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Developing our understanding of nutrition in depression

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Abstract

Research to date has convincingly demonstrated that nutrition impacts depression. Population-based studies have shown that diet, food types, dietary supplements, gut bacteria, endocrine systems and obesity all play a role in depression. While nutrition could provide an important therapeutic opportunity in depression, clinical trials have not shown clinically meaningful results, and it appears unlikely that nutrition is a central determinant of depression. Conversely, however, prior research is inconclusive to inferring that nutrition does not have a clinically significant effect. This would require elucidating precisely when nutrition affects depression which necessitates an alternative, more granular, model for the nutrition–depression interaction. The network theory of mental disorders, which studies how mental disorders arise from a causally related network of symptoms and external factors, is proposed as an alternative model for understanding the complexity of the nutrition–depression link. This approach would uncover which relationships, between aspects of nutrition and depression symptoms, warrant further study at a population and laboratory level. Furthermore, from within nutrition science, is a movement dubbed 'New Nutrition Science' (NNS) that aims to integrate biological, social and environmental determinants of nutrition. NNS is important to nutrition–depression research which has yet to reveal how social factors impact the nutrition–depression interaction. Network theory methodology is fully compatible with the network modelling already used in NNS. Embracing both network theory and NNS in future research will develop a full and complex understanding of nutrition in depression.

Key words: **Depression: Nutrition: Network theory: New Nutrition Science: Mental health**

The link between nutrition and depression has been extensively studied. There is a great breadth of scientific inquiry into the relationship encompassing work on diet, food types, dietary supplements, gut bacteria, endocrine systems and obesity. Population-level studies have repeatedly demonstrated a link between aspects of nutrition and depression (e.g.[1–3]). This replicable finding has obvious clinical bearing. Indeed, while, in the current epoch, we are observing the 'double burden of malnutrition' (rising obesity and undernutrition)[4], a significant proportion of patients with depression consume high-energy, nutrient-poor diets[5,6], and psychiatric medications are well documented to affect appetite and satiety[6]. Nutrition may be an important novel addition to the available interventions in depression.

Approximately one-third of patients experience depression that is resistant to typical pharmacological therapies[7,8]. Combination with psychotherapy improves symptoms and reduces remission rates, but a significant treatment-resistant population remains[9,10]. Other therapeutic options such as atypical antipsychotic medications, electroconvulsive therapy or ketamine may have troublesome side effects, require specialist psychiatric input or not be widely available[10,11]. Nutritional interventions may offer a widely available adjunct to the first-line management of depression. Importantly, while other external stressors to mental health are not within a clinician's remit to intervene on (e.g. social deprivation, relationship breakdown, traumatic life events), a nutritional change, while challenging, is achievable (e.g. in obesity[12–14]).

However, two issues remain in giving population-level findings' clinical bearing. The first is that, although population-level study has consistently shown an interaction between nutrition and depression, effect sizes are not clinically significant (e.g.[15]). Given that changing diets is difficult to achieve[14], the current evidence does not support the widespread use of nutritional interventions in depression. The second issue is that understanding is lacking in *how* exactly nutrition should intervene in depression, that is, which aspects of nutrition impact which depressive symptoms. These two issues are highly related, as, if it is the case that clinically insignificant effect sizes at a population level are due to certain nutritional factors impacting depression meaningfully, but only affecting parts (select symptoms) of depression, or certain subgroups of patients with depression, then, in select clinical presentations, implementing dietary change would be indicated.

Abbreviation: RCT, randomised controlled trial.

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Although it remains possible that nutrition has an evenly distributed, clinically insignificant effect across depression symptoms, it is important to establish for certain whether this is the case, because nutritional interventions, if effective, would be widely available across a range of healthcare settings and because research into nutrition and depression continues apace, but with an uncertain rationale. Overall, the current evidence is inconclusive to inferring that nutrition does not have a clinically significant effect in depression.

Theoretical and laboratory-level research into the depression–nutrition link has provided important insight into how nutrition intervenes in depression and identified areas for further interrogation at a population level. However, bridging theoretical and laboratory research with population-level study has proved difficult. One issue is in defining the importance of a single cellular or metabolic event within a complex human diet. Another is in accounting for the varied environmental contexts that people are exposed to, which may change how laboratory findings, revealed under controlled conditions, operate. A case study of this challenge is observed with research into the gut–brain axis, where convincing animal model findings (e.g.[16]) have shown variable benefit when translated into clinical trials (e.g. with probiotics, see ref.[17]).

An alternative theoretical model for the relationship between nutrition and depression is proposed – drawing from the network theory of mental disorders, outlined by Borsboom[18]. The network theory of mental disorders claims that mental disorders are not single entities but dependent on an interaction of multiple internal and external phenomena. This approach applied to studying the nutrition depression link would (a) reveal a more granular understanding of *how* nutrition affects depression at the population level and (b) provide a framework in which to embed laboratory-level findings to understand how they are contingent on wider human physiology and environmental contexts. It is not claimed here that prior research either at the laboratory or population level has been inadequate in methodology or scientific rigour. Indeed, it is hoped that network theory methodology would reveal relationships, between aspects of nutrition and depression symptoms, that warrant further study at a population and laboratory level.

