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THE EFFECT OF NUTRITION ON MENTAL HEALTH: A FOCUS ON INFLAMMATORY MECHANISMS

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SUMMARY

Neuropsychiatric disorders are closely associated with a persistent low-grade inflammatory state. This suggests that the development of psychopathology is not only limited to the brain, but rather involves an additional systemic aspect, accounting for the large body of evidence demonstrating co-presentation of mental illness with chronic inflammatory conditions and metabolic syndromes. Studies have shown that inflammatory processes underlie the development of neuropsychiatric symptoms, with recent studies revealing not only correlative, but causative relationships between the immune system and psychopathology.

Lifestyle factors such as diet and exercise may influence psychopathology, and this may occur via a bidirectional relationship. Mental illness may prevent health-seeking behaviours such as failing to maintain a balanced diet, whilst adopting a 'healthy' diet rich in fruits, vegetables and fish alongside nutritional supplementation correlates with a reduction in psychiatric symptoms in patients. Obesity and the gut microbiome have proven to be further factors which play an important role in inflammatory signalling and the development of psychiatric symptoms. In a related paper we focus on the role of exercise (another significant lifestyle factor) on mental health (Venkatesh et al. 2020).

Lifestyle modifications which target diet and nutrition may prove therapeutically beneficial for many patients, especially in treatment-resistant subgroups. The current evidence base provides equivocal evidence, however future studies will prove significant, as this is a highly attractive therapeutic avenue, due to its cost efficacy, low side effect profile and preventative potential. By promoting lifestyle changes and addressing the limitations and barriers to adoption, these therapies may prove revolutionary for mental health conditions.

Key words: *diet – nutrition – inflammation - mental health - neuropsychiatric disorders*

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INTRODUCTION

Neuropsychiatric disorders are closely associated with a persistent systemic low-grade inflammatory state, suggesting that the development of psychopathology is not only limited to the brain, but also comprises a systemic aspect, accounting for the large body of evidence demonstrating the concomitant presentation of mental illness with chronic inflammatory conditions and metabolic syndromes. This co-presentation may provide an evolutionary advantage as depressive symptoms may co-exist with social withdrawal and low energy, creating the conditions to recover and rehabilitate. However, with prolonged mental illness and chronic inflammatory states, this can instead prove to be crippling for many patients (Rosenblat et al. 2014).

Studies in both animal and human models have shown that inflammatory processes underlie the development of neuropsychiatric symptoms. Inflammation and oxidative stress can act in synchrony to further perpetuate the inflammatory processes. In situations of chronic disease, this process may continue in the brain, an organ particularly vulnerable to tissue injury, further causing symptoms of neuropsychiatric disease (Ng et al. 2008). Recent studies have revealed not only correlative, but causative relationships between the immune system and psychopathology.

The modulation of lifestyle factors such as diet and exercise can influence psychopathology, and this may occur via a bidirectional relationship. Mental illness may prevent health-seeking behaviours such as failing to maintain a balanced diet, whilst adopting a 'healthy' diet rich in fruits, vegetables and fish alongside nutritional supplementation correlates with a reduction in psychiatric symptoms in patients. It is recognised that obesity is another significant factor correlated with the development of neuropsychiatric symptoms and in part due to the effect of dysregulated insulin signalling and downstream inflammation. Studies in rodent models have further found the gut-microbiota-brain to play an important role in inflammatory signalling between the enteric and central nervous system, further elucidating a potential association between nutrition and psychopathology.

Lifestyle modifications which target diet and nutrition may prove therapeutically beneficial for many patients, especially in treatment-resistant subgroups. The current evidence base provides equivocal evidence, however future studies will prove highly significant, as this is a highly desirable therapeutic avenue, due to its cost efficacy, low side effect profile and preventative potential. By promoting healthy dietary lifestyle changes and addressing the limitations and barriers to adoption, these therapies may prove revolutionary for mental health conditions.

