

# **Nutrient deficiencies common within non-omnivorous diets and their association with depression: A systematic review and meta-analysis**

## **Abstract**

**Introduction:** Depression is a prevalent and debilitating health issue within the modern world and may be concern for populations that consume non-omnivorous diets. Nutrient deficiencies that are common within non-omnivorous diets have been shown to be associated with depression and this could explain in part, the higher rates of depression among non-omnivorous individuals. This systematic review and meta-analysis investigated the degree of association between nutrient deficiencies common within non-omnivorous diets (vitamin D, vitamin B12, zinc, iron and omega 3) and depression and explored the other possible pathophysiological and causal relationships that surround it.

**Methods:** A systematic review and meta-analysis was conducted on 140 observational studies published between 1999 and 2019, over 38 different countries, including 790,846 participants. Analyses were carried out across the five nutrients using multiple types of effect size data investigating both nutrient deficiency and sufficiency in relation to depression risk.

**Results:** Vitamin D deficiency was shown to significantly increase depression risk by 20% (OR = 1.20, 95% CI 1.11–1.31, P = < 0.00001) and vitamin D sufficiency was shown to significantly reduce depression risk by 32% (OR = 0.68, 95% CI 0.52 – 0.89, P = 0.004). Vitamin B12 deficiency was shown to significantly increase depression risk by 46% (OR = 1.46, 95% CI 1.00 – 2.13, P = 0.05) and vitamin B12 sufficiency was shown to significantly reduce depression risk by 24% (OR = 0.76, 95% CI 0.63 – 0.91, P = 0.003). Zinc deficiency was not significantly associated with depression (OR = 1.23, 95% CI 0.93 – 1.63, P = 0.15) but zinc sufficiency was shown to significantly reduce depression risk by 34% (OR = 0.66, 95% CI 0.57 – 0.76, P = < 0.00001). Iron deficiency was shown to significantly increase depression risk by 37% (OR = 1.37, 95% CI 1.10 – 1.70, P = 0.005) and iron sufficiency was shown to significantly reduce depression risk by 16% (OR = 0.84, 95% CI 0.76 – 0.93, P = 0.0005). Omega 3 deficiency was shown to significantly increase depression risk by 47% (OR = 1.47, 95% CI 1.02 – 2.11, P = 0.04) and omega 3 sufficiency was shown to significantly reduce depression risk by 21% (OR = 0.79, 95% CI 0.72 – 0.87, P = < 0.00001).

**Conclusion:** In conclusion, the link between the nutrients covered in this review and their association with depression were all shown to be significant apart from the association between zinc deficiency and depression. Nutrient deficiencies that were shown to be common within non-omnivorous diets may explain the higher rates of depression seen in populations that follow these diets, although there are other causal relationships that are worth considering when drawing inferences from the results in this review.

## **Keywords**

Depression, Nutrient Deficiency, Veganism, Vegetarianism, Non-Omnivorous

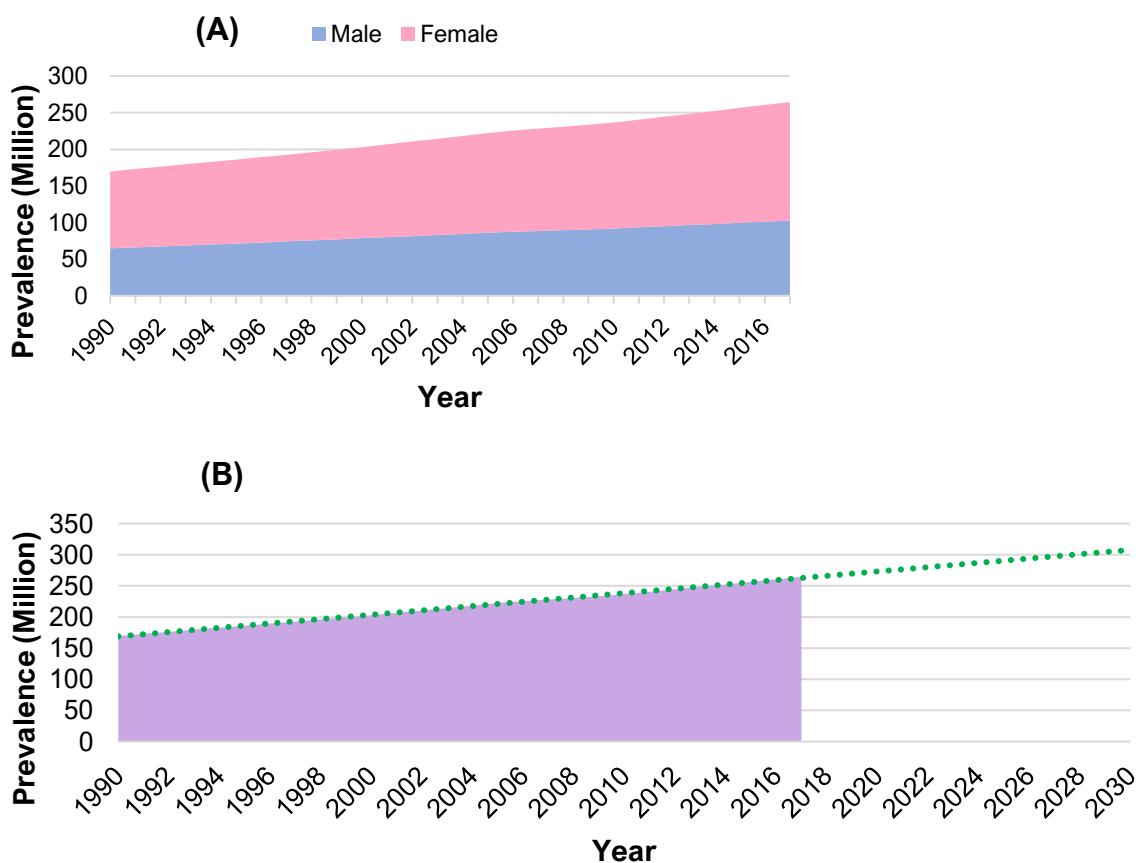
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# Introduction

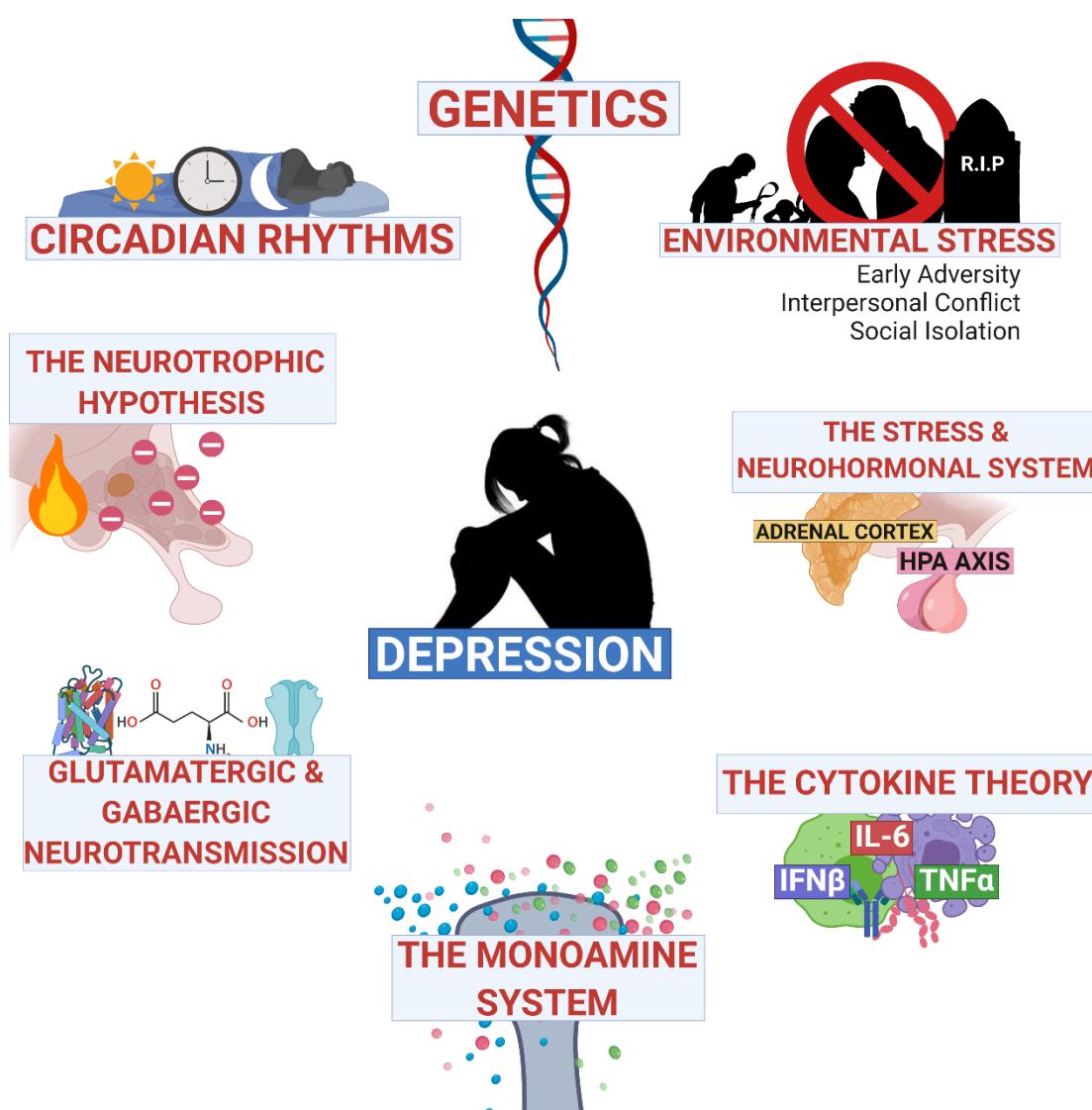
Depression can be defined as a state of low mood or aversion to activity, which is characterised as a chronic or recurrent condition that can have profound and debilitating effects on psychosocial, vocational, academic and family functioning (Zwart et al., 2019). Over the past three decades, depressive disorders have become one of the leading causes of non-fatal health loss globally (James et al., 2018), with an estimated prevalence of 264.46 million of the population suffering with the disorder in 2017, 61% being female and 39% being male (**Figure 1.0A**). A projection estimating the total number of people to be suffering with depression globally to be over 300 million by the year 2030 can also be seen in **Figure 1.0B**. It is the most significant factor relating to suicide, which is a leading cause of death in young people, the elderly and especially in male populations (Bachmann, 2018; Bertolote et al., 2004; Ferrari et al., 2014; Saveanu & Nemeroff, 2012).



**Figure 1.0A.** Total number of people of all ages with depression, differentiated by sex and based on medical, epidemiological data, surveys and meta-regression modelling of the global depression trend between the years 1990 and 2017. **Figure 1.0B.** Not differentiated by sex but with the addition of a 13 year projection to the year 2030 (GBD, 2018).

# Depression

Depression is a multifactorial and complex health disorder and is presented in people with a high level of intrapersonal variability, which makes treating it difficult (Saveanu & Nemeroff, 2012). The nature of depression is heterogenous in how it manifests and comes in a variety of forms related to symptomology (melancholic, atypical, psychotic, or anxious), onset, recurrence, severity and polarity (unipolar vs bipolar) (Thase, 2013). The main hypothesised systems and factors related to the pathophysiology of depression are outlined in **Figure 1.1**.



**Figure 1.1.** The systems hypothesised and the factors to influence, the pathophysiology of depression.

## **Genetics**

The link for a genetic component within depression can be seen in family, twin and adoption studies. A meta-analysis by Sullivan et al., (2000) analysed familial epidemiological studies of major depression and found that the heritability of major depression is likely to be in the range of 31 - 42%, but noted that this is likely to be underestimated and the level of heritability could be significantly higher. Family studies also showed a two to threefold increase in risk of depression in first-degree offspring of depressed people. More recent papers have shown similar associations for the heritability of depression, but found that it is stronger when inherited maternally compared to paternally (Kendler et al., 2001, 2006).

When looking at previous gene association studies, conflicting results have been found with trying to identify a strong association with specific causative genes and the pathogenesis of depression (Lohoff, 2010). It is likely the case, that the predisposition of depression is a result of multiple genes, contributing and interacting together, which supports the idea that depression is a multifaceted heterogenous disorder (Ebmeier et al., 2006; Shadrina et al., 2018). More recently, over 100 independent genetic variants have been suggested to have a potential association with the risk of depression in multiple genome-wide studies (Howard et al., 2018; Hyde et al., 2016; Wray et al., 2018). Later, a meta-analysis of those genome-wide studies found 87 of the 102 variants to be significantly associated with depression (Howard et al., 2019).

Epigenetics, which is the modification of gene expression—often as a result of external or environmental factors—has been linked with the aetiology of depression. A growing body of literature shows that epigenetic changes are a primary mechanistic intermediary by which environmental stress, such as childhood abuse, influences genetic material, that contributes to the development of psychological disorders (Park et al., 2019). Multiple genes have been identified to be involved in stress-associated epigenetic changes that correlate with depression. Genes associated with serotonergic signalling (SLC6A4), glucocorticoid signalling (NR3C1, FKBP5) and neurotrophin (BDNF) are the most promising candidates for further study regarding gene-environment (GxE) interactions (Heim & Binder, 2012; Park et al., 2019).

## **Environmental Stress**

Environmental stress in the form physical, sexual and emotional childhood abuse have all been associated with depression in adult life (Gallo et al., 2018; McCauley et al., 1997; Mullen et al., 1996; Negele et al., 2015; D. Wang et al., 2018; E. A. Young et al., 1997). One study found that traumatic experiences during childhood are mediated by the accumulative effect of chronic stress (allostatic load), which is represented as a multi-system measure of emotional dysregulation (Scheuer et al., 2018). Others have acknowledged this as a mediatory link (Huh et al., 2017), but also suggested that problems with interpersonal functioning and social relationships could have other mediatory factors with childhood abuse and depression (Christ et al., 2019). A study by Klumparendt et al., (2019) postulated a mediational path model to account for the association between childhood maltreatment and depressive symptoms. The model included emotional dysregulation, but also insecure attachment, depressogenic attributional style (internal, stable and global causal interpretations of negative events) and posttraumatic stress disorder (PTSD), whereby all were found to have a direct impact on depressive symptoms, mediated by childhood maltreatment.

In adult life, environmental stress that leads to PTSD has been found to be a comorbidity of depression, with approximately half of people with PTSD also suffering with depression (Campbell et al., 2007; Flory & Yehuda, 2015). Other life stresses that have been related to the progression of depressive symptoms have also been investigated; grief and bereavement (Buckley et al., 2012; Ghesquiere et al., 2014; Keyes et al., 2014; Zisook & Shear, 2009), divorce or separation (Field et al., 2009; Rhoades et al., 2011; Richards et al., 1997; Sbarra et al., 2014; Verhallen et al., 2019) and poor social relationships (Barger et al., 2014; Teo et al., 2013).

## The Stress & Neurohormonal System

Humans respond to stress by activating a multitude of different behavioural and physiological actions, and the hormonal response to stress is fundamentally regulated by the hypothalamic-pituitary-adrenal (HPA) axis. Corticotropin-releasing hormone (CRH) is released by the hypothalamus when the perception of psychological stress is experienced by cortical brain regions. CRH then stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH), of which stimulates the release of the stress hormone cortisol into the bloodstream, via the adrenal glands (Smith & Vale, 2006).

Elevated concentrations of CRH in cerebrospinal fluid (CSF) have been found in depressed patients, this—in part—supports the theory that hypersecretion of CRH contributes to the hyperactivity of the HPA axis characteristic in depression (Nemeroff et al., 1984). Other studies have shown similar findings, with CRH neurons being hyperactive in major depressed patients (Raadsheer et al., 1994), and a reduced number of CRH binding sites in the frontal cortex of suicide victims compared with controls (Nemeroff et al., 1988).

Differences are evident between the sexes, females have been shown to have a greater response to stress and have a higher resistance to glucocorticoid feedback (E. A. Young, 1998). Males appear to be more physiologically reactive to stress related achievement challenges, whereas females tend to be more physiologically reactive to stress related to social rejection challenges (Stroud et al., 2002).

Studies that looked at cortisol awakening response (CAR) in depressed patients found increased levels compared to controls, but highlighted the complexity of the association, due to the variability of stress sensitivity and pre-emptive coping of stress among individuals (Dedovic & Ngiam, 2015; Dienes et al., 2013). Contrasting data showed there to be a blunted response rather than exacerbated HPA reactivity (Huber et al., 2006; Stetler & Miller, 2005). These inconsistencies in the data may be explained by a non-linear relationship, where an inverted U-shaped association has been found in CAR, evening cortisol and dexamethasone suppression data in depression. This could better describe the link between stress and depression (Wardenaar et al., 2011).

## The Cytokine Theory

The cytokine theory of depression has also been proposed, with substantial evidence indicating that chronic inflammation, or a sustained activation of the immune system—promoting proinflammatory cytokines—plays a key part of the underlying pathophysiology in depression (Currier & Nemeroff, 2010).

There are multiple proinflammatory cytokines that have been implicated in depression and have been shown to influence certain aspects and symptoms associated with depression. Interleukin 1 $\beta$  (IL-1 $\beta$ ), interleukin-2 (IL-2), interleukin-6 (IL-6), interferon alpha (IFN $\alpha$ ), interferon beta (IFN $\beta$ ) and tumour necrosis factor-alpha (TNF $\alpha$ ) have been shown to elicit sickness behaviours such as fatigue and soporific effects, which are similar to behaviours synonymous with anxiety and depression (Hymie Anisman et al., 2005; Schiepers et al., 2005). Interleukin-2 (IL-2) has also been shown to elicit anhedonia, another key symptom of depression (Hymie Anisman et al., 2005). IFN $\alpha$ , IFN $\beta$  and interferon gamma (IFN $\gamma$ ) have been shown to cause cognitive impairment and induce depressive mood directly, based on immunotherapy data (Loftis & Hauser, 2004; Schiepers et al., 2005). C-reactive protein (CRP) has also been shown to be significantly higher in depressed patients compared to healthy controls (Lanquillon et al., 2000). When investigating the relationship between proinflammatory cytokines and the severity and development of depression symptomology, studies have found a moderate to significant correlation to describe the association (H. Anisman et al., 1999; Mohr et al., 2001; Vogelzangs et al., 2016; J. J. Young et al., 2014).

Cytokines have been shown to modulate neuroendocrine function such as the hyperactivity of the HPA axis (Chrousos, 1995; Silverman et al., 2005; Silverman & Sternberg, 2012), glucocorticoids also happen to be one of most potent anti-inflammatory agents produced by the body (Yang et al., 2012). Hyperactivity of the HPA axis is a marker of glucocorticoid resistance, which implies the ineffective action on target tissues and dysfunctional negative feedback (Zunszain et al., 2011). Glucocorticoid resistance is known as a major barrier to the treatment of common inflammatory diseases, this is because it reduces the anti-inflammatory effectiveness that glucocorticoid therapies provide (Barnes, 2010; Barnes & Adcock, 2009). The number and/or function of glucocorticoid receptors are also reduced in depressed patients (Pariante & Miller, 2001),

which illustrates the interrelationship between the immune and neuroendocrine systems and how both may contribute to the pathophysiology of depression.

Inflammation and certain proinflammatory cytokines have been found to have profound effects on other systems that also mediate the severity and development of depression. Serotonin levels have been shown to be reduced when circulating cytokines are high, this is said to be due to a reduction in the serotonin precursor tryptophan (Bell et al., 2001; Myint & Kim, 2003; Wilson & Warise, 2008), which is a result of cytokine activation of the kynurenine pathway and this depletes tryptophan (Miller et al., 2013). Excess inflammation has been found to reduce dopamine synthesis (Felger, 2017; Miller et al., 2013) and cause ineffective glutamate receptor activation which disrupts the neural plasticity balance and excitatory neurotransmission in the brain, leading to depression (Haroon & Miller, 2017; McNally et al., 2008; Müller & Schwarz, 2007).

## The Monoamine System

The hypothesis that depression is a cause of chemical imbalances in the brain was first outlined by Schildkraut (1965) in his paper “The Catecholamine Hypothesis of Affective Disorders”. He reviewed data from pharmacological studies and discussed the common mechanistic action of anti-depressant drugs on mediating the bioavailability of catecholamines. This led him to postulate that some types of depression could be associated with a decrease in the level of norepinephrine and dopamine in the brain. Later, the role of serotonin was also considered when tryptophan—a precursor for serotonin—was fed to depressed patients and it potentiated similar anti-depressant effects comparable to earlier medications (Coppen, 1967). This drove a more widely accepted “monoamine hypothesis of depression”, which claims that depression is caused by a deficit in monoaminergic neurotransmission (noradrenergic, dopaminergic and serotonergic) (Perez-Caballero et al., 2019). Most of these serotonergic, noradrenergic and dopaminergic neurons are located throughout the midbrain and brainstem nuclei and communicate to areas of the entire brain (Hasler, 2010).

The activity of serotonergic neurons have been demonstrated to be reduced in depressed patients, with low levels of serotonin metabolites being associated with a history of planned and more medically damaging suicide attempts (J. J. Mann et al., 1996). Another study found an abnormal reduction in serotonin 1A receptors in depressed

subjects with PET imaging (W. C. Drevets et al., 1999). A more recent study by Nautiyal and Hen, (2017) reviewed the evidence supporting the role for serotonin receptors in depression. They highlighted 15 known receptors that have been implicated with depression, with specific attention to the serotonin 1A and 1B receptors, which they noted were most studied and supported for this serotonergic associated depression.

The action of norepinephrine reuptake inhibitors have been said to target depression with reducing the loss of interest and energy (D. Nutt et al., 2007), it also plays a determinant role in intellect and executive functioning regulation cognition, which is a vital component for healthy social relationships (Moret & Briley, 2011). A meta-analysis found that a dual serotonin/norepinephrine reuptake inhibitor (Venlafaxine) was statistically superior than just the class of serotonin reuptake inhibitors for treating depression (Nemeroff et al., 2008). This indicates there is some potential benefit to having increased levels of norepinephrine for depressive symptomology. Although another meta-analysis of monoamine depletion studies found that the depletion of catecholamine precursors in healthy volunteers does not result in depressive mood (Ruhé et al., 2007). Which gives rise to a complex interrelationship that exists with different monoamines and the aetiology of depression.

Dopamine's role in depression is similar to norepinephrine as it reduces the loss of positive affect, however it is considered to be more associated with our ability to experience pleasure, rather than providing us with motivation and energy. This is considered to be an important modulator of human behaviours (eating, social and sexual), which is primarily mediated by the activation of dopaminergic neurons (Saveanu & Nemeroff, 2012). Dopamine system dysregulation and the absence of being able to experience pleasure—a key symptom of depression—is involved in the downregulation of the dopaminergic system (Belujon & Grace, 2017).

## **Glutamatergic and Gabaergic Neurotransmission**

The dysfunction of the glutamate neurotransmitter system is another avenue of research that has been explored within depression aetiology. The amino acid glutamate—which is the brains primary excitatory neurotransmitter and is closely linked with stress and the neuroendocrine system (Kendell et al., 2005)—has been shown to be higher than normal in depressed patients (Altamura et al., 1993; J. S. Kim et al., 1982; Mauri et al., 1998). However, a recent meta-analysis by Moriguchi et al., (2019) found that glutamate and its metabolites are lower among depressed patients compared with controls. Certain compounds that inhibit glutamate release demonstrated antidepressant properties (Kendell et al., 2005), as well as ketamine which is a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist (Zarate et al., 2006). These results conflict, but they show that glutamate levels are altered, and a degree of dysfunction within this system exists, with people suffering from depression.

Gamma-aminobutyric acid (GABA) is a neurotransmitter in the brain and has the primary role of reducing neuronal excitability throughout the nervous system, and it is also interlinked with stress. Psychological stress is a key factor in depression and has been shown to downregulate GABAergic neurotransmission (Hasler et al., 2010). A reduction in GABA concentration has been seen in the prefrontal brain regions of unmedicated depressed adults derived from magnetic resonance spectroscopy (Hasler et al., 2007). GABA concentration has also been found to be lower in depressed people in two recent meta analyses (Godfrey et al., 2018; Romeo et al., 2017).

## **The Neurotrophic Hypothesis**

It is said that reoccurring psychological stress and depressive episodes can cause morphological and neuroplastic changes in different regions in the brain (hippocampus, amygdala, dorsomedial prefrontal cortex, dorsolateral prefrontal cortex, and anterior cingulum) (Frodl et al., 2008; Jaggar et al., 2019). Longer periods of untreated depressive episodes were associated with reductions in hippocampal volume, this association went away if depressive episodes were treated with antidepressants (Sheline et al., 2003). This finding was replicated elsewhere (Bremner et al., 2000), and volume loss in other regions of the brain was also discovered in individuals with major depressive disorder (K. Zhao et

al., 2017). Findings like these has given rise to the neurotrophic theory of depression, which demonstrates that psychological stress decreases the expression of a protein called brain-derived neurotrophic factor (BDNF) which supports the survival of existing neurons and mediates growth of new ones (Duman & Monteggia, 2006; E. J. Huang & Reichardt, 2001).

The evidence for abnormally low levels of BDNF and their association with depression is strong, three meta analyses found significantly low levels of BDNF in patients with major depressive disorder (Brunoni et al., 2008; Kishi et al., 2017; Sen et al., 2008). The BDNF/depression relationship is strengthened further when looking at antidepressants and their ability to increase peripheral BDNF (Brunoni et al., 2008; Zhou et al., 2017) or to block the down-regulation of BDNF levels in response to stress (Nibuya et al., 1995).

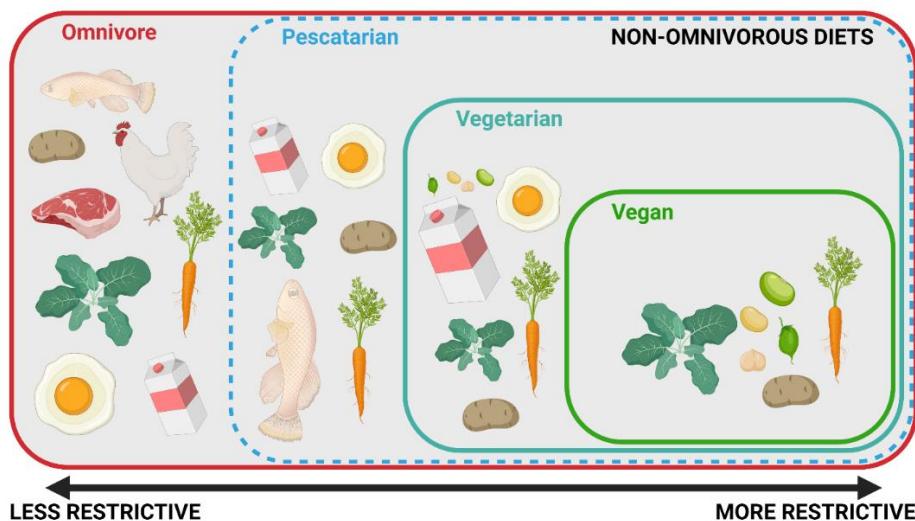
## Circadian Rhythms

The circadian rhythm represents the physiological and psychological fluctuations that follow a day-night cycle and is primarily dictated by the light and darkness changes in an organisms environment (Vitaterna et al., 2001). It is known that sleep disorder is a core symptom related to depression, with around 75% of depressed patients suffering from insomnia (Baglioni et al., 2011; D. Nutt et al., 2008; M. J. Peterson & Benca, 2006). REM sleep abnormalities have also been found to be predictive of unipolar major depression in adolescents, with several candidate genes suggested to be involved with this relationship (Hasler et al., 2004). Circadian disturbances can be observed in the diurnal mood variations common within depression, there are many patients that exhibit a daily pattern of depressive symptoms, with an increase in severity in the morning (Gordijn et al., 1994; Tölle & Goetze, 1987; Wirz-Justice, 2008). The sleep-wake cycle and circadian phase modulates the mood even in healthy subjects (Boivin et al., 1997), so for subjects that already have compromised regulation of mood, circadian phases could have more profound influence on their symptoms. Within young adults with unipolar depression, subjects with disorganised or a delayed circadian rhythm were associated with worse psychiatric profiles compared to subjects with normal or a conventional circadian rhythm (Robillard et al., 2018).

## Non-Omnivorous Diets

The popularity of “vegetarian”, “plant-based” and “vegan” diets has increased dramatically over the last 10 years in western societies. This can be seen by the number of scientific publications, using those specific search terms and within Google Trends data (Medawar et al., 2019).

Omnivorous diets are associated with humans as it is attributed to animals that can eat and survive on both plant and animal-based foods (Brooker, 2008). It can also be defined as a non-restricted diet in respect to animal-based foods, and therefore non-omnivorous diets can be defined as any diet that imposes a restriction in respect to animal-based foods. Non-omnivorous diets are largely categorised as either pescatarian, vegetarian or vegan diets which have greater degrees of animal-based food restriction (**Figure 1.2**).



**Figure 1.2.** The various types of diet across a spectrum in relation to the exclusion of animal-based foods. Non-omnivorous diets include: Pescatarian, vegetarian and vegan. Omnivore diet is unrestricted in respect to the consumption of animal-based foods.

The restriction of animal-based foods that are imposed by different types of non-omnivorous diets, can result in a variety of nutrients being difficult to obtain in sufficient quantities (Murphy & Allen, 2003). This can be partly explained by the impaired bioavailability of some micronutrients that are obtained via plant foods (Platel & Srinivasan, 2016). Nutrients such as non-heme iron and zinc (from cereals), can be affected by the inhibition of polyphenols, phytates, heat processing and soluble dietary fibre in plant foods causing poor bioavailability (Gibson et al., 2006, 2018; Platel & Srinivasan, 2016).

There is a significant lack of vitamin B12 in plant-based foods (Obeid et al., 2019), making it difficult to obtain without fortification or supplements. Vitamin B12 is only synthesised by certain bacteria, which can be transferred and accumulate in animal tissue, especially within the ruminant gut (e.g. sheep, cattle), but can also be found in phytoplankton through a symbiotic relationship with bacteria present in their stomachs (F. Watanabe & Bito, 2018). Unusual plant-based sources of vitamin B12 could be considered, such as edible algae, mushrooms or fermented beans and vegetables which vary contain amounts of vitamin B12 (Watanabe et al., 2014).

Other nutrients that could be difficult to obtain whilst following a non-omnivorous diet (excluding pescatarian) are certain omega-3 fatty acids, such as eicosapentaenoic (EPA) and docosahexaenoic acid (DHA), which are the fatty acids that are primarily associated with proper biological functioning and many health benefits (Swanson et al., 2012). These are not widely available in whole food plant-based sources and are mainly found in algae-consuming fish or marine invertebrates (Monroig et al., 2013; Peltomaa et al., 2017). There is a more abundant plant based omega-3 fatty acid called alpha-linolenic acid (ALA), but this doesn't have the same health benefits that EPA and DHA provides (Swanson et al., 2012). ALA can be found primarily in seed oils (flaxseed and chia seeds), nuts (walnuts) and hemp (Lane et al., 2014) and it has the ability to convert into EPA and DHA, but this conversion is very poor, rendering ALA an inadequate source for obtaining both EPA and DHA (Cholewski et al., 2018; Köhler et al., 2017; Lane et al., 2014).

There is only a limited number of foods that naturally contain vitamin D, some of these sources include fish, egg yolk, fortified milk and liver which are all animal-based (Cribb et al., 2015; Jungert et al., 2014; Lamberg-Allardt, 2006). Other sources can be found in sun soaked wild mushrooms, which are the only significant plant based sources of vitamin D (Black et al., 2017; Jäpel & Jakobsen, 2013; Teichmann et al., 2007). Vitamin D from wild mushrooms comes in the form of ergocalciferol (D2), which has been shown to be less efficacious in raising serum 25-hydroxyvitamin D (25[OH]D) compared to cholecalciferol (D3) (Shieh et al., 2016; Tripkovic et al., 2012), which is only found in the animal sources listed previously (Lamberg-Allardt, 2006; Nair & Maseeh, 2012). The difficulties to obtain certain nutrients when following a non-omnivorous diet could result in a greater risk of creating deficiencies in those nutrients, when not aided by fortified foods or supplements (Craig, 2010).

## Vitamin D Deficiency

Within populations that follow non-omnivorous diets, the risk of deficiency is higher than in populations that follow omnivorous diets (Craig, 2009), and in vegan populations specifically, vitamin D intake (including supplementation) did not reach the daily recommended value (Kristensen et al., 2015). A summary of the studies that investigated vitamin D status within non-omnivorous diets are listed in **Table 1.0**.

**Table 1.0.** A summary of results for observational and intervention studies investigating vitamin D status within populations that consume non-omnivorous and omnivorous diets.

