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Review

Nutritional Psychiatry: Where to next?

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ABSTRACT

The nascent field of 'Nutritional Psychiatry' offers much promise for addressing the large disease burden associated with mental disorders. A consistent evidence base from the observational literature confirms that the quality of individuals' diets is related to their risk for common mental disorders, such as depression. This is the case across countries and age groups. Moreover, new intervention studies implementing dietary changes suggest promise for the prevention and treatment of depression. Concurrently, data point to the utility of selected nutraceuticals as adjunctive treatments for mental disorders and as monotherapies for conditions such as ADHD. Finally, new studies focused on understanding the biological pathways that mediate the observed relationships between diet, nutrition and mental health are pointing to the immune system, oxidative biology, brain plasticity and the microbiome-gut-brain axis as key targets for nutritional interventions. On the other hand, the field is currently limited by a lack of data and methodological issues such as heterogeneity, residual confounding, measurement error, and challenges in measuring and ensuring dietary adherence in intervention studies. Key challenges for the field are to now: replicate, refine and scale up promising clinical and population level dietary strategies; identify a clear set of biological pathways and targets that mediate the identified associations; conduct scientifically rigorous nutraceutical and 'psychobiotic' interventions that also examine predictors of treatment response; conduct observational and experimental studies in psychosis focused on dietary and related risk factors and treatments; and continue to advocate for policy change to improve the food environment at the population level.

Contents

1. Introduction

The field of 'Nutritional Psychiatry' is relatively new. While there had been a focus on the possible utility of omega-3 fatty acid and folate

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supplementation in mood disorders during previous decades (e.g. Su et al., 2003; Stoll et al., 1999; Taylor et al., 2004), as well as a number of observational studies focusing on the intake of single nutrients or foods (e.g. Morris et al., 2003; Hibbeln, 1998), the first studies to examine and establish a link between overall diet quality and the common mental disorders, depression and anxiety, were not published until the last decade (Jacka et al., 2010a; Akbaraly et al., 2009; Sanchez Villegas et al., 2009). Given that nutritional research has, justifiably, moved away from a focus on single foods or nutrients, cognisant of the fact that humans do not consume these in isolation (Hu, 2002) and that what we eat in excess is as important as what we do not eat enough of, these initial studies were influential and prompted a wider and more nuanced interest in this topic. We coined the term 'Nutritional Psychiatry' in order to promote a new field of research focused on developing a comprehensive, cohesive and scientifically rigorous evidence base to support a shift in thinking around the role of diet and nutrition in mental health (Sarris et al., 2015a,b). This narrative review and commentary provides an update on the field as it stands to date. It incorporates a discussion of the methodological issues and challenges, and identifies and discusses significant gaps in the literature with a view to informing the developing research agenda.

2. Observational Data in Humans

Since the initial studies the field has grown rapidly, with published observational studies originating in many different countries. In 2013–14, the evidence base was advanced enough for systematic reviews, and there were several published examining the evidence for a relationship between measures of diet quality and mental disorders, particularly depression. Two of these incorporated a meta-analysis. In one of these studies, 20 observational studies out of a possible 45 were considered methodologically rigorous to be included in the systematic review (Lai et al., 2013). Of these, 13 studies (four cohort and nine cross-sectional) had dietary exposures of sufficient similarity to be included in a meta-analysis. The results suggested that higher intakes of a 'healthy' diet (i.e. fruit, vegetables, fish, and whole grains) were associated with a reduced likelihood of depression (OR: 0.84; 95% CI: 0.76, 0.92). There was little evidence of publication bias. The trend for an association between consuming a 'western' (unhealthy) dietary pattern and depression (OR: 1.17; 95% CI: 0.97, 1.41) was not statistically significant in the meta-analysis, likely due to insufficient power as a result of the small number of included studies (Lai et al., 2013). The second meta-analysis, which included eight cohort studies and one case-control study, identified a dose-response association between high adherence (pooled effect estimate = 0.68, 95% CI: 0.54–0.86) and moderate adherence (pooled effect estimate 0.77, 95% CI: 0.62–0.95) to a Mediterranean diet and the risk for depression (Psaltopoulou et al., 2013). In common with the Lai et al. study (Lai et al., 2013), the study failed to find evidence of publication bias.

