



Nutritional medicine as mainstream in psychiatry

Jerome Sarris, Alan C Logan, Tasnime N Akbaraly, G Paul Amminger, Vicent Balanzá-Martínez, Marlene P Freeman, Joseph Hibbeln, Yutaka Matsuoka, David Mischoulon, Tetsuya Mizoue, Akiko Nanri, Daisuke Nishi, Drew Ramsey, Julia J Rucklidge, Almudena Sanchez-Villegas, Andrew Scholey, Kuan-Pin Su, Felice N Jacka, on behalf of The International Society for Nutritional Psychiatry Research

Psychiatry is at an important juncture, with the current pharmacologically focused model having achieved modest benefits in addressing the burden of poor mental health worldwide. Although the determinants of mental health are complex, the emerging and compelling evidence for nutrition as a crucial factor in the high prevalence and incidence of mental disorders suggests that diet is as important to psychiatry as it is to cardiology, endocrinology, and gastroenterology. Evidence is steadily growing for the relation between dietary quality (and potential nutritional deficiencies) and mental health, and for the select use of nutrient-based supplements to address deficiencies, or as monotherapies or augmentation therapies. We present a viewpoint from an international collaboration of academics (members of the International Society for Nutritional Psychiatry Research), in which we provide a context and overview of the current evidence in this emerging field of research, and discuss the future direction. We advocate recognition of diet and nutrition as central determinants of both physical and mental health.

Introduction

Pharmacologically focused approaches have achieved a moderate reduction in the worldwide burden of poor mental health; however, indicators suggest that the burden of disease attributable to mental disorders will continue to rise worldwide during the coming decades.^{1,2} Mental disorders in general, and major depression and anxiety disorders in particular, account for a large burden of disability worldwide.² Rapid urbanisation, and an overall transition from traditional lifestyles (concerning diet, physical activity, and social structures), which are some of the most pressing global and environmental issues of our time, have both been linked to increases in depression and other mental disorders.³ Indisputably, depression and other common mental disorders are already, and will probably become increasingly, part of an epidemic of comorbidity between physical and mental ill-health, with diet being a crucial common determinant.⁴

The current state, wherein populations in both developed and emerging economies preferentially consume nutrient-poor, energy-dense, highly processed foods, is historically unique—many people are both overfed and undernourished. Although caloric intake has increased, many individuals in affluent, developed nations do not meet the recommended intakes of several brain-essential nutrients, including B-group vitamins, zinc, and magnesium.⁵ Although slight improvements have been detected in the dietary intakes of sugar and fats between 2003–04 and 2009–10, documented intakes of nutrient-rich and fibre-rich vegetables and whole grains are far lower than recommended.⁶ These profound changes in dietary habits, along with tobacco use, insufficient physical activity, and harmful alcohol and recreational drug use, have resulted in an epidemic of ill health. The major non-communicable diseases, along with mental disorders, are expected to cost the worldwide economy US\$47 trillion from 2014 to 2020, if no substantial and effective action is taken.⁷

A traditional whole-food diet, consisting of higher intakes of foods such as vegetables, fruits, seafood, whole

grains, lean meat, nuts, and legumes, with avoidance of processed foods, is more likely to provide the nutrients that afford resiliency against the pathogenesis of mental disorders. The mechanisms by which nutrition might affect mental health are, at least superficially, quite obvious: the human brain operates at a very high metabolic rate, and uses a substantial proportion of total energy and nutrient intake; in both structure and function (including intracellular and intercellular communication), it is reliant on aminoacids, fats, vitamins, and minerals or trace elements.^{3,8} Dietary habits modulate the functioning of the immune system, which also moderates the risk for depression.⁸ The antioxidant defence system, which is also implicated in mental disorders, operates with the support of nutrient cofactors and phytochemicals. Additionally, neurotrophic factors make essential contributions to neuronal plasticity and repair mechanisms throughout life, and these too are affected by nutritional factors.⁹

The purpose of this Personal View is to provide a platform for robust debate in the specialty, particularly regarding the need to move towards a new integrated framework in psychiatry, whereby consideration of nutritional factors should be standard practice. To provide a well informed and respected consensus statement¹⁰ and viewpoint on this position, we formed an international collaboration of academic authors from members of the International Society for Nutritional Psychiatry Research (ISNPR). In this Personal View, we outline the supportive evidence underpinning the proposed paradigm shift, and present our perspective about the future direction of nutritional medicine in psychiatry.