- *Results that support the hypothesis that vitamin D status (measured as intake, serum or plasma) is significantly lower within non-omnivores compared with omnivores.*
- *Results that are statistically insignificant or where significance was not tested or could not be tested.*
- *Results that support the hypothesis that vitamin D status is significantly higher within non-omnivores compared with omnivores.*

Study	Study Type	Measurement	Diets Compared	Results
(Wilmana et al., 1979)	Cross-Sectional, Two-arm study	Plasma 25-hydroxyvitamin D	Omnivore and vegetarian	● Vegetarians had lower vitamin D in plasma compared to omnivores (significant)
(Lamberg-Allardt et al., 1993)	Case Control, Five-arm study	Vitamin D intake, Serum 25-hydroxyvitamin D	Omnivore, pescatarian, lacto-ovo-vegetarian, vegetarian (with vitamin D supplements) and strict vegetarian (vegan)	● Strict vegetarians had the lowest vitamin D intake compared to other groups and omnivores were had highest vitamin D intake compared to all groups (significant)
(Outila et al., 2000)	Cohort, Three-arm study	Vitamin D intake, Serum 25-hydroxyvitamin D	Omnivore, lacto-vegetarian and vegan	● Vegans and lacto-vegetarians had lower vitamin D intake than omnivores (significant) ● Vegans and lacto-vegetarians had lower vitamin D in serum than omnivores in winter months (significant)
(Larsson & Johansson, 2002)	Cross-Sectional, Two-arm study	Vitamin D intake	Omnivore and vegan	● Vegans had lower vitamin D intake compared to omnivores (significant)
(Davey et al., 2003)	Cohort, Four-arm study	Vitamin D intake	Omnivore, pescatarian, vegetarian and vegan	● Vegans had the lowest Vitamin D intakes compared to omnivores and pescatarians/vegetarians had intermediate values (Significance was not tested)
(Dunn-Emke et al., 2005)	Randomised Prospective Trial, Single-arm study	Vitamin D intake	Vegan	● The vegan diet intervention did not achieve adequate levels of vitamin D intake (significance was not tested)
(Fontana et al., 2005)	Case Control, Two-arm study	Serum 25-hydroxyvitamin D	Omnivore and vegetarian	● Vegetarians had lower intake of vitamin D than omnivores (not tested for significance) ● Vegetarians had higher vitamin D in serum than omnivores (significant)
(J. Chan et al., 2009)	Cohort, Three-arm study	Vitamin D intake, Serum 25-hydroxyvitamin D	Omnivore, semi vegetarian and vegetarian	● No difference in vitamin D in serum between vegetarians and omnivores (non-significant) ● Vegetarians had lower vitamin D intake compared with omnivores (non-significant)
(Ambroszkiewicz et al., 2010)	Cross-sectional, Single-arm study	Serum 25-hydroxyvitamin D	Vegan	● Vegans had lower vitamin D in serum compared to daily reference value (significance was not tested)

(Crowe et al., 2011)	Cross-Sectional, Four-arm study	Vitamin D intake, plasma 25-hydroxyvitamin D	Omnivore, pescatarian, vegetarian and vegan	<ul style="list-style-type: none"> <li>• Vegans had the lowest Vitamin D intakes compared to omnivores and pescatarians/vegetarians had intermediate values (significant)</li> <li>• Vegans had the lowest Vitamin D in plasma compared to omnivores and pescatarians/vegetarians had intermediate values (significant)</li> </ul>
(Laskowska-Klita et al., 2011)	Cross-Sectional, Two-arm study	Vitamin D intake, Serum 25-hydroxyvitamin D	Omnivore and vegetarian	<ul style="list-style-type: none"> <li>• Vegetarians had three-fold lower vitamin D intake compared to daily reference value (significance was not tested)</li> <li>• Vegetarians had half the vitamin D in serum compared to daily reference value (significance was not tested)</li> </ul>
(Ho-Pham et al., 2012)	Cohort, Two-arm study	Serum 25-hydroxyvitamin D	Omnivore and vegan	<ul style="list-style-type: none"> <li>• A greater percentage of vegans were deficient via serum vitamin D level than omnivores (significant)</li> </ul>
(Baig et al., 2013)	Cross-Sectional, Two-arm study	Vitamin D intake, Serum 25-hydroxyvitamin D	Omnivore and vegetarian	<ul style="list-style-type: none"> <li>• Vegetarians had vitamin D insufficiency and omnivores had severe vitamin D deficiency (significant)</li> </ul>
(N. S. Rizzo et al., 2013)	Cross-Sectional, Five-arm study	Vitamin D intake	Omnivore, semi-vegetarian, pescatarian, lacto-ovo-vegetarian and strict vegetarian	<ul style="list-style-type: none"> <li>• Strict vegetarians had the lowest vitamin D intake compared to omnivores (significant)</li> </ul>
(Elorinne et al., 2016)	Cross-Sectional, Two-arm study	Vitamin D intake, Serum 25-hydroxyvitamin D	Omnivore and vegan	<ul style="list-style-type: none"> <li>• Vegans had lower vitamin D intake compared to omnivores (significant)</li> <li>• Vegans had lower vitamin D in serum compared to omnivores (significant)</li> </ul>
(Schüpbach et al., 2017)	Cross-Sectional, Three-arm study	Vitamin D intake	Omnivore, vegetarian and vegan	<ul style="list-style-type: none"> <li>• Vegans had lower vitamin D intake compared to vegetarians (significant)</li> <li>• Vegetarians had lower vitamin D intake compared to omnivores (significant)</li> </ul>
(Nebi et al., 2019)	Cross-Sectional, Three-arm study	Vitamin D intake, Serum 25-hydroxyvitamin D	Omnivore, vegetarian and vegan	<ul style="list-style-type: none"> <li>• Omnivores and vegans had higher vitamin D intakes compared to vegetarians (non-significant)</li> <li>• Omnivores and vegans had higher vitamin D in serum compared to vegetarians (non-significant)</li> </ul>
(Xie et al., 2019)	Cross-Sectional, Three-arm study	Vitamin D intake, Serum 25-hydroxyvitamin D	Omnivore, vegetarian and vegan	<ul style="list-style-type: none"> <li>• Vegetarians had lower vitamin D intake than omnivores (significant)</li> <li>• Vegans had lower vitamin D in serum than omnivores (significant)</li> </ul>

## Vitamin B12 Deficiency

Vitamin B12 is found almost exclusively in animal-based foods, which makes populations that follow non-omnivorous diets—that are not well formulated with fortified foods or supplements—at a higher risk of vitamin B12 deficiency (Zeuschner et al., 2013). A summary of the observational studies that investigated vitamin B12 status within non-omnivorous diets are listed in **Table 1.1**.

Many reviews to date have looked across different types of non-omnivorous diets and their association with vitamin B12 deficiency. A consistent finding across these reviews is that vitamin B12 deficiency is common among vegetarians and vegans are at even higher risk, especially without appropriate supplementation (Allen, 2008; Wolfgang Herrmann & Geisel, 2002; R. Pawlak et al., 2014; Roman Pawlak et al., 2013; G. Rizzo et al., 2016; Woo et al., 2014).

A case study on a 14-year-old girl—who suffered from severe neurological disturbances—followed a strict vegetarian diet without vitamin B12 supplementation. Her symptoms were resolved completely following a treatment with vitamin B12, which highlights the importance of vitamin B12 for neurological health, but also that strict vegetarian diets (void of vitamin B12 supplementation) are at high risk of vitamin B12 deficiency (Ashkenazi et al., 1987). A systematic narrative review on vegan and vegetarians diets in pregnancy found that the data is limited and heterogeneous in these populations, but still acknowledged the nutrients iron and vitamin B12 requiring considerable attention to prevent deficiency (Piccoli et al., 2015). A position paper of the nutrition committee, German Society for Paediatric and Adolescent Medicine stated that if a vegan diet is followed over an extended period, it will lead to vitamin B12 deficiency and that supplementation is required to prevent this (Rudloff et al., 2019).

**Table 1.1.** A summary of results for observational studies investigating vitamin B12 status within populations that consume non-omnivorous and omnivorous diets.

- *Results that support the hypothesis that vitamin B12 status (measured as intake, serum cobalamin or serum holotranscobalamin (holoTC)) is significantly lower within non-omnivores compared with omnivores.*
- *Results that are statistically insignificant.*

Study	Study Type	Measurement	Diets Compared	Results
(Bar-Sella et al., 1990)	Cross-Sectional, Two-arm study	Serum cobalamin	Omnivore and vegan	● Vegans had lower serum cobalamin compared to omnivores (significance not tested)
(Janelle & Barr, 1995)	Cross-Sectional, Three-arm study	Vitamin B12 intake	Omnivore, vegetarian and vegan	● Vegetarians and vegans had lower vitamin B12 intakes compared to omnivores (significant)
(Herrmann et al., 2001)	Cross-Sectional, Four-arm study	Serum cobalamin	High meat eaters, low meat eaters, vegetarian and vegan	● Vegetarians and vegans had lower serum cobalamin compared to high meat eaters (non-significant) ● Low meat eaters had lower serum cobalamin compared to high meat eaters (significant)
(Waldmann et al., 2005)	Cross-Sectional, Two-arm study	Serum cobalamin	Strict vegan and moderate vegan	● Strict vegans had lower serum cobalamin than moderate vegans (significant)
(Majchrzak et al., 2006)	Cross-Sectional, Three-arm study	Vitamin B12 intake, plasma cobalamin	Omnivore, vegetarian and vegan	● Vegans had lower vitamin B12 intake than vegetarians and omnivores (significant) ● Vegans had lower plasma cobalamin than vegetarians and omnivores (significant) ● Vegans had lower vitamin B12 intake than vegetarians (significant)
(Gilsing et al., 2010)	Cross-Sectional, Three-arm study	Vitamin B12 intake, serum cobalamin	Omnivore, vegetarian and vegan	● Vegetarians had lower vitamin B12 intake than omnivores (significant) ● Vegans had lower serum cobalamin than vegetarians (significant) ● Vegetarians had lower serum cobalamin than omnivores (significant)
(Naik et al., 2018)	Cross-Sectional, Single-arm study	Serum cobalamin and plasma holoTC	Vegetarian	● 60% of vegetarians were deficient measured by serum cobalamin (significance cannot be tested) ● 76% of vegetarians were deficient measured by plasma holoTC (significance cannot be tested)
(Selinger et al., 2019)	Cross-Sectional, Two-arm study	Serum cobalamin and holoTC	Omnivore and vegan	● Vegans had lower serum cobalamin compared to non-vegans (significant) ● There was no significant difference in serum holoTC between the groups (non-significant)
(Gallego-Narbón, Zapatera, Barrios, et al., 2019)	Cross-Sectional, Two-arm study	Serum cobalamin	Vegetarian and vegan	● There was no significant difference in serum cobalamin between the groups (non-significant)

## Zinc Deficiency

Zinc deficiency among people that follow non-omnivorous diets is common and has been demonstrated within the literature when comparing the intakes of vegetarians, vegans and omnivores, but also when comparing the levels of zinc in serum, hair and saliva (Freeland-Graves, 1988). A summary of observational studies and their results are displayed in **Table 1.2.**

Two reviews suggested that zinc from vegetarian diets tend to be lower due to the exclusion of red meat and a higher consumption of phytic acid from sources such as whole grains, legumes, seeds and nuts (Hunt, 2002, 2003). A meta-analysis of 6 observational studies confirmed this in pregnant women, they found vegetarians had significantly lower dietary zinc intake compared to non-vegetarian controls (Foster et al., 2015). Another meta-analysis of 26 studies by the same author demonstrated similar results, they found dietary zinc intakes and serum zinc concentrations were significantly lower in people following vegetarian diets compared to non-vegetarians (Foster et al., 2013). A later review by Foster & Samman (2015) concluded from the available evidence, that serum zinc is found to be significantly lower in vegetarians compared to omnivores. A study by Saunders et al., (2013) reviewed the literature and came to different conclusions, they suggested that vegetarians had similar serum zinc concentrations to non-vegetarians and had no greater risk of deficiency despite the differences in intake if the diet is well formulated. This was mirrored in another review on young children, they suggested that a well formulated vegetarian diet may overcome any inherent zinc deficiencies that could arise, but also found that within strict vegan diets the risk of deficiency is much higher (Gibson et al., 2014).

**Table 1.2.** A summary of results for observational studies investigating zinc status within populations that consume non-omnivorous and omnivorous diets.

- Results that support the hypothesis that zinc status (measured as intake, saliva, hair, plasma, erythrocyte or serum) is significantly lower within non-omnivores compared with omnivores.
- Results that are statistically insignificant or where significance was not tested or could not be tested.

Study	Study Type	Measurements	Diets Compared	Results
(Freeland-Graves et al., 1980)	Cross-Sectional, Two-arm study	Zinc in serum, saliva and hair	Omnivore, vegetarian and vegan	<ul style="list-style-type: none"> <li>● Vegetarians had lower zinc saliva levels than omnivores; vegans had the lowest mean level (significant)</li> <li>● Vegetarians had lower zinc hair levels than omnivores (significant)</li> <li>● Vegetarians had lower zinc serum levels than omnivores (non-significant)</li> </ul>
(Bakan et al., 1993)	Cross-Sectional, Two-arm study	Zinc intake	Omnivore and vegetarian	<ul style="list-style-type: none"> <li>● Vegetarians had lower zinc intakes compared to omnivores (significant)</li> </ul>
(Donovan & Gibson, 1995)	Cross-Sectional, Three-arm study	Zinc in serum, hair and intake	Omnivore, semi-vegetarian and lacto-ovo-vegetarian	<ul style="list-style-type: none"> <li>● Lacto-ovo-vegetarians and semi-vegetarians had lower zinc intake than omnivores (non-significant)</li> <li>● Lacto-ovo vegetarians had lower zinc in serum and hair levels compared with omnivores (non-significant)</li> </ul>
(Janelle & Barr, 1995)	Cross-Sectional, Three-arm study	Zinc intake	Omnivore, vegetarian and vegan	<ul style="list-style-type: none"> <li>● Vegetarians and vegans had lower zinc intakes compared to omnivores (significant)</li> </ul>
(Davey et al., 2003)	Cohort, Four-arm study	Zinc intake	Omnivore, pescatarian, vegetarian and vegan	<ul style="list-style-type: none"> <li>● Vegans had the lowest zinc intakes compared to omnivores and pescatarians/vegetarians had intermediate values (significance was not tested)</li> </ul>
(de Bortoli & Cozzolino, 2009)	Cross-Sectional, Single-arm study	Zinc in erythrocytes	Vegetarian	<ul style="list-style-type: none"> <li>● Vegetarians had lower zinc in erythrocytes compared to daily reference value (significant)</li> </ul>
(Schüpbach et al., 2017)	Cross-Sectional, Three-arm study	Zinc in plasma & zinc intake	Omnivore, vegetarian and vegan	<ul style="list-style-type: none"> <li>● Vegans had lower zinc plasma levels than vegetarians (significant)</li> <li>● Vegetarians had lower zinc plasma levels than omnivores (significant)</li> <li>● A greater percentage of vegans were deficient via plasma zinc level than vegetarians (significant)</li> <li>● A greater percentage of vegetarians were deficient via plasma zinc levels than omnivores (significant)</li> <li>● There was no significant difference in zinc intake between all groups (non-significant)</li> </ul>
(Nebl et al., 2019)	Cross-Sectional, Three-arm study	Zinc in serum and intake	Omnivore, vegetarian and vegan	<ul style="list-style-type: none"> <li>● Vegetarians and vegans had lower zinc intakes compared to omnivores (non-significant)</li> <li>● Vegetarians and vegans had lower zinc serum levels compared to omnivores (non-significant)</li> </ul>

## Iron Deficiency

Iron deficiency among non-omnivorous can be seen more commonly in restrictive vegetarian diets (e.g. vegan and macrobiotic), and although western vegetarians tend to have a better iron status than those in developing countries—due to higher variety of foods available—special attention should be considered when formulating non-omnivorous diets to ensure deficiency is avoided (Craig, 1994). A results summary of the observational studies investigating iron status in non-omnivores can be seen in **Table 1.3**.

Vegetarian diets among younger populations have been studied, a review by Pawlak and Bell (2017) discovered that inadequate iron status is a common nutritional problem among both vegetarian and omnivorous children, yet stated it is largely more prevalent among vegetarians. This was also concluded by a consensus paper by the German Society for Paediatric and Adolescent Medicine, and made the point that vegetarian diets in childhood and adolescence may require close monitoring and supervision by a paediatrician, to ensure nutritional adequacy (Rudloff et al., 2019). Another review aligns similarly to this, although they put the emphasis on restrictive vegetarian diets (e.g vegan) and recommended the use of supplements where necessary (Gibson et al., 2014). When looking at adults, similar findings have been found. A literature review by Pawlak et al (2016) concluded iron to be a nutrient of concern for vegetarians, which was mainly indicative of reduced ferritin levels below the recommended cut-off values. A systematic review and meta-analysis—that looked into the effect of vegetarian diets on iron status in adults—presented results that found vegetarians were more likely to have a poorer iron status (measured by serum ferritin) when compared with non-vegetarians (Haider et al., 2018).

**Table 1.3.** A summary of results for observational studies investigating iron status within populations that consume non-omnivorous and omnivorous diets.

- Results that support the hypothesis that iron status (measured as intake, in serum iron/ferritin or plasma ferritin) is significantly lower within non-omnivores compared with omnivores.
- Results that are statistically insignificant or where significance was not tested or could not be tested.
- Results that support the hypothesis that iron status is significantly higher within non-omnivores compared with omnivores.

Study	Study Type	Measurement	Diets Compared	Results
(Sharma et al., 1994)	Cross-Sectional, Two-arm study	Serum iron and ferritin	Omnivore and vegetarian	<ul style="list-style-type: none"> <li>● Vegetarians had lower serum iron than omnivores (significant)</li> <li>● Vegetarians had lower serum ferritin than omnivores (significant)</li> </ul>
(Alexander et al., 1994)	Cross-Sectional, Two-arm study	Iron intake and serum ferritin	Omnivore and vegetarian	<ul style="list-style-type: none"> <li>● Vegetarians had lower iron intake than omnivores (significant)</li> <li>● Vegetarian females had lower serum ferritin than omnivores (significant)</li> </ul>
(Shaw et al., 1995)	Cross-Sectional, Two-arm study	Plasma ferritin	Omnivore and vegetarian	<ul style="list-style-type: none"> <li>● Vegetarians had lower plasma ferritin than omnivores (significant)</li> </ul>
(Pongstaporn & Bunyaratavej, 1999)	Cross-Sectional, Two-arm study	Serum ferritin	Omnivore and vegetarian	<ul style="list-style-type: none"> <li>● Vegetarians had lower serum ferritin than omnivores (significant)</li> </ul>
(Ball & Bartlett, 1999)	Cross-Sectional, Two-arm study	Iron intake and serum ferritin	Omnivore and vegetarian	<ul style="list-style-type: none"> <li>● There was no significant difference in iron intake between vegetarians and omnivores (non-significant)</li> <li>● Vegetarians had lower serum ferritin than omnivores (significant)</li> </ul>
(Obeid et al., 2002)	Cross-Sectional, Three-arm study	Serum iron	Semi vegetarians, vegetarians and vegans	<ul style="list-style-type: none"> <li>● There was no significant difference in serum iron between the groups (non-significant)</li> </ul>
(Waldmann et al., 2004)	Cross-Sectional, Single-arm study	Iron intake and serum ferritin	Vegan	<ul style="list-style-type: none"> <li>● 42% of vegans had a daily intake of iron under the daily recommended value (significance not tested)</li> <li>● 40% of vegans were considered iron deficient based serum ferritin levels &lt; 12ng/ml (significance not tested)</li> </ul>
(M.-H. Kim et al., 2007)	Cross-Sectional, Two-arm study	Serum ferritin	Omnivore and vegetarian	<ul style="list-style-type: none"> <li>● Vegetarians had lower serum ferritin than omnivores (significant)</li> </ul>
(Yen et al., 2008)	Cross-Sectional, Two-arm study	Iron intake, serum iron and ferritin	Omnivore and vegetarian	<ul style="list-style-type: none"> <li>● Omnivores had lower iron intake than vegetarians (significant)</li> <li>● There was no difference in serum iron between the groups (non-significant)</li> <li>● Vegetarians had lower serum ferritin than omnivores (significant)</li> </ul>
(Kajanachumpol et al., 2011)	Cross-Sectional, Two-arm study	Serum iron and ferritin	Omnivore and vegan	<ul style="list-style-type: none"> <li>● Vegans had lower serum iron than omnivores (significant)</li> <li>● Vegans had lower serum ferritin than omnivores (significant)</li> </ul>
(Deriemaeker et al., 2011)	Cross-Sectional, Two-arm study	Serum iron and ferritin	Omnivore and vegetarian	<ul style="list-style-type: none"> <li>● Vegetarians had lower serum iron than omnivores (non-significant)</li> <li>● Vegetarians had lower serum ferritin than omnivores (non-significant)</li> </ul>
(Hawk et al., 2012)	Cross-Sectional, Two-arm study	Iron intake, serum iron and ferritin	Omnivore and vegetarian	<ul style="list-style-type: none"> <li>● There was no significant difference in iron intake between the groups (non-significant)</li> <li>● There was no significant difference in serum iron between the groups (non-significant)</li> <li>● There was no significant difference in serum ferritin between the groups (non-significant)</li> </ul>

(Leonard et al., 2014)	Cross-Sectional, Two-arm study	Serum ferritin	Omnivore and vegetarian	<ul style="list-style-type: none"> <li>Vegetarians had lower serum ferritin than omnivores (significant)</li> </ul>
(Śliwińska et al., 2018)	Cross-Sectional, Two-arm study	Ferritin	Vegetarian and vegan	<ul style="list-style-type: none"> <li>Serum ferritin was decreased in the vegetarian and vegan groups (significant)</li> </ul>
(Gallego-Narbón, Zapatera, & Vaquero, 2019)	Cross-Sectional, Two-arm study	Serum iron and ferritin	Vegetarian and vegan	<ul style="list-style-type: none"> <li>There was no significant difference between the groups in serum iron and ferritin (non-significant)</li> </ul>

## Omega 3 Deficiency

Populations that follow non-omnivorous diets have a greater risk of impaired essential fatty acid status, which is primarily due to limited availability of plant based EPA and DHA and the poor conversion of ALA to EPA and DHA (B. C. Davis & Kris-Etherton, 2003). There are many observational studies that show deficiencies in total omega 3 fatty acids, EPA and DHA among populations that follow vegetarian and vegan diets compared to omnivorous and pescatarian diets. A results summary of the observational studies investigating this can be seen in **Table 1.4**.

Studies reviewing the essential fatty acid status of non-omnivorous have come to similar conclusions. A reviewer investigated the EPA and DHA status of pregnant non-omnivorous women compared with omnivorous controls, they found that EPA and DHA intake and levels were lower in vegetarians and vegans compared to omnivores. They also discovered that infants born to vegan mothers had a lower EPA and DHA status compared to infants born to omnivore mothers (Burdge et al., 2017). Another study reviewed omega 3 fatty acids in the vegan diet specifically, they found that in most studies, vegans consume low to zero amounts of EPA and DHA unless they take supplements. They also found that plasma, erythrocytes, adipose, serum and platelet levels of EPA and DHA are lower in vegans than omnivores (Burns-Whitmore et al., 2019). This was also replicated in a review that look at DHA by itself, they found that preformed DHA in the diet of omnivores explains the higher levels that are seen in blood and tissue samples compared with vegetarians (Sanders, 2009).

**Table 1.4.** A summary of results for observational studies investigating omega 3 status within populations that consume non-omnivorous and omnivorous diets.

- *Results that support the hypothesis that omega 3 status (measured as intake, in serum, plasma, adipose tissue, erythrocytes, platelets or breast milk) is significantly lower within non-omnivores compared with omnivores.*
- *Results that are statistically insignificant or where significance was not tested or could not be tested.*
- *Results that support the hypothesis that omega 3 status is significantly higher within non-omnivores compared with omnivores.*

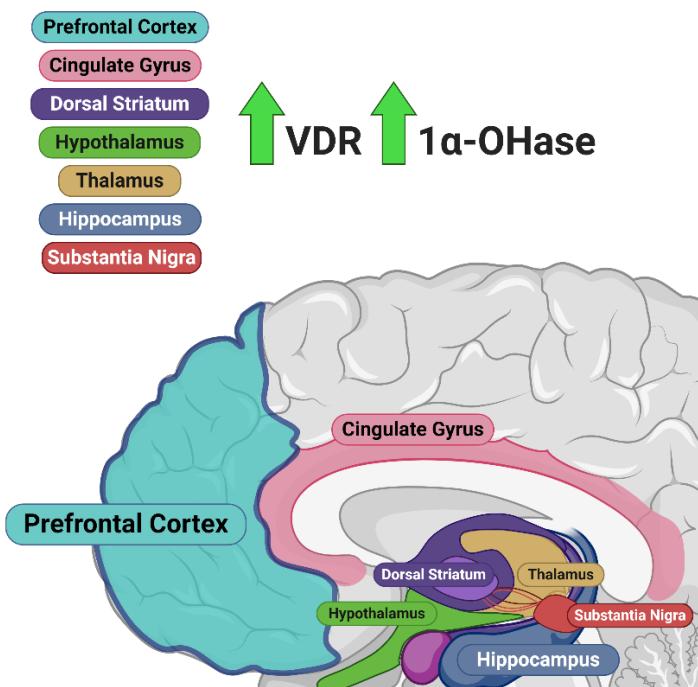
Study	Study Type	Measurement	Diets Compared	Results
(Sanders et al., 1978)	Cross-Sectional, Two-arm study	Plasma EPA and DHA	Omnivore and vegan	<ul style="list-style-type: none"> <li>● Vegans had lower plasma EPA than omnivores (significant)</li> <li>● Vegans had lower plasma DHA than omnivores (significant)</li> </ul>
(Sanders & Roshanai, 1992)	Cross-Sectional, Two-arm study	Platelet EPA and DHA	Omnivore and vegan	<ul style="list-style-type: none"> <li>● Vegans had lower platelet EPA than omnivores (significance was not tested)</li> <li>● Vegans had lower platelet DHA than omnivores (significance was not tested)</li> </ul>
(Agren et al., 1995)	Cross-Sectional, Two-arm study	Erythrocyte EPA and DHA	Omnivore and vegan	<ul style="list-style-type: none"> <li>● Vegans had lower erythrocyte EPA than omnivores (significant)</li> <li>● Vegans had lower erythrocyte DHA than omnivores (significant)</li> </ul>
(Conquer & Holub, 1997)	Cohort, Two-arm study	Serum EPA and DHA	Omnivore and vegetarian	<ul style="list-style-type: none"> <li>● There was no significant difference in EPA between groups (non-significant)</li> <li>● There was no significant difference in DHA between groups (non-significant)</li> </ul>
(D. Li et al., 1999)	Cross-Sectional, Two-arm study	Plasma total n-3, EPA and DHA	Omnivore and vegetarian	<ul style="list-style-type: none"> <li>● Vegetarians had lower total n-3 in plasma than omnivores (significant)</li> <li>● Vegetarians had lower plasma EPA than omnivores (significant)</li> <li>● Vegetarians had lower plasma DHA than omnivores (significant)</li> </ul>
(H. Y. Lee et al., 2000)	Cross-Sectional, Two-arm study	Serum total n-3, EPA and DHA	Omnivore and vegetarian	<ul style="list-style-type: none"> <li>● Vegetarians had lower serum total n-3 than omnivores (significant)</li> <li>● Vegetarians had lower serum EPA than omnivores (significant)</li> <li>● Vegetarians had lower serum DHA than omnivores (significant)</li> </ul>
(Manjari et al., 2001)	Cross-Sectional, Two-arm study	Serum EPA and DHA	Omnivore and vegetarian	<ul style="list-style-type: none"> <li>● Vegetarians had lower serum EPA than omnivores (significant)</li> <li>● Vegetarians had lower serum DHA than omnivores (significant)</li> </ul>
(Rosell et al., 2005)	Cross-Sectional, Three-arm study	Plasma EPA and DHA	Omnivore, vegetarian and vegan	<ul style="list-style-type: none"> <li>● Vegans had lower plasma EPA than vegetarians (significant)</li> <li>● Vegetarians had lower plasma EPA than omnivores (significant)</li> <li>● Vegans had lower plasma DHA than vegetarians (significant)</li> <li>● Vegetarians had lower plasma DHA than omnivores (significant)</li> </ul>
(N. Mann et al., 2006)	Cross-Sectional, Four-arm study	Total n-3 intake, plasma EPA and DHA	High meat omnivore, moderate meat omnivore, vegetarian and vegan	<ul style="list-style-type: none"> <li>● Vegans and vegetarians had lower total n-3 intake than high and moderate omnivores (significant)</li> <li>● Vegans and vegetarians had lower plasma EPA than high and moderate omnivores (significant)</li> <li>● Vegans and vegetarians had lower plasma DHA than high and moderate omnivores (significant)</li> </ul>

<b>(Kornsteiner et al., 2008)</b>	Cross-Sectional, Four-arm study	Total n-3 intake, erythrocyte EPA and DHA	Omnivore, semi-omnivore, vegetarian and vegan	<ul style="list-style-type: none"><li>● Vegans had lower total n-3 intake than vegetarians (significant)</li><li>● Vegetarians had lower total n-3 intake than omnivores (significant)</li><li>● Vegans had lower erythrocyte EPA than vegetarians (significant)</li><li>● Vegetarians had lower erythrocyte EPA intake than omnivores (significant)</li><li>● Vegans had lower erythrocyte DHA than vegetarians (significant)</li><li>● Vegetarians had lower erythrocyte DHA intake than omnivores (significant)</li></ul>
				<ul style="list-style-type: none"><li>● Omnivores had lower erythrocyte EPA than vegans (significant)</li><li>● There was no significant difference in erythrocyte DHA between groups (non-significant)</li></ul>
<b>(Sarter et al., 2015)</b>	Cross-Sectional, Two-arm study	Erythrocyte EPA and DHA	Omnivore and vegan	<ul style="list-style-type: none"><li>● Vegetarians had lower serum EPA than omnivores (significant)</li><li>● Vegetarians had lower serum DHA than omnivores (significant)</li></ul>
<b>(Elorinne et al., 2016)</b>	Cross-Sectional, Two-arm study	Serum EPA and DHA	Omnivore and vegetarian	<ul style="list-style-type: none"><li>● Vegetans had lower plasma EPA compared to omnivores (significant)</li><li>● Vegetans had lower plasma DHA compared to omnivores (significant)</li></ul>
<b>(Pinto et al., 2017)</b>	Cross-Sectional, Two-arm study	Plasma and erythrocyte EPA and DHA	Omnivore and vegan	<ul style="list-style-type: none"><li>● Vegans had lower erythrocyte EPA compared to omnivores (significant)</li><li>● Vegans had lower erythrocyte DHA compared to omnivores (significant)</li></ul>
				<ul style="list-style-type: none"><li>● Vegans had lower serum total n-3 than vegetarians (significant)</li><li>● Vegans had lower serum EPA than vegetarians (non-significant)</li><li>● Vegans had lower serum DHA than vegetarians (significant)</li></ul>
<b>(Salvador et al., 2019)</b>	Cross-Sectional, Two-arm study	Serum total n-3, EPA and DHA	Omnivore and vegetarian	<ul style="list-style-type: none"><li>● Omnivores had lower breast milk total n-3 than vegetarians (significant)</li><li>● Vegetarians had lower breast milk total n-3 than vegans (significant)</li></ul>
<b>(Perrin et al., 2019)</b>	Cross-Sectional, Three-arm study	Breast milk total n-3	Omnivore, vegetarian and vegan	<ul style="list-style-type: none"><li>● Vegetarians had lower adipose tissue EPA compared to omnivores (significant)</li><li>● Vegans and vegetarians had lower adipose tissue EPA compared to pescatarians (significant)</li></ul>
<b>(Miles et al., 2019)</b>	Cross-Sectional, Five-arm study	Adipose tissue EPA and DHA	Omnivore, semi-vegetarian, pescatarian, vegetarian and vegan	<ul style="list-style-type: none"><li>● Vegetarians had lower adipose tissue EPA compared to omnivores (significant)</li><li>● Vegans and vegetarians had lower adipose tissue EPA compared to pescatarians (significant)</li></ul>

# Linking Nutrient Deficiencies to Depression

## Vitamin D Deficiency

The mechanism that links vitamin D deficiency to depression is not fully understood. Although inferences can be made from immunohistochemical staining data within human brain regions, where vitamin D receptors (VDR) and the enzyme responsible for converting vitamin D into its active form ( $1\alpha$ -OHase) have been found to be substantially distributed in multiple regions in the brain (**Figure 2.0**) (D. W. Eyles et al., 2005).



**Figure 2.0** The brain regions that were found to have intense immunoreactivity in both VDR and  $1\alpha$ -OHase (Eyles et al., 2005).

Some of these regions have been shown to be involved in the pathophysiology of depression, with different changes that are apparent in each region among individuals who suffer from depression (**Table 2.0**). Other possible mechanisms related to vitamin D and depression include the role the nutrient plays in brain development (Eyles et al., 2003), but also within immunomodulation and how vitamin D relates to the proinflammatory cytokine theory of depression (McCann & Ames, 2008).

