in light and moderate physical activity than non-depressed adults (Song et al., 2012). In a longitudinal study of over 9,000 people, regular physical activity was associated with a reduced likelihood of depressive symptoms at follow-up (Azevedo Da Silva et al., 2012).

Although not as extensive, investigations into sedentary behaviours have also largely confirmed a positive relationship with depression. In a systematic review of seven observational and four intervention studies on adult populations, Teychenne and colleagues (2010) confirmed that, on balance, sedentary behaviours such as watching television or using the computer were associated with an increased risk of depression. However, evidence was limited by methodological weaknesses in most studies.

The efficacy of exercise as a treatment for depression is summarised in over a dozen recent reviews. In a meta-analysis on supervised and unsupervised physical activity interventions among healthy adults, Conn (2010) concluded that physical activity interventions had a moderate inhibitory effect on depressive symptoms in adults with and without clinical depression (mean effect size of 0.37 for supervised and 0.52 for unsupervised physical activity studies). Carek and colleagues (2011) maintained from a review of the literature that exercise compared favourably to antidepressant medications as a first-line treatment for mild-to-moderate depression and also improved depressive symptoms when used as an adjunct to medications. Similar antidepressant effects were also found in trials comparing exercise with cognitive-behavioural therapy (Rimer et al., 2012). Despite these positive findings there is a paucity of research demonstrating long-term beneficial effects of exercise in patients with clinical depression (Krogh et al., 2011).

4.3.1. Exercise and its effect on inflammation

Although a single bout of exercise provokes an acute inflammatory response, primarily in IL-6 (release from muscle increases up to 100-fold during contractile exercise), exercise is followed by an increase in anti-inflammatory cytokines (Pedersen and Fischer, 2007) and a decreased production of the pro-inflammatory cytokines TNF-α and IL-1β (Pedersen et al., 2003). Data also suggest that exercise-induced IL-6 inhibits TNF-α production in the presence of low-grade inflammation (Starkie et al., 2003).

Four recent reviews have primarily revealed anti-inflammatory effects from long-term exercise (Beavers et al., 2010, Mathur and Pedersen, 2008, Ploeger et al., 2009, Thomas and Williams, 2008). In a systematic review of 19 studies on the inflammatory effects of acute and chronic exercise in children and adults, Ploeger et al. (2009) concluded that training programs can attenuate chronic inflammation in some patients with chronic inflammatory disease; however, the exercise training-induced response appeared highly dependent on the type of disease, severity of the disease and the frequency, duration and intensity of the exercise intervention.

Lower inflammatory biomarker concentrations, particularly CRP, and to a lesser extent IL-6, are observed across a wide range of individuals performing more frequent and intense physical activity (Plaisance and Grandjean, 2006, Taaffe et al., 2000). This inverse relationship between CRP and physical activity is consistently seen in men, and to a lesser extent in women (Beavers et

al., 2010). In adults, investigations using self-reported measures of physical activity have demonstrated that physically-active individuals have CRP concentrations 19–35% lower than less active individuals (Plaisance and Grandjean, 2006). While these inflammatory markers are attenuated following adjustment for adiposity, a significant relationship between inflammatory biomarkers and physical activity persists (Abramson and Vaccarino, 2002).

In sum, while most studies demonstrate anti-inflammatory effects of exercise in adults and children, the relationship is influenced by a number of factors including the population studied, the type, frequency and duration of exercise, pre-existing medical conditions and initial levels of inflammation. Thus, further studies are required to enable more definitive conclusions, particularly in patients suffering from depression.