Meanwhile, from within the nutrition canon, a paradigm that increasingly incorporates social factors into nutrition research (see[19]) could further our understanding of the nutrition–depression link. Social factors, often controlled for in studying the nutrition–depression interaction, could be relevant in two important ways. Firstly, if nutrition is a key way in which certain social determinants affect depression, then, in those social contexts, nutritional interventions are more likely to be effective (see graphical abstract, depicting the two pathways by which social factors could affect depression). Secondly, it is important to reveal whether the impact of nutrition on depression is dependent on social factors, that is, are social factors effect modifiers on the causal pathway between nutrition and depression. Network theory methodology could again be employed here and is fully compatible with the network modelling already used in nutrition science to understand the multifarious (including social) causes of nutritional health.

Nutrition and depression, what is known currently?

Research covering a large swathe of nutrition literature has identified the relevance of nutrition to depression. These include studies on diet, food types, dietary supplements, gut bacteria, endocrine systems and obesity in depression.

Healthy diets reduce the risk of depression onset and reduce depressive symptoms[2,15,20–22]. Additionally, unhealthy diets increase depression risk and depressive symptoms[21,22]. For example, Molendijk *et al.*[15], in a large meta-analysis, demonstrated that population adherence to healthy diets had a significant linear relationship ($P < 0{\cdot}01$) with reducing depression risk (OR: 0·64–0·78). Jacka[21] and Conner *et al.*[23], meanwhile, have shown dietary interventions improve depressive symptoms in randomised controlled trials (RCT).

Certain food types also affect depression. Foods with low glycaemic index are associated with lower risk of depression[3]. Meanwhile, foods with high inflammatory potential, measured using the dietary inflammatory index, have shown to negatively affect depression in a large (n 43 685) female cohort[24].

Dietary supplements Mg, Zn, Fe, n-3 fatty acids and vitamin B_9 have all shown some benefit in depression[1,25,26], although there is some complexity in how dosing of supplements changes their impact[1].

The 'gut–brain axis', the interactions between the brain and microbiome, is a growing research area. Probiotics (capsules containing certain bacterial strains) have shown significance in reducing depression symptoms[1,27–30], although there is inconsistency in these findings, which is further discussed below[29].

Relatively few population-based human studies have examined the endocrine system in depression. The gut hormone ghrelin may slightly reduce depression symptoms[31], possibly due to its effects in improving sleep[31,32]. Given the role of obesity[33] and the metabolic syndrome[34] in depression, pioglitazone, used in type II diabetes mellitus, has also been studied. In a meta-analysis, pioglitazone, which has anti-inflammatory and insulin-sensitising properties, induced higher remission rates of depressive episodes (OR: 3·3) even in patients without the metabolic syndrome[35].

Interpretation and clinical relevance

The above findings convincingly indicate that nutrition impacts depression. However, beyond using these findings to inform public health guidance (as advocated by refs.[2,15,21,36]) authors argue that clinical applications should be postponed until research can clarify the mechanisms by which nutrition affects depression[1,2,15,20,22,25,26]. There remain challenges both at the population level of study and at the theoretical or laboratory level of study in generating this kind of mechanistic understanding.

Population-level challenges. Despite much population-level research being top-tier according to the hierarchy of evidence (meta-analyses/systematic reviews[37]), studies have yet to generate a mechanistic understanding of how nutrition and depression interact. Additionally, although this research has demonstrated that nutrition impacts depression, it has not revealed clinically meaningful effect sizes. For example, in

a meta-analysis, methylfolate reduced depression symptoms 0·78 points on the HAM-D 17 depression scale[38], meanwhile another meta-analysis showed the number needed to treat with a high quality diet to prevent one case of depression was 47 participants[15].

Given these small effect sizes, it is unlikely that any one nutritional intervention acts on a 'central determinant' of depression – as argued by Molendijk *et al.*[15]. The theoretical model, in which nutritional interventions act on depression as a single construct, is dominant in the population-level research canon. In these studies, 'depression', as an entity, is positioned as a latent variable, affected by a nutritional change, whose improvement is inferred from a change in depressive symptoms or rate of depression onset as a measurable outcome variable. While this is the logical starting point for evaluating the interaction between nutrition and depression, it is unlikely that understanding of nutrition's clinical significance in depression will be advanced further using the same model. It is common in the literature to suggest further population-level research without proposing an alternative model for understanding the nutrition–depression link (e.g. with more participants[20], or more targeted RCT[1,22] or using randomised prevention trials[15]).