Concordant with these meta-analyses arising from adult data, there are now many cross-sectional and prospective observational studies reporting inverse associations between adherence to healthy dietary patterns and reduced risk for or likelihood of mental health disturbances in children and adolescents, while unhealthy dietary habits are positively associated with mental health problems. These relationships are, also in common with the adult data, usually observed to be independent of other key health behaviours, including physical activity and smoking, but are also independent of key environmental factors such as socioeconomic circumstances, family conflict, poor family functioning and social support, and adolescent dieting behaviours (Jacka et al., 2011, 2010b, 2013a). They are even documented in very young children, suggesting important opportunities for preventive interventions focused on prenatal and early life nutritional exposures (Jacka et al., 2013b; Pina-Camacho et al., 2015). A systematic review in 2014 confirmed an association between higher unhealthy diets and poor mental health in children and adolescents (O'Neil et al., 2014a), although this review now requires updating.

The findings of the studies included in these systematic reviews and meta-analyses are notable for their consistency across countries, cultures and age groups. At their core, the many and varied versions of a 'healthy' diet comprise higher intakes of nutrient-dense plant based foods and quality sources of protein. Thus, healthy diets in Spain, Norway, Japan, Australia, China, the UK, and the many other countries from which the published data are derived, are unified in being characterized by these dietary components, despite differing on culturally specific foods. On the other hand, 'western' diets are more homogeneous in their composition due to their common source (i.e. industry). What is also notable is that the relationship between both healthy and unhealthy diets and mental health are consistently independent of each other, indicating that each (i.e. low intakes of healthy, nutrient and fibre-dense foods and higher intakes of processed, sugary and fat-laden foods) are associated with poor mental health via potentially different, although overlapping, pathways. Finally, the extant evidence largely supports a causal relationship between diet quality and depression on the basis of the Bradford Hill criteria: that of consistency, with concordant findings and effect sizes across cultures, genders and age groups, with multiple methods used to assess diet quality and mental health; biological gradient; temporality; biological plausibility; and coherence of the findings with what we already know about the impact of habitual diet on noncommunicable disorders (Jacka et al., 2012a).

However, while many results from more recent population-based studies support the systematic reviews, there are negative findings. In particular, one prospective study from the very large Nurses Health Study failed to find strong evidence for the hypothesized relationship between diet quality and depression in women after adjustments (Chocano-Bedoya et al., 2013). Moreover, while a large repeated cross-sectional study (n = 296,121) reported consistent inverse relationships between fruit and vegetable intake and major depressive disorder (McMartin et al., 2013), a more recent longitudinal study in the same population, utilizing data from more than eight thousands Canadians, found that the inverse relationship between fruit and vegetable intake and depression observed in univariate analyses was attenuated by the addition of other measures of health behaviours to the model (Kingsbury et al., 2015). Another large Australian cohort study also reported that the weak relationships arising from univariate analyses were attenuated by adjustment for other health behaviours or by measures of socioeconomic position in younger and middle-aged groups. However, associations between dietary patterns and depression over time remained significant in the older cohort (Jacka et al., 2014a). On the other hand, when the dietary data from the Nurses Health Study were re-analysed according to the 'inflammatory potential' of the diet, by use of a Dietary Inflammatory Index (DII), the DII did predict depression over twelve years of follow up (Lucas et al., 2013). These studies point to the need to identify and address critical methodological issues, including those relating to the measurement and quantification of diet, and issues relating to the shared variance between lifestyle factors, such as diet, smoking and exercise.

3. Methodological Issues

Methods for accurately measuring people's dietary intakes remain problematic. Extensive research in nutritional epidemiology points to high levels of measurement error with the use of the various methods for capturing dietary intakes (e.g. Freedman et al., 2014). Given that there is also error associated with the measurement of mental health, the relationships between diet and health outcomes may be obscured and attenuated by measurement error. However, an equally important issue relates to the methods chosen to examine associations between 'diet quality' and health outcomes. In many studies, diet quality is measured using a priori dietary quality indexes derived from recommended dietary guidelines, or by other composite measures of dietary intake.