INFLAMMATION IS A CENTRAL UNDERLYING DRIVER PROCESS FOR PSYCHOPATHOLOGY

Inflammatory processes have been shown to underly psychopathology. This has been shown through experimental induction of inflammation in healthy volunteers preceding development of psychiatric disturbances, and also the co-occurrence of systemic chronic inflammatory conditions with cognitive impairment that can greatly detriments patients' quality of life (Borsini et al. 2017; Drevets et al. 2008). Genetic studies have added further weight to this association between the immune system and mental health (Sekar et al. 2016). Longitudinal research has demonstrated that elevated Interleukin 6 (IL-6) in childhood may predispose to depression and psychosis later in a dose-dependent fashion (Khandaker et al. 2014). However, whether the inflammation is a cause or consequence of psychopathology is yet to be determined. The Insight study aims to evaluate the therapeutic benefits of targeting IL-6 in patients with depression and evidence of inflammation and this randomised controlled trial is likely to provide further evidence for the field (Khandaker et al. 2018).

Inflammatory pathways such as the kynurenine pathway have been implicated in contributing to chronic background inflammation by reducing the availability of tryptophan and by encouraging the production of free radical and potent neurotoxins (O'Connor et al. 2009, Vancassel et al. 2018). Studies have shown that targeting these inflammatory pathways may prove especially useful in therapeutically intractable subgroups that have a background level of inflammation (Mondelli et al. 2015). In a related paper, we discuss these concepts in further detail (Venkatesh et al. 2020) (Figure 1).

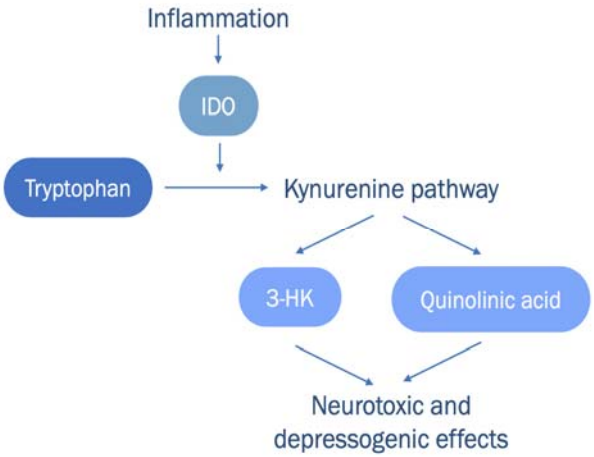

Figure 1. Inflammation shifts the metabolism of tryptophan to the kynurenine pathway. This increases the production of 3-hydroxykynurenine (3-HK) and quinolinic acid (an NMDA receptor antagonist) which may contribute to neuropsychiatric disorders (Figure adapted from O'Connor et al. (2009) and Vancassel et al. (2018))

NUTRITION PLAYS A KEY ROLE IN PSYCHOPATHOLOGY VIA INFLAMMATORY MECHANISMS

The bidirectional relationship of nutrition with mental health conditions

Individuals with a poor diet are at a greater risk of developing psychopathology. A large body of evidence supports this association particularly with regards to one of the most common mental health conditions, depression. A meta-analysis showed that adherence to a 'healthy' diet was significantly associated with a lower risk of developing depressive symptoms (Molendijk et al. 2018). A similar study determined a significant relationship between increased saturated fatty acid (SFA) intake and the risk of developing depression later in life (Sánchez-Villegas et al. 2011). One group employed a pseudo-panel approach to assessing whether obesity causes depression and found that an increased BMI was significantly associated with increased frequency of depressive symptoms (Ha et al. 2017). A meta-analysis assessing the longitudinal relationships between depression and obesity found that not only did obesity predispose to depression by 55% but also that the opposite was true and depressed individuals were at a 55% greater risk of developing obesity (Luppino et al. 2010). This suggests the converse relationship, that mental health illnesses can affect the dietary intake and patterns of an individual. Further evidence corroborates this as one prospective cohort study showed that the atypical form of depression is a significant predictor of obesity (Lasserre et al. 2014). This evidence strongly points towards a bidirectional relationship with mental health conditions.

There is now evidence to suggest that these pathways may be due to the direct effect nutrition has on downstream inflammatory pathways which lead to the development of psychopathology. A comprehensive review of the literature reveals three main aspects of nutrition that contribute to pro- or anti-inflammatory states. The first is the variation in dietary patterns and the concept that diets may be rich in pro- or anti-inflammatory foods. These differing nutritional constituents may have a direct effect on the level of chronic systemic inflammation in the body. Secondly, it may be that the dietary pattern itself is not significant, but rather the overall surplus of food intake combined with lack of exercise creates a positive energy balance leading to obesity which itself is inflammatory. Lastly, emerging research into the gut-microbiota-brain axis suggests that the early gut microbiome may affect mental health, primarily through its effects on brain function and development at an early age.