**Table 2.0** A summary of the brain region changes that have been found in people who suffer from depression.

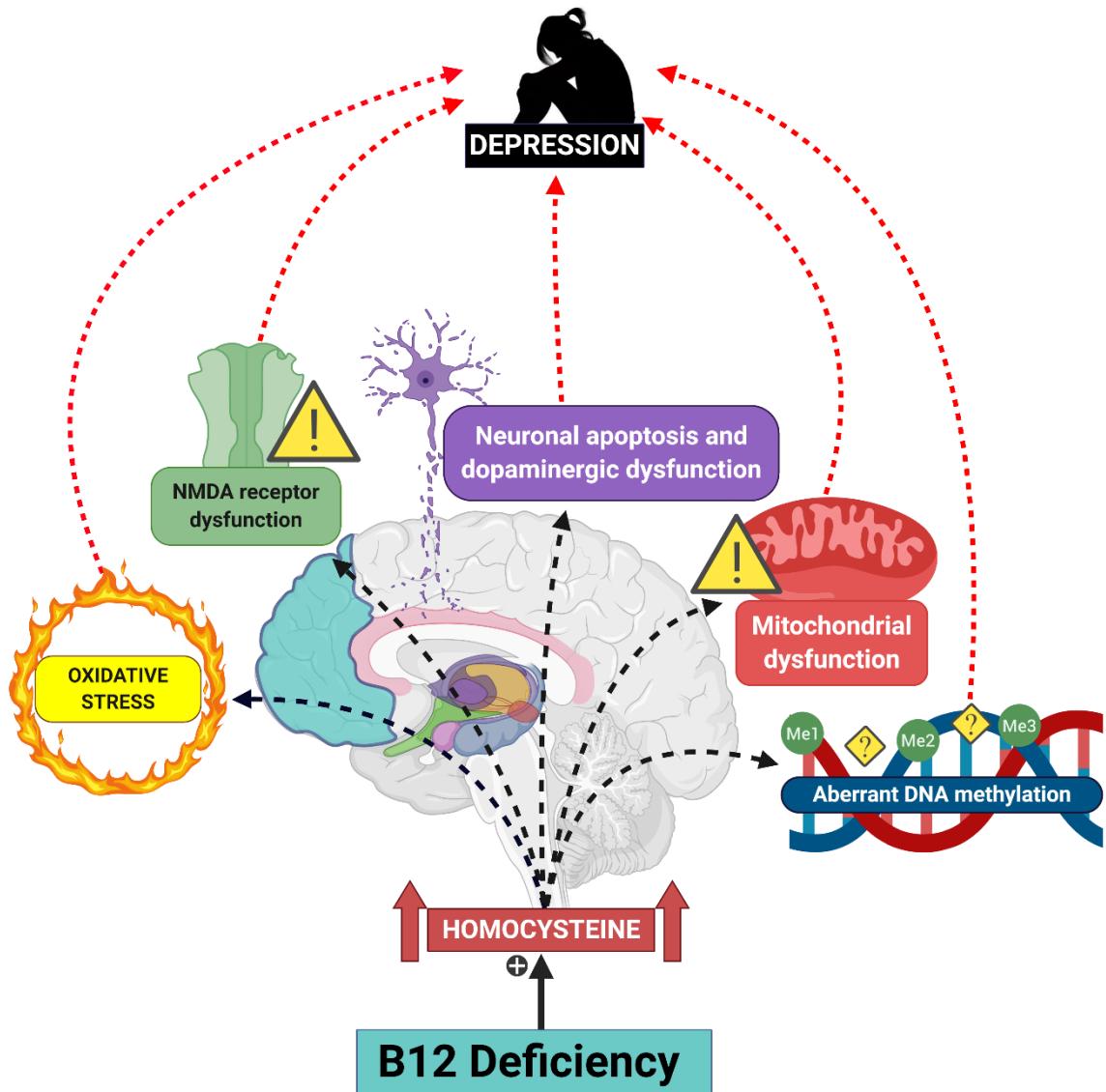
Region	Changes to regions related to depression pathophysiology	Reference
Prefrontal Cortex	Adverse changes to neural plasticity	(Liu et al., 2017)
Hippocampus	Adverse changes to neural plasticity	(Liu et al., 2017)
Cingulate Gyrus	Reduction in region volume	(Drevets et al., 2008)
Dorsal Striatum	Alterations in corticostriatal connectivity	(Kerestes et al., 2015)
Hypothalamus	Involved in neurohormonal system of depression	(Bao & Swaab, 2018)
Thalamus	An increased number of regional neurons	(Leonard et al., 2014)
Substantia Nigra	A loss of dopaminergic neurons	(Wen et al., 2016)

## Vitamin B12 Deficiency

Vitamin B12 deficiency has been associated with neurological and psychiatric manifestations, including irritability, depression, dementia, impaired memory and psychosis (Hutto, 1997; Lindenbaum et al., 1988; Oh & Brown, 2003). The main mechanism that is known to be implicated in the link between vitamin B12 deficiency and depression is homocysteine (Moustafa et al., 2014). Homocysteine has been shown to influence many pathways in the brain that are also involved in the pathophysiology of psychiatric disorders (**Table and Figure 2.1**).

**Table 2.1** A summary of the evidence showing the pathophysiological pathways that could be implicated in depression caused by B12 deficiency mediated by elevated homocysteine.

Pathophysiology Pathway	Reference
Homocysteine → Oxidative Stress	(Tyagi et al., 2005)
Oxidative stress → Depression	(Michel et al., 2012)
Homocysteine → NMDA receptor dysfunction	(Poddar & Paul, 2009)
NMDA receptor dysfunction → Depression	(Lakhan et al., 2013)
Homocysteine → Neuronal apoptosis and dopaminergic dysfunction	(Duan et al., 2002; Kruman et al., 2000)
Neuronal apoptosis and dopaminergic dysfunction → Depression	(Belujon & Grace, 2017; Duman, 2009)
Homocysteine → Mitochondrial dysfunction	(Fiddian-Green & Massachusetts, 2002)
Mitochondrial dysfunction → Depression	(Bansal & Kuhad, 2016)
Homocysteine → Aberrant DNA methylation	(Kinoshita et al., 2013)
Aberrant DNA methylation → Depression	(Li et al., 2019)



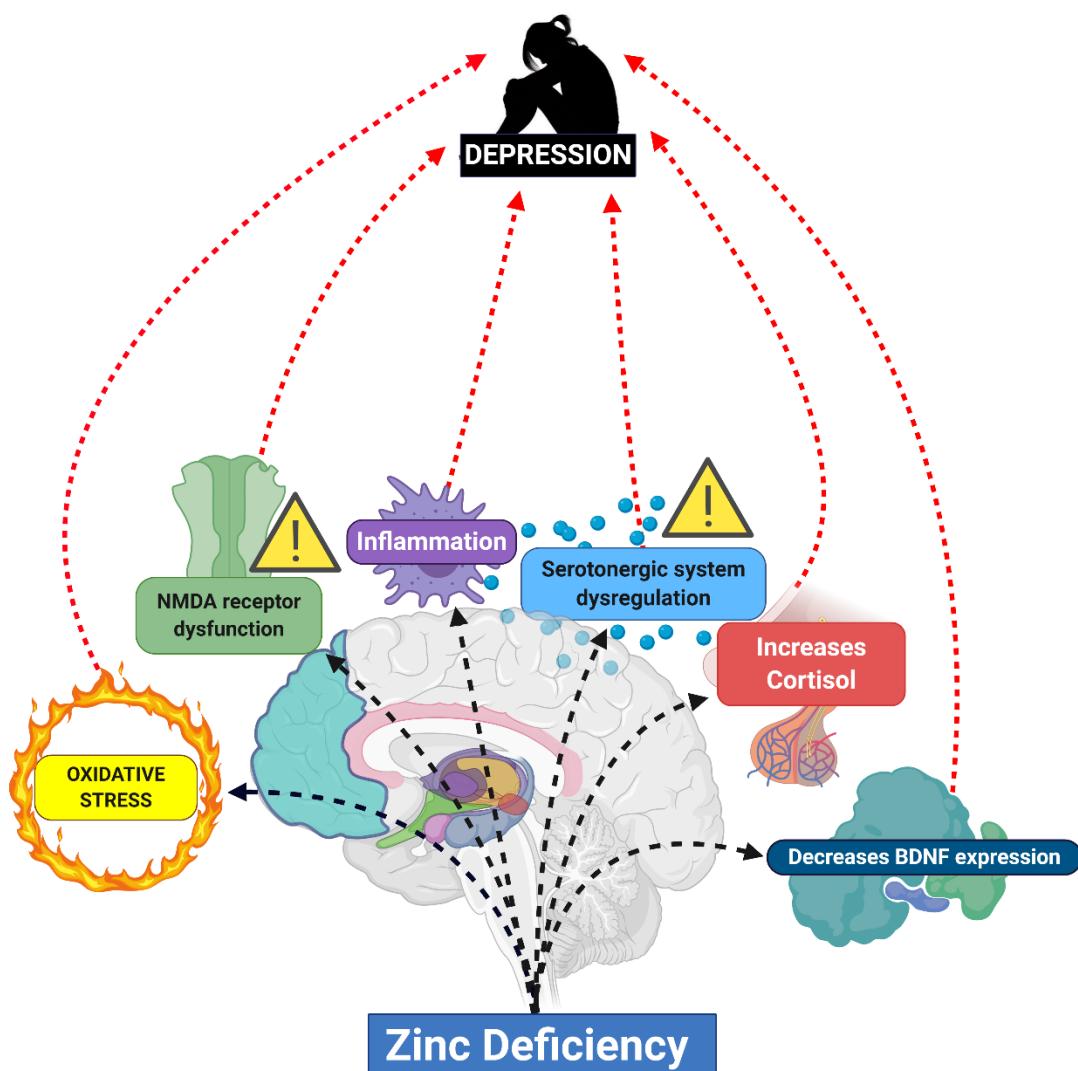
**Figure 2.1** The pathophysiological pathways that could be implicated in depression caused by B12 deficiency, mediated by elevated homocysteine.

## Zinc Deficiency

Zinc is responsible for the activity of key enzymes involved in neuronal metabolism and is a modulator of synaptic activity and neuronal plasticity in both development and adulthood (Gower-Winter & Levenson, 2012). There are many possible mechanisms that could be implicated in the pathophysiology depression due to zinc deficiency, one being zinc's ability to modulate NMDA receptor activity (Petrilli et al., 2017), but also other mechanistic links have been explored (**Table** and **Figure 2.2**).

**Table 2.2** A summary of the evidence showing the pathophysiological pathways that could be implicated in depression caused by zinc deficiency.

Pathophysiology Pathway	Reference
Zinc Deficiency → Oxidative Stress	(Eide, 2011)
Oxidative stress → Depression	(Michel et al., 2012)
Zinc Deficiency → NMDA receptor dysfunction	(Młyniec, 2015)
NMDA receptor dysfunction → Depression	(Lakhan et al., 2013)
Zinc Deficiency → Inflammation	(Kido et al., 2019)
Inflammation → Depression	(Loftis & Hauser, 2004)
Zinc Deficiency → Serotonergic system dysregulation	(Doboszewska et al., 2017)
Serotonergic system dysregulation → Depression	(Cowen & Browning, 2015)
Zinc Deficiency → Increases cortisol	(Takeda et al., 2016)
Increases cortisol → Depression	(Keller et al., 2017)
Zinc Deficiency → Decreases BDNF expression	(Fazzini et al., 2018)
Decreases BDNF expression → Depression	(Solati et al., 2015)



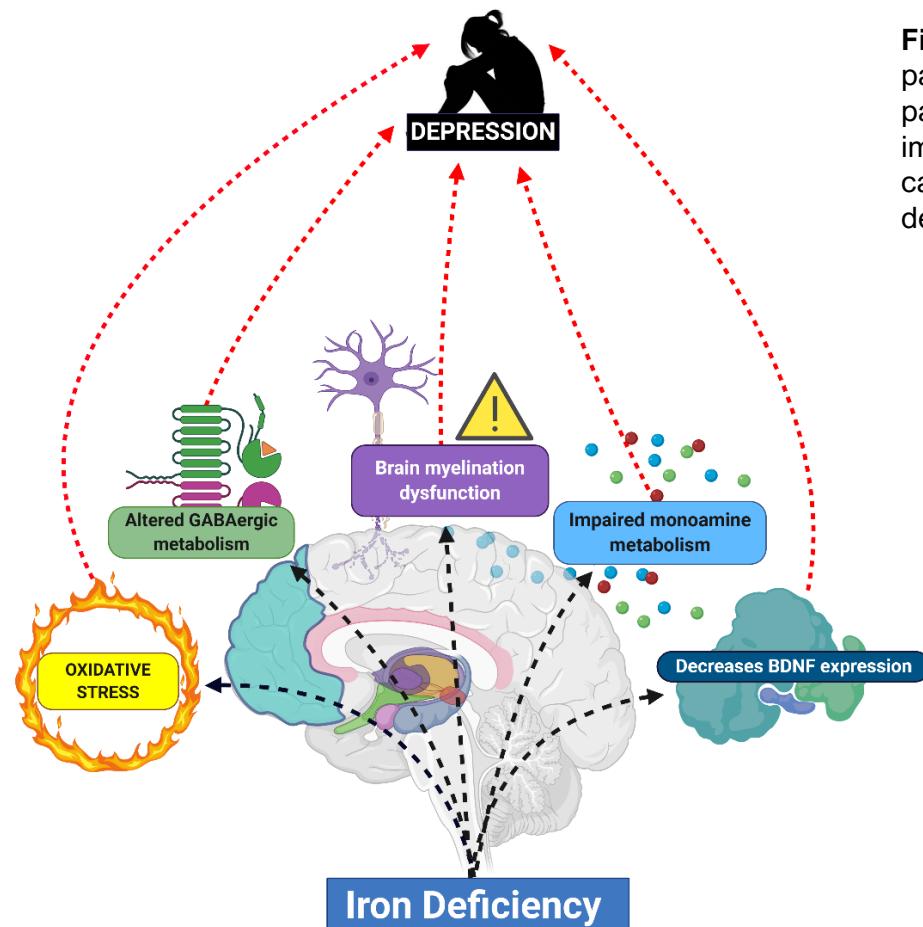
**Figure 2.2** The pathophysiological pathways that could be implicated in depression caused by zinc deficiency

## Iron Deficiency

Iron is an important nutrient for brain development and behaviour (Georgieff, 2008; Yafeng Wang et al., 2019). Many potential pathways exist that have linked iron deficiency to depression, such as the influence it has on dopamine and GABA metabolism (Kim & Wessling-Resnick, 2014), but also on oxidative stress, brain myelination and BDNF expression (Table and Figure 2.3).

**Table 2.3** A summary of the evidence showing the pathophysiological pathways that could be implicated in depression caused by zinc deficiency.

Pathophysiology Pathway	Reference
Iron Deficiency → Oxidative stress	(Coghetto Baccin et al., 2009)
Oxidative stress → Depression	(Michel et al., 2012)
Iron Deficiency → Altered GABAergic metabolism	(Rao et al., 2003)
Altered GABAergic metabolism → Depression	(Lener et al., 2017)
Iron Deficiency → Brain myelination dysfunction	(Connor & Menzies, 1996)
Brain myelination dysfunction → Depression	(Williams et al., 2019)
Iron Deficiency → Impaired monoamine metabolism	(Kim & Wessling-Resnick, 2014)
Impaired monoamine metabolism → Depression	(D. J. Nutt, 2008)
Iron Deficiency → Decreases BDNF expression	(Tran et al., 2009)
Decreases BDNF expression → Depression	(Solati et al., 2015)



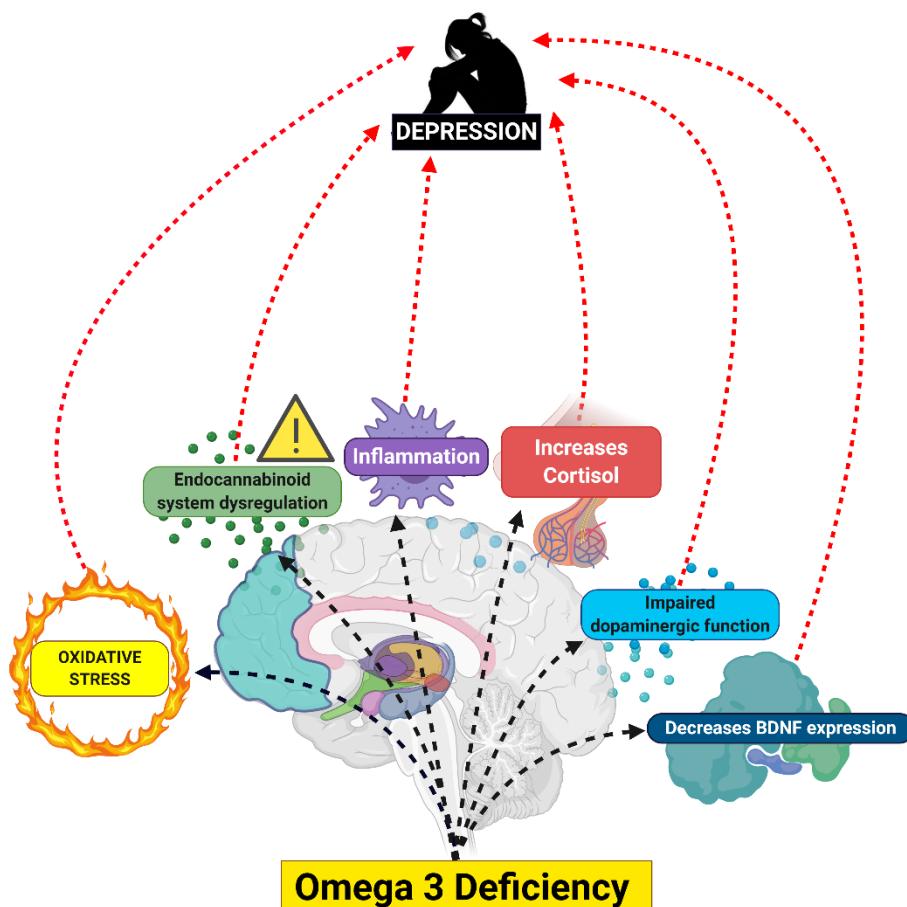
**Figure 2.3** The pathophysiological pathways that could be implicated in depression caused by iron deficiency.

## Omega 3 Deficiency

The importance of omega 3 fatty acids for brain function is illustrated by the fact that the central nervous system has the highest concentration of lipids after adipose tissue (Larrieu & Layé, 2018). Its involvement in depression aetiology and potential pathophysiological pathways can be seen in **Table 2.4** and **Figure 2.4**.

**Table 2.4** A summary of the evidence showing the pathophysiological pathways that could be implicated in depression caused by zinc deficiency.

Pathophysiology Pathway	Reference
Omega 3 Deficiency → Oxidative stress	(Wu et al., 2004)
Oxidative stress → Depression	(Michel et al., 2012)
Omega 3 Deficiency → Endocannabinoid system dysregulation	(Lafourcade et al., 2011)
Endocannabinoid system dysregulation → Depression	(W.J. Huang et al., 2016)
Omega 3 Deficiency → Inflammation	(Joffre et al., 2019)
Inflammation → Depression	(Loftis & Hauser, 2004)
Omega 3 Deficiency → Increases Cortisol	(Mocking et al., 2013)
Increases Cortisol → Depression	(Keller et al., 2017)
Omega 3 Deficiency → Impaired Dopaminergic Function	(Healy-Stoffel & Levant, 2018)
Impaired Dopaminergic Function → Depression	(Healy-Stoffel & Levant, 2018)
Omega 3 Deficiency → Decreases BDNF expression	(Wu et al., 2004)
Decreases BDNF expression → Depression	(Solati et al., 2015)



**Figure 2.4** The pathophysiological pathways that could be implicated in depression caused by omega 3 deficiency.

## Depression in Non-omnivores

Conflicting results can be seen across various study designs that have tried to investigate the link between depression and non-omnivorous diets. A systematic review of randomised controlled trials, that looked at the effectiveness of plant-based diets in promoting the well-being of type 2 diabetic patients, found that plant-based diets—that are accompanied with educational interventions—can significantly improve psychological health (Toumpanakis et al., 2018). Another systematic review on the effects of plant-based diets on the body and brain concluded that there is a lack of interventional studies about the cognitive effects of plant-based diets, and therefore a causal link in regards to mental and neurological health has yet to be demonstrated (Medawar et al., 2019). A cross-sectional study on Seventh Day Adventists concluded that vegetarian diets do not adversely affect mood despite the low intake of omega-3 fatty acids (Beezhold et al., 2010). More recently the same author conducted a randomised control trial on three dietary groups (omnivores, pescatarians and vegetarians), but they found no significant differences in depression improvement across all testing between the groups (Beezhold & Johnston, 2012).

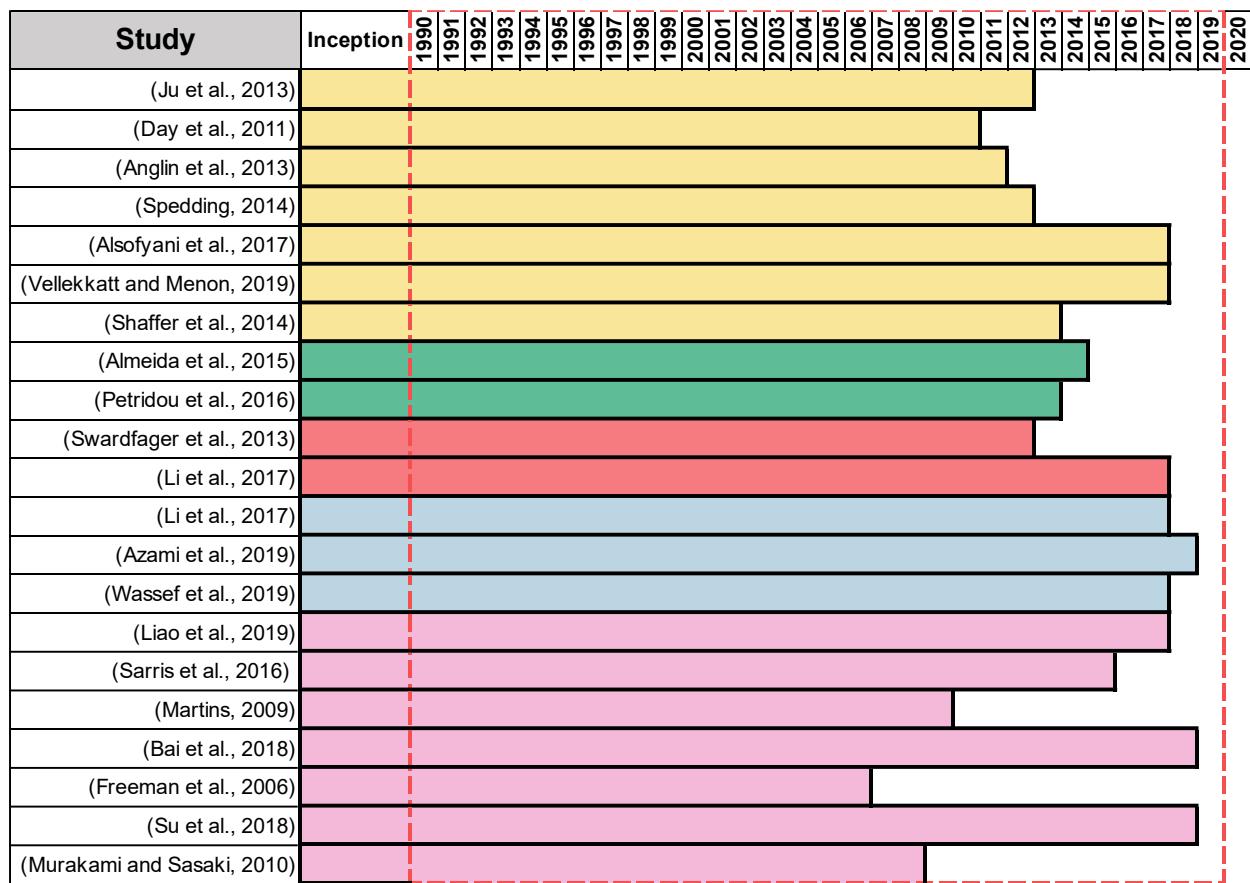
In contrast, a cross-sectional study found that omnivorous diet patterns were associated with significantly reduced odds of major depression in men (50%) and a significantly lower chance of psychological distress in women (25%) (Salehi-Abargouei et al., 2019). Other cross-sectional data showed similar associations, a study that looked at vegetarianism, depression and personality found significantly higher scores of depression and neuroticism in vegetarian and semi-vegetarian groups compared with omnivores (Forestell & Nezlek, 2018)

Two case studies found psychiatric symptoms to be concurrent with consuming a non-omnivorous diet. A vegetarian female patient was reported with a clinical case of delirium, further investigation discovered that the patient had vitamin B12 deficiency and the authors attributed this to her strict vegetarian diet (Mavrommatti & Sentissi, 2013). Another case study of a 47-year old woman with a history of psychosis was found to also be deficient in vitamin B12, this patient has also been following a strict vegan diet for 7 years. An oral dose of 1000 µg of vitamin B12 was supplemented and within six months her psychiatric symptoms had relieved (Bachmeyer et al., 2019).

Ten observational studies—that looked at this association—found that there is a 0.4 to 3.3 times higher risk ( $<0.05$ ) for depression when consuming non-omnivorous diets compared to omnivorous diets (Baines et al., 2007; Burkert et al., 2014; Hibbeln et al., 2018; Jacka, Pasco, et al., 2012; Kapoor et al., 2017; Larsson & Johansson, 2002; X. Li et al., 2019; Matta et al., 2018; Meesters et al., 2016; Michalak et al., 2012).

Three other observational studies that investigated the same association came to different conclusions. The results of two large longitudinal studies found no significant difference between the two diet types (Lavallee et al., 2019; Northstone et al., 2018) and a cross-sectional study of 892 South Asians in the United States found there to be a significant reduction (43%) in depression, when consuming a vegetarian diet compared to a non-vegetarian diet (Yichen Jin et al., 2019). However, a recent systematic review that compared meat-consumers to meat-abstainers found a significantly greater prevalence in the risk of depression in participants who avoided meat consumption (Dobersek et al., 2020).

Causality for the strong association demonstrated above between depression and non-omnivorous diets is multifactorial and largely unknown. Therefore, the purpose of this systematic review and meta-analysis is to elucidate—or to rule out—the possible links between the nutrient deficiencies, that are common among non-omnivorous diets and their associated with depression. The selection of the nutrients for this review was based on the current published meta-analyses that looked at different nutrient deficiencies and depression, but also the nutrients that are more common to be deficient among non-omnivores (based off available data displayed above). A summary of the published meta analyses, that investigated the rates of depression among populations with nutrient deficiencies that are analysed in this review, is illustrated in **Figure 3.0**.



Key	
Vitamin D	Yellow
Vitamin B12	Green
Zinc	Red
Iron	Light Blue
Omega-3	Pink
This Review	Dashed Red Box

**Figure 3.0** Graph to show the current published systematic reviews and meta analyses that investigated the association with nutrient deficiencies and depression. Also shown; the year range of the papers published that were covered by each of the reviews within their respective search criteria. The year range of the papers published that were covered by this review are also shown.

This systematic review and meta-analysis will specifically look at the nutrient levels of vitamin D, vitamin B12, zinc, iron and omega-3 and their association with depression rates within observational data. The therapeutic effect of supplementing with these nutrients will not be explored, therefore interventional data will not be the focus of this review. Whilst additional avenues of causality will be explored within this review, understanding the association with nutrient levels and depression may help to uncover other causal starting points that link non-omnivorous diets to psychological disorders, for future study.

# Methods

## Search Strategy

PubMed, CINAHL and Medline were the databases chosen for the searches within this review. Search strings for PubMed and CINAHL were formulated using the advanced search builder within PubMed, as both databases utilise identical Boolean syntax in their searches. The search string was copied from PubMed and pasted directly into the CINAHL search box. Search strings for Medline was built using Web of Sciences advanced search builder as Web of Science uses a different Boolean-like syntax. Search strings for all nutrients and databases can be seen in **Appendix 1**.

Search terms and filters for each nutrient search were decided upon using an adapted PICO-like model to identify the population (**P**), outcome (**O**), intervention/exposure (**I**), study characteristics (**S**) and exclusionary terms (**E**) in each case. Only the intervention/exposure component changed between independent searches for each nutrient, all other elements remained the same across the searches, an example of one search within in this review can be seen in **Table 3.0**. The terms that are highlighted with a red border in **Table 3.0** change with each search performed.

Identifying the terms that were used in the construction of each search was carried out using PubMed's MeSH (Medical Subject Headings) search function to gather as many different MeSH terms that were associated to the specific search element. MeSH terms are official medical words or phrases that represent a biomedical concept/topic, they allow the ability to search for multiple associated terms using just one term (Baumann, 2016). Medline and CINAHL also utilise MeSH terms, which made the cross-database searches with the same terms viable.

**Table 3.0.** An example of how the vitamin D search was constructed, including the search terms, filters used and Boolean logic. Structured around the PICO-like model ‘POISE’.

**Green** text indicates the MeSH terms used.

The **Red** border highlights the intervention/exposure terms that change for each search.

**Pink** text indicates the search filters used in the review

Blue text indicates the Boolean operators used in the example search string

**Black** text the non-MeSH terms used.

O	I	E	P	S
Depression	Vitamin D Deficiency	Psychotic Disorders	[Age = Adult 19+ years]	[Results by year = 1999 to 2019]
OR	OR	OR	[Species = Humans]	
Depressive Disorder	Cholecalciferol	Postpartum Period		
OR	OR	Autistic Disorder		
Mental Health	Calcitriol	Schizophrenia		
OR	OR	OR		
Mental Disorders	Vitamin D	Anorexia Nervosa		
OR	OR	OR		
Depressive Disorder, Major	25-Hydroxyvitamin D 2	Alzheimer Disease		
AND	OR	Dementia		
	Hypovitaminosis D	OR		
		Supplementation		
	NOT			

The search filters were then applied once the initial searches strings were formulated. The following filters were applied to both PubMed and Medline databases: **[Species = Humans]**, **[Age = Adult 19+ years]** and **[Results by year = 1999 to 2019]**. CINAHL database does not utilise the ‘species’ filter so only ‘age’ and ‘results by year’ were used on the CINAHL searches.

The title review of the remaining search results was performed firstly on the PubMed database, the title reviews for CINAHL and Medline were performed after. Duplicate studies were excluded during the CINAHL and Medline title reviews by cross referencing with the PubMed results. Further exclusion of studies was carried out for all databases during the abstract and full text review process, an overview of the entire study selection process from the initial search up to the full text review can be seen in **Figure 4.0.**

## Eligibility Criteria

Cross-sectional, longitudinal and case control studies were included in the analysis for the review, interventional studies that looked at the therapeutic effects of nutrient supplementation on depression were disregarded, as the focus of the analysis was primarily on the effect of nutrient deficiencies on depression. Systematic reviews, meta analyses and uncontrolled case studies were not considered in this review, only observational data that investigated the associative relationship between nutrient levels and rates of depression were considered.

Studies that were published in the last 20 years were included within this review, the decision to not include studies from database inception was based on previously published systematic reviews and meta analyses that investigating the same associations. These reviews (in **Figure 3.0**) that conducted searches from database inception found a very limited amount of studies that preceded the year 1999. Moreover, the purpose of this review was to update and build upon those reviews already published—that investigated the association between depression and the nutrient deficiencies chosen in this review—not to replicate the work that has already been done. The total number of studies across all nutrients, that were excluded due to the **[Results by year = 1999 to 2019]** filter was 1687 (as seen in **Figure 3.0**). Thus, the decision was also to reduce the number of non-useable studies that would be put forward for title review, that streamlined the review process.

## Population

The target population of this review included adult subjects (19+ years) of both sexes that were tested for depression and nutrient status using established testing methods. Studies that analysed the nutrient effects on populations that had other psychological disorders such as autism, schizophrenia, psychotic disorders or dementia were not included. Studies that investigated nutrient effects on pregnant subjects were also excluded from the analysis

## **Exposure**

Vitamin D, Vitamin B12, Zinc, Iron and Omega-3 were the nutrients chosen as the exposures for the analysis. Measurement of these exposures included nutrient intakes (based off multiple methods of dietary measurement, e.g. dietary recall or food frequency questionnaire) and direct measurement of nutrient levels over various methods (e.g. adipose fatty acid, serum or plasma). Studies that measured foods (e.g. fish intake) or nutrient ratio levels (e.g AA/DHA) were not included. Subgroup analyses was performed where there were clear differences in the exposure measurement method (e.g. serum and nutrient intake) or within different component measures (e.g. EPA, DHA or total omega 3).

Dichotomous (e.g cut-off or lowest vs highest ‘tile of nutrient level/intake) and continuous (e.g. with every 1% increase of nutrient level) variables were included but were sub-grouped accordingly or included within a separate forest plot if the effect direction was opposite to each other. The nutrient threshold that was used across different studies varied, some studies used thresholds that coincided with deficiency/sufficiency cut-offs, others did not. All studies that used different thresholds were included in the analyses but were also sub-grouped accordingly.