4.3.2. Exercise and its effect on neurotransmitters

The antidepressant effects of exercise may be due to its capacity to modify monoamine communication. In animal studies, running increased plasma free tryptophan, brain tryptophan, and levels of the serotonin metabolite, 5-HIAA (Bailey et al., 1993, Chaouloff et al., 1985). Human trials also provide evidence of exercise and its serotonin-enhancing effects. For example, untrained participants randomly assigned to an aerobic exercise group experienced greater changes in serum serotonin levels compared to those in a stretching-control group (Wipfli et al., 2011). Tryptophan availability, the precursor to serotonin, is also increased after acute exercise (Melancon et al., 2012). Three weeks of exercise training also influenced serotonin receptors and serotonin transporters in sedentary males as demonstrated by increased levels of 5-HT transporters (5-HTT) and 5-HT_{2A} receptors on isolated platelet membranes. In contrast, four weeks of excessive training in well-trained athletes did not change 5-HTT, and 5-HT_{2A} receptor density declined. This suggests that the impact of exercise on serotonin neurotransmission may depend on the training state of athletes and extent of exertion (Weicker and Struder, 2001).

Exercise is also able to modify dopamine and noradrenergic transmission as evidenced by increased tyrosine hydroxylase expression (Foley and Fleshner, 2008, Kim et al., 2011), elevated striatal dopamine D_2 receptor expression (Vuckovic et al., 2010) and increased noradrenaline levels (Dishman, 1997) in rats exposed to chronic exercise. However, acute exercise comprising 30 minutes of vigorous exercise in healthy adult volunteers with a history of regular exercise did not change synaptic dopamine concentrations (Wang et al., 2000).

4.3.3. Exercise and its effect on oxidative stress

There is mounting evidence to suggest that exercise is accompanied by an increased generation of free radicals, resulting in measurable elevations in oxidative stress biomarkers after both acute aerobic (Benitez-Sillero et al., 2011, Bloomer, 2008, Fogarty et al., 2011) and anaerobic exercise (Bloomer and Goldfarb, 2004, Pittaluga et al., 2006, Vollaard et al., 2005). Given the substantial evidence for the protective effects of exercise on oxidative stress-associated diseases, this seems paradoxical. However, it is argued that chronic exercise leads to exercise-induced adaptation and resistance (Cooper et al., 2002, Radak et al., 2008). The exercise-induced ROS formation evokes specific adaptation, comprising up-regulation in endogenous antioxidant defences, increased antioxidant/oxidative damage-repairing enzyme activity, increased resistance to oxidative stress, and lowered levels of oxidative damage. This adaptive response seems to be systemic, affecting skeletal muscle, liver, and the brain (Radak et al., 2008). Gomez-Cabrera et al (2008) argue that because exercise results in an up-regulation of powerful antioxidant enzymes, exercise itself can be considered an antioxidant despite generating free radicals.

4.3.4. Exercise and its effect on the HPA axis

The relationship between exercise and HPA activity is complex as it is influenced by duration, type, intensity and chronicity of exercise; characteristics of the stressor used; and characteristics of the population studied (Campeau et al., 2010, Leal-Cerro et al., 2003, Mastorakos et al., 2005, Stranahan et al., 2008). In an animal study, four weeks of swimming exercise was associated with reduced levels of serum corticosterone and depressive behaviours in rats exposed to high levels of glucocorticoids prenatally (Liu et al., 2012a). In another study, the HPA axis response to lower-intensity stressors decreased in rats exposed to 6 weeks (but not 1 or 3 weeks) of intermittent, voluntary wheel running, although no change occurred following exposure to more intense stressors (Campeau et al., 2010). The complexity of the relationship between exercise and HPA responsivity was further demonstrated by Droste et al. (2003) who reported that HPA responses in exercising mice were differently influenced by the stressor used and the novelty of the environment.

