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Nutrition and depression: Summary of findings from the EU-funded MooDFOOD depression prevention randomised controlled trial and a critical review of the literature

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Abstract

This paper discusses the emerging field of nutritional psychology and provides an update on the now completed EU-funded *MooDFOOD* depression prevention randomised controlled trial that assessed the effects of two nutrition-based interventions for the prevention of depression in overweight or obese adults with at least mild symptoms of depression. We first outline the problem of major depression, the most common form of psychopathology and the largest contributor to global disability, and then give an overview of the connection between nutrition and depression; separating the evidence according to prevention and treatment of depression. The extant literature is reviewed, and we examine the implications for both prevention and treatment. Questions are posed for further research in this emerging and important area.

Keywords: depression, diet, nutrients, omega-3 fatty acids, supplements

Introduction

Depression

Depression is highly prevalent (Wittchen *et al*. 2011; Kessler & Bromet 2013) and has become a major public health challenge. It is ranked by the World Health Organization (WHO) as the single largest contributor to global disability (World Health Organization 2017) and a major contributor to suicidal behaviour (Hegerl *et al*. 2019). Depression is enormously detrimental economically with global annual associated costs estimated to stand at $1 trillion (Chisholm *et al*. 2016). While there are psychological and pharmacological treatments available, efficacy in both has been shown to be modest (Cuijpers *et al*. 2016; Cipriani *et al*. 2018), and it has been suggested that psychotherapy treatment effects may have been overestimated (Cuijpers *et al*. 2019).

The problem is exacerbated because more than half of individuals develop recurrent or chronic depression,

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spending some 20% of their life with a depressive disorder (Cuijpers, Beekman & Reynolds 2012). While many do receive benefit from treatment, the proportion of patients in remission following psychological or pharmacological treatment is not high, typically less than 50% (Kolovos *et al*. 2017; Van Bronswijk *et al*. 2019). There are also a number of barriers to seeking help including a systemic lack of economic, social, scientific and human resources (Kakuma *et al*. 2011; Becker & Kleinman 2013) and individual-level barriers, including perceived stigma, recognising symptoms and a preference for self-reliance (Gulliver, Griffiths & Christensen 2010). Unfortunately, this means that most people in need of treatment for mental health problems do not actually receive any (Kessler *et al*. 2005). It has been argued that even if we could collectively overcome these barriers to treatment and achieve 100% treatment coverage, the reduction in the burden associated with affective disorders would only be modest (approximately 35%) (Andrews *et al*. 2004). This speaks to the need for more efficacious interventions (treatment and prevention) for current depression that is both scalable and accessible. In addition, researchers are now increasingly focussing on prevention intervention strategies.

With a realisation that relying on treatment only is unlikely to be enough to help everyone in need, depression prevention interventions have now become a global priority (Cuijpers, Beekman & Reynolds 2012; Ebert & Cuijpers 2018). Although it was once thought by the National Institute of Mental Health that prevention of depression was not a realistic goal, 'In general, the onset of a clinical depression cannot be prevented' (Muñoz, Beardslee & Leykin 2012), subsequent work has shown that prevention interventions can be a viable and effective approach to depression. For example, a systematic review of psychological interventions for the prevention of major depressive disorder in a range of different samples (*e.g*. adolescents, adults, primary care samples, pregnant women and post-stroke patients) found that interventions were able to reduce the risk of major depression by 21% on average compared with control groups (van Zoonen *et al*. 2014). No differences were found in this review between intervention types. That is, cognitive behavioural therapy, interpersonal psychotherapy or other (*e.g*. problem solving). In fact, a number of novel approaches to preventing depression have yielded positive results including parental programmes (Yap *et al*. 2016), mindfulness (Raes *et al*. 2014) and exercise (Harvey *et al*. 2018). Another emerging area with potential is nutritional psychology.