## **Outcome**

Studies that measured depression using an established threshold-based scale were included, studies that used generalised health/wellbeing scales were excluded from the analysis. There was no subgrouping or exclusion based off different types of established depression measurement, as this would make aggregating data for the meta analyses difficult. Studies that used the same depression scales sometimes used different thresholds to diagnose depression, this did not influence the way the data was dealt with in the analyses either.

## **Statistical Testing**

Studies that tested the association between nutrient status and depression with odds ratio, hazard ratio and correlation coefficients were included within the analysis. Studies that only reported beta-coefficients and no raw data to calculate more appropriate effect sizes were excluded. A study that looked into the use of beta-coefficients in meta analyses discussed the topic: “A beta coefficient is a partial coefficient that reflects the influence of all predictor variables in a multiple regression model. Logic dictates that unless an effect-size metric reflects a simple bivariate or zero-order relationship between two variables, effect sizes cannot be meaningfully combined and aggregated across studies.” They also proposed a formula to convert beta coefficients into correlation coefficients, but the use of this formula was beyond the scope of this review (Peterson & Brown, 2005). Other studies were excluded that reported effect sizes that were less common and could not be aggregated with other studies of the same variables.

## **Statistical Analysis**

Statistical analyses, forest plots, funnel plots and heterogeneity for all non-correlative data (odds/hazard ratio) was calculated using Review Manager software (Review Manager (RevMan), version: 5.3. 2014). Statistical analyses, forest plots and heterogeneity for correlative data (correlation coefficients) was calculated using Comprehensive Meta-Analysis software (Comprehensive Meta-Analysis Software (CMA), version: 3. 2013). Statistical tests for publication bias for all data and funnel plots for correlative data was performed and calculated using Meta-Essentials: Workbooks for meta-analysis (Suurmond et al., 2017).

## **Effect Size**

Within each nutrient meta-analysis, studies were grouped based on effect size type and effect direction. Data cannot be aggregated together into one forest plot if the effect size type is different (hazard ratio, odds ratio or correlation coefficient) or if the effect direction are in opposition of each other. For example, effects sizes that express the odds of nutrient sufficiency to reduce depression risk cannot be aggregated with effect sizes that express the odds of nutrient deficiency to increase depression risk. The distinct groups that data was aggregated into, along with the types of effect sizes are described in **Appendix 2**. Fully adjusted effect sizes were put forward for the analysis over crude effect sizes when reported by studies.

## **Heterogeneity**

Heterogeneity was measured using Cochran's Q test and heterogeneity between studies was assumed when the probability value was  $< 0.1$  and the  $I^2$  statistic was  $> 50\%$ . All heterogenous datasets used a random effects model for the analysis and all homogenous datasets used a fixed effects model for the analysis.

## **Risk of Bias Assessment**

Risk of bias across studies was determined using statistical tests and funnel plots to assess publication bias and asymmetry across studies within data sets. Statistical tests used were the Egger's regression (Egger et al., 1997) and Begg and Mazumdar rank correlation test (Begg & Mazumdar, 1994), funnel plots were performed to test for subjective asymmetry. Publication bias was only assessed on data sets that had  $\geq 10$  studies/data entries included within the analysis, this was due to the lack power that the regression and rank correlation tests hold to test publication bias, when the number of studies/data entries is less than 10 or substantial publication bias is not present in the data set (Sterne et al., 2000).

# Results

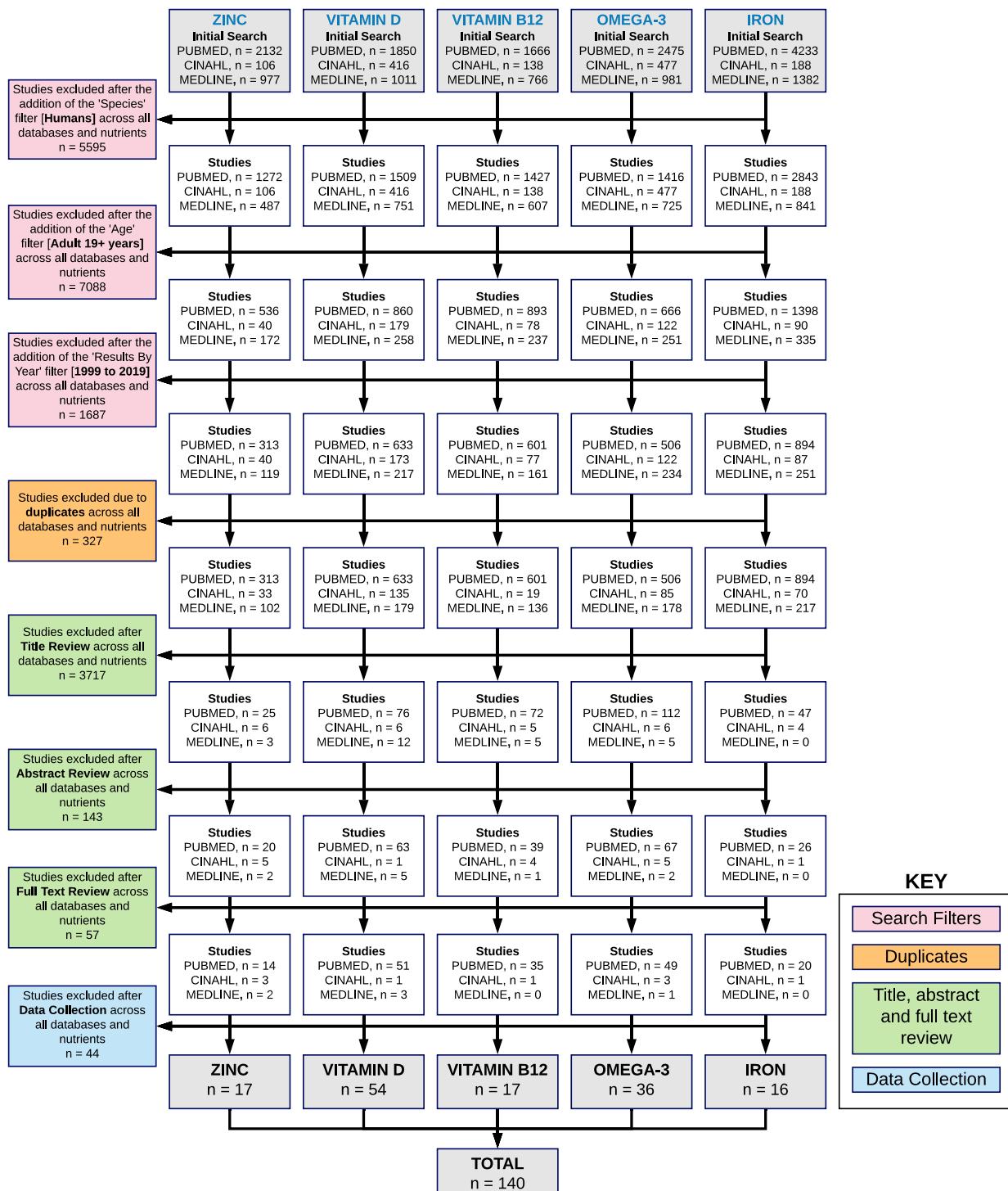
The initial search across all databases and nutrients produced a total of 18,798 studies, after filters were applied and duplicates were removed, there remained a total of 1,154 studies to be put forward for title review. Out of those studies, 384 abstracts were screened, and 241 studies went forward for full text review. After the full text review, 190 studies remained for data collection, during this process a further reduction across all nutrients was made which resulted in a remaining 140 studies. A summary of the reasons for study exclusion, at the data collection stage, can be seen in **Table 4.0** and the entire study selection process is illustrated in **Figure 4.0**. There were also some cases where depression was measured against multiple nutrients within the same study, this resulted in the sharing and duplication of 6 studies across different nutrient analyses.

**Table 4.0** A summary of the reasons for study exclusion at the data collection stage.

<p><b>1</b> study was excluded for <b>Vitamin D</b> during data collection:</p> <ul style="list-style-type: none"><li>• 1 study was excluded due to no other data to aggregate with.</li></ul>
<p><b>19</b> studies were excluded for <b>Vitamin B12</b> during data collection:</p> <ul style="list-style-type: none"><li>• 2 studies were excluded due to only reporting beta-coefficients in results.</li><li>• 1 study was excluded due to subjects being pregnant.</li><li>• 11 studies were excluded due to only reporting associations between homocysteine and depression.</li><li>• 1 study was excluded due to inappropriate exposure measure.</li><li>• 4 studies were excluded due to reported data having no other data to aggregate with.</li></ul>
<p><b>2</b> studies were excluded for <b>Zinc</b> during data collection:</p> <ul style="list-style-type: none"><li>• 2 studies were excluded due to reported data having no other data to aggregate with.</li></ul>
<p><b>5</b> studies were excluded for <b>Iron</b> during data collection:</p> <ul style="list-style-type: none"><li>• 4 studies were excluded due to only reporting beta-coefficients in results.</li><li>• 1 study was excluded due to inappropriate exposure measure.</li></ul>
<p><b>17</b> studies were excluded for <b>Omega 3</b> during data collection:</p> <ul style="list-style-type: none"><li>• 6 studies were excluded due to only reporting beta-coefficients in results.</li><li>• 3 studies were excluded due to subjects being pregnant.</li><li>• 3 study was excluded due to inappropriate exposure measure.</li><li>• 5 studies were excluded due to reported data having no other data to.</li></ul>

There was a total of 790,847 participants across all 140 studies that were published between 1999 and 2019, over 38 different countries that were included in the analyses for all nutrients and their association with depression.

## Study Selection



**Figure 4.0** The study selection matrix for Zinc, Vitamin D, Vitamin B12, Omega-3 and Iron for all databases used in the review.

# Study Characteristics and Meta-Analyses

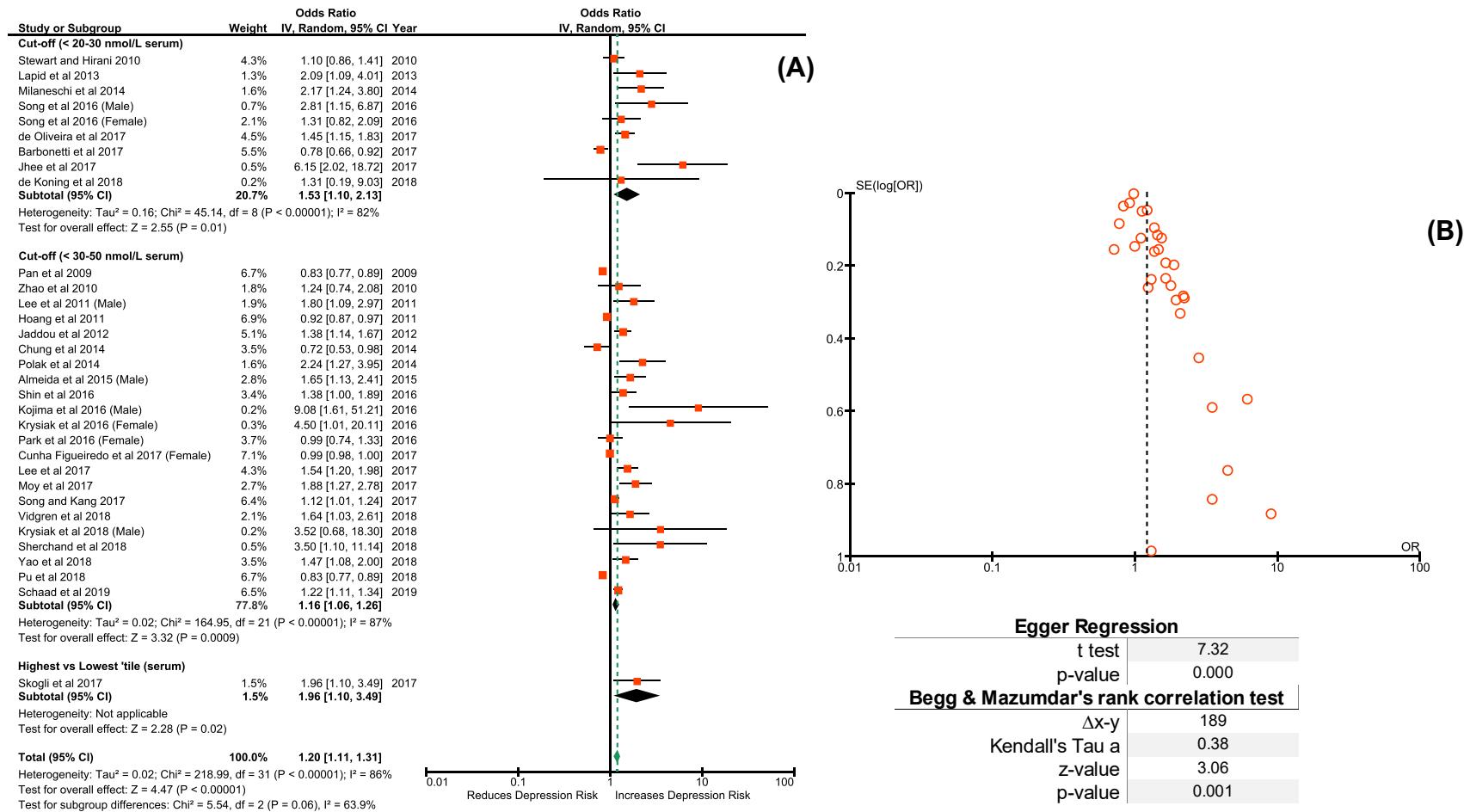
## Vitamin D

**Table 5.0** Study Characteristics for studies included in **Figure 5.0A** and adjustments made for confounders.

Author, Year	Study Design	Country	Population	n	Vitamin D Measurement	Depression Testing & threshold	Confounders Adjusted
(Barbonetti et al., 2017)	Cross-Sectional	Italy	Male & Female (20 - 89 years)	100	Cut-off < 25 nmol/L	BDI-II, ≥14	Sex, BMI, season, activity, time since injury, intake of psychotropic medications, leisure time, and spinal cord independence measure
(de Koning et al., 2018)	Cohort	Netherlands	Male & Female (>55 years)	2019	Cut-off < 30 nmol/L	CES-D, ≥16	Age, sex, education, and season
(de Oliveira et al., 2017)	Cross-Sectional	UK	Male & Female (≥50 years)	5870	Cut-off < 30 nmol/L	CES-D, ≥16	Age, sex, season, waist circumference, wealth, smoking, exercise, CVD, non-CVD conditions, difficulties in activities of daily living and memory score
(Jhee et al., 2017)	Cross-Sectional	Korea	Male & Female (60 - 80 years)	533	Cut-off < 25 nmol/L	KNHANES V, VI	Age, sex, BMI, alcohol, smoking, suicidal idea. EQ5D index, HTN, DM, hemoglobin, glucose, total cholesterol, eGFR and proteinuria
(Lapid et al., 2013)	Cross-Sectional	USA	Male & Female (≥60 years)	1618	Cut-off < 25 nmol/L	HICDA	Age, sex and ERA score
(Milaneschi et al., 2014)	Cohort	Korea	Male & Female (20 - 70 years)	2316	Cut-off < 20 nmol/L	IDS, ≥26	Age, sex, BMI, season marriage status, smoking, DM, stroke, angina and CRP level.
(Song et al., 2016)	Cross-Sectional	Korea	Male & Female (65 - 95 years)	2853	Cut-off < 25 nmol/L	CES-D, ≥16 GDS, ≥5	Age, BMI, study year, month of assay, PTH, comorbidities, smoking, alcohol, exercise, sleep, income, education, cohabitation status, and residential area
(Stewart & Hirani, 2010)	Cross-Sectional	UK	Male & Female (≥65 years)	2070	Cut-off < 25 nmol/L	GDS, ≥5	Age, sex, BMI, season, vitamin D supplement intake, social class, smoking, long-standing limiting illness and subjective general health status
(Almeida et al., 2015)	Cohort	Australia	Male (71 – 88 years)	3105	Cut-off < 50 nmol/L	PHQ-9, ≥10	Age, smoking, season living arrangements, and CHD or stroke
(Chung et al., 2014)	Cross-Sectional	Korea	Male & Female (≥20 years)	3570	Cut-off < 50 nmol/L	KNHANES-V	Age, sex, BMI, season, income, education, marital status, body weight control, perceived body shape, alcohol behaviour, smoking status and physical activity
(Cunha Figueiredo et al., 2017)	Cohort	Brazil	Female (20 - 40 years)	322	Cut-off < 50 nmol/L	EPDS, ≥13	Age, gestational age, pre-pregnancy body mass index, self-reported skin colour, previous history of depression, education, alcohol intake and smoking habit
(Hoang et al., 2011)	Cross-Sectional	USA	Male & Female (≥40 years)	12594	Cut-off < 50 nmol/L	CES-D, ≥10	Age, BMI, education, and thyrotropin
(Jaddou et al., 2012)	Cross-Sectional	Jordan	Male & Female (50 - 70 years)	4002	Cut-off < 50 nmol/L	DASS, ≥14	Age, sex, marital status, education, BMI, serum creatinine, number of chronic diseases, smoking, exercise, and altitude
(Kojima et al., 2016)	Cross-Sectional	Hawaii	Male (60.8 years (x̄))	64	Cut-off < 50 nmol/L	GDS, ≥5	Age, BMI and race
(Krysiak et al., 2016)	Case Control	Poland	Female (20 - 40 years)	42	Cut-off < 50 nmol/L	BDI-II, ≥14	n/a
(Krysiak et al., 2018)	Case Control	Poland	Male (18 - 40 years)	47	Cut-off < 50 nmol/L	BDI-II, ≥14	n/a

(Lee et al., 2011)	Cohort	IT, BE, PL, SE, UK, ES, HE and EE	Male (40-79 years)	3369	25.0 - 49.9 nmol/L	BDI-II, ≥14	Age, BMI, smoking, alcohol, activity, physical function, morbidities, adverse life events and psychotropic drug use.
(Lee et al., 2017)	Cross-Sectional	Korea	Male & Female (20 - 88 years)	7198	Cut-off < 50 nmol/L	KNHANES V	Age, sex, BMI, season, smoking, alcohol, exercise, income, education, marital status, changes in bodyweight, perceived body shape and cholesterol
(Moy et al., 2017)	Cross-Sectional	Netherlands	Male & Female (18 - 65 years)	770	Cut-off < 50 nmol/L	DASS, >9	BMI, smoking, alcohol, physical activity, chronic diseases and creatinine clearance
(Pan et al., 2009)	Cross-Sectional	China	Male & Female (50 - 70 years)	161	Cut-off < 50 nmol/L	HAMD ≥ 8	Age, sex, BMI, urban/rural, activity, smoking, number of chronic diseases, social activity level, marital status, income, geographic location
(Park et al., 2016)	Cross-Sectional	Malaysia	Female (≥20 years)	15695	Cut-off < 50 nmol/L	KNHANES-V	Age, race, BMI, metabolic syndrome, depression, PTH and MCS and PCS scores.
(Polak et al., 2014)	Cross-Sectional	Korea	Male & Female (≥20 years)	615	Cut-off < 43.9nmol/L	CES-D, ≥16	Age, sex, obesity, education, occupation, economic status, marital status, exercise, chronic disease, subjective health status, alcohol, and smoking
(Pu et al., 2018)	Cross-Sectional	China	Male & Female (25 - 75 years)	161	Cut-off < 50 nmol/L	HAMD ≥ 8	Age, sex, BMI, marital status, education, disease duration, DAS28-ESR, HAQ, VAS, CRP, treated by TNFi and treated by prednisone
(Schaad et al., 2019)	Cross-Sectional	USA	Male & Female (18 - 64 years)	381818	Cut-off < 50 nmol/L	ICD-9-CM, DSM-V	Age, sex, vitamin D diagnosis, MTF location, service type, career type, career progression, and associated encounters as a continuous variable
(Sherchand et al., 2018)	Cross-Sectional	New Zealand	Male & Female (17 - 25 years)	300	Cut-off < 50 nmol/L	BDI, ≥10	Age, sex, race, BMI, and time spent outdoors
(Shin et al., 2016)	Cross-Sectional	Nepal	Male & Female (≥18 years)	52228	Cut-off < 50 nmol/L	GDS, ≥3	BMI, geographical region, marital status, activity, socioeconomic status, education and employment
(Song & Kang, 2017)	Cohort	Korea	Male & Female (32 - 89 years)	204	Cut-off < 50 nmol/L	PHQ-9, ≥ 10	Age, sex, BMI, NYHA functional class, LVEF, aetiology of HF, total comorbidities, and use of antidepressants
(Vidgren et al., 2018)	Cross-Sectional	Finland	Male & Female (53 - 73 years)	1602	Cut-off < 50 nmol/L	DSM-III, ≥4	Age, sex, examination year/month, economic status, marital status, leisure-time, activity, energy intake, alcohol, intake of fruits, berries, vegetables, omega-3 and mental diseases.
(Yao et al., 2018)	Cross-Sectional	China	Male & Female (>100 years)	940	Cut-off < 50 nmol/L	GDS >6	Age, sex, ethnicity, education, living conditions, social interactions, lifestyles, ADL impairments, outdoor activities, BMI, SBP, DBP, TG, TC, FBG, ALB, Hb, estimated GFR, visual impairments, and auditory impairments
(Zhao et al., 2010)	Cross-Sectional	USA	Male & Female (≥20 years)	3916	37.5 - 50 nmol/L Highest vs Lowest Tertile Vitamin D	PHQ-9, ≥10	Age, sex, race, BMI, alcohol, activity, education, marital status, cotinine, and chronic diseases
(Skogli et al., 2017)	Cross-Sectional	Canada	Male & Female (18-58 years)	1699	Lowest Tertile Vitamin D	K6, ≥13	Age, sex, marital status, days spent out on the land, feeling of being alone, income and smoking.

The overall effect when all studies were pooled together showed a 20% greater risk for depression across all vitamin D categories (OR = 1.20, 95% CI 1.11–1.31, P = < 0.00001) (**Figure 5.0A**). Description of subgroup analyses, heterogeneity and publication bias is included in **Appendix 3.1**.



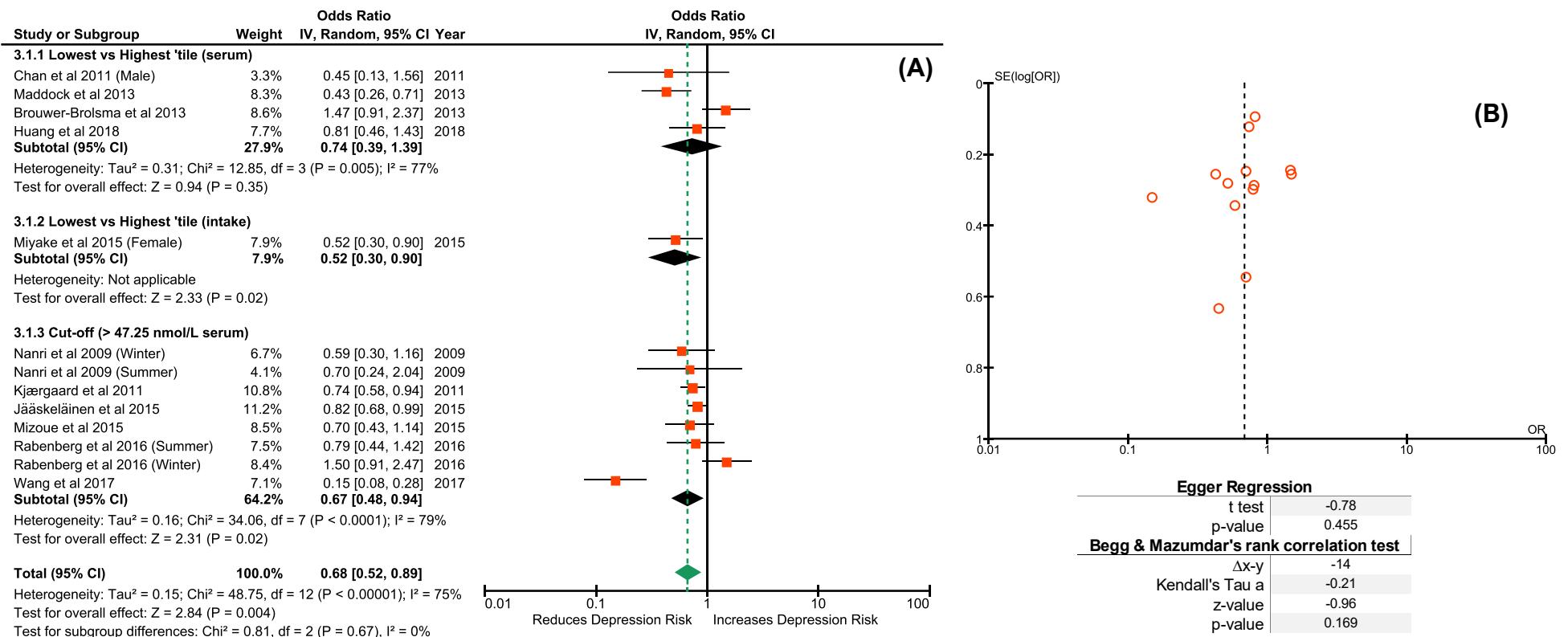
**Figure 5.0A** - Forest plot displaying the odds ratio (OR) of depression for three subgroups with different categories for vitamin D deficiency. The red squares to the right of the midline indicate that the category for vitamin D deficiency listed was associated with an increased risk for depression. The black diamonds indicate the subtotal OR for each subgroup and the green diamond and vertical dotted line indicates the total OR for the entire dataset. The horizontal black lines represent the 95% confidence intervals for the associated OR. **Figure 5.0B** – Funnel plot illustrating the level of asymmetry in the data set. Red circles in the plot represent the individual studies and the vertical dotted black line represents the overall effect in the data set. Egger Regression and Begg & Mazumdar's rank correlation test to show statistical significance for publication bias in the data set.

A random effects model was used as heterogeneity was assumed

**Table 5.1** Study Characteristics for studies included in **Figure 5.1** and adjustments made for confounders.

Author, Year	Study Design	Country	Population	n	Vitamin D Measurement	Depression Testing & threshold	Confounders Adjusted
(Brouwer-Brolsma et al., 2013)	Cross-Sectional	Netherlands	Male & Female (>65 years)	127	Lowest vs Highest tertile Serum 25(OH)D	CES-D, ≥16	Age, sex, body mass index, education, smoking, physical activity, alcohol intake, and season
	Cohort	China	Male (≥65 years)	629	Lowest vs Highest quartile Serum 25(OH)D	GDS, ≥8	Age, BMI, education, PASE, number of ADLs, DQI, smoking status, alcohol use, season of measurement, number of chronic diseases, GDS category and serum (In)PTH concentration
(Huang et al., 2018)	Cross-sectional	USA	Male & Female (20 - 85 years)	2791	Lowest vs Highest quartile Serum 25(OH)D	PHQ-9	Age, sex, BMI, family PIR race/ethnicity, education, marital status smoking history and examination time
	Cohort	UK	Male & Female (≥45 years)	7401	Lowest vs Highest quartile serum 25(OH)D	MHI-5, < 53	Sex, BMI, season, socioeconomic position, smoking, activity, leisure time, sun-cover, blistering after sunburn and actively seeking a sun tan.
(Maddock et al., 2013)	Cross-Sectional	Japan	Female (26 - 36 years)	1745	Lowest vs Highest Quartile Vitamin D intake	CES-D, ≥16	Age, gestation, region of residence, number of children, family structure, history of depression, family history of depression, smoking, second-hand smoke exposure at home and at work, employment; household income, education, body mass index, intake of saturated fatty acids, and intake of eicosapentaenoic acid plus docosahexaenoic acid.
(Mizoue et al., 2015)	Cross-Sectional	Finland	Male & Female (30 - 79 years)	5371	56–134 nmol/L	BDI, ≥10	Age, sex, BMI, season, education, leisure-time, activity, smoking, alcohol, BP, HDL, TAG, fasting glucose
(Nanri et al., 2009)	Longitudinal	Norway	Male & Female (30-87 years)	8120	56.7–182.50 nmol/L	SCL-10, ≥1.85	Age, sex, BMI, GFR, marital status, education, alcohol consumption, physical activity and chronic disease
(Wang et al., 2017)	Cross-Sectional	Japan	Male & Female (19–69 years)	1786	> 75nmol/L	CES-D, ≥16	Age, sex, BMI, smoking, alcohol, factory, marital status, job, overtime/shift work, job strain, sleep, activity, kcal intake, folate, vitamin B6, n-3 PUFA, magnesium, iron and leisure-time
(Rabenberg et al., 2016)	Cross-Sectional	China	Male & Female (25 - 80 years)	2786	> 47.25 nmol/L	PHQ-9, ≥10	Age, sex, BMI, season, education, marital status, family history of mental illness, use of insulin, activity, medication adherence score, Hs-CRP, FBG and HbA1c
(Chan et al., 2011)	Cross-Sectional	Germany	Male & Female (18-79 years)	3263	60-347 nmol/L	PHQ-9, ≥ 10	Age, sex, socioeconomic status, partnership, municipality size, country of birth, obesity, physical functioning, eGFR, smoking, alcohol and sport activity.
(Jääskeläinen et al., 2015)	Cross-Sectional	Japan	Male & Female (21-67 years)	527	> 82 nmol/L	CES-D, ≥16	Age, sex, BMI, job, marital status, occupation, non-job activity, smoking, alcohol and folate

The overall effect when all studies were pooled together showed a 32% reduced risk for depression across all vitamin D categories (OR = 0.68, 95% CI 0.52 – 0.89, P = 0.004) (**Figure 5.1A**) Description of subgroup analyses, heterogeneity and publication bias is included in **Appendix 3.1**.



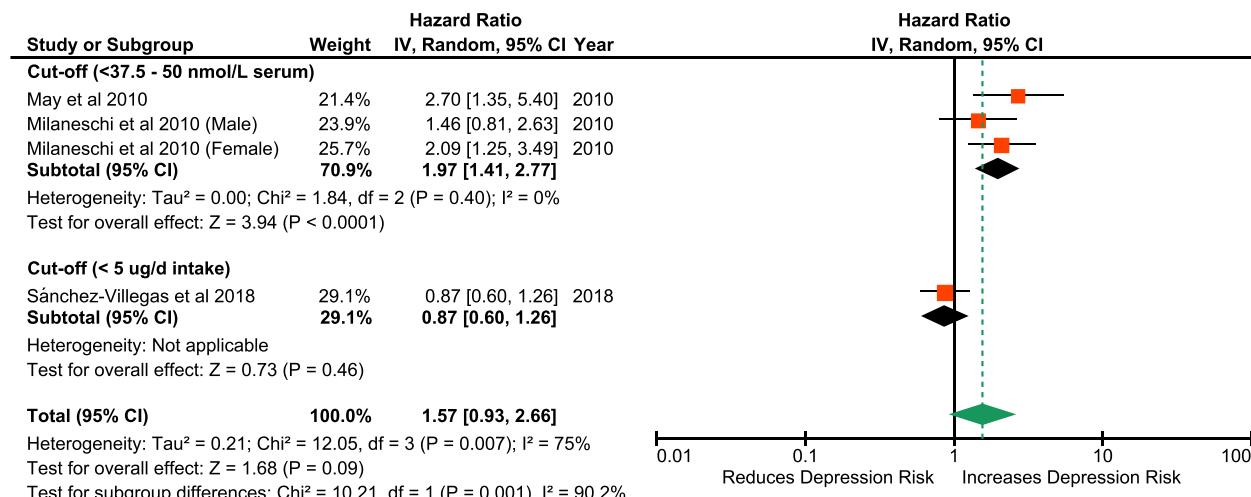
**Figure 5.1A** - Forest plot displaying the rOR of depression for three subgroups with different categories for vitamin D sufficiency. The red squares to the left of the midline indicate that the category for vitamin D sufficiency listed was associated with a reduced risk for depression. The black diamonds indicate the subtotal rOR for each subgroup and the green diamond and vertical dotted line indicates the overall effect for the entire dataset. The horizontal black lines represent the 95% confidence intervals for the associated rOR. **Figure 5.1B** – Funnel plot illustrating the level of asymmetry in the data set. Red circles in the plot represent the individual studies and the vertical dotted black line represents the overall effect in the data set. Egger Regression and Begg & Mazumdar's rank correlation test to show statistical significance for publication bias in the data set.

A random effects model was used as heterogeneity was assumed.

**Table 4.2** Study Characteristics for studies included in **Figure 4.2** and adjustments made for confounders.

Author, Year	Study Design	Country	Population	n	Vitamin D Measurement	Depression Testing	Confounders Adjusted
(May et al., 2010)	Cohort	US	Male & Female ( $\geq 50$ years)	7358	< 37.5 nmol/L serum	ICD-9	Age, sex, DM, hypertension, hyperlipidaemia, CAD, prior MI, heart failure, CVA, TIA, A-fib, prior fracture, PVD and renal failure
(Milaneschi et al., 2010)	Cohort	Italy	Male & Female ( $\geq 65$ years)	954	< 50 nmol/L serum	CES-D, $\geq 16$	Age, season baseline CES-D, ADL disabilities, use of antidepressants, number of chronic diseases, SPPB and high PTH
(Sánchez-Villegas et al., 2018)	Cohort	Spain	Male & Female (26 - 54 years)	13983	Vitamin D inadequacy (intake < 5 ug/d)	DSM-IV	Age, sex, physical activity, BMI, energy intake, special diets, smoking, alcohol intake and prevalence of CVD, HTA, or T2DM

The overall effect when all studies were pooled together showed a 57% greater risk for depression across all vitamin D categories (OR = 1.57, 95% CI 0.93 – 2.66, P = 0.09) (**Figure 5.2**). Description of subgroup analyses, heterogeneity and publication bias is included in **Appendix 3.1**.