Current evidence

In the past several years, links have been established between nutritional quality and mental health, and scientifically rigorous studies have made important contributions to the understanding of the role of nutrition in mental health. Many epidemiological studies, including prospective studies, have shown

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The Melbourne Clinic (J Sarris PhD), and Royal Melbourne Hospital (F N Jacka PhD), Department of Psychiatry, The University of Melbourne, Richmond, Melbourne, VIC, Australia; Centre for Human Psychopharmacology, Swinburne University of Technology, Hawthorn, VIC, Australia (J Sarris, A Scholey PhD); Complementary Alternative Medicine and Nutrition Research (CAMNR), Calabasas, CA, USA (A C Logan BA); INSERM U710 (Institut National de la Santé et de la Recherche médicale), University of Montpellier, Montpellier, France (T N Akbaraly PhD); Department of Epidemiology and Public Health, University College London, London, UK (T N Akbaraly); Orygen Youth Health Research Centre, Parkville, VIC, Australia (G P Amminger MD); Teaching Unit of Psychiatry and Psychological Medicine, La Fe University and Polytechnic Hospital, University of Valencia Medical School, Centro de Investigación Biomédica En Red de Salud Mental (CIBERSAM), Valencia, Spain (V Balanzá-Martínez MD); Perinatal and Reproductive Psychiatry (M P Freeman MD), and Depression and Clinical Research Program (D Mischoulon MD), Massachusetts General Hospital, Boston, MA, USA; National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD, USA (J Hibbeln MD); Department of Clinical Epidemiology, Translational Medical Center (Y Matsuoka MD), and Department of Mental Health Policy and Evaluation, National Institute of Mental Health (D Nishi MD), National Center

of Neurology and Psychiatry, Kodaira, Tokyo, Japan; Department of Epidemiology and Prevention, Center for Clinical Sciences, National Center for Global Health and Medicine, Shijuku-ku, Tokyo, Japan (T Mizoue MD, A Nanri MD); Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, USA (D Ramsey MD); Department of Psychology, University of Canterbury, Christchurch, New Zealand (J J Rucklidge PhD); Department of Clinical Sciences, University of Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain (A Sanchez-Villegas PhD); Department of Psychiatry & Mind-Body Interface Laboratory (MBI-Lab), China Medical University Hospital, and Graduate Institute of Neural and Cognitive Sciences, China Medical University, Taichung, Taiwan (K P Su MD); School of Medicine, Deakin University, IMPACT Strategic Research Centre, Geelong, VIC, Australia (F N Jacka); Murdoch Children's Research Centre, Parkville, VIC, Australia (F N Jacka); and Black Dog Institute, Hospital Road Prince of Wales Hospital, Randwick, NSW, Australia (F N Jacka)

Correspondence to: Dr Jerome Sarris, The Melbourne Clinic, 2 Salisbury Street, Richmond, Melbourne, VIC 3121, Australia
jsarris@unimelb.edu.au

associations between healthy dietary patterns and a reduced prevalence of, and risk for, depression^{11,12} and suicide.¹³ Maternal and early-life nutrition is also emerging as a determinant of later mental health outcomes in children,^{14,15} and severe macronutrient deficiencies during crucial developmental periods have long been implicated in the pathogenesis of both depressive and psychotic disorders.^{16,17}