Nutrition and depression

The aetiology of depression is complex and not yet fully understood but is thought to involve cognitive (Watkins 2008; Gotlib & Joormann 2010), genetic (Mullins & Lewis 2017) and environmental (LeMoult *et al*. 2020) factors, as well as physiological factors such as hormones (Owens *et al*. 2014), inflammatory markers (Lamers *et al*. 2019) and arousal and wakefulness regulation (Hegerl & Hensch 2014; Jawinski *et al*. 2019). Lifestyle factors are also thought to play a role, including most notably sleep, exercise and diet (Lopresti, Hood & Drummond 2013). We note that the relationship between diet, nutrition and mood is complex and likely to involve interactions and reciprocal relationships between subsystems. For example, it is suggested that stress and depression can shape gut microbiota, which in turn may affect stress and depression (Madison & Kiecolt-Glaser 2019). It is also increasingly recognised that modern lifestyles may lead to unhealthy diets, which may in turn contribute to both an obesogenic (García, Long & Rosado 2009; Blüher 2019) and depressogenic social environment (Hidaka 2012). The obesity global pandemic (Abarca-Gómez *et al*. 2017) could be linked to depression as the two factors often co-occur (Sutaria *et al*. 2019). Obesity and depression may have a bi-directional relationship where increase in one is associated with increase in the other over time (Luppino *et al*. 2010; Marmorstein, Iacono & Legrand 2014). Furthermore, obesity and depression might share common biological mechanisms (Milaneschi *et al*. 2019), including, for example, inflammatory processes (Bullmore 2018).

One emerging approach to either the prevention or treatment of depression aims to improve diet and nutritional status. Under this framework, it is acknowledged that diet and nutritional status have an important yet complex relationship with mental health (Sanchez-Villegas & Martínez-González 2013; Sarris *et al*. 2015; Jacka 2017; Lassale *et al*. 2019), and perhaps with depression in particular (Marx, Hoare & Jacka 2019). Theoretically, nutrients from diet or supplements are able to treat or prevent depression in two main ways: helping the brain to function well and providing neuroprotective effects. It has been shown, for example, that omega-3 fatty acids have pluripotent beneficial effects in the brain by upregulating adult neurogenesis (Beltz *et al*. 2007) and brain-derived neurotrophic factor (BDNF) protein expression (Wu, Ying & Gomez-Pinilla 2004; Rao *et al*. 2007), promoting metabolism, release, uptake and receptor functions of key neurotransmitter systems (*e.g*. serotonin and

dopamine) (Grosso *et al*. 2014a) and regulating stress via the Hypothalamic-Pituitary-Adrenal Axis (Thesing *et al*. 2018). Neuroprotection from nutrients may come in the form of anti-inflammatory processes (Wall *et al*. 2010), reducing apoptosis (Harms *et al*. 2011) and reducing oxidative stress (Lima *et al*. 2018).

Research has assessed the links between specific nutrients and the prevention or treatment of depression. For example, dietary omega-3 is associated with a reduced risk of depression (Grosso *et al*. 2016), omega-3 supplementation versus placebo has demonstrated a beneficial effect on depressive symptoms (Liao *et al*. 2019) and vitamin D supplementation may benefit those with clinical depression (for a review on the connection between vitamin D and depression see Parker, Brotchie & Graham 2017). However, it has also been argued that single nutrient supplementation is unlikely to be maximally effective, given that nutrients are not consumed in isolation (Opie *et al*. 2015). A whole-diet approach on the other hand accounts for the complex interplay between known and unknown nutrients in the diet. Research in this area focuses on high-quality diets that are nutrient dense and low in ultra-processed foods (*e.g*. the Mediterranean diet or traditional diet). There is robust observational evidence to suggest that such high-quality diets are at least associated with lower risk of incident depression (Molendijk *et al*. 2018; Lassale *et al*. 2019; Nicolaou, Colpo & Vermeulen 2019) and in addition, there is likely to be a complex bidirectional relationship between the two (Elstgeest *et al*. 2019). However, more work in this nascent field is needed to test the causal status of nutrients and diet quality and the prevention of depression; in particular, more randomised controlled nutritional intervention trials (RCTs) are required.