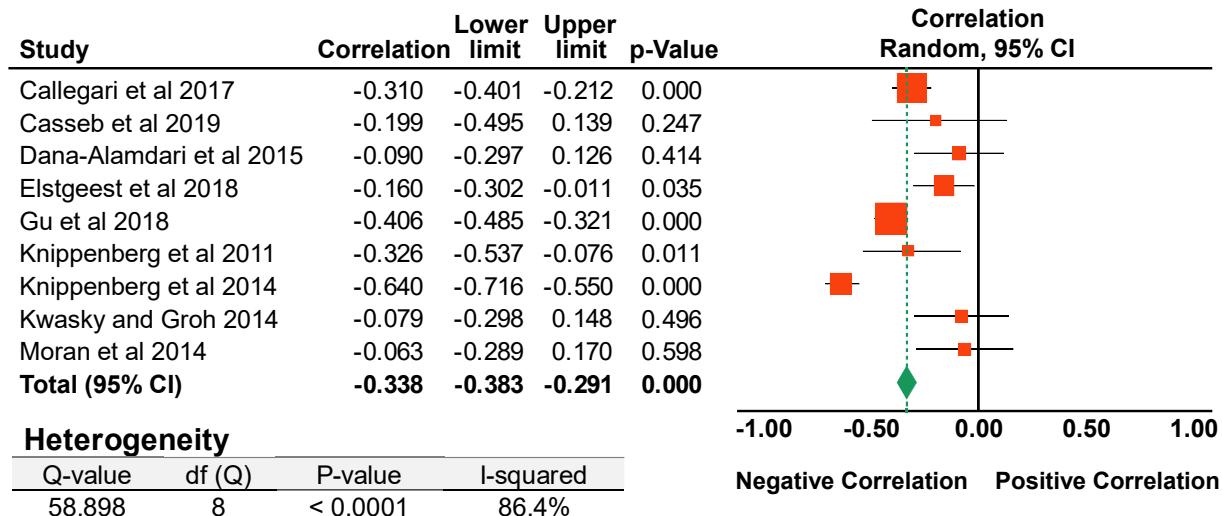
**Figure 5.2** - Forest plot displaying the hazard ratio (HR) of depression for two subgroups with different categories for vitamin D deficiency. The red squares to the right of the midline indicate that the category for vitamin D deficiency listed was associated with a reduced risk for depression. The black diamonds indicate the subtotal HR for each subgroup and the green diamond and vertical dotted line indicates the total HR for the entire dataset. The horizontal black lines represent the 95% confidence intervals for the associated HR.

A random effects model was used as heterogeneity was assumed.

**Table 5.3** Study Characteristics for studies included in **Figure 5.3** and adjustments made for confounders.

Author, Year	Study Design	Country	Population	n	Vitamin D Measurement	Depression Testing	Confounders Adjusted
(Callegari et al., 2017)	Cross-Sectional	Australia	Female (16 - 25 years)	353	Vitamin D Level x PHQ-9	PHQ-9 ≥10	Age, season, height, Weight, COC use, vitamin D supplementation and sun exposure
(Casseb et al., 2019)	Cross-Sectional	Brazil	Male & Female (26 - 47 years)	36	Vitamin D level x BDI	BDI, ≥14	n/a
(Dana-Alamdar et al., 2014)	Case Control	Iran	Male & Female (18 - 63 years)	85	Vitamin D x HRSD	HRSD, DSM-IV	n/a
(Elstgeest et al., 2018)	Cohort	Netherlands	Male & Female (55 - 65 years)	173	Vitamin D Level x CES-D	CES-D, ≥16	Age, sex, education level, body mass index, physical activity, alcohol use, smoking and baseline standardised/deseasonalised 25(OH)D concentration
(Gu et al., 2018)	Cross-Sectional	China	Male & Female (18 - 80 years)	402	Vitamin D level x HAMD	HAMD ≥ 8	n/a
(Knippenberg et al., 2011)	Cross-Sectional	Netherlands	Male & Female (21 - 80 years)	59	Vitamin D Level	HADS ≥ 8	Age, EDSS score, HADS and MFI
(Knippenberg et al., 2014)	Cohort	Tasmania	Male & Female (21 - 77 years)	198	Lowest vs Highest serum 25(OH)D (> 80nmol/L)	HADS ≥ 8	Age, sex, initial EDSS score, initial disease duration, immunomodulatory therapies, BMI and season
(Kwasky & Groh, 2014)	Cohort	USA	Female (18 - 24 years)	77	Vitamin D serum x BDI-II	BDI-II ≥14	n/a
(Moran et al., 2015)	Cross-Sectional	Australia	Female (18-45 years)	73	Vitamin D Level x HADS	HADS ≥ 8	Age, BMI

The overall effect when all studies were pooled together showed a weak to moderate negative correlation between vitamin D level and depression ( $r = -0.338$ , 95% CI –0.383 to –0.291,  $P = 0.0001$ ) (**Figure 5.3**). Description of subgroup analyses, heterogeneity and publication bias is included in **Appendix 3.1**.



**Figure 5.3** - Forest plot displaying the correlation coefficient (CC) between vitamin D level and depression severity. The red squares to the left of the midline indicate that there is a negative correlation between vitamin D level and depression. The green diamond and vertical dotted line indicate the total CC for the entire dataset. The horizontal black lines represent the 95% confidence intervals for the associated CC.

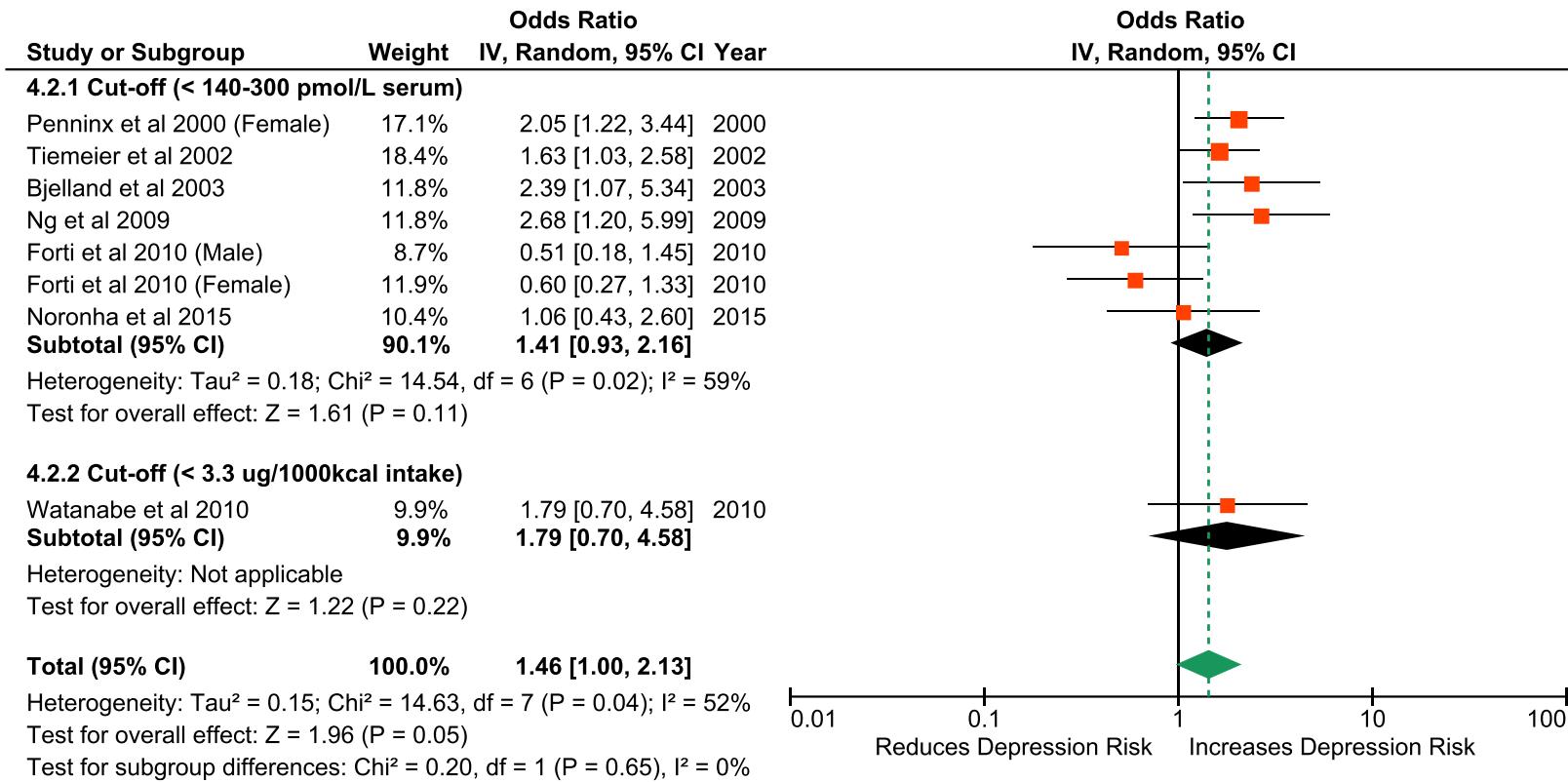
A random effects model was used as heterogeneity was assumed.

## Vitamin B12

**Table 6.0** Study Characteristics for studies included in **Figure 6.0** and adjustments made for confounders.

Author, Year	Study Design	Country	Population	n	Vitamin B12 Measurement	Depression Testing	Confounders Adjusted
(Ng et al., 2009)	Cross-sectional	Singapore	Male & Female (55 - 91 years)	669	Serum B12 (180 pmol/L)	GDS	Age, sex, housing size, education, and social network and support, smoking, alcohol, underweight, obese, antidepressant use, depression-inducing drugs, number of comorbidities, instrumental activity of daily living disability, activity of daily living disability, unintended weight gain or loss, daily vitamin B12, folate supplement, anaemia, albumin, and creatinine.
(Bjelland et al., 2003)	Cross-sectional	Norway	Male & Female (46 - 74 years)	5948	Highest vs Lowest (B12 serum - < 230 pmol/L)	HADS-A	Age, sex, smoking status and educational level
(Forti et al., 2010)	Cohort	Italy	Male & Female (> 65 years)	457	Vitamin B12 deficiency (< 250 pmol/l) Vitamin B12 Deficiency (<258 pmol/litre) - Sever versus no depression	GDS	Age, education, serum creatinine, MMSE score, physical disability, comorbidity, history of CVD, history of stroke, metabolic syndrome,
(Penninx et al., 2000)	Cross-sectional	USA	Female (> 65 years)	700	Vitamin B12 deficiency (<258 pmol/litre)	GDS	Age, race, education, income, body mass index, serum creatinine level, congestive heart failure, cancer, diabetes, and disability in activities of daily living.
(Tiemeier et al., 2002)	Case Control	Netherlands	Male & Female (> 55 years)	528	Vitamin B12 deficiency (<258 pmol/L)	DSM-IV	Age, sex, education, smoking, alcohol intake, score on the Mini-Mental State Examination, score on the Stanford Health Assessment Questionnaire, a measure of disability in activities of daily living, cardiovascular risk factors: history of stroke, history of myocardial infarction, and systolic blood pressure.
(Noronha et al., 2015)	Cross-sectional	Portugal	Male & Female (65 - 101 years)	84	Serum B12 (< 400 pg/ml)	CES-D	n/a
(Watanabe et al., 2010)	Cross-sectional	Japan	Female (20 - 41 years)	86	B12 intake (< 3.3ug/1000kcal)	CES-D	n/a

The overall effect when all studies were pooled together showed a 46% greater risk for depression across all vitamin B12 categories (OR = 1.46, 95% CI 1.00 – 2.13, P = 0.05) (**Figure 6.0**). Description of subgroup analyses, heterogeneity and publication bias is included in **Appendix 3.2**.



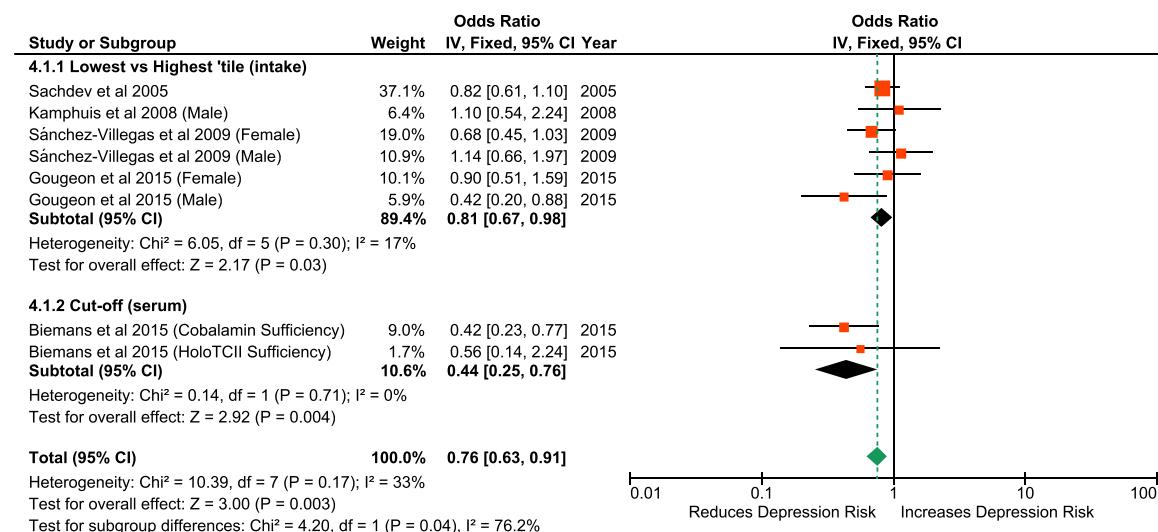
**Figure 6.0** - Forest plot displaying the OR of depression for two subgroups with different categories for vitamin B12 deficiency. The red squares to the right of the midline indicate that the category for vitamin D deficiency listed was associated with an increased risk for depression. The black diamonds indicate the subtotal OR for each subgroup and the green diamond and vertical dotted line indicates the total OR for the entire dataset. The horizontal black lines represent the 95% confidence intervals for the associated OR.

A random effects model was used as heterogeneity was assumed

**Table 6.1** Study Characteristics for studies included in **Figure 6.1** and adjustments made for confounders.

Author, Year	Study Design	Country	Population	n	Vitamin B12 Measurement	Depression Testing	Confounders Adjusted
(L. Gougeon et al., 2016)	Cross-sectional	Canada	Male & Female (67 - 84 years)	1368	Lowest vs Highest Tertile (B12 intake)	GDS	Age, physical activity, functional autonomy, stressful life events and total energy intake
(Kamphuis et al., 2008)	Cross-sectional	Netherlands	Male (70 - 90 years)	332	Lowest vs Highest Quintile (B12 intake)	SDS	Age, years of education, living alone, physical activity, energy intake, self-reported health, disability in activities of daily living and cognitive functioning.
(Sachdev et al., 2005)	Cross-sectional	Australia	Male & Female (60 - 64 years)	412	Lowest Quartile vitamin B12	PHQ-9	Sex, physical health, smoking, highest quartile creatinine and lowest quartile homocysteine
(Sánchez-Villegas et al., 2018)	Cross-sectional	Spain	Male & Female (21 - 65 years)	9670	Lowest vs Highest Quintile (B12 intake)	Author formulated	Age, body mass index, physical activity, marital status, smoking, unemployment status, cardiovascular diseases, cancer, incapacitating diseases, energy intake, omega-3 fatty acids intake, alcohol intake and self-perceived personality traits
(Biemans et al., 2015)	Cross-sectional	Netherlands	Male & Female (49 - 74 years)	550	Total Cobalamin sufficiency (>148 pmol/L), HoloTCII sufficiency (> 21 pmol/L)	Combined (WHO, CES-D, ICPC)	Age, sex, ethnicity, duration of type 2 diabetes, HbA1c, MDRD, diastolic tension, cholesterol/HDL-cholesterol ratio, cigarette pack years, dementia, dementia for depression, neuropathy, nephropathy, retinopathy, calcium, H2RA, PPI and gastrointestinal disease

The overall effect when all studies were pooled together showed a 24% reduced risk for depression across all vitamin B12 categories (OR = 0.76, 95% CI 0.63 – 0.91, P = 0.003) (**Figure 6.1**). Description of subgroup analyses, heterogeneity and publication bias is included in **Appendix 3.2**.



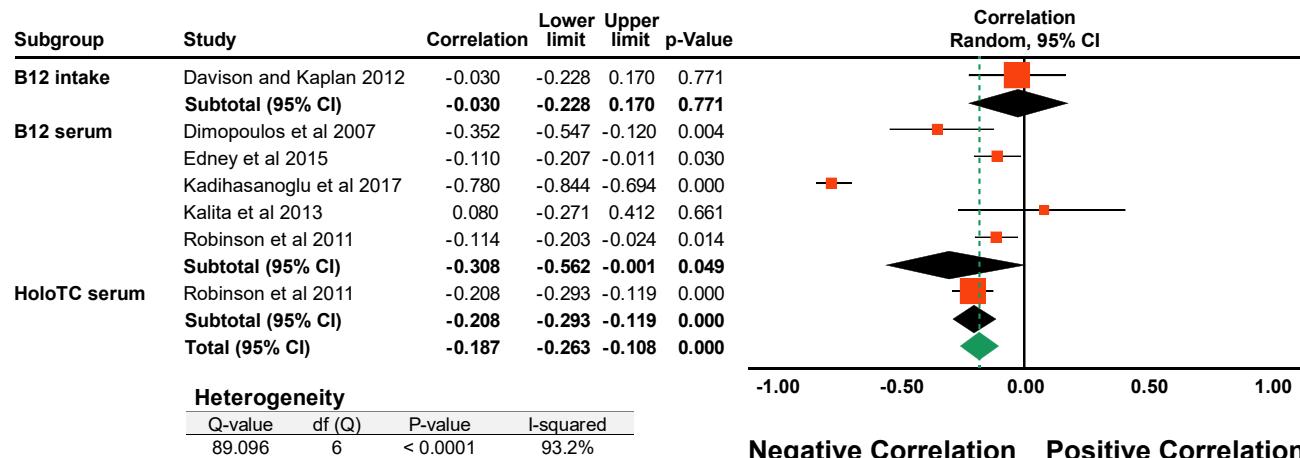
**Figure 6.1** - Forest plot displaying the rOR of depression for two subgroups with different categories for vitamin B12 sufficiency. The red squares to the left of the midline indicate that the category for vitamin B12 sufficiency listed was associated with a reduced risk for depression. The black diamonds indicate the subtotal rOR for each subgroup and the green diamond and vertical dotted line indicates the total rOR for the entire dataset. The horizontal black lines represent the 95% confidence intervals for the associated rOR.

A fixed effects model was used as heterogeneity was not assumed.

**Table 6.2** Study Characteristics for studies included in **Figure 6.2** and adjustments made for confounders.

Author, Year	Study Design	Country	Population	n	Vitamin B12 Measurement	Depression Testing	Confounders Adjusted
(Dimopoulos et al., 2007)	Case Control	Greece	Male & Female (> 60 years)	66	Serum B12	GDS	n/a
(Edney et al., 2015)	Cross-sectional	Australia	Male & Female (64 - 91 years)	391	Serum B12	PANAS	n/a
(Kadihasanoglu et al., 2017)	Case Control	Turkey	Male (18 - 40 years)	109	Serum B12	BDI-II	n/a
(Kalita et al., 2013)	Case Control	India	Male & Female (12 - 68 years)	33	Serum B12	HADS	n/a
(Robinson et al., 2011)	Cross-sectional	Ireland	Male & Female (72 - 84 years)	466	Serum B12 & HoloTCII	CES-D	Age, sex, social class, living alone, smoking status, serum creatinine, MMSE, instrumental activities of daily living, physical self-maintenance scale, alcohol intake, life satisfaction index, loneliness score, homocysteine, presence or absence of angina, hypertension, stroke, history of angioplasty, myocardial infarction or coronary artery bypass grafting
(Davison & Kaplan, 2012)	Cross-sectional	Canada	Male & Female ( $\geq 18$ years)	97	Vitamin B12 intake (food & supplement intake via 3-day food dairy)	HDRS $\geq 17$	n/a

The overall effect when all studies were pooled together showed a weak negative correlation between vitamin D level and depression ( $r = -0.187$ , 95% CI –0.263 to –0.108,  $P = 0.0001$ ) (**Figure 6.2**). Description of subgroup analyses, heterogeneity and publication bias is included in **Appendix 3.2**.



**Figure 6.2** - Forest plot displaying the CC between vitamin B12 level and depression severity. The red squares to the left of the midline indicate that there is a negative correlation between vitamin B12 level and depression. The green diamond and vertical dotted line indicate the total CC for the entire dataset. The horizontal black lines represent the 95% confidence intervals for the associated CC.

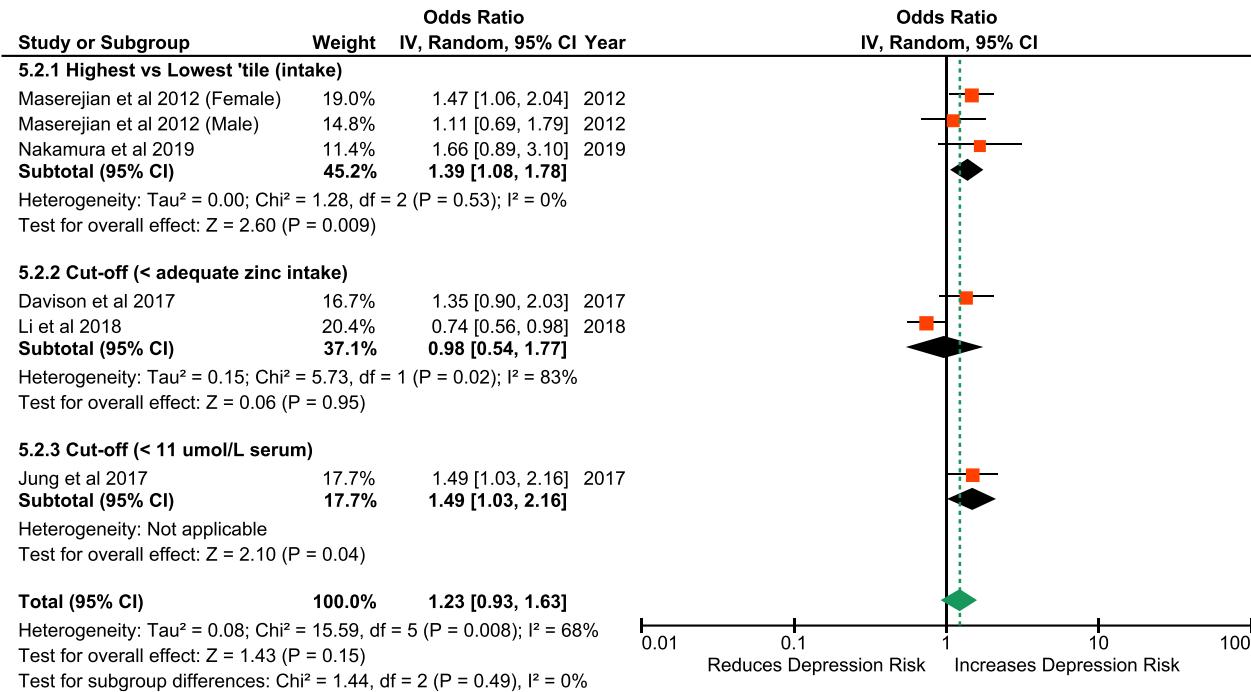
A random effects model was used as heterogeneity was assumed.

## Zinc

**Table 7.0** Study Characteristics for studies included in **Figure 7.0** and adjustments made for confounders.

Author, Year	Study Design	Country	Population	n	Zinc Measurement	Depression Testing	Confounders Adjusted
(Maserejian et al., 2012)	Cross-sectional	USA	Male & Female (30 - 79 years)	3708	Highest vs Lowest Quartile (intake)	CES-D	Age, race/ethnicity, socioeconomic status, BMI, physical activity, smoking status, total energy intake and any antidepressant/antipsychotic medication use, diabetes, prostatitis, American Urological Association Symptom Index score for lower urinary tract symptoms, alcohol intake cardiac disease and arthritis/rheumatism.
(Nakamura et al., 2019)	Cross-sectional	Japan	Male & Female (18 - 79 years)	2089	Highest vs Lowest Quartile (intake)	K6	Age and sex, smoking, alcohol drinking, body mass index, shift work, intake of Vitamin C, B6, B12, folic acid, PUFA, medications for hypertension, hyperlipidaemia, and diabetes.
(Li et al., 2018)	Cross-sectional	China	Male & Female ( $\geq 18$ years)	14834	Below RDA for zinc intake via 24-hour dietary recall	PHQ-9 $\geq 10$	Age, sex, BMI, race, educational level, smoking status, family income, work activity, recreational activity, hypertension, diabetes and total daily energy intake
(Davison et al., 2017)	Cross-sectional	Canada	Male & Female (19 - 70 years)	15546	Suboptimal Zinc Intake (based of food security survey)	CCHS	n/a
(Jung et al., 2016)	Cross-sectional	Germany	Male & Female (60 - 84 years)	1514	Zinc Deficiency (< 11 umol/L)	GDS	Age, sex, BMI, TSH, Vitamin B12, Vitamin D, Magnesium, Folate, CRP, Cognitive impairment, Poor Sleep quality, Morbidity Index and total daily energy intake

The overall effect when all studies were pooled together showed a 23% greater risk for depression across all zinc categories (OR = 1.23, 95% CI 0.93 – 1.63, P = 0.15) (**Figure 7.0**). Description of subgroup analyses, heterogeneity and publication bias is included in **Appendix 3.3**.



**Figure 7.0** - Forest plot displaying the OR of depression for three subgroups with different categories for zinc deficiency. The red squares to the right of the midline indicate that the category for zinc deficiency listed was associated with an increased risk for depression. The black diamonds indicate the subtotal OR for each subgroup and the green diamond and vertical dotted line indicates the total OR for the entire dataset. The horizontal black lines represent the 95% confidence intervals for the associated OR. A random effects model was used as heterogeneity was assumed

**Table 7.1** Study Characteristics for studies included in **Figure 7.1** and adjustments made for confounders.

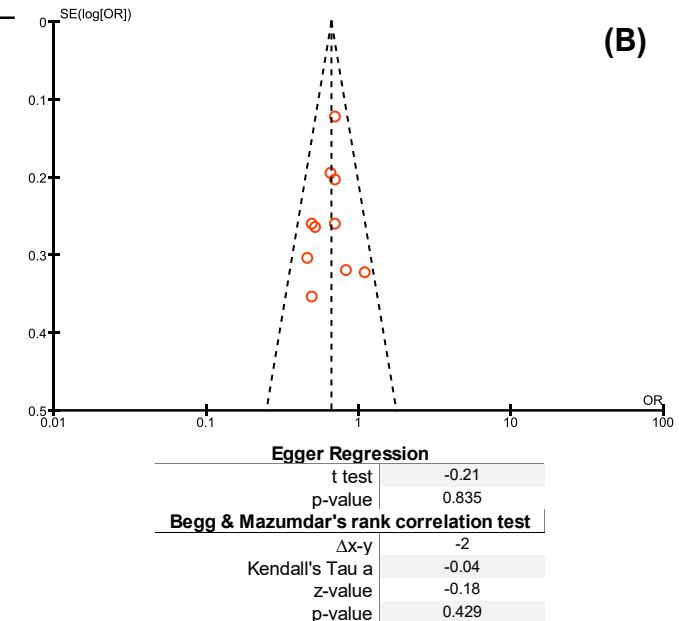
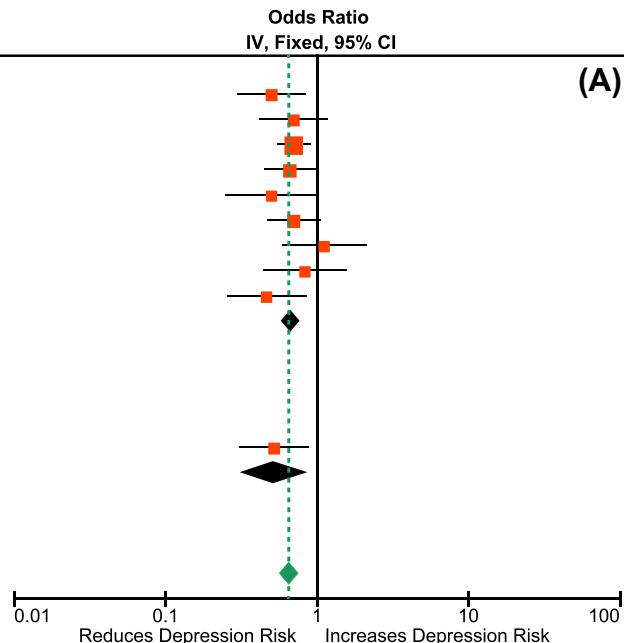
Author, Year	Study Design	Country	Population	n	Zinc Measurement	Depression Testing	Confounders Adjusted
(Kim et al., 2018)	Cross-sectional	Korea	Male & Female (> 22 years)	1748	Lowest vs Highest Tertile	Single Question/Author formulated	Age, smoking, alcohol consumption, physical activity, BMI, total body fat percentage, eGFR levels and fat, carbohydrate, and protein intake per day
(Li et al., 2018)	Cross-sectional	USA	Male & Female (> 18 years)	14834	Lowest vs Highest Quartile	PHQ-9	Age, sex, BMI, race, educational level, smoking status, family income, work activity, recreational activity, hypertension, diabetes and total daily energy intake
(Miki et al., 2015)	Cross-sectional	Japan	Male & Female (19 - 69 years)	2006	Lowest vs Highest Tertile	CES-D	n/a
(Poudel-Tandukar et al., 2016)	Cross-sectional	Nepal	Male & Female (18 - 60 years)	311	Lowest vs Highest Tertile	BDI-Ia	Age, sex, alcohol intake, smoking, physical activity, body mass index, history of any disease in past twelve months, CD4 $\beta$ T-cell count, anti-retroviral therapy and C-reactive protein
(Thi Thu Nguyen et al., 2019)	Cross-sectional	Japan	Male & Female (> 65 years)	1423	Lowest vs Highest Quartile	GDS-15 $\geq$ 6	Age, BMI, living status, having a job status, married status, smoking status, alcohol consumption, total energy, hypertension, diabetes, hyperlipidaemia
(Vashum et al., 2014)	2x Cohorts	Australia	Male & Female (55 - 85 years)	12656	Lowest vs Highest Quintile	CES-D	n/a
(Yary & Aazami, 2012)	Cross-sectional	Malaysia	Male & Female (26 - 39 years)	402	Absent vs Present DRI of Zinc	CES-D	Age, sex, BMI, monthly expenses, close friends, living in campus, smoking, physical inactivity, education, and marital status
(Jacka, Maes, et al., 2012)	Cross-sectional	Australia	Female (20 - 94 years)	1046	Zinc intake and categorical depression	DSM-IV	Energy Intake

The overall effect when all studies were pooled together showed a 34% reduced risk for depression across all zinc categories (OR = 0.66, 95% CI 0.57 – 0.76, P = < 0.00001) (**Figure 7.1A**). Description of subgroup analyses, heterogeneity and publication bias is included in **Appendix 3.3**.