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These include indices such as the Healthy Eating Index (HEI), various indices based on national dietary guidelines, or numerous measures of Mediterranean Diet. Diet quality is also assessed by the use of dietary pattern analysis, which is a *post priori* method affording the determination of habitual dietary patterns in the data at hand. Such studies commonly identify two main dietary patterns that reflect healthy dietary habits (often named 'prudent' or 'wholesome') and unhealthy dietary patterns ('western'). There is evidence that (e.g. Jacka et al., 2010a) the use of dietary pattern analysis, using factor analytical approaches, yields better results as these derived their patterns from the data and sample at hand, rather than from imposing an a priori diet quality score on dietary information derived from a particular population. As an exemplar, imposing a Mediterranean-style dietary index is likely problematic in non-Mediterranean cultures. However, newer methods, such as the use of a DII (Lucas et al., 2013; O'Neil et al., 2015), are less influenced by cultural contexts and are starting to be more widely applied.

Another methodological issue that can obscure and complicate the assessment of the diet-mental health relationship relates to the covariance between health behaviours such as diet, physical activity and smoking. As these health behaviours are all associated with depression in a bidirectional manner, as well as being correlated with each other, teasing apart the relative contribution of each to the variance in depression and understanding how each interacts with each other can complicate the interpretation of the results of observational studies. As such, caution should be employed in such interpretation. Similarly, while sensitivity analyses and study design attempt to assess reverse causality (e.g. Jacka et al., 2015a) and residual and unmeasured confounding by other important factors, such as socioeconomic position (Jacka et al., 2014a), the limitations of observational study designs must always be recognised. Less commonly-utilized statistical approaches to data analysis, such as structural equation modeling, may help to mitigate some of the most pernicious issues relating to residual confounding in observational studies (Westfall and Yarkoni, 2016). Animal experiments also offer an important contribution to our understanding, as they allow for manipulation of diet in a controlled way; however, animal and human biology and nutritional needs differ substantially and the limitations here are also clear.

Finally, intervention studies using randomised controlled trial designs are considered the gold standard in determining causality, but these are fraught when it comes to diet. Ensuring and accurately measuring dietary adherence is far more challenging in nutrition than in almost any other field of research. Moreover, such studies – by their nature – preclude the possibility of double-blinding, predisposing to issues such as expectation bias and a failure of allocation concealment. However, some studies are beginning to yield important and valuable insights into causality, prevention and treatment and these are now considered.

4. Intervention Data in Humans

The European PREDIMED study (Estruch et al., 2013) represents the largest dietary intervention attempted to date. In this study, older adults with elevated risk factors for cardiac events were randomised to one of three dietary conditions: one of two forms of a Mediterranean diet or a 'low fat' control condition, based on American Heart Association dietary guidelines. Participants received individualised and group support for dietary change and adherence, as well as being provided with some relevant foods. The primary outcome of PREDIMED was cardiovascular events and the study was successful in showing that a Mediterranean diet could protect against such outcomes (Estruch et al., 2013). However, although not statistically powered to assess de novo depression as an outcome, post hoc analyses of the self-reported depression data from PREDIMED suggested a non-significant trend towards the prevention of depression by the Mediterranean diet supplemented with nuts (OR = 0.78 (0.55–1.10)), and this was statistically significant in those with type 2 diabetes, who comprised approximately half the study sample (OR = 0.59 (0.36–0.98)) (Sanchez-Villegas et al., 2013). In another randomised prevention trial, dietary coaching used as a control condition was unexpectedly equivalent to problem-solving therapy in both preventing clinical depression (Stahl et al., 2014) and improving health-related quality of life (Jimenez et al., 2015) in disadvantaged older Americans.