Nevertheless, nutrition-based approaches are attractive candidates for mental health prevention strategies for a number of reasons including the fact that they have the potential to reach a large number of people and have additional wide-ranging positive health benefits including promoting healthy immune function (Wintergerst, Maggini & Hornig 2007), and reducing negative effects of diabetes (Salas-Salvadó *et al*. 2015), heart disease (Grosso *et al*. 2017) and cancer (Aune *et al*. 2011). In addition, healthy diets can encourage healthy weight loss which may itself provide wide-ranging health benefits, potentially including preventing depression. Several studies have shown positive effects of behavioural weight control on both depressed mood and weight (*e.g*. Brinkworth *et al*. 2009; Faulconbridge *et al*. 2018) and as a result, nutritional interventions could also lead to health economic benefits (Gyles *et al*. 2012). The recently completed *MooDFOOD* intervention (Roca *et al*. 2016; Bot *et al*. 2019) is one such randomised controlled prevention trial that investigated the role of nutrition and nutrition-related psychological factors on depression.

The MooDFOOD prevention trial and interventions

Mental health interventions can be comprised of either treatment or prevention strategies and we argue that the distinction is important in depression, while recognising that the boundaries between the two can be somewhat fuzzy. Primary prevention interventions are often classified in two main ways, as *universal*, applied to the whole population for the benefit of all or *targeted* strategies that focus on sub-populations at elevated risk for a disorder. The latter can be subdivided into *selective prevention*, which focusses on known risk factors for disorder (*e.g*. being overweight or obese) and *indicated prevention*, where subpopulations have symptoms that may suggest emerging disorder. Treatment interventions on the other hand are focussed on individuals who have already received a clinical diagnosis and may target *de novo* episodes of depression or help patients with chronic depression to prevent relapse and recurrence. In the latter case, the line between treatment and prevention becomes blurred, including as it does secondary prevention. The *MooDFOOD* trial adopted the definition recommended by the American Institute of Medicine that prevention refers to those interventions that occur prior to the onset of clinical disorder for individuals who have elevated symptoms of disorder but who do not currently meet the criteria for a clinical disorder (O'Connell, Boat & Warner 2009).

Participants in the *MooDFOOD* trial (Roca *et al*. 2016; Cabout, Brouwer & Visser 2017; Bot *et al*. 2019) were overweight or obese [mean body mass index (BMI) = 31.4], aged 18-75 years (mean = 46.5 years) with at least mild symptoms of depression but no current depressive episode or diagnosis in the past 6 months. Participants were randomised to daily multi-nutrient supplementation versus pill placebo, and to a nutritionally based psychological therapy; a multi-modal food-related behavioural activation intervention (F-BA); versus no behavioural activation intervention, for a 12-month period. In this 2 x 2 factorial trial design, participants were therefore allocated to one of four arms: F-BA plus supplements (n = 256), no F-BA plus supplements

($n = 256$), F-BA plus placebo ($n = 256$) or no F-BA plus placebo ($n = 257$). Measures were collected at baseline (T0), 3 months (T3), 6 months (T6) and at 12 months (T12; end of trial).

Multi-nutrient supplementation intervention

The daily multi-nutrient supplement included one capsule of long-chain omega-3 fatty acids containing 1412 mg of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (ratio 3:1) and a pill containing selenium (30 μg), folic acid (400 μg) and vitamin D3 (20 μg) along with calcium (100 mg). The matched placebos used included one capsule of sunflower oil (57% linoleic acid, 30% oleic acid) and one pill with filling materials (microcrystalline cellulose; corn starch; polyvinylpyrrolidone; crosslinked carboxymethylcellulose sodium; magnesium stearate and magnesium silicate).