A recent systematic review has now confirmed a relation between unhealthy dietary patterns and poorer mental health in children and adolescents.¹⁸ In view of the early age of onset for depression and anxiety, these data suggest that diet is a key modifiable intervention target for prevention of the initial incidence of common mental disorders. Indeed, although not statistically powered to assess the prevention of de-novo depression, results from the large European PREDIMED study¹⁹ showed a strong trend towards a reduced risk for incident depression for individuals randomly assigned to a Mediterranean diet with nuts, and this protective effect was particularly evident in those with type 2 diabetes. Similarly, results of an indicated prevention trial²⁰ showed that dietary counselling was as effective as psychotherapy at prevention of transition to case-level depression in older adults. A randomised controlled trial designed to test the efficacy of dietary improvement as a treatment for major depression is underway.²¹

Convincing data suggest that select nutrient-based supplements (in isolation, or in combination),²² might provide many neurochemical modulatory activities that are beneficial in the management of mental disorders. Examples of these nutrient-based supplements include omega-3 fatty acids, S-adenosyl methionine (SAME), N-acetyl cysteine (NAC), zinc, B vitamins (including folic acid), and vitamin D. Various clinical investigations support the potential usefulness of omega-3 fatty acids for disorders including, but not limited to, bipolar depression, post-traumatic stress disorder, and major depression, and they are indicated in the prevention of psychosis.²³ Omega-3 fatty acids can provide a range of neurochemical activities via the following mechanisms: modulation of neurotransmitter (noradrenaline, dopamine, and serotonin) re-uptake, degradation, synthesis, and receptor binding; anti-inflammatory and anti-apoptotic effects; and the enhancement of cell membrane fluidity and neurogenesis via upregulation of brain-derived neurotrophic factor (BDNF).^{23,24}

SAME is an endogenous sulphur-containing compound that is an important neurochemical component involved in the one-carbon cycle responsible for the methylation of neurotransmitters that regulate mood. Clinical trials have shown that SAME is an effective antidepressant,²⁵ and clinically significant augmentation effects occur with antidepressants.²⁶ NAC has evidence of efficacy in bipolar depression, schizophrenia, trichotillomania, and other compulsive and addictive behaviours.²⁷ This aminoacid-based compound has

glutamate modulatory effects, and anti-inflammatory, antioxidant, and neuroprotective activity.²⁷ Zinc is an abundant trace element that is involved in cytokine modulation and hippocampal neurogenesis via upregulation of BDNF, and also modifies N-methyl-D-aspartate and glutamate activity.²⁸ Zinc deficiency has been linked to increased depressive symptoms, and evidence is emerging that zinc supplementation improves depressed mood, mainly as an adjunctive intervention with antidepressants.²⁸

B vitamins are needed for proper neuronal function, and a deficiency of B9 (folate) has been reported in depressed populations, and in poor responders to antidepressants.²⁹ Several studies have assessed the antidepressant effect of folic acid with concomitant antidepressant use, and results of most either showed an increase in the proportion of participants who had an antidepressant response, or improved the onset of response. Vitamin D is a neurosteroid, with data suggesting that low maternal concentrations are implicated in schizophrenia risk, and deficiency is likewise linked to increased depressive symptoms.³⁰ A combination of nutrients that match the natural physiological needs of the body, and also better represent the broad range of nutrients present in food, might prove even more effective than isolated nutrients alone.³¹

Future direction

During the past several years, high-quality research into nutrition and mental health—a specialty that has been neglected—has grown rapidly and is finally starting to develop its potential. In view of the changes related to rapidly growing urbanicity and the globalisation of the food industry, resulting in profound shifts away from traditional dietary patterns, the ways in which overall diet and specific nutritional elements, multivitamin interventions, or both can affect mental health clearly need to be identified. In view of the widespread use of nutrient supplements by individuals with and without mental disorders, scientifically rigorous methods should be used to assess the efficacy of these supplements and to identify what dose of a nutrient supplement is needed, by whom, when, and under what circumstances. From this resultant research, the evidence needs to be communicated to clinicians via educational programmes, and to the wider public via public health campaigns. Formal medical education should include training that focuses on the role of diet and nutrients in brain function and mental health.