The evidence for anti-inflammatory mechanisms of nutritional variation in mental health

Dietary patterns

Mediterranean-style diets have been shown to be protective in the development of mental disorders whereas

Western diets which are typically much richer in (SFAs) and refined sugars may have the opposite effect. A meta-analysis conducted by Lai et al. showed that a diet which is high in fruit, vegetables, fish and whole grains reduced the odds of developing depression (Lai et al. 2014). Furthermore, there is a large body of evidence which confirms that this pattern of dietary intake is associated with reduced all-cause mortality. The anti-inflammatory nature of these foods may be the linking factor by which there is reduced prevalence of mental health conditions. Conversely, the high SFAs have a largely pro-inflammatory effect which may influence the underlying pathology through various mechanisms.

Diets rich in pro-inflammatory foods such as SFAs may lead to the development of psychiatric symptoms. Animal models suggest that these effects are mediated through elevated levels of cytokines which result in downstream low-grade inflammation. Rats fed a high fat diet (60%) for 16 weeks exhibited anxiety and anhedonic behaviour (Dutheil et al. 2016). Researchers found that this was accompanied by increased levels of cytokines, primarily IL-1β, IL-6 and TNF-α in the hippocampus – a structure which is intimately involved in learning, memory and the target of many antidepressants. Similarly, abnormalities and alterations in the levels of inflammatory cytokines has been well established in patients with schizophrenia and these changes are more distinct in treatment-resistant patients. Moreover, a higher ratio of omega-6 to omega-3 intake, which is a key feature of Western diets, has been associated with systemic inflammatory conditions such as cardiovascular disease and cancer, whereas a low ratio has suppressive effects on inflammation (Simopoulos 2002).

Neuroinflammation may also be affected by foods with anti-inflammatory properties such as polyunsaturated fatty acids (PUFAs). PUFAs are an integral part of the neuronal cell membrane, with both anti-inflammatory and anti-apoptotic properties. The literature suggests two main omega-3 PUFAs of note, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), that have long been associated with cardiovascular health and recent evidence suggests they may hold some significance in mental health too. Indeed, McNamara et al. conducted post-mortem analyses of patients with depression and found that there was a deficit of DHA in the orbitofrontal cortex of these patients (McNamara et al. 2007). A further study assessed whether these effects could be reversed by supplementation of the EPA (Mocking et al. 2016), which found a beneficial effect comparable to that of antidepressant administration.

Vitamin D has also been identified as an anti-inflammatory nutrient. Low levels of Vitamin D3 have been associated with depression and attention deficit hyperactivity disorder (ADHD). A randomised control trial assessed the outcomes of supplementing Vitamin D3 in clozapine-treated schizophrenic patients (Krivoy et al. 2017). Findings showed that although there was no improvement in the positive symptoms (psychosis), supplementation was associated with enhanced cognitive ability. Despite this positive response, the evidence base for Vitamin D3 supplementation in mental health conditions is poor and requires further investigation.

Obesity

Obesity is a highly prevalent condition affecting our population today and is defined as a BMI of greater than 30. It is a multifactorial disease which draws on both genetic and environmental factors and is strongly associated with increased morbidity and mortality. A bidirectional relationship between obesity and psychiatric disorders is evident, particularly with disorders of mood and cognition. A meta-analysis conducted by Luppino et al. found conclusive evidence that there is a strong reciprocal relationship between obesity and depression and that having one condition significantly predisposes to developing the other (Luppino et al. 2010).

The development of dementia is well known to be linked to inflammatory risk factors such as obesity and other metabolic syndromes such as type 2 diabetes mellitus, insulin resistance and hypertension (de la Torre 2013). Moreover, a 27-year longitudinal population-based study illustrated that obesity in middle-age correlated with a 74% significantly increased risk of developing dementia in later life (Whitmer et al. 2005). This study not only suggests that obesity is correlated with dementia, but that this relationship may, in fact, be highly preventable. Alzheimer's dementia is a subtype of dementia which is characterised by the production of Aβ amyloid plaques in the brain and research into the role of inflammation in Alzheimer's dementia found that obese patients with dementia had increased systemic amyloid levels in blood plasma which was reduced with active weight loss (Jahangiri et al. 2013). Another study revealed enhanced permeability of the blood-brain barrier in individuals who were overweight or obese in middle-age (Gustafson et al. 2007).