MooDFOOD trial food-related behavioural activation intervention

The *MooDFOOD* F-BA prevention intervention was based on the standard behavioural activation therapy (BA) for depression model (Richards *et al*. 2017; Veale 2008; Watkins *et al*. 2011; Watkins *et al*. 2016) which uses self-monitoring, functional analysis and activity scheduling to encourage individuals to increase their engagement with activities rather than avoid them (Ekers *et al*. 2014; Richards *et al*. 2016). There was strong emphasis on changing habitual behaviour by identifying triggers, planning alternative responses and repeating behaviours routinely to develop healthy habits, focussing on both dietary habits (*e.g*. reducing snacking and encouraging a Mediterranean-style diet) and the mood-food relationship (*e.g*. reducing emotional eating). The F-BA intervention was delivered by psychologists, who were trained by a nutritionist, and consisted of up to 21 sessions, initially individual weekly (15) and fortnightly sessions, and subsequently monthly group (6) sessions.

There was no evidence in the *MooDFOOD* trial main analyses that either intervention was efficacious in preventing episodes of clinical depression over a 12-month period. However, in subsequent sensitivity analyses, F-BA was shown to reduce symptoms of depression for those with high baseline levels and there was a depression-prevention effect of F-BA when intervention adherence was taken into account (Bot *et al*. 2019). The results for individual nutritional supplements and the F-BA and their implications in the context of current research are discussed below.

Evidence with respect to nutritional supplements

There was neither evidence of prevention of depressive episodes nor any beneficial effects on depressive symptoms for daily nutrient-supplementation in the *MooDFOOD* trial, and there was even evidence that depressive symptom outcomes were worse for those taking supplements versus placebo (Bot *et al*. 2019). This latter result is mirrored by that of a recent treatment study that administered a combination nutraceutical supplement to treat patients with clinical depression (Sarris *et al*. 2019). In this study, the placebo was also shown to be superior in reducing depressive symptoms in patients, in this case over an 8-week period. The authors point to the interesting possibility that single nutrients may be more effective than a 'shotgun' approach. However, it is also important to remain open to the possibility that nutritional supplementation may confer iatrogenic effects on individuals with mental health problems, or for those at risk of ill mental health. In both the *MooDFOOD* prevention trial and the above treatment trial reported by Sarris *et al*., the data suggest that nutritional supplements compared less favourably than placebo. However, it is important to note that neither intervention was associated with a *rise* in depressive symptoms *per se*. Therefore, a more important concern may be that, equipped with a misguided belief that nutritional supplements are efficacious, people with an unfolding serious mental illness may forgo seeking treatments that are known be effective. There is also a risk that with an erroneous belief in a 'magic healthy pill', some individuals will not see the need to follow healthy diets and lifestyles. In this regard, we urge caution for recommending multi-supplements for the prevention of depression and echo a recent statement that physicians should not recommend omega-3 supplements for reducing depression risk (Deane *et al*. 2019).

The evidence for the efficacy of nutritional supplements in depression is to some extent moderated by treatment versus prevention, as shown by the equivocal results produced from meta-analyses of RCTs on the treatment effect of omega-3 on depression. While some have found that initial positive results may be explained by publication bias (Bloch & Hannestad 2012) or that effects are only small and unlikely to be clinically meaningful (Appleton *et al*. 2016), others have shown more substantial beneficial treatment effects (Grosso 2014a; Mocking *et al*. 2016; Bai *et al*. 2018; Firth *et al*. 2019a; Liao *et al*. 2019). While effect sizes are generally found to be small to

moderate (Firth *et al*. 2019b), these are comparable to those found for anti-depressants (Schalkwijk *et al*. 2014). Interestingly, however, one meta-analysis (Hallahan *et al*. 2016) found that omega-3 bestowed clinical benefits for those diagnosed with depression but no evidence for reduction of depressive symptoms for populations without a depression diagnosis (although see Grosso *et al*. 2014a for an alternative view). Similarly, one meta-analysis (Mocking *et al*. 2016) found greater treatment effects for depressed patients who were also taking anti-depressants. In support of this important distinction in the results between treatment and prevention studies, the more recent meta-analysis on the effect of omega-3 on the *prevention* of depression (*MooDFOOD* trial included) found no evidence of a prophylactic effect (Deane *et al*. 2019). It should be noted, however, that there is a paucity of research on prevention and more is needed to draw firmer conclusions. In conclusion, current evidence suggests no prevention effect of omega-3 on depression.