Investigations into the relationship between exercise and HPA activity in human populations have primarily examined the effect of acute activity on measures such as cortisol and ACTH. Studies on the influence of chronic exercise on HPA activity, and in particular on the HPA response to stressors, are sparse. In general, acute exercise elevates cortisol levels, although this most consistently occurs following moderate-to-severe intensity activity (Hill et al., 2008). In a study on women of varying age and fitness, ACTH levels recovered slowly in older women, particularly those with low fitness levels (Traustadottir et al., 2004). In a study on female adolescents with mild-to-moderate depression, 8 weeks of an exercise regimen improved depressive symptoms and was associated with reductions in 24 hour urinary cortisol levels (Nabkasorn et al., 2006). In another study on patients with chronic low back pain, twelve weeks of high-intensity aerobic exercise was associated with reductions in pain, enhanced mood and improvements in HPA responsiveness to the dexamethasone suppression test (Chatzitheodorou et al., 2008).

4.3.5. Exercise and its effect on neuroprogression

Evidence of the beneficial effects of exercise on brain function is summarised in three recent reviews (Cotman et al., 2007, Dishman et al., 2006, Vivar et al., 2012). Exercise is associated with enhanced adult hippocampal neurogenesis and increased activity-dependent synaptic plasticity. According to Cotman et al. (2007), enhanced hippocampal neurogenesis and increased synaptic plasticity are the most reproducible effects of exercise in the rodent brain. In both young and old animals, exercise stimulated neural progenitor populations, increased the number of new neurons, and promoted survival of these new cells (Brandt et al., 2010, Olson et al., 2006, Wu et al., 2008). In animal studies, exercise also increased BDNF in several brain regions, and there was increased insulin-like growth factor-1 (IGF-1) gene expression and peripheral circulating levels of IGF-1 (Ding et al., 2006, Schwarz et al., 1996). In a review on the effects of exercise on peripheral BDNF in human subjects, it was concluded that exercise temporarily elevated basal BDNF and possibly up-regulated BDNF cellular processing (i.e. synthesis, release, absorption and degradation) (Knaepen et al., 2010). However, there have been no reported findings of long-lasting BDNF responses to acute exercise or training.

Human studies on the effects of exercise-induced BDNF changes in depressed populations are still preliminary, although BDNF levels were transiently increased in elderly women with

remitted major depression (Laske et al., 2010) and in unmedicated patients suffering from major depressive disorder (Gustafsson et al., 2009).

4.3.6. Exercise and its effect on mitochondria

An accumulating body of literature has demonstrated that endurance exercise effectively stimulates mitochondrial biogenesis in a wide range of tissues including skeletal muscle, adipose tissue, liver, brain, and kidney (Little et al., 2011). Vina et al. (2009) concluded that exercise, and particularly aerobic exercise, activated mitochondriogenesis in young animals, although its influence on older animals required further investigation. Eight weeks of treadmill training in a murine model augmented mitochondrial function, as reflected by increased mitochondrial enzyme activities, maximal rate of ATP synthesis in isolated mitochondria, and whole-body maximal O_2 uptake (Chow et al., 2007). Lanza et al. (2009) reviewed a number of studies which demonstrated that older adults enrolled in exercise training programs respond with increased VO_2 peak, mitochondrial content, oxidative enzyme activities, muscle protein synthesis rates, mitochondrial protein gene transcripts, and mitochondrial DNA copy number.

5. Conclusion and directions for future research

While the importance of lifestyle factors such as diet, exercise and sleep are generally acknowledged in the research literature on major depression, the mechanisms of their potential influence are often not fully appreciated. As illustrated in figure 3, diet, exercise and sleep can influence several physiological pathways associated with depression. A bi-directional relationship likely exists between depression and these lifestyle factors, thereby creating a potentially increasing cycle of influence. Key symptoms of major depression include changes in appetite, sleep, energy and general motivation levels; all likely to have significant effects on diet, exercise and obviously sleep patterns. The importance of these lifestyle factors was highlighted in a recent paper by Jacka et al (2012) who argued that depression should be included under the umbrella of non-communicable diseases influenced by lifestyle factors, with increasing efforts directed toward prevention through the promotion of lifestyle changes.