While these preliminary findings suggest that dietary interventions or improvement may be useful for preventing depression, up until recently there were no rigorous intervention studies explicitly designed to take a dietary approach to treatment in populations with existing mental disorders (Opie et al., 2015a). We have now just published the first study to do so and the results are noteworthy. In the SMILES study (O'Neil et al., 2013; Jacka et al., 2017) we aimed to investigate the efficacy of an adjunctive dietary improvement program for the treatment of major depressive episodes using a 12-week, parallel group, single blind randomised controlled trial design. The intervention comprised the 'Mod*i*MedDiet', which is rich in vegetables, fruit and whole grains, with an emphasis on increased consumption of oily fish, extra virgin olive oil, legumes and raw unsalted nuts. However, in contrast to traditional Mediterranean diets, it advocates for moderate consumption of red meat (Jacka et al., 2012b) and dairy. Participants, most of whom were already receiving psychotropic medications and/or psychotherapy, received seven individual dietary coaching sessions of approximately 60 min each, delivered by an accredited dietitian, and the control group received manualised social support ('Befriending') to the same schedule and intensity. The results were notable, with the intervention group demonstrating significantly greater improvement between baseline and 12 weeks than the control group with a very large effect size (Cohen's d −1.16: 95% CI: −1.73, −0.59) and a number needed to treat (NNT) of 4.1 (Jacka et al., 2017). Secondary outcomes were also concordant with the primary outcome measure and all effects were independent of any changes in BMI, self-efficacy, smoking rates and/or physical activity. Finally, dietary adherence correlated strongly with improvements in mood. These results provide the first RCT evidence for dietary improvement as a treatment strategy for treating major depressive episodes, as well as providing intervention evidence supporting causality. Importantly, the study also tells us that working with patients with mental illness to help them to achieve dietary improvements is feasible, despite the fatigue and reduced motivation often associated with depression. On the other hand, the relatively small sample size and the inability to blind participants to group allocation are clear limitations to this study, which now requires replication using larger study samples.

5. Diet or Supplements?

Supplements in nutrition interventions have often been used to avoid the difficulties of addressing dietary intakes; however, it needs to be stressed that diet and nutritional supplements are not equivalent (Lichtenstein and Russell, 2005) and data supporting the utility of such supplementation in mental illness are somewhat limited and equivocal to date. The exception to this is omega-3 fatty acid supplements, which have a more extensive evidence base, particularly for the use of supplements containing a higher proportion of EPA compared to DHA (Sublette et al., 2011) and as an adjunctive treatment for mood disorders including bipolar depression (Sarris et al., 2012).

Sarris et al. reviewed the literature on nutritional supplements for major depressive disorder and found little support for these as monotherapies, but concluded that there was evidence for the utility of folic acid, S-adenosyl-methionine (SAMe), omega-3 fatty acids, and L-tryptophan as adjunctive therapies (Sarris et al., 2009). A more recent systematic review and meta-analysis of nutraceuticals as adjunctive therapies for depression confirmed the efficacy of SAMe, omega 3, methylfolate and Vitamin D, but provided only limited support for zinc, folic acid, vitamin C, and tryptophan (Sarris et al., 2016). Almeida et al. also

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conducted a recent systematic review and meta-analysis of the literature on the short and long term impact of Vitamin B12 and folate as a treatment for depression (Almeida et al., 2015). They concluded that the evidence did not support these B-group vitamins as a short-term treatment, but that they might offer some preventive potential over the longer term. Other nutraceuticals with methods of action focused on addressing the pathophysiological aberrations that characterise many psychiatric disorders, such as inflammation, oxidative stress, reduced neurogenesis, and mitochondrial dysfunction, have shown considerable promise. For example, *N*-acetyl cysteine (NAC) – a bioavailable amino acid that upregulates glutathione and modulates glutamatergic, neurotropic, and inflammatory pathways – has shown preliminary efficacy as an adjunctive treatment in schizophrenia and bipolar depression (Berk et al., 2008a,b), but not in major depressive disorder (Berk et al., 2014).