For treatment of depression, however, the extant research suggests that omega-3 may be effective as an adjunct to pharmacotherapy in terms of acceleration of response or augmenting non-response (Schefft *et al*. 2017), or as a monotherapy (Hallahan *et al*. 2016). EPA has been shown to more effective than DHA (Martins, Bentsen & Puri 2012) and recommendations for the optimal efficacious dose of EPA have been given at approximately 1-2 grams (Guu *et al*. 2019), although one meta-analysis found the most effective dose was $\leq$ 1 g/day (Liao *et al*. 2019). In addition, omega-3 may exert a stronger beneficial effect for more severe cases of depression (Bloch & Hannestad 2012; Martins, Bentsen & Puri 2012), although this effect cannot be considered a consistent finding (Grosso *et al*. 2014b; Mocking *et al*. 2016).

Although there is less evidence available with which to assess the efficacy of supplementation with nutrients other than omega-3 in the treatment of depression (see Firth *et al*. 2019b for a review), a small number of RCTs have suggested that vitamin D supplementation may reduce depressive symptoms as a monotherapy (Vellekkatt & Menon 2019). In the general population, however, there is evidence for little to no beneficial effects of vitamin D supplementation on depressive symptoms (Elstgeest *et al*. 2017; De Koning *et al*. 2019), while it is not currently possible to exclude the possibility of a small beneficial effect for those with low baseline levels of vitamin D (Elstgeest *et al*. 2018) until further studies have been completed. One trial underway is the *VITAL-DEP* study which is assessing the effect of vitamin D and omega-3 supplementation on reducing the risk of clinical depressive syndrome as well as the effect on mood symptom scores as measured by the Patient Health Questionnaire (Okereke *et al*. 2018). The results of such trials will be informative and add to the evidence base, enabling stronger conclusions to be made in the future.

In addition, again with only limited evidence available, findings from meta-analysis suggests that folate (Roberts, Carter & Young 2018) or zinc (Schefft *et al*. 2017) may be beneficial for patients with depressive disorders as an adjunctive therapy to anti-depressant medication. As an illustrative example of the findings, one RCT administering a daily supplement of 25 mg of zinc versus placebo in combination with a tricyclic anti-depressant (Imipramine), depressive symptoms in the zinc group significantly reduced for those with treatment-resistant depression (Siwek *et al*. 2009). Conversely, there is clearer evidence from RCTs showing that supplementation with magnesium does not improve symptoms in depressed patients (Phelan *et al*. 2018). In conclusion, the current evidence does not support the use of supplements for the prevention of depression. Although caution is advised and more trials are required, there is some evidence to suggest that omega-3 may give some benefit to individuals already diagnosed with clinical depression, as an adjunctive treatment or possibly as a monotherapy. A dearth of RCTs for other nutrients prevents firmer conclusions being drawn.

Evidence from behavioural approaches

The F-BA did not prevent incidence of depression in the *MooDFOOD* trial, yet secondary analyses suggested that the intervention may be effective for those adhering highly to the intervention. These exploratory analyses showed that for those with high adherence, the F-BA lead to a 22% reduction in the incidence of clinical depression over the course of the trial, an effect which is comparable with previous psychological prevention interventions (van Zoonen *et al*. 2014). Secondary analyses also showed that the F-BA reduced symptoms of depression at 12-month follow-up for those with higher initial severity of depressive symptoms (Bot *et al*. 2019).

Although it is certainly possible that the underlying cause of the reduction in symptoms seen for some participants in the F-BA trial arm could be the (relatively small) reduction in unhealthy food consumption and increase in healthy food consumption (Grasso *et al*. 2019), our more recent analyses suggest that it is

unlikely that targeting food consumption alone will have a strong effect of reducing symptoms of depression. In mediation analyses on the *MooDFOOD* trial data, we found no evidence to suggest that increasing diet quality or reducing snacking *per se* explained the apparent small beneficial effect of F-BA on depressive symptoms (Owens *et al*., manuscript submitted for publication). In this analysis, we did, however, find that reductions in negative responses to food cues (*i.e*. unrestrained eating and emotional eating) partially explained the link. This is consistent with previous analyses linking depression to these unhealthy eating styles in the *MooDFOOD* cohort (Paans *et al*. 2018). This evidence leads us to speculate that learning alternative habitual, healthier responses to such cues may be a modifiable target for future interventions. A similar view can be found in research with patients with obesity, where it has been proposed that the interaction between psychological habits, mood and emotional dysregulation is thought to be key in reducing clinical obesity (see Raman, Smith & Hay 2013).