<<<insert Figure 3 near here>

While these lifestyle factors are significant in the etiology and maintenance of depression, a multitude of other lifestyle influences may also be important. These include chronic stress, social influences, mental and physical effects associated with medical diseases, alcohol and other drug use, chronic pain and even exposure to sunlight/vitamin D. It is these influences, plus a large array of psychological, genetic and biological factors that often make the treatment of depression difficult. Basic interventions comprising attention towards one cause and/or one biochemical mechanism (e.g., targeting a single neurotransmitter disturbance) makes the goal of remission or recovery less likely. This was highlighted in a recent study where giving simple written recommendations about lifestyle changes for sleep hygiene, physical activity, diet, and sunlight exposure enhanced outcomes to standard antidepressant treatment (Garcia-Toro et al., 2012). Remission/response rates reached 60% in the combined treatment group compared with only 10% in the anti-depressant only group.

Future research needs to be directed toward better understanding the role that diet, exercise, sleep and other lifestyle factors play in depression and other mental health conditions. While this review provides a comprehensive coverage of the research literature, with a specific emphasis on the biological effects of these lifestyle factors on depression, a future more systematic review with well-defined search strategies and inclusion criteria would be beneficial to further elucidate the role these lifestyle factors play in depression, particularly those addressing diet.

A limitation associated with many of the studies reviewed is that significant portions were correlational and/or epidemiological, thereby limiting conclusions about causation. Other influences such as general healthy lifestyle behaviours, socioeconomic status and medical illnesses are examples of confounding factors that may have influenced findings in some studies. Given these and other confounding influences, a significant barrier associated with studies on dietary intervention is being able to accurately provide direct evidence that dietary change causes improvements in mental health. Increasing attention toward randomised, placebo-controlled treatment studies may help to elucidate the mediating roles that these lifestyle factors play in major depression. A paucity of treatment studies has investigated dietary interventions in depressed populations; however, an inherent problem relates to identifying methods to blind such interventions for participants and investigators. While this may be possible with single nutrients or foods, it is likely that the benefits of diet are derived from consuming a range of complementary foods, particularly those characteristic of Mediterranean diets (Ghiselli et al., 1997, Milaneschi et al., 2011). It is also important that increasing attention be given to measuring changes in important biomarkers associated with inflammation, oxidative stress, HPA regulation, neuroprogression, monoamine and mitochondrial function. Measuring changes in biomarkers and assessing their relationship with affective and behavioural changes should provide a greater understanding of mechanisms of action associated with depression.

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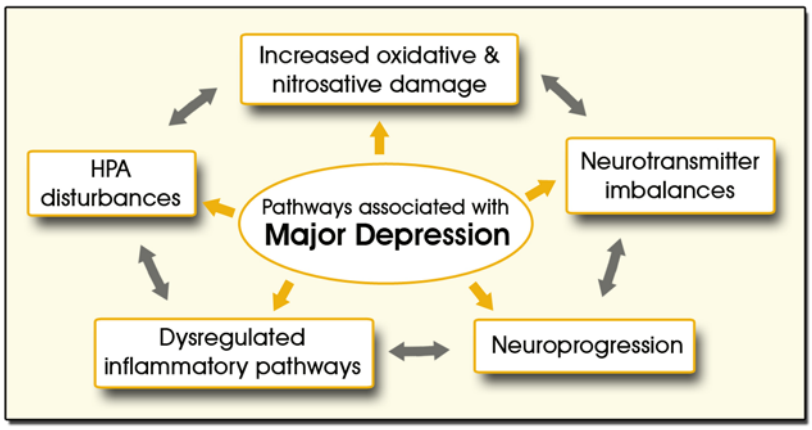