Study or Subgroup	Weight	Odds Ratio IV, Fixed, 95% CI Year
<b>5.1.1 Lowest vs Highest 'tile (intake)</b>		
Yary and Aazami, 2012	7.4%	0.50 [0.30, 0.83] 2012
Vashum et al 2014 (Cohort A)	7.4%	0.70 [0.42, 1.17] 2014
Vashum et al 2014 (Cohort B)	33.3%	0.70 [0.55, 0.89] 2014
Miki et al 2015	13.2%	0.66 [0.45, 0.97] 2015
Poudel-Tandukar et al 2016	4.0%	0.50 [0.25, 1.00] 2016
Li et al 2018	12.2%	0.70 [0.47, 1.04] 2018
Kim et al 2018	4.8%	1.11 [0.59, 2.09] 2018
Thi Thu Nguyen et al 2019 (Male)	4.9%	0.83 [0.44, 1.55] 2019
Thi Thu Nguyen et al 2019 (Female)	5.4%	0.46 [0.26, 0.84] 2019
<b>Subtotal (95% CI)</b>	<b>92.8%</b>	<b>0.67 [0.58, 0.78]</b>
Heterogeneity: Chi <sup>2</sup> = 6.53, df = 8 (P = 0.59); I <sup>2</sup> = 0%		
Test for overall effect: Z = 5.40 (P < 0.00001)		

#### 5.1.2 Cut-off (zinc intake and categorical depression)

Jacka et al 2012	7.2%	0.52 [0.31, 0.87] 2012
<b>Subtotal (95% CI)</b>	<b>7.2%</b>	<b>0.52 [0.31, 0.87]</b>
Heterogeneity: Not applicable		
Test for overall effect: Z = 2.48 (P = 0.01)		
<b>Total (95% CI)</b>	<b>100.0%</b>	<b>0.66 [0.57, 0.76]</b>
Heterogeneity: Chi <sup>2</sup> = 7.40, df = 9 (P = 0.60); I <sup>2</sup> = 0%		
Test for overall effect: Z = 5.86 (P < 0.00001)		
Test for subgroup differences: Chi <sup>2</sup> = 0.87, df = 1 (P = 0.35), I <sup>2</sup> = 0%		



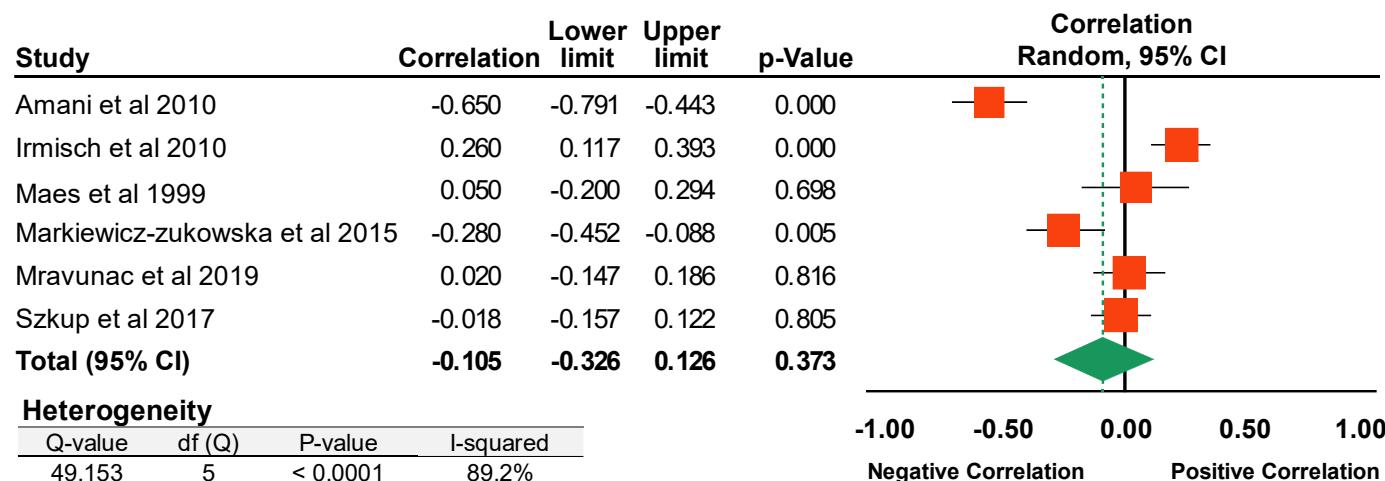
**Figure 7.1A** - Forest plot displaying the rOR of depression for two subgroups with different categories for zinc sufficiency. The red squares to the left of the midline indicate that the category for zinc sufficiency listed was associated with a reduced risk for depression. The black diamonds indicate the subtotal rOR for each subgroup and the green diamond and vertical dotted line indicates the total rOR for the entire dataset. The horizontal black lines represent the 95% confidence intervals for the associated rOR. **Figure 7.1B** – Funnel plot illustrating the level of asymmetry in the data set. Red circles in the plot represent the individual studies, the vertical dotted black line represents the overall effect in the data set and the diagonal dotted black lines represent the 95% confidence intervals. Egger Regression and Begg & Mazumdar's rank correlation test to show statistical significance for publication bias in the data set.

A fixed effects model was used as heterogeneity was not assumed.

**Table 7.2** Study Characteristics for studies included in **Figure 7.2** and adjustments made for confounders.

Author, Year	Study Design	Country	Population	n	Zinc Measurement	Depression Testing	Confounders Adjusted
(Amani et al., 2010)	Case-control	Iran	Male & Female (19 - 22 years)	46	Serum Zn x BDI	BDI	n/a
(Irmisch et al., 2010)	Case-control	Germany	Male & Female (21 - 70 years)	176	Serum Zn x BDI	BDI	Age, sex and body-mass-index
(Maes et al., 1999)	Case-control	Belgium	Male & Female (42 - 68 years)	63	Serum Zn x HDRS	HDRS	n/a
(Markiewicz-Żukowska et al., 2015)	Cohort	Poland	Male & Female (60 -102 years)	100	Serum Zn x GDS	GDS	n/a
(Mravunac et al., 2019)	Cross-sectional	Australia	Male & Female (66-75 years)	139	Serum Zn x HADS	HADS	n/a
(Szkup et al., 2017)	Case-control	Poland	Women (42 - 70 years)	198	Serum Zn x BDI	BDI	n/a

The overall effect when all studies were pooled together showed a weak negative correlation between serum zinc level and depression ( $r = -0.105$ , 95% CI -0.326 to 0.126,  $P = 0.373$ ) (**Figure 7.2**). Description of subgroup analyses, heterogeneity and publication bias is included in **Appendix 3.3**.



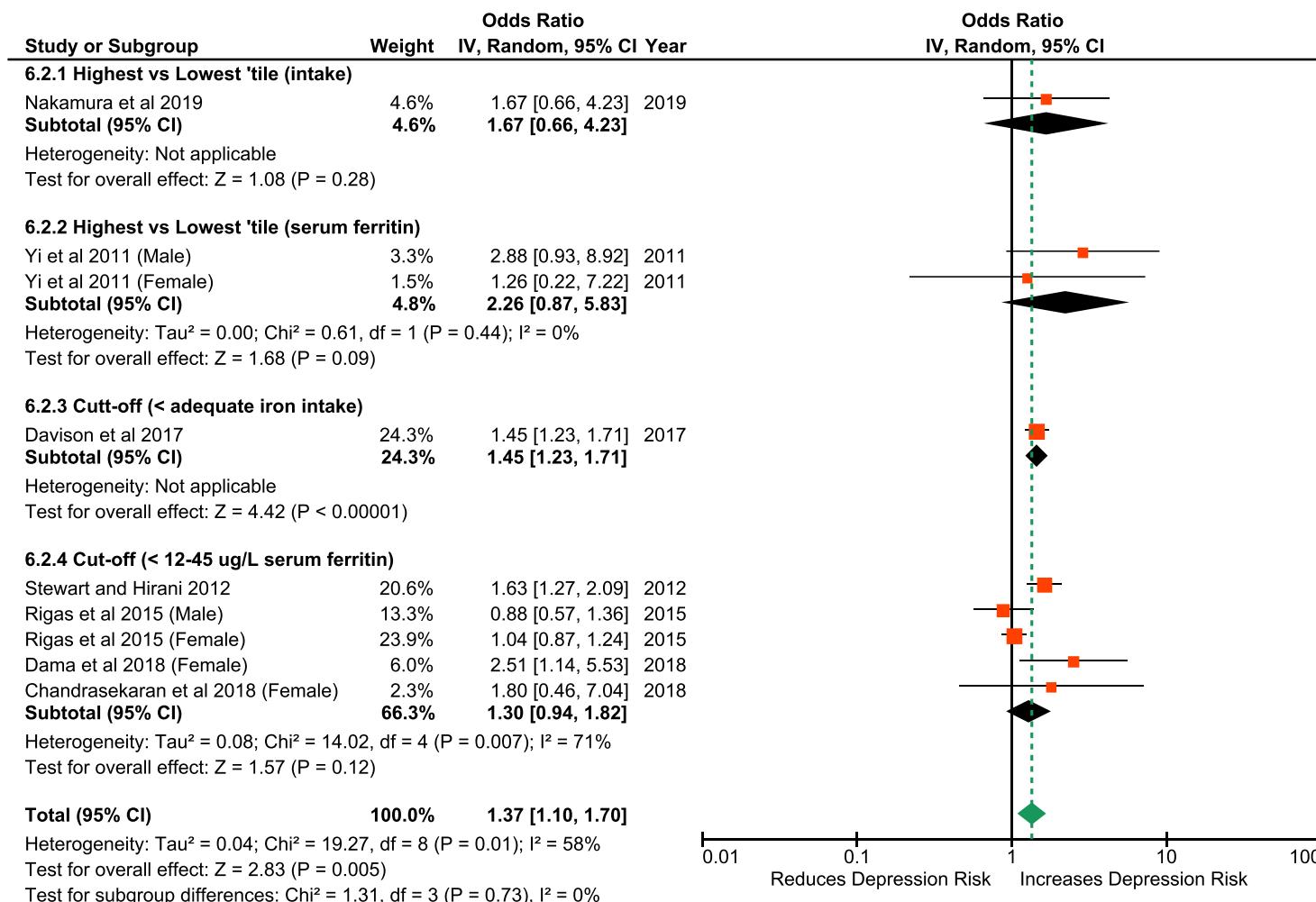
**Figure 7.2** - Forest plot displaying the CC between zinc level and depression severity. The red squares to the left of the midline indicate that there is a negative correlation between zinc level and depression. The green diamond and vertical dotted line indicate the total CC for the entire dataset. The horizontal black lines represent the 95% confidence intervals for the associated CC. A random effects model was used as heterogeneity was assumed.

## Iron

**Table 8.0** Study Characteristics for studies included in **Figure 8.0** and adjustments made for confounders.

Author, Year	Study Design	Country	Population	n	Iron Measurement	Depression Testing	Confounders Adjusted
(Nakamura et al., 2019)	Cross-sectional	Japan	Male & Female (18 - 79 years)	2089	Highest vs Lowest Quartile of Iron intake	K6 ≥13	Age and sex, smoking, alcohol drinking, body mass index, shift work, intake of Vitamin C, B6, B12, folic acid, PUFA, medications for hypertension, hyperlipidaemia, and diabetes.
(Yi et al., 2011)	Cross-sectional	Japan	Male & Female (29 - 56 years)	528	Highest vs Lowest Quartile Serum ferritin (ug/L)	CES-D ≥19	Age, marital status, study site, occupational physical activity, social status, body mass index, non-job physical activity, current smoking, current drinking, and serum folate
(Davison et al., 2017)	Cross-sectional	Canada	Male & Female (19 - 70 years)	15546	Suboptimal Iron Intake (based of food security survey)	CCHS	n/a
(Chandrasekaran et al., 2018)	Cohort	Canada	Female (≥18 years)	103	1st quartile Serum ferritin (ug/L)	EPDS ≥ 10	Age, parity, prenatal vitamins, breastfeeding at week 6
(Dama et al., 2018)	Cross-sectional	Canada	Female (21 - 33 years)	142	Iron Deficiency (Serum Ferritin <12 ug/L)	EPDS ≥12	History of depression, a history of anxiety, overweight or obesity, multiparity, and current use of iron supplements
(Rigas et al., 2015)	Cross-sectional	Denmark	Male & Female (18 - 67 years)	16375	Iron Deficiency (Serum Ferritin <15 ug/L)	HRQL, MCS (low)	Age, BMI, smoking status, number of donations within the past 3 years, and CRP levels
(Stewart & Hirani, 2012)	Cross-sectional	UK	Male & Female (≥65 years)	1875	Iron Deficiency (Serum Ferritin < 45 ug/L)	GDS-10 ≥3	Age, sex, occupation, multivitamin intake, smoking status, body mass index, hypertension, heart disease, stroke, diabetes, and cancer

The overall effect when all studies were pooled together showed a 37% greater risk for depression across all iron categories (OR = 1.37, 95% CI 1.10 – 1.70, P = 0.005) (**Figure 8.0**). Description of subgroup analyses, heterogeneity and publication bias is included in **Appendix 3.4**.



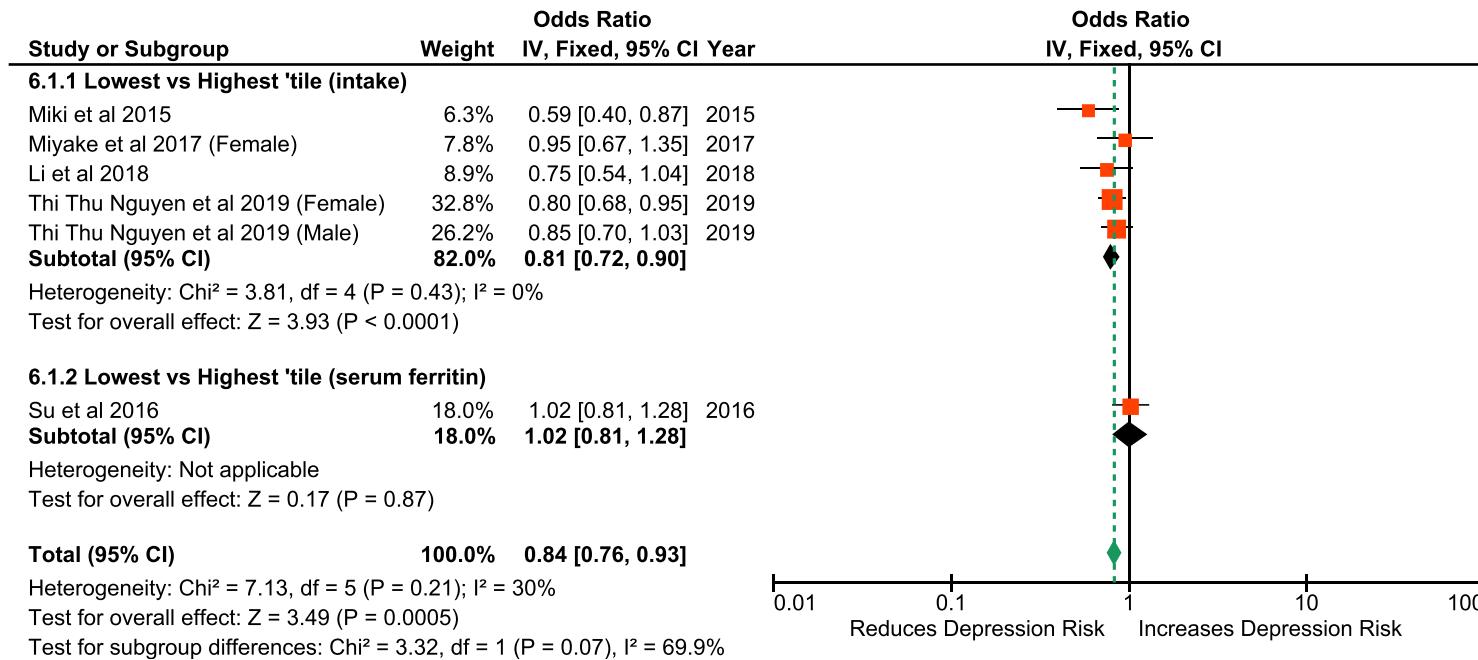
**Figure 8.0** - Forest plot displaying the OR of depression for four subgroups with different categories for iron deficiency. The red squares to the right of the midline indicate that the category for iron deficiency listed was associated with an increased risk for depression. The black diamonds indicate the subtotal OR for each subgroup and the green diamond and vertical dotted line indicates the total OR for the entire dataset. The horizontal black lines represent the 95% confidence intervals for the associated OR.

A random effects model was used as heterogeneity was assumed

**Table 8.1** Study Characteristics for studies included in **Figure 8.1** and adjustments made for confounders.

Author, Year	Study Design	Country	Population	n	Iron Measurement	Depression Testing	Confounders Adjusted
(Li et al., 2018)	Cross-sectional	China	Male & Female ( $\geq 18$ years)	14834	Lowest vs Highest quartile of Iron intake via 24-hour dietary recall	PHQ-9 $\geq 10$	Age, sex, BMI, race, educational level, smoking status, family income, work activity, recreational activity, hypertension, diabetes and total daily energy intake
(Miki et al., 2015)	Cross-sectional	Japan	Male & Female (19 - 69 years)	2006	Lowest vs Highest tertile of Iron intake	CES-D $\geq 16$	Age, sex, site, marital status, job grade, night or rotating shift work, overtime work, physical activity at work and housework or while commuting to work, leisure-time physical activity, smoking, alcohol drinking, total energy intake, and intake of folate, vitamin C, vitamin B6, vitamin B12, and n-3 polyunsaturated fatty acids.
(Miyake et al., 2017)	Cross-sectional	Japan	Female (21 - 33 years)	1745	Lowest vs Highest quartile of Iron intake	CES-D $\geq 16$	Age, gestation, region of residence, number of children, family structure, history of depression, family history of depression, smoking, second-hand smoke exposure at home and at work, employment, household income, education, body mass index, and intake of saturated fatty acids, eicosapentaenoic acid plus docosahexaenoic acid, calcium, vitamin D, and isoflavones.
(Thi Thu Nguyen et al., 2019)	Cross-sectional	Japan	Male & Female ( $> 65$ years)	1423	Lowest vs Highest Quartile Intake	GDS-15 $\geq 6$	Age, BMI, living status, having a job status, married status, smoking status, alcohol consumption, total energy, hypertension, diabetes, hyperlipidaemia
(Su et al., 2016)	Cohort	China	Male & Female (36 - 60 years)	3839	Lowest vs Highest quartile of serum ferritin	SDS $\geq 40$	Age, sex, body mass index, smoking status, drinking status, physical activity, marital status, total energy intake, household incomes, employment status, educational levels, visiting friends, living alone, metabolic syndrome, diabetes, history of inflammatory diseases, intake of EPA + DHA and white blood cell counts.

The overall effect when all studies were pooled together showed a 16% reduced risk for depression across all zinc categories (OR = 0.84, 95% CI 0.76 – 0.93, P = 0.0005) (**Figure 8.1**). Description of subgroup analyses, heterogeneity and publication bias is included in **Appendix 3.4**.



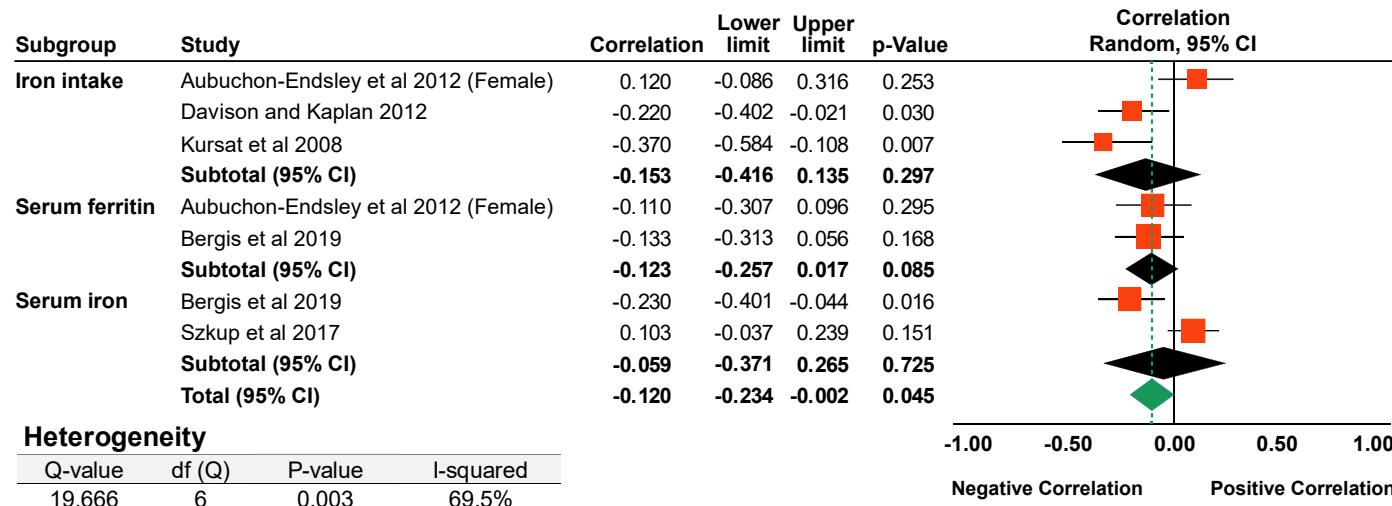
**Figure 8.1** - Forest plot displaying the rOR of depression for two subgroups with different categories for iron sufficiency. The red squares to the left of the midline indicate that the category for iron sufficiency listed was associated with a reduced risk for depression. The black diamonds indicate the subtotal rOR for each subgroup and the green diamond and vertical dotted line indicates the total rOR for the entire dataset. The horizontal black lines represent the 95% confidence intervals for the associated rOR.

A fixed effects model was used as heterogeneity was not assumed.

**Table 8.2** Study Characteristics for studies included in **Figure 8.2** and adjustments made for confounders.

Author, Year	Study Design	Country	Population	n	Iron Measurement	Depression Testing	Confounders Adjusted
(Aubuchon-Endsley et al., 2012)	Cross-sectional	USA	Female (21 - 33 years)	93	Serum Ferritin (ug/L) & Iron intake (mg)	SCL-90-R	n/a
(Bergis et al., 2019)	Cross-sectional	Germany	Male & Female (18-85 years)	109	Serum Iron & Ferritin (ug/dL)	CES-D ≥16, DSM-V	n/a
(Szkup et al., 2017)	Case-control	Poland	Women (42 - 70 years)	198	Serum iron (mg/L) x BDI	BDI ≥12	n/a
(Davison & Kaplan, 2012)	Cross-sectional	Canada	Male & Female (≥18 years)	97	Iron intake (food & supplement intake via 3-day food diary)	HDRS ≥17	n/a
(Kursat et al., 2008)	Cross-sectional	Turkey	Male & Female (40 - 70 years)	52	Iron intake (est via subjective global assessment) x TDQS	TDQS ≥19	n/a

The overall effect when all studies were pooled together showed a weak negative correlation between iron level and depression ( $r = -0.120$ , 95% CI -0.234 to -0.002,  $P = 0.045$ ) (**Figure 8.2**). Description of subgroup analyses, heterogeneity and publication bias is included in **Appendix 3.4**.



**Figure 8.2** - Forest plot displaying the CC between iron level and depression severity. The red squares to the left of the midline indicate that there is a negative correlation between iron level and depression. The green diamond and vertical dotted line indicate the total CC for the entire dataset. The horizontal black lines represent the 95% confidence intervals for the associated CC.

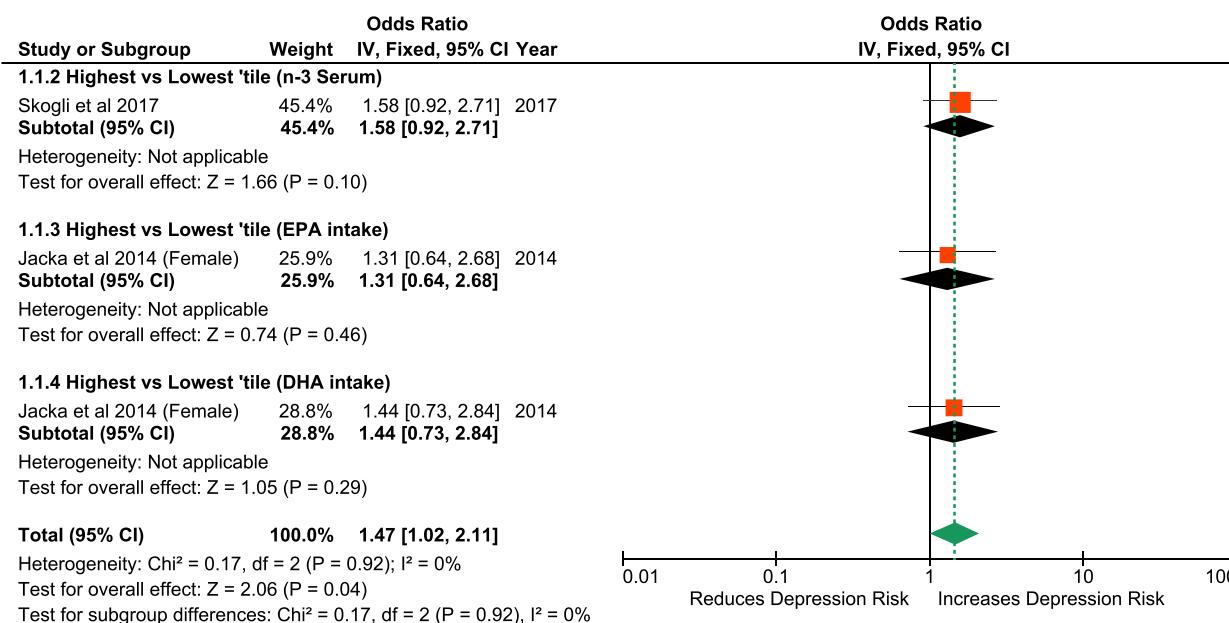
A random effects model was used as heterogeneity was assumed.

## Omega 3

**Table 9.0** Study Characteristics for studies included in **Figure 9.0** and adjustments made for confounders.

Author	Study Design	Country	Population	n	Omega-3 Measurement	Depression Testing	Confounders Adjusted
(Jacka et al., 2013)	Cross-Sectional	Australia	Female (20 - 93 years)	935	Highest vs Lowest tertile (Est. EPA and DHA intake via FFQ)	GHQ, DSM-IV-TR	History of pregnancy
(Skogli et al., 2017)	Cross-Sectional	Canada	Male & Female ( $\geq 18$ years)	1244	Highest vs Lowest tertile (Serum n-3)	K6, $\geq 13$	Age, sex, marital status, days spent out on the land, feeling of being alone, income and smoking.

The overall effect when all studies were pooled together showed a 47% greater risk for depression across all omega 3 categories (OR = 1.47, 95% CI 1.02 – 2.11, P = 0.04) (**Figure 9.0**). Description of subgroup analyses, heterogeneity and publication bias is included in **Appendix 3.5**.



**Figure 9.0** - Forest plot displaying the OR of depression for three subgroups with different categories for omega 3 deficiency. The red squares to the right of the midline indicate that the category for omega 3 deficiency listed was associated with an increased risk for depression. The black diamonds indicate the subtotal OR for each subgroup and the green diamond and vertical dotted line indicates the total OR for the entire dataset. The horizontal black lines represent the 95% confidence intervals for the associated OR.

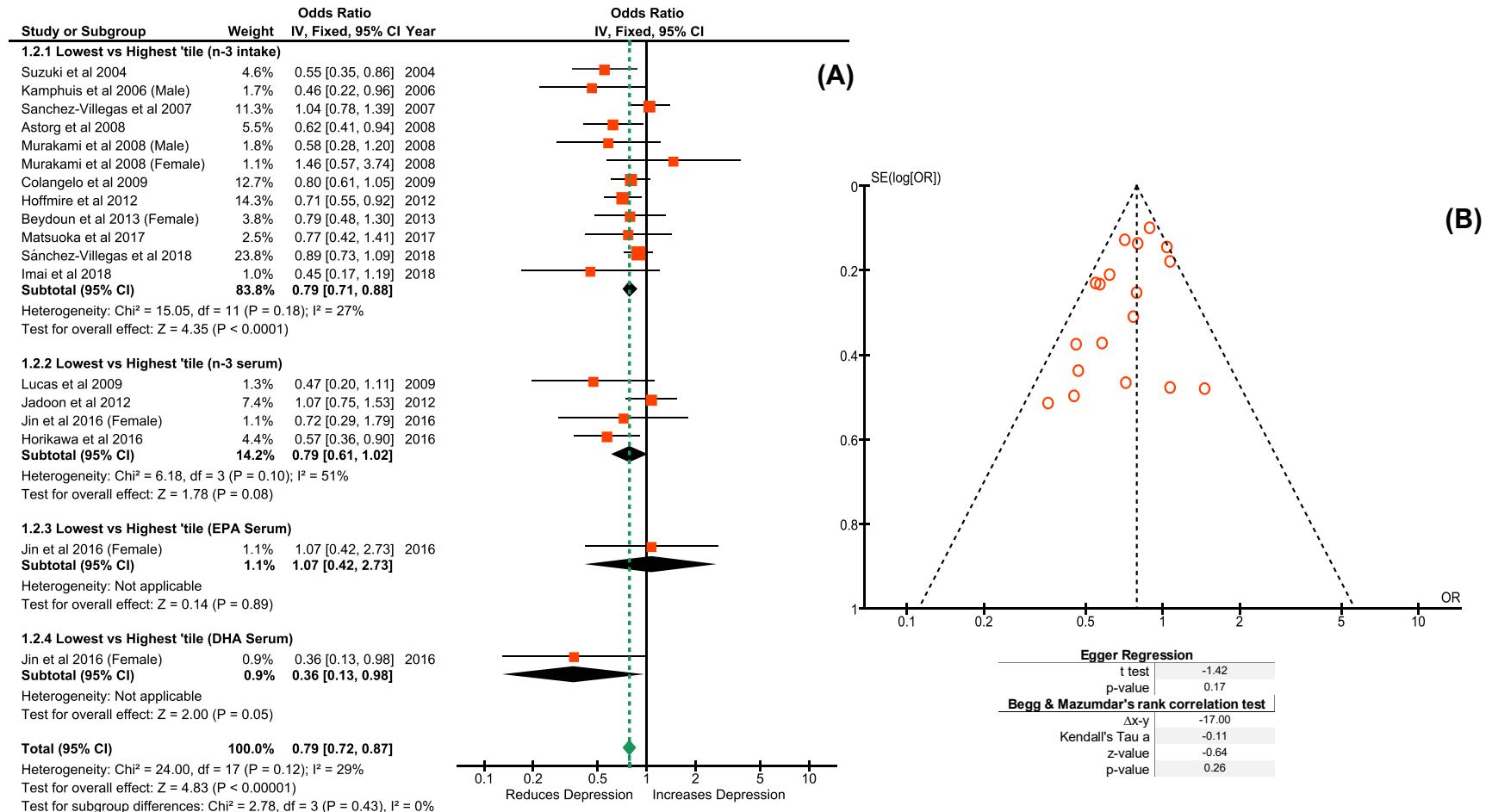
*A fixed effects model was used as heterogeneity was not assumed.*

**Table 9.1** Study Characteristics for studies included in **Figure 9.1** and adjustments made for confounders.

Author, Year	Study Design	Country	Population	n	Omega-3 Measurement	Depression Testing	Confounders Adjusted
(Suzuki et al., 2004)	Cross-Sectional	Japan	Male & Female (54 - 74 years)	771	Est. Total n-3 intake via FFQ	HADS ≥ 5	Age, sex, performance status, clinical stage, histology, pain, breathlessness, employment, smoking, alcohol consumption, and body mass index as covariates.
(Kamphuis et al., 2006)	Cross-Sectional	Netherlands	Male (70 - 90 years)	332	Est. Total n-3 intake via 2-week dietary recall	ZSDS ≥50	Age, years of education, BMI, smoking, alcohol consumption, systolic blood pressure, physical activity, and energy intake.
(Sanchez-Villegas et al., 2007)	Cohort	Spain	Male & Female (28 - 52 years)	7903	Est. energy adjusted n-3 intake via FFQ	Author formulated	Age, sex, incapacitating disease, energy intake, physical activity during leisure time, change in physical activity since baseline.
(Murakami et al., 2008)	Cross-Sectional	Japan	Male & Female (21 - 67 years)	517	Est. energy adjusted n-3 intake via Diet Recall	CES-D ≥16	Age, body mass index, workplace, marital status, occupational physical activity, leisure-time physical activity, current smoking, current alcohol drinking, and job stress score.
(Astorg et al., 2008)	Case Control	France	Male & Female (40 - 56 years)	1233	Est. n-3 intake > 0.10% of total energy intake via FFQ	No. of antidepressant prescriptions, >1	Age, intervention group (vitamin/mineral supplement or placebo), family status (living alone or in couple), education level and tobacco use
(Colangelo et al., 2009)	Cohort	USA	Male & Female (18 - 30 years)	3317	Est. EPA + DHA intake via FFQ	CES-D ≥16	Age, race, sex, educational level, body mass index, cigarettes/d, alcohol intake, total physical activity, marital status, employment status, income, and intakes of linoleic acid, folic acid.
(Lucas et al., 2009)	Cross-Sectional	Canada	Female (18 - 74 years)	368	Serum n-3	PDISQS-14 >39	Age, sex, good relationship with the community, CAGE score≥2, depression in lifetime, no recent stress events, coastal region and abused sexually.
(Hoffmire et al., 2012)	Cross-Sectional	USA	Male & Female (≥20 years)	9276	Est. energy adjusted EPA + DHA intake via FFQ	PHQ, ≥5	Age, race, sex, educational level, marital status, smoking and general health status, antidepressant use and fish oil supplementation in the last 30 days, and average total caloric intake from 24-hour dietary recall.
(Jadoon et al., 2012)	Cross-Sectional	Taiwan	Male & Female (60 - 86 years)	132	Serum n-3	HDRS >5	None
(Beydoun et al., 2013)	Cross-Sectional	USA	Female (30 - 65 years)	1746	Est. n-3 % of total energy intake via 2-day dietary recall	CES-D ≥16	Age, sex, race/ethnicity, marital status, education, poverty-income ratio, smoking and drug use status, measured BMI, and selected nutrients as well as total energy intake, namely B-vitamins (vitamins B-6 and B-12 and total folate), total carotenoids, and vitamins A, C, and E.
(Horikawa et al., 2016)	Cross-Sectional	Japan	Male & Female (≥40 years)	2129	Serum n-3	CES-D ≥16	Age, sex, BMI, education level, marital status, smoking status, alcohol consumption, physical activity, employment status and medical history.