The F-BA in *MooDFOOD* has also been shown to be feasible to carry out and was acceptable to the majority of participants in the *MooDFOOD* trial (Owens *et al*., manuscript submitted for publication), which leaves open the possibility of refining and further developing this novel approach to depression prevention, combining both nutritional and psychological/behavioural components. In this study, we found a clear preference for individual versus group, which has also been found for mental health treatment in primary care (Lang 2005). When designing interventions it is important to consider patient preference, a factor that can predict good outcomes for individuals, as shown by a recent study with depressed patients showing a preference for one treatment over another (person-centred counselling vs. low intensity cognitive behavioural therapy) predicted the best treatment outcomes (Cooper *et al*. 2018). Furthermore, evidence from meta-analysis has demonstrated smaller therapeutic effects for group versus individual psychotherapy for depressed patients (Cuijpers *et al*. 2014).

Whole-diet approaches

When comparing the evidence of whole-diet interventions on depressive and anxiety symptoms, a recent meta-analysis of 16 RCTs (the vast majority assessing non-clinical depression) suggests that the whole-diet approach may provide a small yet significant positive benefit in reducing symptoms of depression (Firth *et al*. 2019a). Effect sizes (Hedge's *g*) for the interventions were similar for depressive symptoms when comparing those that aimed to improve nutrition [K (number of studies) = 9, 0.365] and those aiming to reduce fat intake (K = 4, 0.477), while the effect size was smaller for those interventions focussing on weight loss (K = 4, 0.212). Fifteen studies in this review of the literature were comprised of non-clinical populations, with a single study, the *SMILES* trial, using a clinical depression sample (Jacka *et al*. 2017). This study observed a very large difference in the reduction of depression symptoms for a dietary support group versus a social support group (Cohen's d effect size of –1.16). The only other whole-diet RCT for clinical depression that we are aware of, and not included in the recent review by Firth *et al*. (2019a) is the *HELFIMED* trial (Parletta *et al*. 2019). This trial recruited patients with general practitioner (GP)-reported or self-reported depression and randomised them to either a 'MedDiet' group receiving nutrition education from dietitians and nutritionists, Mediterranean-style food hampers, cooking workshops and fish oil supplements for 6 months, or to fortnightly social groups for 3 months. The results showed statistically significant reductions in symptoms of depression for the MedDiet group, where 60% fewer participants experienced 'extremely severe' depression. A further clinical trial to look out for with results forthcoming is the *PREDI-DEP* trial. This trial is assessing the effect a dietitian-led Mediterranean-style diet supplemented with olive oil on the prevention of the *recurrence* of disorder for participants with a history of clinical depression (Sánchez-Villegas *et al*. 2019).

Role of weight loss

The focus of the *MooDFOOD* trial was on the prevention of depression and the change in depressive symptoms rather than weight loss *per se* and consistent with this, trial participants lost less than 1 kilogram of weight in the trial arms (0.3–0.8 kg), after 1 year of being in the study, with no significant difference between trial arms (Bot *et al*. 2019). Interventions that specifically target weight loss with psychotherapy, however, have been shown to reduce emotional eating and cognitive restraint, but current meta-analytic evidence suggests that cognitive behavioural therapy specifically for weight loss (CBTWL) is not superior to other interventions for depression (Jacob *et al*. 2018). In this recent meta-analysis, the majority of studies were not designed specifically to reduce depression but interestingly one included study

with obese women (Pagoto *et al*. 2013) which used BA (as did *MooDFOOD*), reported reductions in depressive symptoms and associated weight loss. More recently, the *RAINBOW* RCT for patients with both obesity and high levels of depressive symptoms showed that an integrated intervention including a weight loss programme and psychological therapy including BA, reduced both BMI and depressive symptoms (Ma *et al*. 2019). In this study, baseline depressive symptoms on the Patient Health Questionnaire were higher than in the *MooDFOOD* trial (13.8 vs. 7.4 in *MooDFOOD*), adding credence to the suggestion that behavioural approaches may be more effective for individuals with a higher level of baseline symptomatology.