There is growing evidence that dysregulated insulin signalling is an important pathway by which metabolic conditions such as obesity exert their inflammatory effects on the brain. It is understood that obesity may lead to systemic insulin resistance which will in turn result in reduced insulin signalling in the brain. The physiological effects of this will include alterations in cerebral glucose metabolism but this has also been associated with increased levels of monoamine oxidases (MAO) and enhanced dopamine clearance. As illustrated by the monoamine hypothesis of depression and the dopamine hypothesis of schizophrenia, this activity is negatively correlated with psychiatric symptoms. In mice, this was investigated using a brain-specific knockout of the insulin receptor and it was shown to lead to anxiety and depressive behaviours (Kleinridders et al. 2015). Further investigation showed that this behaviour was in fact allayed by administration of MAO inhibitors.

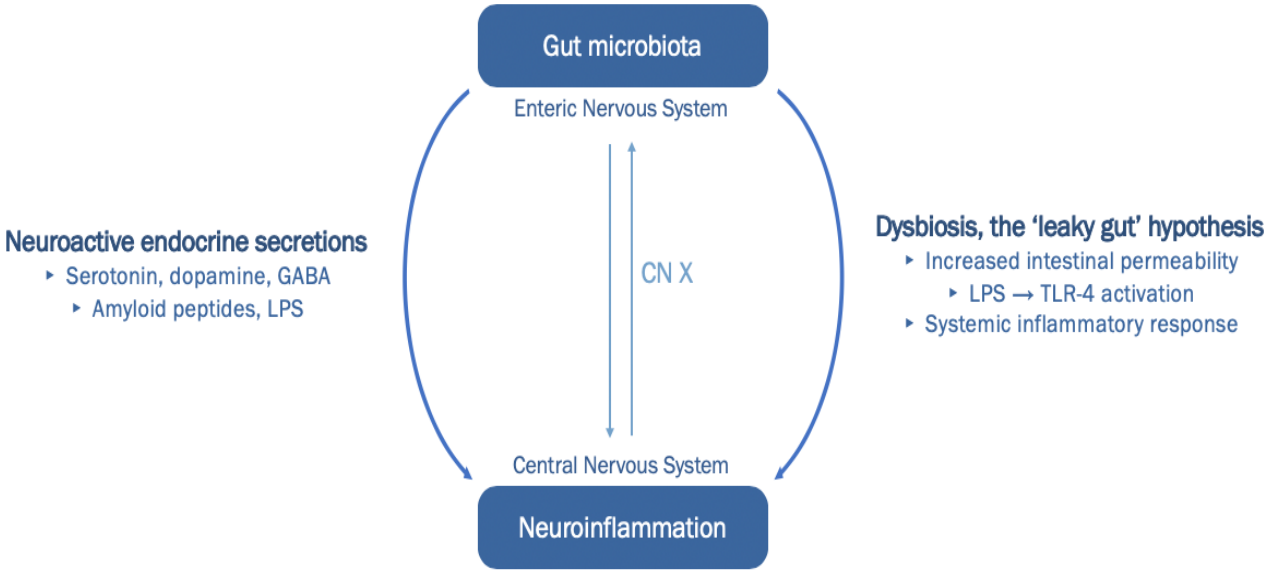

Figure 2. The gut-microbiota-brain axis is the communication pathway by which the enteric nervous system can communicate with the central nervous system by means of the vagus nerve (CN X). The gut microbiota may be able to influence neuroinflammation by two hypotheses: (i) neuroactive endocrine secretions, (ii) dysbiosis, or the 'leaky gut hypothesis; and thereby contribute to neuropsychiatric disease

It is worth mentioning that obesity will have a direct effect on mental health due to social and cultural factors. In the western world, low BMI is seen as desirable attribute and thus individuals who are obese are more likely to suffer from low self-esteem and body dysmorphic disorders, which is conducive to the development of psychiatric disorders, particularly mood disorders.