Figure 1. Multiple pathways associated with major depression

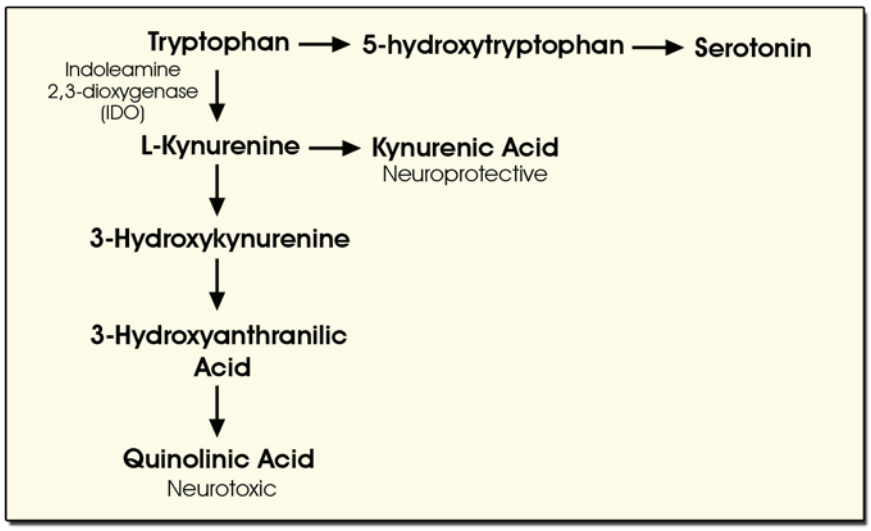

Figure 2. Kynurenine pathway and its metabolites.

The kynurenine pathway starts with the degradation of tryptophan by the enzyme, indoleamine 2,3-dioxygenase (IDO) which is upregulated by pro-inflammatory cytokines (e.g. IFN-γ, TNF-α, IL-, IL-6). These TRYCATS (tryptophan catabolites along the IDO pathway) have neuroprotective and neurotoxic effects on the CNS and influence monoaminergic transmission.

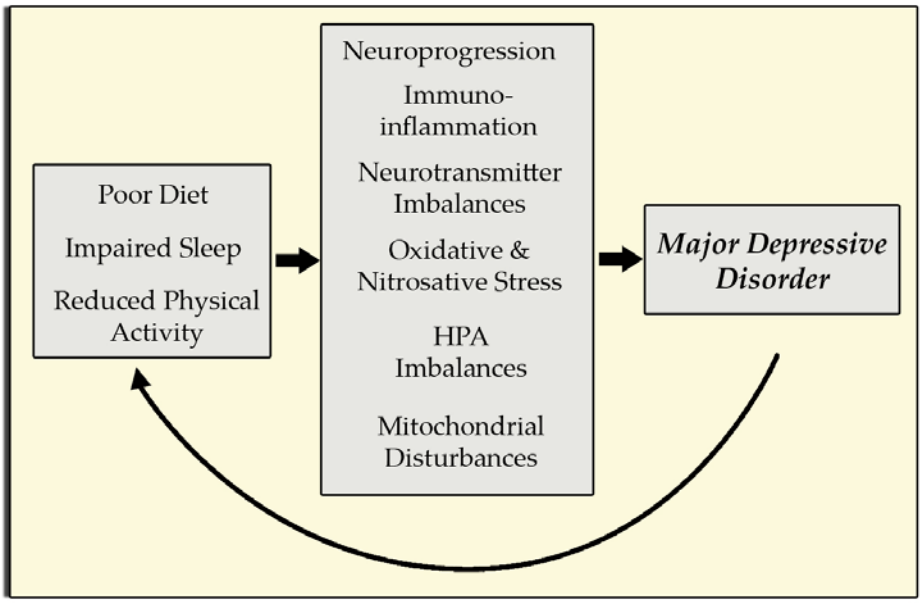

Figure 3. Potential mechanisms of diet, sleep and exercise on major depression.

Diet, sleep and exercise are associated with depression. These lifestyle factors influence a number of biological processes associated with major depression including neurotransmitter transmission, immuno-inflammation, oxidative and nitrosative stress, HPA balance, neuroprogression and mitochondrial health. Suffering from depression is also likely to lead to changes in diet, sleep and exercise, creating a vicious cycle of change.