Conclusions and future directions

The nutrition-based approach to treat or prevent depression reviewed here is a promising emerging field that warrants further investigation. Treatment and prevention of common mental health problems, such as depression, is a pressing global priority and more resources should be devoted to understanding what works and for whom. We do not underestimate the need for treatment of depression and indeed believe that more resources should be devoted to develop new treatments than is currently the case. We do emphasise, however, the need for greater efforts on prevention. As has been pointed elsewhere, our society tends to focus on the 'rule of rescue' rather than prevention. However, this may well be 'collective health care myopia' (O'Connell, Boat & Warner 2009). Prevention efforts are not visible in the same way that treatment effects are but can deliver cost-effective outcomes (Ebert & Cuijpers 2018). It is also important to consider that even small reductions in depressive symptoms on a population scale are likely to produce an enormous public health benefit (Muñoz *et al*. 2016).

Although there are still very few RCTs assessing integrative nutritional and psychological approaches to depression prevention, the current literature includes evidence, albeit limited, that nutritional supplements are *not* effective for the prevention of depression. It therefore remains an open question as to whether future nutrition-based interventions will have the ability to prevent depression. There is some evidence, on the other hand, for small beneficial effects of omega-3 supplements in the treatment of depression as an adjunctive therapy. Whole-diet approaches may yield beneficial effects on depressive symptoms in clinical depression (see the *SMILES* trial; Jacka *et al*. 2017), although the majority of studies have used non-clinical populations (Firth *et al*. 2019b). This latter fact leaves open the possibility that there is potential for depression prevention effects through whole-diet approaches, but more research is needed in this area to ascertain this.

We have also noted here that we should proceed with caution to ensure that we do not cause harm, either directly through any iatrogenic effects (*e.g*. negative effects of supplements) or by inadvertently signposting those in need, whether they are patients with clinical depression or individuals with elevated symptoms or with known risk factors for disorder, to ineffective interventions, when they might otherwise seek help from interventions known to be efficacious.

Moreover, there are a number of important questions that remain unanswered in the emerging area of nutritional psychology including but not limited to, what components make an intervention work? For whom will they be most effective? What are the underlying mechanisms at play? Are they more effective for prevention or treatment? Under which conditions will an intervention work and when will they not? For example, in the *MooDFOOD* depression prevention trial, the behavioural intervention was only able to prevent depression in those with good adherence to the protocol and was only able to reduce symptoms of depression for those with higher initial symptom levels. Several nutrition-related candidate mechanisms of action are plausible in depression prevention and treatment interventions, and future research needs to tease these out. For example, is change in nutrient status the key intervention ingredient (or perhaps only in those with an initially low status), or perhaps, as we have ventured, swapping a range of unhealthy behaviours for more healthy ones, and making these habitual?

Equally, we need to know whether these types of intervention are more effective as an indicated prevention when a disorder is unfolding, or as a treatment for severely depressed patients, or alternatively, more as recurrence prevention. Who should deliver the intervention to maximise its effectiveness? For instance, in the review of diet quality interventions on depression (Firth *et al*. 2019a), involvement of a nutritional professional (*e.g*. dietitians or nutritionists) in delivering dietary interventions was associated with a significant reduction in depressive symptoms, whereas interventions without such involvement fared no better than control. We also do not know what the optimal nutrient levels should be for mental health and wellbeing and so a nutrition-based intervention may be