Psychiatric disorders can also predispose to the development of obesity and in fact one study showed that depressed patients have a 58% increased chance of becoming obese (Luppino et al. 2010). This risk relationship was also significantly greater than the chance of becoming overweight, thus suggesting a dose-dependent relationship between depression and BMI. The inherent pathology of mental health conditions such as depression involves changes in appetite. It has been shown that atypical depression in particular is associated with increased appetite and subsequent increase in bodyweight. Other symptoms such as low mood and energy in depression, or avolition in schizophrenia, often lead to individuals adopting an unhealthy lifestyle which may involve overeating or lack of regular exercise. There is also evidence that psychiatric conditions may have a causal link with obesity through neuroendocrine pathways and long-term activation of the HPA axis. This can involve enhanced levels of cortisol and insulin which can lead to insulin resistance and subsequent dysregulated insulin signalling. Furthermore, it is important to note that weight gain is often a side effect of many commonly prescribed psychiatric drugs. It is thought that this is primarily due to the effects of medications interacting with the central appetite and feeding centres in the brain.

Gut microbiota

The gut microbiota refers to the community of bacteria that inhabit the gut environment and the genetic makeup is referred to as the gut microbiome. It has been determined that this will vary with age, gender and other environmental factors and in human populations, differing diets lead to differences in the gut microbiome. It is theorised that the composition of the early gut microbiome may affect adult behaviour, in terms of the development of neuropsychiatric symptoms, primarily through the effects on early-life brain function and development. This is thought to stem from enteric nervous system signalling to the central nervous system (CNS) through the vagus nerve: a communication pathway known as the gut-microbiota-brain axis (Figure 2).

Our understanding of the workings of this axis comes chiefly from rodent models. Feeding high-fat diets to mice for 8 weeks induced a depressed phenotype in these animals which was accompanied by decreased population of Bacteroidetes in the gut (Hassan et al. 2019). A similar study showed that simply transplanting the faecal microbiota from depressed human patients into mice induced anhedonic and anxiety-like behaviours (Zheng et al. 2016). These studies strongly suggest that there is an association between the gut microbiome and psychiatric symptoms. Another group assessed whether ingestion of the probiotic bacteria Lactobacillus by mice would affect their behaviour (Bravo et al. 2011). The study showed anxiolytic and antidepressive effects of this particular probiotic, but also that these effects did not occur in vagotomised mice.

The gut is known to secrete neuroactive compounds such as serotonin, dopamine and GABA. 'Chemical im-

balances' in these substances have been implicated in the pathogenesis of mood disorders and schizophrenia and thus it is thought that secretion allows for increased bioavailability in the CNS which may contribute to alterations in levels of these compounds. Similarly, secretions of potentially harmful substances such as amyloid peptides and lipopolysaccharides (LPS) are thought to increase the permeability of the blood brain barrier (BBB) and contribute to some degree of neuroinflammation.

Another theory as to how the gut induces an inflammatory state is illustrated by the 'leaky gut' hypothesis which states that alterations to the composition of gut microbiota, 'dysbiosis', may result in the development of psychiatric disorders by inducing an immune response which leads to low-grade inflammation. It has emerged this dysbiotic state and the production of potential pathogens leads to an increased permeability of the intestinal wall which allows for leakage of substances such as LPS into the bloodstream. LPS acts upon toll-like receptor (TLR) 4 to induce a systemic inflammatory response. TLR-4 activation has been implicated in many other metabolic inflammatory conditions such as increased dietary fat intake, obesity and dysregulated insulin signalling.

Therapeutic implications, limitations and barriers to adoption

Current management of psychiatric disorders primarily consists of pharmacological and psychological therapies (i.e. cognitive behavioural therapy). However, these interventions are only effective in treating around half of the disease burden with large number of patients being treatment-resistant. From the evidence as presented above, diet and nutrition play a highly significant role in the development of mental health conditions. Further investigation to enhance our understanding may allow for careful manipulation of these biochemical and physiological systems to provide therapeutic benefit to patients.