Recommendations for governments to take more substantive actions to improve food quality and promote healthier dietary practices should be considered to address the substantial burden of disease that results from unhealthy diets. Importantly, the activities of the food industry need to be examined at a governmental level, and relevant policies need to be designed to reduce the worldwide burden of physical and mental ill-health attributable to poor diet.⁴ Such policies are advised to

stimulate substantial public change in dietary habits back towards a traditional whole-food diet (dependent on the culture). Further, better education of the public and clinicians about the role of nutrients in the brain, and the link to mental health, is crucially needed.

Conclusions

Present treatment of psychiatric disorders can be improved and greater attention can be given to preventive efforts. As a result of the immense burden of mental disorders, modifiable targets to reduce the incidence of mental disorders are now urgently needed. Diet and nutrition offer key modifiable targets for the prevention of mental disorders, having a fundamental role in the promotion of mental health. Now is time for the recognition of the importance of nutrition and nutrient supplementation in psychiatry. Nutritional medicine should now be considered as a mainstream element of psychiatric practice, with research, education, policy, and health promotion supporting this new framework.

Contributors

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References

- Baxter AJ, Patton G, Scott KM, Degenhardt L, Whiteford HA. Global epidemiology of mental disorders: what are we missing? *PLoS One* 2013; **8**: e65514.
- Whiteford HA, Degenhardt L, Rehm J, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet* 2013; **382**: 1575–86.
- Logan AC, Jacka FN. Nutritional psychiatry research: an emerging discipline and its intersection with global urbanization, environmental challenges and the evolutionary mismatch. *J Physiol Anthropol* 2014; **33**: 22.
- Jacka FN, Sacks G, Berk M, Allender S. Food policies for physical and mental health. *BMC Psychiatry* 2014; **14**: 132.
- Parker E, Goldman J, Moshfegh A. America's nutrition report card: comparing WWEIA, NHANES 2007–2010 usual nutrient intakes to dietary reference intakes. *FASEB J* 2014; **28** (suppl): 384.2.
- Bowman S, Friday J, Thoeirig R, Clemens J, Moshfegh A. Americans consume less added sugars and solid fats and consume more whole grains and oils: changes from 2003–04 to 2009–10. *FASEB J* 2014; **28** (suppl): 369.2.
- WHO. Global action plan for the prevention and control of noncommunicable diseases 2013–2020. Geneva: World Health Organisation, 2013.
- Berk M, Williams LJ, Jacka FN, et al. So depression is an inflammatory disease, but where does the inflammation come from? *BMC Med* 2013; **11**: 200.
- Molendijk ML, Bus BA, Spinhoven P, et al. Serum levels of brain-derived neurotrophic factor in major depressive disorder: state-trait issues, clinical features and pharmacological treatment. *Mol Psychiatry* 2011; **16**: 1088–95.
- Sarris J, Logan A, Akbaraly T, et al. International Society for Nutritional Psychiatry Research consensus position statement: nutritional medicine in modern psychiatry. *World Psychiatry* (in press).
- Lai JS, Hiles S, Bisquera A, Hure AJ, McEvoy M, Attia J. A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults. *Am J Clin Nutr* 2014; **99**: 181–97.
- Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kosti R, Scarmeas N. Mediterranean diet, stroke, cognitive impairment, and depression: a meta-analysis. *Ann Neurol* 2013; **74**: 580–91.
- Nanri A, Mizoue T, Poudel-Tandukar K, et al, and the Japan Public Health Center-based Prospective Study Group. Dietary patterns and suicide in Japanese adults: the Japan Public Health Center-based Prospective Study. *Br J Psychiatry* 2013; **203**: 422–27.
- Jacka FN, Ystrom E, Brantsaeter AL, et al. Maternal and early postnatal nutrition and mental health of offspring by age 5 years: a prospective cohort study. *J Am Acad Child Adolesc Psychiatry* 2013; **52**: 1038–47.
- Steenweg-de Graaff J, Tiemeier H, Steegers-Theunissen RP, et al. Maternal dietary patterns during pregnancy and child internalising and externalising problems. The Generation R Study. *Clin Nutr* 2014; **33**: 115–21.
- Brown AS, Susser ES, Lin SP, Neugebauer R, Gorman JM. Increased risk of affective disorders in males after second trimester prenatal exposure to the Dutch hunger winter of 1944–45. *Br J Psychiatry* 1995; **166**: 601–06.
- Susser ES, Lin SP. Schizophrenia after prenatal exposure to the Dutch Hunger Winter of 1944–1945. *Arch Gen Psychiatry* 1992; **49**: 983–88.