Finally, some in the field have argued that the use of single nutrient supplements is flawed as a strategy, given that nutrients are not ever consumed singly in the diet and that humans have evolved to require a broad range of nutrients. In their recent systematic review, which included open label trials and case studies in addition to randomised placebo-controlled trials, Rucklidge and Kaplan (2013) noted the lack of trials of combined multivitamin-mineral formulations in populations with clinical depressive, anxiety or psychotic disorders. However, two randomised, double-blind, placebo-controlled trials of such formulations in adult ADHD (Rucklidge et al., 2014) and for antisocial behaviour in young adult prisoners (Gesch et al., 2002) offer support for such an approach to treatment. Certainly, an assumption that greater efficacy might be attainable using simultaneous and synergistic combinations of nutraceuticals has merit, and a trial of a multi-component nutrient formula, in combination with NAC, for the treatment of bipolar depression is currently underway (Dean et al., 2015). More research in this field is warranted and this is discussed further below.

6. Where to Now?

The field of Nutritional Psychiatry is only just starting to generate data of the quality and consistency required to change public health recommendations and clinical practice. However, we have recently argued for such changes on the basis of the precautionary principle and the imperative to find new ways to address the very high burden of illness associated with mental disorders, and the fact that these are shared risk factors across the suite of non-communicable disorders with which mental disorders are so commonly comorbid (Dash et al., 2016). Such recommendations, including dietary recommendations (Opie et al., 2015b), are also cognizant of the substantial burden of disease associated with the profound and detrimental changes to food systems globally (G. B. D. Risk Factors Collaborators et al., 2015) and the urgent need for governments to address food policy to support better population health (Jacka et al., 2014b).

While we wait for such changes, there is much to be done to advance this nascent field. Firstly, there is a clear need to now refine, replicate and scale-up dietary interventions aimed at both preventing and treating common mental disorders (Sanchez-Villegas et al., 2013; O'Neil et al., 2013). The use of technology and the internet is one feasible way in which scaling up could be achieved. Given that emerging evidence suggests highly individualized responses to food intake, further research should utilise new sources of data and statistical methodologies for developing predictive algorithms and individualized dietary recommendations (Zeevi et al., 2015). Moreover, given the role of prenatal and early life nutrition in influencing physical and mental health outcomes in children, public health strategies for improving nutrition during pregnancy should also be developed, implemented and evaluated (O'Neil et al., 2014b; Jacka and Berk, 2014).

Another key imperative is to home in on the biological pathways that mediate the diet-mental health link. Previous discussions have centered on inflammatory (Berk et al., 2013) and oxidative stress (Moylan et al., 2014) pathways, as well as brain plasticity (Jacka et al., 2015b) and the new evidence regarding intestinal permeability (Maes et al., 2012) and the gut microbiota (Dash et al., 2015; Sandhu et al., 2017). In particular, the gut-brain axis is an increasing focus of attention, given the recent understanding regarding the importance of the gut microbiota in influencing brain and behaviour (Cryan and Dinan, 2012) and the recognition that diet is a key modulator of gut microbiota and gut health. Indeed, recent animal work suggests that more than half of the variance in gut microbiota can be accounted for by dietary changes (Zhang et al., 2010), while both short and long term diets have a profound influence on the microbial profiles of humans (Wu et al., 2011). The consumption of complex carbohydrates, plant-based foods/fruits and vegetables (Wu et al., 2011; Albenberg and Wu, 2014) positively influence microbial composition, synthesis of anti-inflammatory metabolites, and host health, while high fat diets (HFD) in animals appear to trigger microbial dysbiosis, intestinal permeability ('leaky gut') and inflammation (Kim et al., 2012), with behavioural disruptions that are independent of obesity (Bruce-Keller et al., 2015). Emerging evidence, although preliminary (Allen et al., 2016; Tillisch et al., 2013; Akkasheh et al., 2016), also supports the investigation of probiotics – termed 'psychobiotics' (Dinan et al., 2013) – as psychotropic medications, while fermented foods (Kim et al., 2016) may also be a useful dietary strategy for mental and brain health. Equally important to consider is the emerging evidence regarding the noxious impact of components of 'junk' and processed foods, including dietary emulsifiers (Chassaing et al., 2015), artificial sweeteners (Suez et al., 2014) and high-fat, refined-sugar diets (e.g. Molteni et al., 2002; Morrison et al., 2010; Zainuddin and Thuret, 2012) on gut and brain health.