The novel field of nutritional psychiatry harnesses our current understanding of diet and its role in mental health with a view to managing and treating some of these conditions. A comprehensive literature search to ascertain effectiveness of using diet as treatment reveals equivocal data. One randomised control trial analysed the benefits of implementing a modified Mediterranean diet in patients with depression (Jacka et al. 2017). Over the course of twelve weeks, individuals underwent weekly diet and nutritional counselling. Their results show a significant improvement in depression scores of the Mediterranean diet cohort (using the Montgomery-Åsberg Depression Rating Scale) compared to the control group and indeed a significant number of individuals achieved remission. Moreover, a further meta-analysis revealed that adherence to a Mediterranean diet resulted in low depression scores in a dose-response manner (Molendijk et al. 2018). Similarly adopting a diet with a low-inflammatory index may be of particular significance as it may provide a reduction in the low-grade chronic inflammation. Ketogenic diets are high-fat, low-carbohydrate diets which have an anti-inflammatory effect. This diet has been used in the treatment of neuropsychiatric conditions such as epilepsy and Alzheimer's disease and has shown to result in improved cognition (Brietzke et al. 2018). Further approaches in nutritional psychiatry include nutraceutical interventions which involves targeting specific nutritional alterations known to be involved in inflammation and psychopathology. As mentioned earlier PUFAs have been shown to have a beneficial effect in depression as well as other conditions such as ADHD and Alzheimer's disease. Recent evidence suggests that simply supplementing either DHA or EPA is insufficient for therapeutic benefit and rather the ratio of these substances is important. As illustrated by many clinical trials, it seems as though a dose with high EPA:DHA ratio is more effective in treating symptoms of depression, whereas doses of high DHA:EPA are more effective in improving cognition (Song et al. 2016).

Targeting the gut-microbiota-brain axis has been suggested by prebiotics (non-digestible food components such as complex carbs which are thought to nurture and cultivate enteric flora as well as by the ingestion of probiotic microorganisms in foods such as natural bio-yoghurt. The latter may be of particular importance in older patients as it is known that the population of gut microbiota decreases with age.

The evidence for the effectiveness of using nutrition in treating disorders is promising but inconclusive and there are many more questions to be answered. Of the studies conducted, many are relatively short-term, often under 6 months, and thus the impact of a long-term dietary change remains unknown. Despite psychiatric disorders and variations in the gut microbiome having a significant genetic and environmental component, most of the research has been conducted in Western countries or with populations composed mainly of Caucasian individuals. Similarly, even though nutritional interventions are likely to have been used in treatment-resistant subgroups of patients, our understanding of the benefit of nutritional interventions in varying severity of mental illness is lacking. Another noteworthy point is that a modified diet may only be of benefit in specific psychiatric conditions. For example, a systematic review assessing the effectiveness of nutritional supplementation in children with autism spectrum disorder revealed inconclusive evidence for beneficial use (Sathe et al. 2017). However, it was noted that not surprisingly there is often a very low side-effect profile associated with nutritional therapies.

In the future, with greater understanding of nutritional psychiatry and its effectiveness in treating neuropsychiatric disorders, it is hoped that 'healthy' dietary strategies will be adopted by patients. A scoping review analysing the barriers to 'healthy eating' in young adults found the key barriers to include, relative indifference of

men to health-conscious behaviours, unhealthy diets adopted by friends and family as well as the financial and time aspects of purchasing and preparing foods (Munt et al. 2017).

With the increasing prevalence of mental health conditions, it is likely that public health strategies will be in important aspect of implementing beneficial dietary changes through routes such as education for school children and governmental policy changes affecting food growers and manufacturers. Public health interventions such as these may have a great impact in increasing awareness of the bidirectional relationship between nutrition and mental health as well as potentially preventing the development of mental health and inflammatory conditions early in life.

CONCLUSIONS AND FUTURE DIRECTIONS

The evidence presented suggests that inflammation is indeed a significant factor affecting psychopathology and that modulating lifestyle factors such as nutrition and exercise (Venkatesh et al. 2020) could prove therapeutically beneficial for many patients. However, future research is necessary to better characterise the relationship between inflammation, nutrition and psychopathology as well as to assess the potential therapeutic benefits. In particular, long-term studies to determine the impact of particular nutritional interventions on psychopathology are needed and this may pave the way to implementing personalised lifestyle prescriptions with regards to nutrition.

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Contribution of individual authors:

Shantal D. Edirappuli & Ashwin Venkatesh carried out the literature search and wrote the paper.

Rashid Zaman conceived the idea of the paper, reviewed the literature and wrote the final draft.

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