- 18 O'Neil A, Quirk SE, Housden S, et al. Relationship between diet and mental health in children and adolescents: a systematic review. *Am J Public Health* 2014; **104**: e31–42.
- 19 Sánchez-Villegas A, Martínez-González MA, Estruch R, et al. Mediterranean dietary pattern and depression: the PREDIMED randomized trial. *BMC Med* 2013; **11**: 208.
- 20 Stahl ST, Albert SM, Dew MA, Lockovich MH, Reynolds CF 3rd. Coaching in healthy dietary practices in at-risk older adults: a case of indicated depression prevention. *Am J Psychiatry* 2014; **171**: 499–505.
- 21 O'Neil A, Berk M, Itsiopoulos C, et al. A randomised, controlled trial of a dietary intervention for adults with major depression (the "SMILES" trial): study protocol. *BMC Psychiatry* 2013; **13**: 114.
- 22 Rucklidge JJ, Kaplan BJ. Broad-spectrum micronutrient formulas for the treatment of psychiatric symptoms: a systematic review. *Expert Rev Neurother* 2013; **13**: 49–73.
- 23 Mischoulon D, Freeman MP. Omega-3 fatty acids in psychiatry. *Psychiatr Clin North Am* 2013; **36**: 15–23.
- 24 Sarris J, Mischoulon D, Schweitzer I. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. *J Clin Psychiatry* 2012; **73**: 81–86.
- 25 Sarris J, Papakostas GI, Vitolo O, Fava M, Mischoulon D. S-adenosyl methionine (SAME) versus escitalopram and placebo in major depression RCT: efficacy and effects of histamine and carnitine as moderators of response. *J Affect Disord* 2014; **164**: 76–81.
- 26 Papakostas GI, Mischoulon D, Shyu I, Alpert JE, Fava M. S-adenosyl methionine (SAME) augmentation of serotonin reuptake inhibitors for antidepressant nonresponders with major depressive disorder: a double-blind, randomized clinical trial. *Am J Psychiatry* 2010; **167**: 942–48.
- 27 Berk M, Malhi GS, Gray LJ, Dean OM. The promise of N-acetylcysteine in neuropsychiatry. *Trends Pharmacol Sci* 2013; **34**: 167–77.
- 28 Lai J, Moxey A, Nowak G, Vashum K, Bailey K, McEvoy M. The efficacy of zinc supplementation in depression: systematic review of randomised controlled trials. *J Affect Disord* 2012; **136**: e31–39.
- 29 Fava M, Mischoulon D. Folate in depression: efficacy, safety, differences in formulations, and clinical issues. *J Clin Psychiatry* 2009; **70** (suppl 5): 12–17.
- 30 Eyles DW, Burne TH, McGrath JJ. Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. *Front Neuroendocrinol* 2013; **34**: 47–64.
- 31 Rucklidge JJ, Johnstone J, Kaplan BJ. Magic bullet thinking—why do we continue to perpetuate this fallacy? [letter]. *Br J Psychiatry* 2013; **203**: 154–55.