(Jin et al., 2016)	Cross-Sectional	South Korea	Female (48 - 63 years) Male & Female (63 - 82 years)	214	Highest vs Lowest tertile (Serum n-3, EPA, DHA)	BDI ≥14	History of pregnancy, energy intake and diet quality score.
(Matsuoka et al., 2017)	Cross-Sectional	Japan	Female (63 - 82 years)	1181	Est. energy adjusted n-3 intake via FFQ	CES-D ≥16, PHQ-9, DSM-IV	Age, sex, smoking status, alcohol frequency, physical activity, past history of depression, cancer, stroke, myocardial infarction and diabetes mellitus.
(Imai et al., 2018)	Cross-Sectional	Iceland	Male & Female (67 - 93 years)	1571	Est. Total n-3 intake via FFQ	GDS ≥ 5	Age, sex, education, BMI, current smoking, alcohol, partner status, physical activity, and chronic diseases
(Sánchez-Villegas et al., 2018)	Cross-Sectional	Spain	Male & Female (55 - 75 years)	6587	Est. n-3 intake via FFQ	BDI-II, ≥10	Age, sex, marital status, educational level, smoking, physical activity, body mass index, hypercholesterolemia, hypertension, type 2 diabetes mellitus, energy intake and adherence to the Mediterranean diet.

The overall effect when all studies were pooled together showed a 21% reduced risk for depression across all omega 3 categories (OR = 0.79, 95% CI 0.72 – 0.87, P = < 0.00001) (**Figure 9.1A**). Description of subgroup analyses, heterogeneity and publication bias is included in **Appendix 3.5**.



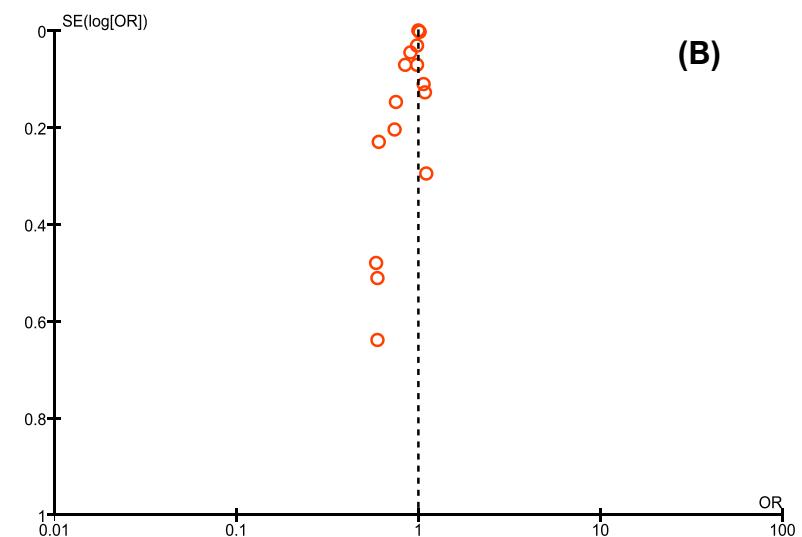
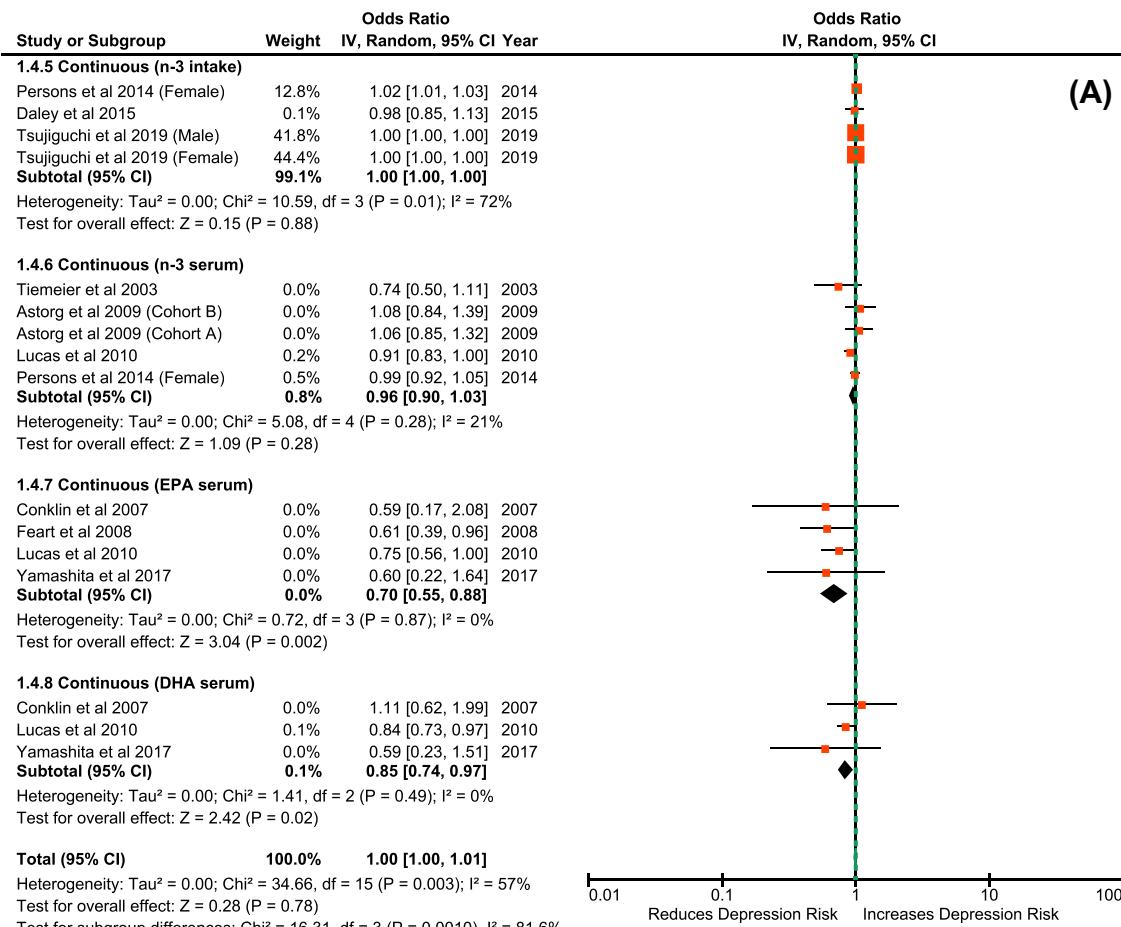
**Figure 9.1A** - Forest plot displaying the rOR of depression for four subgroups with different categories for omega 3 sufficiency. The red squares to the left of the midline indicate that the category for omega 3 sufficiency listed was associated with a reduced risk for depression. The black diamonds indicate the subtotal rOR for each subgroup and the green diamond and vertical dotted line indicates the total rOR for the entire dataset. The horizontal black lines represent the 95% confidence intervals for the associated rOR. **Figure 9.1B** – Funnel plot illustrating the level of asymmetry in the data set. Red circles in the plot represent the individual studies, the vertical dotted black line represents the overall effect in the data set and the diagonal dotted black lines represent the 95% confidence intervals. Egger Regression and Begg & Mazumdar's rank correlation test to show statistical significance for publication bias in the data set.

A fixed effects model was used as heterogeneity was not assumed.

**Table 9.2** Study Characteristics for studies included in **Figure 9.2** and adjustments made for confounders.

Author	Study Design	Country	Population	n	Omega-3 Measurement	Depression Testing	Confounders Adjusted
(Tiemeier et al., 2003) (Conklin et al., 2007)	Case Control	Netherlands	Male & Female (61 - 101 years)	106	Serum n-3	CES-D ≥16, DSM-IV	Age, sex, smoking status, systolic blood pressure, and activities of daily living score.
	Cross-Sectional	USA	Male & Female (30 - 55 years)	116	Serum EPA and DHA	BDI, ≥10	None
(Féart et al., 2008)	Case Control	France	Male & Female (>65 years)	1390	Serum EPA	CES-D, (Male: ≥17, Female: ≥23)	Age, sex, income, marital status, antidepressant treatment, Mini-Mental State Examination score, hypercholesterolemia, number of drugs/d, and weight loss
(Astorg et al., 2009)	Case Control	France	Male & Female (35 - 60 years)	815	Serum n-3	n/a	Age, sex, intervention group (vitamin/mineral supplement or placebo), family status (living alone or in couple), education level (three levels), socio-professional category and tobacco use
(Lucas et al., 2010)	Cross-Sectional	Canada	Male & Female (≥18 years)	746	Serum n-3, EPA and DHA	K6, ≥13, DSM-IV	Age, sex, work, marital status, obesity, alcohol consumption, and income.
(Persons et al., 2014)	Cross-Sectional	USA	Female (63 - 81 years)	7086	Est. n-3 intake via FFQ, Serum n-3	CES-D/DIS	U.S. region, marital status, race, education, income, obesity, high blood pressure, high cholesterol, smoking status, bilateral oophorectomy, arthritis, cardiovascular disease, diabetes, prescription narcotic use, physical activity, and alcohol consumption
(Daley et al., 2015)	Cross-Sectional	Australia	Female (20 - 30 years)	7635	Est. n-3 intake via FFQ	CES-D ≥10	BMI, energy intake, physical activity categorised in total metabolic equivalent, type 2 diabetes, heart disease, postnatal depression, anxiety, a sexually transmitted infection, hepatitis B or C or cancer, severe tiredness, leaking urine, back pain and skin problems, alcohol status, highest qualification completed, pattern of drug use, smoking status, pregnancy status, experienced any kind of abuse in last 3 years, area of residence, ability to manage on income, marital status and whether they had experienced any of twenty-eight major life events in the last 12 months
(Yamashita et al., 2017)	Cohort	Japan	Male & Female (36 - 87 years)	100	Serum EPA and DHA	HADS ≥ 8	Age, sex, body mass index, hypertension, dyslipidaemia, and total score of the Hospital Anxiety and Depression Scale.
(Tsujiguchi et al., 2019)	Cross-Sectional	Japan	Male & Female (≥65 years)	1633	Est. energy adjusted n-3 intake via FFQ	GDS, ≥7	Age, energy, carbohydrate, education, social activity, household size, drinking, smoking, hypertension, diabetes, overweight/obesity and hyperlipidaemia

The overall effect when all studies were pooled together showed a no effect for depression across all omega 3 categories (OR = 1.00, 95% CI 1.00 – 1.01, P = 0.78) (**Figure 9.2A**). Description of subgroup analyses, heterogeneity and publication bias is included in **Appendix 3.5**.



#### Egger Regression

t test	-2.08
p-value	0.057

#### Begg & Mazumdar's rank correlation test

$\Delta x-y$	-8.00
Kendall's Tau a	-0.07
z-value	-0.36
p-value	0.359

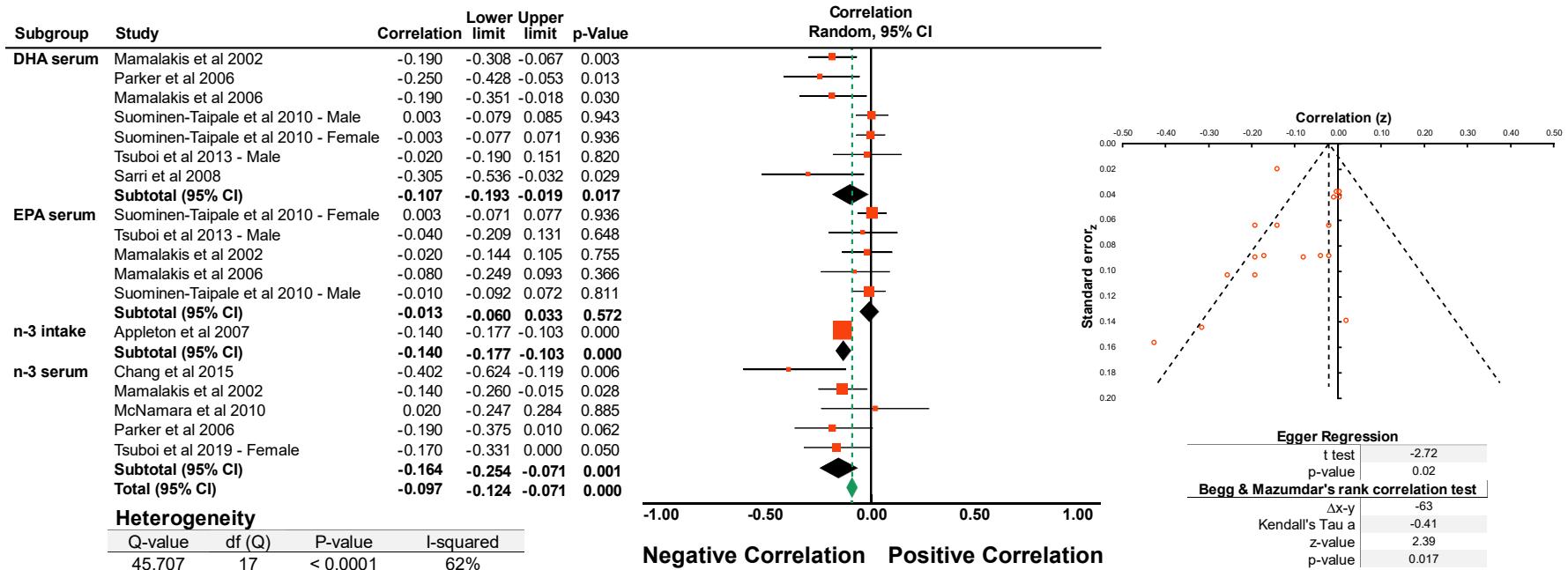
**Figure 9.2A** - A forest plot displaying the continuous odds ratio (cOR) of depression for four subgroups with different categories for omega 3. The red squares to the right of the midline indicate that the category for omega 3 listed was associated with an incremental increased risk for depression. The black diamonds indicate the subtotal cOR for each subgroup and total cOR for the entire dataset is indicated with a dotted green vertical line. The horizontal lines represent the 95% confidence intervals for the associated cOR. **Figure 9.2B** - Funnel plot illustrating the level of asymmetry in the data set. Egger Regression and Begg & Mazumdar's rank correlation test to show statistical significance for publication bias in the data set.

A random effects model was used as heterogeneity was assumed.

**Table 9.3** Study Characteristics for studies included in **Figure 9.3** and adjustments made for confounders.

Author	Study Design	Country	Population	n	Omega-3 Measurement	Depression Testing	Confounders Adjusted
(Mamalakis et al., 2002)	Cross-Sectional	Greece	Male & Female (27 - 53 years)	247	Adipose Fatty Acid (n-3 PUFA, EPA and DHA)	ZSDS ≥50	Age, sex, BMI, dietary total fat, dietary caloric intake, and adipose tissue c18:2n6, c20:2n6, c20:3n6, c20:4n6, sum of n6 fatty acids, c18:3n3, c20:5n3, c22:5n3, and sum of n3 PUFAs.
(Parker et al., 2006)	Cross-Sectional	Australia	Male & Female (55 - 77 years)	97	Serum Fatty acid (DHA)	DMI-18	None
(Mamalakis et al., 2006)	Cross-Sectional	Greece	Male & Female (22 - 58 years)	130	Adipose Fatty Acid (EPA and DHA)	ZSDS ≥50	None
(Parker et al., 2006)	Cross-Sectional	Australia	Male & Female (55 - 77 years)	97	Serum Fatty acid (n-3 PUFA)	DMI-18	None
(Appleton et al., 2007)	Cross-Sectional	UK	Male & Female (>18 years)	2674	Est. Total n-3 intake (g/wk) via FFQ	DASS, ≥14	Age, gender, IMD, date of questionnaire completion
(Sarri et al., 2008)	Case Control	Greek	Male & Female (20 - 60 years)	51	Serum Fatty acid (DHA)	BDI, ≥10	None
(Suominen-Taipale et al., 2010)	Cross-Sectional	Finland	Male & Female (>35 years)	1282	Serum Fatty acid (EPA & DHA)	GHQ	Age, level of education, marital status, smoking history, physical activity, total energy intake (except for the models including serum concentrations of fatty acids), alcohol intake, alcohol-induced intoxication (in the Fishermen Study), BMI, medication for depression or psychiatric disorders, occurrence of physician-diagnosed severe illnesses (i.e. cancer, myocardial infarction, cerebral stroke, diabetes or rheumatoid arthritis), back pain or illness, bronchial asthma and regular use of fish oil supplements.
(McNamara et al., 2010)	Case Control	USA	Male & Female (28 - 52 years)	55	Serum Fatty acid (EPA+DHA)	HDRS >5	None
(Tsuboi et al., 2013)	Cross-Sectional	Japan	Male & Female (19 - 75 years)	133	Serum Fatty acid (n-3 PUFA, EPA & DHA)	CES-D ≥16	Age, sex, BMI, leisure-time physical activities, snacking habit, smoking habit and alcohol consumption.
(Chang et al., 2015)	Cross-Sectional	Taiwan	Male & Female (47 - 77 years)	44	Serum Fatty acid (n-3)	HAMD ≥ 10	Age

The overall effect when all studies were pooled together showed a very weak negative correlation between omega 3 and depression severity ( $r = -0.097$ , 95% CI -0.124 to –0.071,  $P = 0.0001$ ) (**Figure 9.3A**). Description of subgroup analyses, heterogeneity and publication bias is included in **Appendix 3.5**.



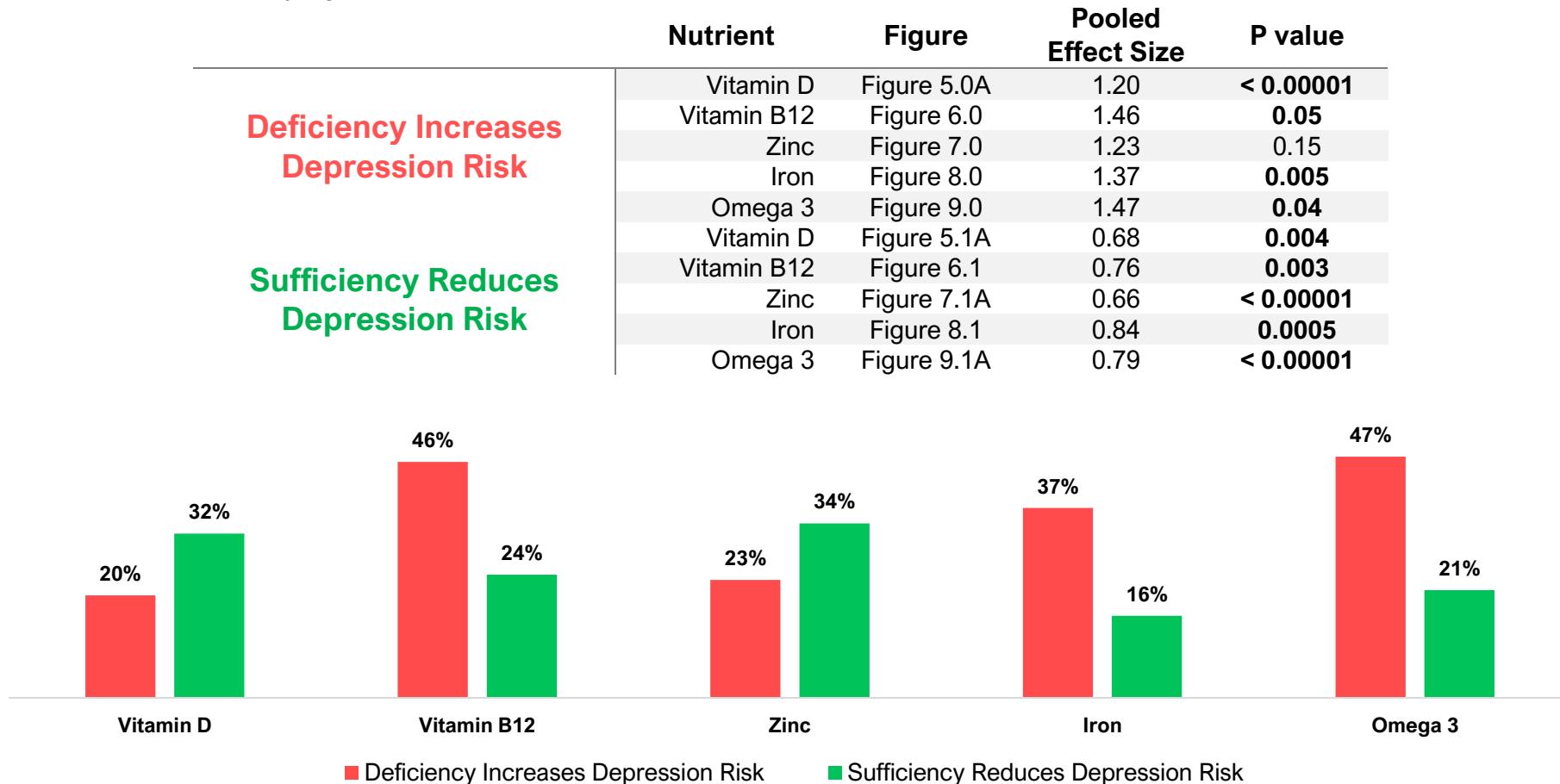
**Figure 9.3A** - Forest plot displaying the CC between omega 3 and depression severity for four subgroups with different categories of omega 3. The red squares to the left of the midline indicate that there is a negative correlation between omega level and depression. The black diamonds indicate the subtotal CC for each subgroup and the green diamond and vertical dotted line indicate the total CC for the entire dataset. The horizontal black lines represent the 95% confidence intervals for the associated CC. **Figure 9.3B** - Funnel plot illustrating the level of asymmetry in the data set. Red circles in the plot represent the individual studies, the vertical dotted black line represents the overall effect in the data set. Egger Regression and Begg & Mazumdar's rank correlation test to show statistical significance for publication bias in the data set.

A random effects model was used as heterogeneity was assumed.

## Totals

**Table 10.0** Summary of results from the main odds ratio meta-analyses of each nutrient and their association with increasing and reducing depression risk.

*P values in bold are statistically significant.*



**Figure 10.0** Summary of results from the main odds ratio meta-analyses of each nutrient and their association with increasing and reducing depression risk, odds ratio converted into percentage of risk increase or reduction.

**Table 10.1** Summary of results from all correlative data meta-analyses of each nutrient and their association with depression.  
*P values in bold are statistically significant.*

Nutrient	Figure	Pooled Correlation Coefficient	Interpretation	P value
Vitamin D	Figure 4.3	-0.338	weak to moderate negative correlation	<b>0.0001</b>
Vitamin B12	Figure 5.2	-0.187	weak negative correlation	<b>0.0001</b>
Zinc	Figure 6.2	-0.105	weak negative correlation	0.373
Iron	Figure 7.2	-0.12	weak negative correlation	<b>0.045</b>
Omega 3	Figure 8.3A	-0.097	weak negative correlation	<b>0.0001</b>

**Table 10.2** Summary of results from additional effect size data meta-analyses for vitamin D and omega 3 and their association with depression.

Nutrient	Figure	Effect Size	Pooled Effect Size	P value
Vitamin D	Figure 4.2	Hazard Ratio	1.57	0.09
Omega 3	Figure 8.2A	Continuous/Incremental Odds Ratio	1.00	0.78

## Discussion

In this review, 140 observational studies were analysed that investigated the relationship between various nutrients and their association with depression. The meta-analyses that pooled odds ratio data on nutrient deficiency, found that deficiency in vitamin D, vitamin B12, iron and omega 3 were significantly associated with increasing depression risk, however zinc deficiency was not. Vitamin B12 and omega 3 deficiency had the strongest effect on increasing depression risk out of all the nutrients (46% and 47% respectively) (**Figure & Table 10.0**). Within the data that investigated nutrient sufficiency and its ability to reduce depression risk, all meta analyses that pooled reverse odds ratio were found to be statistically significant. Zinc and vitamin D sufficiency had the strongest effect on reducing depression risk out of all the nutrients (34% and 32% respectively) (**Figure & Table 10.0**). Meta-analyses that pooled correlative data found that vitamin D, vitamin B12, iron and omega 3 were significantly correlated with depression, although zinc was not. Vitamin D was the only nutrient that had a weak to moderate negative correlation (-0.338), all other nutrients had weak negative correlations (**Table 10.1**). The meta-analyses that pooled other effect size data found no statistical significance in either vitamin D or omega 3, which analysed hazard ratio and continuous/incremental odds ratio respectively (**Table 10.2**).

When looking at previous meta-analyses investigating the nutrients that were covered in this review, similar findings can be seen across several nutrients and their associations with depression.

To date there are only two meta analyses that investigated the relationship between vitamin D deficiency and depression, of which they both found a significant relationship between the two (Alsofyani, Alharbi, & Alanazi, 2017; Anglin et al., 2013). Five meta-analyses investigated the efficacy of vitamin D supplementation on reducing depression (Alsofyani, Alharbi, & Alanazi, 2017; Ju et al., 2013; Shaffer et al., 2014; Spedding, 2014; Vellekkatt & Menon, 2019), two found significant results (Alsofyani, Alharbi, & Alanazi, 2017; Spedding, 2014), and one noted that supplementation was comparable to the effect of anti-depressant medication (Spedding, 2014). Whilst this present review didn't look at the therapeutic effect of vitamin D supplementation on depression specifically, within the data that investigated vitamin D sufficiency, a significant overall effect was found for reducing depression (**Figure 5.1A**).

Two previous meta-analyses looked at the relationship between vitamin B12 and depression, one of which looked specifically at deficiency and depression risk, where they found a significant association only in females (Petridou et al., 2016). The other found no significant association between vitamin B12 as a treatment to decrease depression severity (Almeida et al., 2015). These findings partly mirror the results in this review, where vitamin B12 deficiency has a stronger effect of increasing depression risk than vitamin B12 sufficiency has on reducing depression risk (**Figure 10**). Although no subgroup analyses were done between gender groups.

Looking at previous studies on dietary zinc and depression, two meta-analyses found a significant association between deficiency and risk of depression (Li et al., 2017; Swardfager et al., 2013). In contrast to that, this review found no significance with the overall effect of the data on zinc deficiency and depression risk (**Figure 7.0**), this may have been down to the lack of studies included in the analysis that used blood zinc concentrations as an exposure measure. Swardfager et al., (2013) included seventeen studies measuring peripheral blood zinc concentrations, which may have allowed the elucidation of a stronger association. Within the correlative data between zinc levels and depression, there was also no significance and a weak correlation was found (**Figure 7.2**).

There is a paucity of data that looked at the direct link between iron and depression, one meta-analysis of only 3 studies found a significant inverse association between iron intake and risk of depression (Li et al., 2017). This finding has been replicated in this review, firstly across 5 studies that showed a significant reduction in depression for a higher iron intake and serum ferritin (**Figure 8.1**), secondly within correlative data (**Figure 8.2**) and thirdly across 7 studies showing a significant increase in depression risk for iron deficiency (**Figure 8.0**). Other meta-analyses looked specifically at rates of iron deficiency anaemia and postpartum depression in female populations where significant associations were found (Azami et al., 2019; Wassef et al., 2019).

There were three meta-analyses that looked only at the efficacy of omega 3 fatty acid in its ability to reduce depression. One review of 9 RCTs found mixed results that were not significant (Bai et al., 2018). Two other meta-analyses found more promising results, where they found more efficacy with EPA compared to DHA in treating depression (Liao et al., 2019; Martins, 2009). Mixed results were found in this review compared to previous studies mentioned. In one analysis, serum EPA was found be more associated

with reducing depression risk than serum DHA by 15% (**Figure 9.2A**). All other omega-3 analyses found either no significant difference between EPA and DHA (intake) (**Figure 9.0**), or a greater reduction in depression from erythrocyte DHA compared with EPA. Which can be seen in the subgroup analysis in **Figure 9.1A** and is comprised of the data from a single study (Jin et al., 2016).

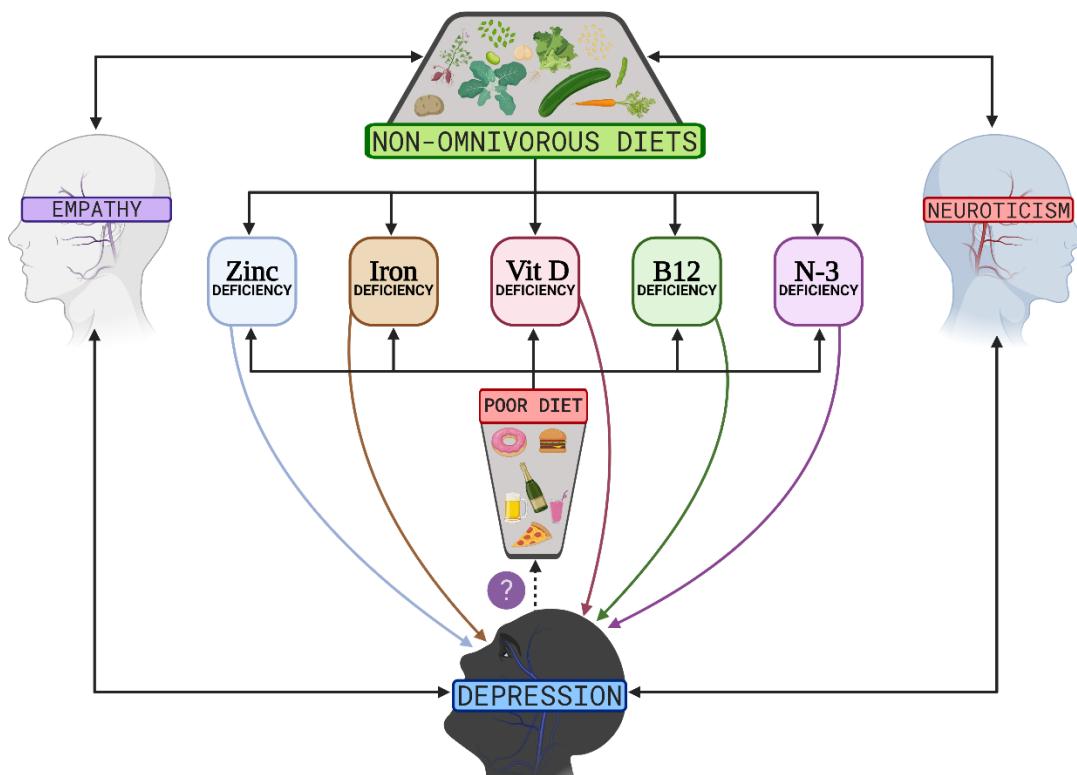
Whilst all but one meta-analysis conducted in this review were found to be significant with a moderate effect, causal inferences cannot be made solely based on the associative data of observational studies. However, there is considerable mechanistic data surrounding each of the nutrients studied, linking deficiency to depression. Therefore, nutrient deficiencies may explain in part, the reason why there are higher rates of depression in non-omnivores.

Possible reverse causalities in the relationship between non-omnivorous diets and depression are also worth considering. Vegans were shown to have higher levels of empathy compared with vegetarians in one study (Kessler et al., 2016) but in another study comparing vegans two both vegetarians and omnivores no differences in empathy was found (Kessler et al., 2018). A study that looked at the brain activation of vegans, vegetarians and omnivores found a higher engagement of empathy related areas while observing negative animal suffering for non-omnivorous compared to omnivores (Filippi et al., 2010). An argument could also be made that non-omnivores are more empathetic than omnivores regarding animals purely by definition. Empathy has been consistently shown to be associated with depression (Bennik et al., 2019; Calandri et al., 2019; Tone & Tully, 2014), which may explain part of the causal relationship between non-omnivores and depression.

Another aspect of psychology that could contribute to the causal map that explains the relationship between non-omnivores and depression is personality. Vegetarians have been shown to have higher rates of trait neuroticism when compared to non-omnivores (Forestell & Nezlek, 2018), and also specifically in the “primary-process subcortical brain emotion system” sadness (Davis & Panksepp, 2011; Sariyska et al., 2019). Neuroticism has been consistently shown as a risk factor for depression (Jylhä & Isometsä, 2006; Klein et al., 2011; Lahey, 2009; Xia et al., 2011), which could provide another link between non-omnivores and depression.

Relationships linking nutrient deficiencies and depression are worth noting, as many studies have consistently shown an association between dietary habits and depression (Lai et al., 2014; O’Neil et al., 2014; T. S. S. Rao et al., 2008; Whitaker et al., 2014). This relationship has been described as complex and bidirectional by some authors, whereby the presence of depression in an individual may result in a poorer diet, but also that a poor diet may cause depression (Jacka et al., 2015). Perhaps as various nutrient deficiencies have also been implicated to play a role in the pathophysiology of depression (J. Kim & Wessling-Resnick, 2014; Larrieu & Layé, 2018; Oh & Brown, 2003; Penckofer et al., 2010; Petrilli et al., 2017). This causal bidirectional relationship has been termed the ‘depression-nutrient intake reverse causality hypothesis’, however when tested across longitudinal data, it has shown to not necessarily explain the relationship between diet and depression (Gougeon et al., 2017; Jacka et al., 2015). A proposed model to conceptualise the results of this review and the current relevant literature surround non-omnivorous diets, nutrient deficiencies and depression can be seen in

**Figure 11.0.**



**Figure 11.0** A model to describe the relationship between non-omnivorous diets and depression. Non-Omnivorous diets and Depression (**NOD**).