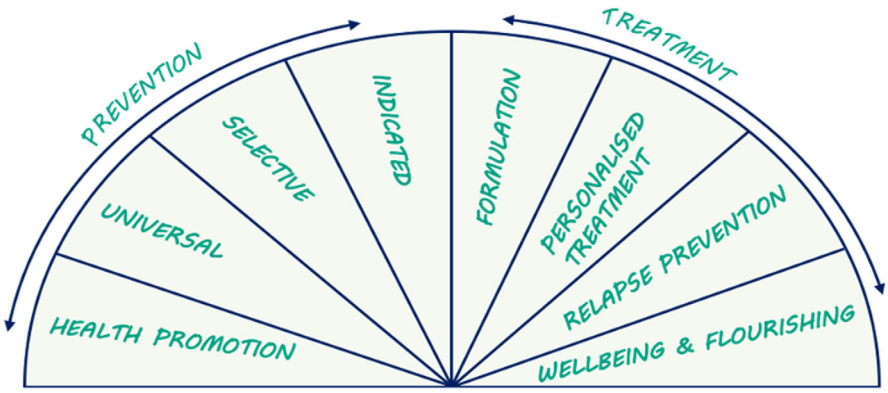

Figure 1 A blended prevention and treatment model for depression based on earlier work (Muñoz, Mrazek & Haggerty 1996; O'Connell, Boat & Warner 2009).

personalised based on, for example, individual differences in initial omega-3 levels or perhaps levels of inflammatory markers or their combination (Guu *et al*. 2019). These and other questions should be the focus of future research and given the often-blurred boundaries between prevention and treatment, a blended model of intervention in depression may be a useful way to plan future work. We illustrate one such model in Figure 1, adapted from O'Connell, Boat and Warner (2009) and applied to the case of depression.

Prevention of depression may begin with health promotion that includes psychoeducation on lifestyle factors known to be important in the etiopathogenesis of the disorder such as diet, sleep and exercise (Lopresti 2019), or more broadly building resilience to stress. Prevention of *de novo* depressions could be approached through universal programmes, such as dietary advice based on national dietary guidelines and promoting positive healthy habits, or used in a selective way for individuals with known risk factors for depression. Alternatively prevention may be indicated, where high levels of symptoms are present in individuals but without disorder (*e.g*. Van Voorhees *et al*. 2009). Personalised, or precision approaches to intervention, including both prevention and treatment, could be facilitated through a person-centred approach of formulation, which summarises and integrates a broad range of biopsychosocial putative causal factors. For example, identifying diet quality, nutrient status, psychological and behavioural patterns as well as somatic and psychological symptoms may guide professionals towards a more tailored intervention for a given individual. Whether these approaches will turn out to be valid is an empirical question and we need to collect sufficient evidence before proceeding. As discussed, depression can run a chronic course and relapse is a major problem (Cuijpers, Beekman & Reynolds 2012) and so future research should also test the best approaches to prevention of relapse or recurrence. Finally, recognising that the ultimate goal for some is not simply the absence of disorder, intervention should ideally also consider ways in which to also enhance more positive outcomes of wellbeing and flourishing (Huppert & So 2013).

Finally, we recognise that depression is a complex and heterogenous problem likely to involve a number of interacting lifestyle factors, not only diet and nutrition. The nature of these interactions and their relative contribution in depression should be the focus of basic science, applied research as well as clinical practice.

In conclusion, the psychological-nutritional approach has shown promise for mental health and depression treatment in particular but more work is needed to understand the optimal strategies for those in need, whether that means health promotion, graded prevention or treatment, recurrence prevention or facilitating greater wellbeing/flourishing, helping people to live the life that they want to. More basic science as well as rigorous, high-quality RCTs conducted in well-described groups (*e.g*. those at higher risk, clinical patients, those with a history of depression) are required to help us understand the underlying mechanisms and moderating factors involved, and to test novel interventions in the emerging field of nutritional psychology.

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Conflict of interest

No conflicts of interest have been declared by any author.

Author contributions

MO was the lead author on the manuscript. All authors contributed to the writing of the manuscript and approved the final version.

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