However, key issues relate to the lack of clarity regarding the potential differential impact of differing dietary fats, such as saturated vs mono vs polyunsaturated fats, as well as carbohydrate intake, on gut health, immune, metabolic and behavioural outcomes, and whether the results of HFD and similar experimental paradigms in animal studies are relevant to humans. These issues are currently subject to intense investigation due to their likely relevance to public health and clinical approaches. Moreover, relationships between diet and bacteria are likely dependent on individual factors, and which dietary patterns and components promote particular microbial populations is not well understood. More human data are urgently needed to understand the complex ways in which dietary intakes influence gut microbiota composition and activity, and to explicate the relationships between gut microbiota and health and a range of environmental exposures, health behaviours, medical conditions, blood biomarkers and mental health.

Another imperative is to move beyond a focus on common mental disorders to investigate diet, as well as diet-related factors including food allergy and gut health, as modifiable risk factors in the serious spectrum of mental illnesses. For example, there are tantalising data from animal models pointing to the potential for the ketogenic diet in animal models of psychosis (Kraeuter et al., 2015) and this could be evaluated as a possible intervention in humans. Similarly, gastrointestinal barrier dysfunction, food sensitivities, inflammation, and the metabolic syndrome are commonly seen in schizophrenia and this warrants research investigating the possible role of such factors in the genesis and progression of psychotic illnesses, and the potential of dietary interventions addressing immune dysfunction, food sensitivities and gut health in those with psychosis. There are data to suggest that targeting inflammation using nutraceutical approaches can prevent emerging psychotic illnesses (Amminger et al., 2010); however, a recent replication study failed to confirm these findings, pointing to both the imperative to replicate early studies and to some of the methodological challenges involved in doing so (McGorry et al., 2017).

Finally, as previously described, the extant nutraceutical literature is currently limited by methodological issues including heterogeneity, a lack of randomisation and/or blinding, small samples sizes, insufficient duration of exposure, and non-representative samples. Therefore, while the use of nutraceuticals represents a potentially useful and

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efficacious approach to mental disorder treatment, more high-quality, rigorous clinical trials are required to understand what agents are useful, to whom, under what circumstances, and at what dosage. Moreover, systematic investigation into the mechanisms and baseline factors that predict treatment response, including the potential role of genetics, inflammation, oxidative stress, and the microbiome in influencing treatment efficacy, is also required. As such, an expansion and improvement of the existing evidence base regarding nutraceutical supplementation is a key and outstanding imperative for this new field.

7. Conclusion and Recommendations for Research

The emerging field of Nutritional Psychiatry offers promise for a new approach to both the prevention and treatment of disorders that account for the leading disability burden globally. Such investigations are also of relevance to neurodevelopmental (Borre et al., 2014) and neurodegenerative disorders (Jacka et al., 2014b, 2015b); these disorders also impose a substantial disease burden and are – to date – largely intractable to prevention and treatment. Key challenges for the field are to now: refine, replicate and scale up clinical and population level dietary interventions; identify a clear set of biological pathways and targets that mediate the identified associations; conduct scientifically rigorous nutraceutical and 'psychobiotic' interventions that also examine predictors of treatment response (e.g. microbiome profiles, baseline nutrient and inflammatory status, dietary and other lifestyle behaviours); and conduct observational and experimental studies in psychosis focused on dietary and related risk factors and treatments. Finally, there is a need to continue to emphasise the likely limitations of dietary change to prevent or treat all cases of mental ill health. Clearly there are many individuals who consume good quality diets and who are metabolically healthy, but still suffer from depression or other disorders. The factors that contribute to the development of mental disorders are complex and multitudinous and dietary change should be considered part of a range of lifestyle strategies, including exercise and smoking cessation, that may support mental health in addition to – rather than instead of – other established interventions. However, given the very large burden of illness imposed by mental disorders and the evidence supporting the importance of nutrition to mental and brain health, it will be critical to continue to liaise with key allies in public health to advocate for policy change to improve the food environment at the population level (Jacka et al., 2014b; Logan and Jacka, 2014), and to develop knowledge and capacity within clinical settings to promote the benefits of dietary improvement for those with mental illnesses.

Conflicts of Interest

Nothing to declare.

Author Contributions

FNJ conceived and wrote this manuscript.

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