## **Strengths & Limitations**

The present study is the first systematic review and meta-analysis to investigate multiple nutrient deficiencies in the wider context of non-omnivorous diets and their association with depression. The large number of studies that were analysed for each nutrient could be seen as a strength, as it represents more of the available data relating to the topic, therefore giving a truer representation of the totality of evidence. This was mainly achieved by a thorough and methodical search strategy from the initial title review through to data extraction, but also allowing a lesser strict exclusion criterion in respect to exposure measures. This could also be considered a limitation as there was numerous ways in which nutrient status was measured (e.g. intake, serum or plasma), although transparency was maintained using appropriate subgrouping where differences in exposure measure existed. This does not excuse the fact that the overall pooled analyses could be vulnerable to this limitation, and in fact this can be seen in the degree of heterogeneity that was present in multiple analyses in this review. An additional limitation was in the lack of discrimination in relation to how nutrient intake was measured across studies, many studies used food frequency questionnaires or dietary recall to measure nutrient intake. Which are known to have inherent bias due to self-reporting and measurement error (Shim et al., 2014).

Another area that could influence the strength of this review can be found in the data extraction process. Most studies adjusted for multiple confounders, in this review the most adjusted effect sizes were preferentially chosen for the final analysis and crude effect sizes were only used in cases where adjusted data was not presented. Although due to the nature of the research question, observational studies—that usually provide lower-quality evidence—were only included to show the association between depression and nutrient deficiency. RCTs would provide more control over confounding factors and future reviews could include these in meta-analyses alongside observational studies, which would further strengthen the evidence. When selecting the types of populations to be included for analyses, the criteria was only set to exclude non-adult populations or individuals who were currently pregnant. Whilst this limited confounding factors to a degree, the lack of exclusion on data related populations that suffered with other disease or health issues, could skew overall effect sizes significantly when aggregated with healthy

populations. When looking at depression measurement, the testing varied across all studies in this review. Most were threshold based, multi-component questionnaires related to traits of depression, however there were many different variations of this way of screening and the lack of a universal way to measure depression is a definite limitation to the consistency of the outcome measure.

The level heterogeneity in this review was substantially high, eleven out of the sixteen total meta analyses conducted had statistical heterogeneity in the pooled analysis and lacked precision (**Appendix 3**). This is mostly caused by the subgrouping of different exposure measures within each nutrient analysis (e.g subgrouping nutrient intake with serum levels or serum EPA with serum DHA). But could also be a product of aggregating sexed data with mixed sex data or aggregating disease suffering cohorts with healthy cohorts. This subgrouping was required to limit the number of distinct forest plots that would need to be generated, to cover all the data put forward for the analysis. Heterogeneity was tested for each separate subgroup for transparency and provides valuable information for future reviews investigating the same question.

Publication bias across studies was tested subjectively for asymmetry using a funnel plot and statistical tests were run to provide significance (**Appendix 3**). Data sets that consisted of 10 or more studies were tested for publication bias only. Two meta-analyses out of a total of six (that were tested for publication bias) showed subjective asymmetry and had statistically significant bias (**Figure 5.0B** and **Figure 9.3B**), one meta analyses presented some asymmetry but didn't have statistically significant bias when tested (**Figure 9.2B**). Lastly, there were three meta-analyses that showed no asymmetry and no significant publication bias after statistical testing (**Figure 5.1B** and **Figure 9.1B**).

## **Implications & Future Directions**

This review demonstrates the importance of ensuring an adequate micronutrient whilst consuming a non-omnivorous diet to mitigate or perhaps treat depression, it should also be viewed as a pilot study that provides an insight into the vast majority of data surrounding the nutrient deficiencies covered in this review and their association with depression. This will allow for future investigations—that focus on single nutrient deficiencies related depression—to provide more precise and comprehensive analyses of the relationships with more control and less heterogeneity. Moreover, it could provide the basis and background for a future meta-analysis that investigates the association between non-omnivores and depression directly.

## **Conclusion**

In conclusion, the link between the nutrients covered in this review and their association with depression were all shown to be significant apart from the association between zinc deficiency and depression. However, a mechanistic rationale exists linking zinc to depression, and sufficiency was found to significantly reduce depression risk. Vitamin B12 and omega 3 deficiency had the strongest effect on increasing depression risk out of all the nutrients (46% and 47% respectively) and zinc and vitamin D sufficiency had the strongest effect on reducing depression risk out of all the nutrients (34% and 32% respectively). Nutrient deficiencies that were shown to be common within non-omnivorous diets may explain the higher rates of depression seen in populations that follow these diets, although there are other causal relationships that are worth considering when drawing inferences from the results in this review.

## **Funding**

Funding was acquired from the University of Suffolk for the software application Comprehensive Meta-Analysis. An academic/non-profit standard 1-year licence was purchased.

## **Acknowledgements**

I wish to acknowledge and thank my dissertation supervisor's Dr Suha Al-Naimi and Dr Manos Georgiadis for their support and guidance throughout and my module leader Dr Fandi Ibrahim for his direction on many aspects related to statistics.

## **Conflicts of Interest**

The author(s) consume omnivorous diets.

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# Appendices

## Appendix 1 – Search Strings

### PubMed/CINAHL

### Medline

Vitamin D	(((((((Vitamin D Deficiency) OR Cholecalciferol) OR Calcitriol) OR Vitamin D) OR 25-Hydroxyvitamin D 2) OR Hypovitaminosis D)) AND (((((Depression) OR Depressive Disorder) OR Mental Health) OR Mental Disorders) OR Depressive Disorder, Major))) NOT (((((((Psychotic Disorders) OR Postpartum Period) OR Autistic Disorder) OR Schizophrenia) OR Anorexia Nervosa) OR Alzheimer Disease) OR Dementia) OR Supplementation))  (((((Transcobalamins) OR Homocysteine) OR Vitamin B 12) OR Vitamin B 12 Deficiency)) AND (((((Depression) OR Depressive Disorder) OR Mental Health) OR Mental Disorders) OR Depressive Disorder, Major))) NOT (((((((Psychotic Disorders) OR Postpartum Period) OR Autistic Disorder) OR Schizophrenia) OR Supplementation) OR Anorexia Nervosa) OR Alzheimer Disease) OR Dementia)
Vitamin B12	TS=(Transcobalamins OR Homocysteine OR Vitamin B 12 OR Vitamin B 12 Deficiency) AND TS=(Depression OR Depressive Disorder OR Mental Health OR Mental Disorders OR Depressive Disorder, Major) NOT TS=(Psychotic Disorders OR Postpartum Period OR Autistic Disorder OR Schizophrenia OR Supplementation OR Anorexia Nervosa OR Alzheimer Disease OR Dementia)
Zinc	(((((Zinc) OR hypozincaemia) OR Zinc Deficiency)) AND (((((Depression) OR Depressive Disorder) OR Mental Health) OR Mental Disorders) OR Depressive Disorder, Major))) NOT (((((((Psychotic Disorders) OR Postpartum Period) OR Autistic Disorder) OR Schizophrenia) OR Anorexia Nervosa) OR Alzheimer Disease) OR Dementia) OR Supplementation)
Iron	TS=(Zinc OR hypozincaemia OR Zinc Deficiency) AND TS=(Depression OR Depressive Disorder OR Mental Health OR Mental Disorders OR Depressive Disorder, Major) NOT TS=(Psychotic Disorders OR Postpartum Period OR Autistic Disorder OR Schizophrenia OR Anorexia Nervosa OR Alzheimer Disease OR Dementia OR Supplementation)
Omega - 3	(((((Iron) OR (ferric compounds)) OR (Anemia, Iron-Deficiency)) AND (((((Depression) OR (Depressive Disorder)) OR (Mental Health)) OR (Mental Disorders)) OR (Depressive Disorder, Major))) NOT (((((((Psychotic Disorders) OR (Postpartum Period)) OR (Autistic Disorder)) OR (Schizophrenia)) OR (Anorexia Nervosa)) OR (Alzheimer Disease)) OR (Dementia)) OR (Supplementation)))  (((((Fatty Acids, Omega-3) OR Docosahexaenoic Acids) OR Eicosapentaenoic Acid) OR Fatty Acids, Essential) OR Omega 3 deficiency)) AND (((((Depression) OR Depressive Disorder OR Mental Health) OR Mental Disorders) OR Depressive Disorder, Major))) NOT (((((((Psychotic Disorders) OR Postpartum Period) OR Autistic Disorder) OR Schizophrenia) OR Anorexia Nervosa) OR Alzheimer Disease) OR Dementia) OR Supplementation))

## **Appendix 2 – Effect Sizes**

### **Odds Ratio**

This group consists of all studies that reported odds ratio as the effect size, showing the relationship between a dichotomous nutrient variable and the odds of increasing depression risk. Typically, data is in the form of a nutrient cut-off/threshold that signifies deficiency or data showing the difference between the highest and the lowest quartiles, with the highest range acting as the reference value = 1.

### **Reverse Odds Ratio**

This group consists of all studies that reported odds ratio as the effect size, showing the relationship between a dichotomous nutrient variable and the odds of decreasing depression risk. Data would also be in the form of a nutrient cut-off/threshold, but it would signify nutrient sufficiency rather than deficiency. However, most of the reverse odds ratio data came in a quartile-based format, which was presented as the difference between the lowest and the highest quartiles, with the lowest range acting as the reference value = 1.

### **Continuous/Incremental Odds Ratio**

Continuous odds ratio data is a group that consists of all studies that reported odds ratio as the effect size but showed the relationship between an incremental decrease in nutrient value and the odds of increasing depression risk with that increment.

### **Hazard Ratio**

Hazard ratio data is a group that consists of all studies that reported hazard ratio as the effect size showing the relationship between a dichotomous nutrient variable and the likelihood of increasing depression risk. Typically, data was in the form of a nutrient cut-off/threshold that signifies deficiency.

## Correlative Data

Correlative data is a group that consists of all studies that reported correlation coefficients as the effect size showing the direct correlative relationship between nutrient level and depression severity. The interpretation of the correlation coefficients were as follows: Strong correlation (+/- 0.7 – 0.9), moderate correlation (+/- 0.4 – 0.7) and weak correlation (+/- 0.1 – 0.3) (Akoglu, 2018).

## Appendix 3 – Subgroup Analyses, Heterogeneity and Publication Bias

### Appendix 3.1 – Vitamin D

#### Figure 5.0

32 studies were analysed that reported odds ratio values for vitamin D deficiency and depression risk (**Figure 5.0A**), the data was stratified into three categorical subgroups for the analysis. Within the Cut-off (< 20-30 nmol/L serum) subgroup, 8 studies showed that when vitamin D serum is < 20-30 nmol/L there is a 53% greater risk for depression (OR = 1.53, 95% CI 1.10 - 2.13, P = 0.01). The Cut-off (< 30-50 nmol/L serum) subgroup contained 22 studies and they showed that when vitamin D serum is < 30-50 nmol/L there is a 16% greater risk for depression (OR = 1.16, 95% CI 1.06–1.24, P = 0.0009). The Highest vs Lowest ‘tile (serum) subgroup only contained 1 study, but it showed that when comparing the highest to the lowest tertile of vitamin D serum (with the highest tertile serving as the reference value = 1), there is an 96% greater risk for depression (OR = 1.96, 95% CI 1.10–3.49, P = 0.02). A random effects model was used for this analysis as heterogeneity was assumed ( $Tau^2 = 0.02$ ;  $Chi^2 = 218.99$ , df = 31, (P = < 0.00001),  $I^2 = 86\%$ ). There was also considerable asymmetry present in the funnel plot (**Figure 5.0B**), the Egger’s regression and Begg & Mazumdar’s rank correlation test found significant publication bias across the studies in the analysis (Egger’s regression; t test = 7.32, P = 0.0001), (Begg & Mazumdar’s rank correlation test;  $\Delta x-y = 189$ , Kendall’s Tau-a = 0.38, z-value = 3.06, P = 0.001).

## **Figure 5.1**

11 studies were analysed that reported reverse odds ratio (rOR) values for vitamin D sufficiency and reduced depression risk (**Figure 5.1A**), the data was stratified into three categorical sub-groups for the analysis. The Lowest vs Highest ‘tile (serum) subgroup contained 4 studies, they showed that when comparing the lowest to highest ‘tile of vitamin D serum (with the lowest ‘tile serving as the reference value = 1), there is a 26% reduction in risk for depression (OR = 0.74, 95% CI 0.39–1.39, P = 0.35). The Lowest vs Highest ‘tile (intake) subgroup, only contained 1 study, but it showed than when comparing lowest to the highest tertile of vitamin D intake (with the lowest ‘tile serving as the reference value = 1), there is a 48% reduction in risk for depression (OR = 0.52, 95% CI 0.30–0.90, P = 0.02). Within the Cut-off (> 47.25 nmol/L serum) subgroup, 6 studies showed that when vitamin D serum is > 47.25 nmol, there is a 33% reduction in depression risk (OR = 0.67, 95% CI 0.48 – 0.94, P = 0.02). A random effects model was used for this analysis as heterogeneity was assumed ( $Tau^2 = 0.15$ ;  $Chi^2 = 48.75$ , df = 12, (P = < 0.00001),  $I^2 = 75\%$ ). There was no apparent asymmetry present in the funnel plot (**Figure 5.1B**), the Egger’s regression and Begg & Mazumdar’s rank correlation test found no significant publication bias across the studies in the analysis (Egger’s regression; t test = -0.78, P = 0.455), (Begg & Mazumdar’s rank correlation test;  $\Delta x-y = -14$ , Kendall’s Tau-a = -0.21, z-value = -0.96, P = 0.169).

## **Figure 5.2**

3 studies were analysed that reported hazard ratio values for vitamin D deficiency and depression risk (**Figure 5.2**), the data was stratified into two categorical sub-groups for the analysis. The Cut-off (< 37.5 - 50 nmol/L serum) subgroup, 2 studies showed that when vitamin D serum is < 37.5 - 50 nmol/L there is a 97% greater risk for depression (OR = 1.97, 95% CI 1.41 - 2.77, P = < 0.0001). Within the Cut-off (< 5 ug/d intake) subgroup, 1 study showed that when vitamin D intake is < 5 ug/d there is a 13% reduction in risk for depression (OR = 0.87, 95% CI 0.60 – 1.26, P = 0.46). A random effects model was used for this analysis as heterogeneity was assumed ( $Tau^2 = 0.21$ ;  $Chi^2 = 12.05$ , df = 3, (P = 0.007),  $I^2 = 75\%$ ). Asymmetry and publication bias were not measured in this dataset as the number of studies was < 10.

### **Figure 5.3**

9 studies were analysed that reported correlation coefficients for vitamin D level and depression severity (**Figure 5.3**), the data was not stratified into subgroups. A random effects model was used for this analysis as heterogeneity was assumed ( $Q$ -value = 58.898,  $df(Q) = 8$ , ( $P = < 0.0001$ ),  $I^2 = 86.4\%$ ). Asymmetry and publication bias were not measured in this dataset as the number of studies was  $< 10$ .

## **Appendix 3.2 – Vitamin B12**

### **Figure 6.0**

7 studies were analysed that reported odds ratio values for vitamin B12 deficiency and depression risk (**Figure 6.0A**), the data was stratified into two categorical sub-groups for the analysis. Within the Cut-off ( $< 140 - 300$  pmol/L serum) subgroup, 5 studies showed that when vitamin B12 serum is  $< 140 - 300$  pmol/L there is a 41% greater risk for depression ( $OR = 1.41$ , 95% CI 0.93 - 2.16,  $P = 0.11$ ). The Cut-off ( $< 3.3$  ug/1000kcal/d intake) subgroup contained 1 study and they showed that when vitamin D intake is  $< 3.3$  ug/1000kcal/d there is a 79% greater risk for depression ( $OR = 1.79$ , 95% CI 0.70 – 4.58,  $P = 0.22$ ). A random effects model was used for this analysis as heterogeneity was assumed ( $Tau^2 = 0.15$ ;  $Chi^2 = 14.63$ ,  $df = 7$ , ( $P = 0.04$ ),  $I^2 = 52\%$ ). Asymmetry and publication bias were not measured in this dataset as the number of studies was  $< 10$ .

### **Figure 6.1**

5 studies were analysed that reported reverse odds ratio (rOR) values for vitamin B12 sufficiency and reduced depression risk (**Figure 6.1**), the data was stratified into two categorical sub-groups for the analysis. The Lowest vs Highest ‘tile (intake) subgroup contained 4 studies, they showed that when comparing the lowest to highest ‘tile of vitamin B12 intake (with the lowest ‘tile serving as the reference value = 1), there is a 19% reduction in risk for depression ( $OR = 0.81$ , 95% CI 0.67 – 0.98,  $P = 0.03$ ). Within the Cut-off (serum) subgroup, 2 studies showed that when cobalamin and holoTC serum levels are sufficient, there is a 66% reduction in depression risk ( $OR = 0.44$ , 95% CI 0.25 – 0.76,  $P = 0.004$ ). A fixed effects model was used for this analysis as heterogeneity was not

assumed ( $\text{Chi}^2 = 10.39$ ,  $\text{df} = 7$ ,  $(P = 0.17)$ ,  $I^2 = 33\%$ ). Asymmetry and publication bias were not measured in this dataset as the number of studies was  $< 10$ .

### Figure 6.2

4 studies were analysed that reported correlation coefficients for vitamin B12 level and depression severity (Figure 6.2), the data was stratified into three categorical subgroups. The B12 intake subgroup contained 1 study, they showed a very weak negative correlation between vitamin B12 intake and depression severity ( $r = -0.030$ , 95% CI - 0.228 to 0.170,  $P = 0.771$ ). The B12 serum subgroup contained 5 studies and they showed a weak to moderate negative correlation between cobalamin serum and depression severity ( $r = -0.308$ , 95% CI - 0.562 to - 0.001,  $P = 0.049$ ). The HoloTC serum subgroup contained 1 study and they showed a weak negative correlation between HoloTC serum and depression severity ( $r = -0.208$ , 95% CI - 0.293 to - 0.119,  $P = 0.0001$ ). A random effects model was used for this analysis as heterogeneity was assumed ( $Q$ -value = 89.096,  $\text{df}(Q) = 6$ ,  $(P = < 0.0001)$ ,  $I^2 = 93.2\%$ ). Asymmetry and publication bias were not measured in this dataset as the number of studies was  $< 10$ .

### Appendix 3.3 – Zinc

#### Figure 7.0

5 studies were analysed that reported odds ratio values for zinc deficiency and depression risk (Figure 7.0), the data was stratified into two categorical sub-groups for the analysis. The Highest vs Lowest ‘tile (intake) subgroup contained 2 studies and it showed that when comparing the highest to the lowest quartile of zinc intake (with the highest quartile serving as the reference value = 1), there is an 39% greater risk for depression ( $\text{OR} = 1.39$ , 95% CI 1.08 – 1.78,  $P = 0.009$ ). Within the Cut-off (< adequate zinc intake) subgroup, 2 studies showed that when zinc intake is not adequate, there is a 2% reduced risk for depression ( $\text{OR} = 1.41$ , 95% CI 0.93 - 2.16,  $P = 0.11$ ). The Cut-off (< 11 umol/L serum) subgroup contained 1 study and they showed that when zinc serum is < 11 umol/L there is a 49% greater risk for depression ( $\text{OR} = 1.49$ , 95% CI 1.03 – 2.16,  $P = 0.04$ ). A random effects model was used for this analysis as heterogeneity was assumed ( $\text{Tau}^2 = 0.08$ ;  $\text{Chi}^2 = 15.59$ ,  $\text{df} = 5$ ,  $(P = 0.008)$ ,  $I^2 = 68\%$ ). Asymmetry and publication bias were not measured in this dataset as the number of studies was  $< 10$ .

### **Figure 7.1**

8 studies were analysed that reported reverse odds ratio (rOR) values for zinc sufficiency and reduced depression risk (**Figure 7.1A**), the data was stratified into two categorical sub-groups for the analysis. The Lowest vs Highest ‘tile (intake) subgroup contained 7 studies, they showed that when comparing the lowest to highest ‘tile of zinc intake (with the lowest ‘tile serving as the reference value = 1), there is a 33% reduction in risk for depression (OR = 0.67, 95% CI 0.58 – 1.78, P = < 0.00001). Within the Cut-off (zinc intake and categorical depression) subgroup, 1 study showed that zinc intake had a 48% reduction in categorical depression risk (OR = 0.52, 95% CI 0.31 – 0.87, P = 0.01). A fixed effects model was used for this analysis as heterogeneity was not assumed (Chi<sup>2</sup> = 7.4, df = 1, (P = 0.6), I<sup>2</sup> = 0%). There was no apparent asymmetry present in the funnel plot (**Figure 7.1B**), the Egger’s regression and Begg & Mazumdar’s rank correlation test found no significant publication bias across the studies in the analysis (Egger’s regression; t test = -0.21, P = 0.835), (Begg & Mazumdar’s rank correlation test; Δx-y = -2, Kendall’s Tau-a = -0.04, z-value = -0.18, P = 0.429).

### **Figure 7.2**

6 studies were analysed that reported correlation coefficients for zinc level and depression severity (**Figure 7.2**), the data was not stratified into categorical subgroups. A random effects model was used for this analysis as heterogeneity was assumed (Q-value = 49.153, df(Q) = 5, (P = < 0.0001), I<sup>2</sup> = 89.2%). Asymmetry and publication bias were not measured in this dataset as the number of studies was < 10.

## **Appendix 3.4 – Iron**

### **Figure 8.0**

7 studies were analysed that reported odds ratio values for iron deficiency and depression risk (**Figure 8.0**), the data was stratified into four categorical sub-groups for the analysis. The Highest vs Lowest ‘tile (intake) subgroup contained 1 studies and it showed that when comparing the highest to the lowest quartile of iron intake (with the highest quartile serving as the reference value = 1), there is an 67% greater risk for depression (OR = 1.67, 95% CI 0.66 – 4.23, P = 0.28). The Highest vs Lowest ‘tile (serum

ferritin) subgroup contained 1 studies and it showed that when comparing the highest to the lowest quartile of serum ferritin (with the highest quartile serving as the reference value = 1), there is an 126% greater risk for depression (OR = 2.26, 95% CI 0.87 – 5.83, P = 0.09). Within the Cut-off (< adequate iron intake) subgroup, 1 study showed that when iron intake is not adequate, there is a 45% increased risk for depression (OR = 1.45, 95% CI 1.23 – 1.71, P = < 0.00001). The Cut-off (< 12 - 45 ug/L serum ferritin) subgroup contained 4 studies and they showed that when serum ferritin is < 12 - 45 ug/L, there is a 30% greater risk for depression (OR = 1.30, 95% CI 0.94 – 1.82, P = 0.12). A random effects model was used for this analysis as heterogeneity was assumed ( $Tau^2 = 0.04$ ;  $Chi^2 = 19.27$ , df = 8, (P = 0.01),  $I^2 = 58\%$ ). Asymmetry and publication bias were not measured in this dataset as the number of studies was < 10.

### **Figure 8.1**

5 studies were analysed that reported reverse odds ratio values for iron sufficiency and reduced depression risk (**Figure 8.1**), the data was stratified into two categorical subgroups for the analysis. The Lowest vs Highest ‘tile (intake) subgroup contained 4 studies, they showed that when comparing the lowest to highest ‘tile of iron intake (with the lowest ‘tile serving as the reference value = 1), there is a 19% reduction in risk for depression (OR = 0.81, 95% CI 0.72 – 0.90, P = < 0.0001). The Lowest vs Highest ‘tile (serum ferritin) subgroup contained 1 study, they showed that when comparing the lowest to highest ‘tile of serum ferritin (with the lowest ‘tile serving as the reference value = 1), there is a 2% increase in risk for depression (OR = 1.02, 95% CI 0.81 – 1.28, P = 0.87). A fixed effects model was used for this analysis as heterogeneity was not assumed ( $Chi^2 = 7.13$ , df = 5, (P = 0.21),  $I^2 = 30\%$ ). Asymmetry and publication bias were not measured in this dataset as the number of studies was < 10.

### **Figure 8.2**

7 studies were analysed that reported correlation coefficients for zinc level and depression severity (**Figure 8.2**), the data was stratified into three categorical subgroups. The iron intake subgroup contained 3 studies and they showed a weak negative correlation between iron intake and depression severity ( $r = -0.153$ , 95% CI -0.416 to 0.135, P = 0.297). The serum ferritin subgroup contained 2 studies, they showed a weak negative correlation between serum ferritin and depression severity ( $r = -0.123$ , 95% CI

- 0.257 to 0.017,  $P = 0.085$ ). The serum iron subgroup contained 2 studies and they showed a very weak negative correlation between serum iron and depression severity ( $r = -0.059$ , 95% CI -0.371 to 0.265,  $P = 0.725$ ). A random effects model was used for this analysis as heterogeneity was assumed ( $Q$ -value = 19.666,  $df(Q) = 6$ , ( $P = 0.003$ ),  $I^2 = 69.5\%$ ). Asymmetry and publication bias were not measured in this dataset as the number of studies was < 10.

## Appendix 3.5 – Omega 3

### Figure 9.0

2 studies were analysed that reported odds ratio values for omega deficiency and depression risk (**Figure 9.0**), the data was stratified into three categorical sub-groups for the analysis. The Highest vs Lowest ‘tile (n-3 serum) subgroup contained 1 study and it showed that when comparing the highest to the lowest quartile of omega 3 serum (with the highest quartile serving as the reference value = 1), there is an 58% greater risk for depression ( $OR = 1.58$ , 95% CI 0.92 – 2.71,  $P = 0.10$ ). The Highest vs Lowest ‘tile (EPA intake) subgroup contained 1 study and it showed that when comparing the highest to the lowest quartile of EPA intake (with the highest quartile serving as the reference value = 1), there is an 31% greater risk for depression ( $OR = 1.31$ , 95% CI 0.64 – 2.68,  $P = 0.46$ ). The Highest vs Lowest ‘tile (DHA intake) subgroup contained 1 study and it showed that when comparing the highest to the lowest quartile of DHA intake (with the highest quartile serving as the reference value = 1), there is an 44% greater risk for depression ( $OR = 1.44$ , 95% CI 0.73 – 2.84,  $P = 0.29$ ). A fixed effects model was used for this analysis as heterogeneity was not assumed ( $\chi^2 = 0.17$ ,  $df = 2$ , ( $P = 0.92$ ),  $I^2 = 0\%$ ). Asymmetry and publication bias were not measured in this dataset as the number of studies was < 10.

### Figure 9.1

15 studies were analysed that reported reverse odds ratio values for omega 3 sufficiency and reduced depression risk (**Figure 9.1A**), the data was stratified into four categorical sub-groups for the analysis. The Lowest vs Highest ‘tile (n-3 intake) subgroup contained 11 studies, they showed that when comparing the lowest to highest ‘tile of omega 3 intake (with the lowest ‘tile serving as the reference value = 1), there is a 21% reduction in risk for depression ( $OR = 0.79$ , 95% CI 0.71 – 0.88,  $P = < 0.0001$ ). Within

Lowest vs Highest ‘tile (n-3 serum) subgroup, 4 studies showed that when comparing the lowest to highest ‘tile of omega 3 serum (with the lowest ‘tile serving as the reference value = 1), there is a 21% reduction in risk for depression (OR = 0.79, 95% CI 0.61 – 1.02, P = 0.08). The Lowest vs Highest ‘tile (EPA serum) subgroup contained 1 study, they showed that when comparing the lowest to highest ‘tile of EPA serum (with the lowest ‘tile serving as the reference value = 1), there is a 7% increase in risk for depression (OR = 1.07, 95% CI 0.42 – 2.73, P = 0.89). Within Lowest vs Highest ‘tile (DHA serum) subgroup, 1 study showed that when comparing the lowest to highest ‘tile of DHA serum (with the lowest ‘tile serving as the reference value = 1), there is a 64% reduction in risk for depression (OR = 0.36, 95% CI 0.13 – 0.98, P = 0.05). A fixed effects model was used for this analysis as heterogeneity was not assumed ( $\text{Chi}^2 = 24$ , df = 17, (P = 12),  $I^2 = 29\%$ ). There was no apparent asymmetry present in the funnel plot (**Figure 9.1B**) and the Egger’s regression and Begg & Mazumdar’s rank correlation test found no significant publication bias across the studies in the analysis (Egger’s regression; t test = -1.42, P = 0.17), (Begg & Mazumdar’s rank correlation test;  $\Delta x-y = -17.00$ , Kendall’s Tau-a = -0.11, z-value = -0.64, P = 0.26).

## **Figure 9.2**

9 studies were analysed that reported continuous odds ratio values for omega deficiency and depression risk (**Figure 9.2A**), the data was stratified into four categorical sub-groups for the analysis. The Continuous (n-3 intake) subgroup contained 3 studies and it showed that with every incremental decrease omega 3 intake, there is no effect to the risk for depression (OR = 1.00, 95% CI 1.00 – 1.00, P = 0.88). Within the Continuous (n-3 serum) subgroup, 4 studies showed that with every incremental decrease omega 3 serum, there is a 4% reduction in risk for depression (OR = 0.96, 95% CI 0.90 – 1.03, P = 0.28). Continuous (EPA serum) subgroup contained 4 studies and it showed that with every incremental decrease EPA serum, there is a 30% reduction in risk for depression (OR = 0.70, 95% CI 0.55 – 0.88, P = 0.002). Within the Continuous (DHA serum) subgroup, 3 studies showed that with every incremental decrease DHA serum, there is a 15% reduction in risk for depression (OR = 0.85, 95% CI 0.74 – 0.97, P = 0.02). A random effects model was used for this analysis as heterogeneity was assumed ( $\text{Tau}^2 = 0.00$ ;  $\text{Chi}^2 = 34.66$ , df = 15, (P = 0.003),  $I^2 = 57\%$ ). There was also evidence of some asymmetry present in the funnel plot (**Figure 9.2B**), although the Egger’s regression and Begg &

Mazumdar's rank correlation test found no significant publication bias across the studies in the analysis (Egger's regression;  $t$  test = - 2.08,  $P$  = 0.057), (Begg & Mazumdar's rank correlation test;  $\Delta x-y$  = - 8.00, Kendall's Tau-a = - 0.07,  $z$ -value = - 0.36,  $P$  = 0.359).

### Figure 9.3

10 studies were analysed that reported correlation coefficients for omega 3 and depression severity (**Figure 9.3A**), the data was stratified into four categorical subgroups. The n-3 intake subgroup contained 1 study and they showed a weak negative correlation between omega intake and depression severity ( $r$  = - 0.140, 95% CI - 0.177 to - 0.103,  $P$  = 0.0001). The n-3 serum subgroup contained 5 studies and they showed a weak negative correlation between omega intake and depression severity ( $r$  = - 0.164, 95% CI - 0.254 to - 0.071,  $P$  = 0.001). The EPA serum subgroup contained 3 studies and they showed a weak negative correlation between omega intake and depression severity ( $r$  = - 0.013, 95% CI - 0.060 to 0.033,  $P$  = 0.572). The DHA serum subgroup contained 5 studies and they showed a weak negative correlation between omega intake and depression severity ( $r$  = - 0.107, 95% CI - 0.193 to - 0.019,  $P$  = 0.017). A random effects model was used for this analysis as heterogeneity was assumed ( $Q$ -value = 45.707,  $df(Q)$  = 17, ( $P$  = < 0.0001),  $I^2$  = 62%). There was considerable asymmetry present in the funnel plot (**Figure 9.3B**), the Egger's regression and Begg & Mazumdar's rank correlation test found significant publication bias across the studies in the analysis (Egger's regression;  $t$  test = -2.72,  $P$  = 0.02), (Begg & Mazumdar's rank correlation test;  $\Delta x-y$  = - 63, Kendall's Tau-a = - 0.41,  $z$ -value = 2.39,  $P$  = 0.017).

## **Appendix 4 – Software Applications**

### **Appendix 4.1 - Biorender**

Biorender was used to create many of the illustrative figures seen in this review (*BioRender*, 2020).

### **Appendix 4.2 - Lucid Chart**

Lucid Chart was used to create the flow diagram figures seen in this review (*Lucid Chart*, 2020).

### **Appendix 4.3 – Zotero**

Search results were compiled using a reference management software (Zotero: The Next Generation Research Tool, version: 5.0.85. Oct 2006; <http://www.zotero.org>).

### **Appendix 4.4 – Review Manager 5**

Statistical analyses, forest plots, funnel plots and heterogeneity for all non-correlative data (odds/hazard ratio) was calculated using Review Manager software (Review Manager (RevMan), version: 5.3. 2014).

### **Appendix 4.5 – Comprehensive Meta-Analysis**

Statistical analyses, forest plots and heterogeneity for correlative data (correlation coefficients) was calculated using Comprehensive Meta-Analysis software (Comprehensive Meta-Analysis Software (CMA), version: 3. 2013).

### **Appendix 4.6 – Meta-Essentials: Workbooks for meta-analysis**

Statistical tests for publication bias for all data and funnel plots for correlative data was performed and calculated using Meta-Essentials: Workbooks for meta-analysis (Suurmond et al., 2017).