Specifically, there are two reasons why positioning depression as a latent variable hinders understanding whether nutritional interventions could be clinically significant: (1) studies cannot provide a detailed interrogation of exactly how nutrition affects depression and (2) studies are required to control for variables, whose interaction with depression and nutrition is of therapeutic interest (e.g. socio-economic factors). Put differently, for a clinician it is important to know if nutrition does not affect all presentations of depression equally and whether certain contexts impact nutrition's interaction with depression.

In a similar vein, Cartwright[39] argues RCT are an excellent method for advancing an 'it works somewhere' claim but do not develop an understanding of *when* an intervention will work, which depends on understanding the wide range of circumstances that determine the efficacy of an intervention. This level of understanding is not developed with RCT as their structure controls for factors that might contaminate an intervention effect on an outcome. It is possible, as some authors have reported, to use meta-analysis to try to tease apart the heterogeneity in the literature. Meta-analysis allows the identification of populations that are sources of heterogeneity in a cohort of multiple populations. For example, Firth *et al.*[1] identified that *n*-3 fatty acids had no efficacy in populations with physical health co-morbidities, and Li *et al.*[25] identified that Mg had its strongest effect on depression in Asian countries. These findings, however, show a degree of *post-hoc* analysis and are not theoretically driven. Meta-analyses, again, are not the best method of *understanding* heterogeneity[40] or, therefore, predicting when interventions will work.

Concluding their review, Jacka[21] posits a future challenge is to 'refine, replicate and scale up clinical and population level dietary interventions'. This will not be possible through population-level research without a shift in the theoretical model, given that nutrition, as discussed, is unlikely to be a central determinant in depression.

Translational challenges. Laboratory and theoretical research has investigated how nutrition might impact depression through gut bacteria, local inflammation, neurotransmitters and gut hormones[41–44]. Some of this work has already translated to clinical trials, for example, with the use of supplements, probiotics and pioglitazone to alleviate depression (see the previous section).

There is a continued difficulty, however, in translating this research to real-world contexts. Human nutrition is complex, composed of innumerable interacting nutrients and affected by external factors (see[45]). Laboratory and theoretical research, meanwhile, interrogates interactions in highly controlled conditions.

This problem of ecological validity is due to initial research and subsequent translational work being unable to account for the *complexity* of human diets and the *contexts* in which they occur. Research on the gut microbiome in depression demonstrates this.

Challenges in gut bacteria–depression research. A replicable finding is that transplanting the microbiome from patients with depression to healthy animals induces depressive symptoms (e.g.[16]; for review, see ref.[46]). Certain bacterial strains (Faecalibacterium, Coprococcus and Dialister bacteria) have also been identified at a human population level to be associated with depression[47]. Exploring this relationship further at a molecular level with animal models of depression has revealed that unfavourable bacterial selection in the gut (termed dysbiosis) negatively affects depressive symptoms. This effect is shown to be mediated by the innate immune system[48], meanwhile certain bacteria (e.g. *Clostridium butyricum*) influence neurotransmitter metabolism with concurrent changes in depressive symptoms[49].

The diversity of evidence implicating gut bacteria in depression has justified the study of probiotic treatment in depression. Systematic review and meta-analysis of these studies have shown positive effects of probiotics on mood[17,27,28,30]. However, there remains a significant heterogeneity in the literature base in terms of the strength of this interaction[17,27,30], and one recent, updated review of RCT concluded that there was no enough evidence currently to support or refute the anti-depressant potential of probiotics (only seven of thirty-two studies showed a significant anti-depressive effect of probiotics[29]).

Two explanations arise from the literature as to why there is a problem in translating prior research into clinical gains. The first is that there has been a focus on a few key bacterial strains (which are those contained in probiotics); the gut microbiome, meanwhile, is composed of hundreds of bacterial strains[41]. Fond *et al.*[17] argue probiotics' limited bacterial content could be the cause for their mixed results in depression and that transplanting the entire faecal microbiome may offer better results. Here, prior research and its translational work fail to account for the *complexity* of nutrition. Indeed, probiotics are one of a growing group of single-agent nutritional interventions treated as pharmacological agents, termed 'nutraceuticals' (alongside vitamins, antioxidants, etc.)[21,50]. Although interesting, they are only a small part of an individual's overall diet, and investigating them in isolation may obscure their exact potential.

The second explanation for the therapeutic inconsistency of probiotics is that research cannot account for the *context* in

which human nutrition occurs. Dysbiosis, the unfavourable shift in gut microbiome composition, has been shown to be affected by inflammation[48], western diet[51] and possibly urban environments[44]. It is not unreasonable to suggest that probiotics will be ineffective when environmental factors overwhelmingly negatively impact gut bacterial composition.

The above example demonstrates that the translational potential of laboratory and theoretical research into the nutrition–depression interaction is dependent on being observant of the complexity and context of human diets.

Network approach to nutrition in depression

A network approach to studying nutrition and depression would enable us to deepen our understanding of the nutrition–depression relationship while retaining ecological validity in our approach.

What is network theory?

The network theory of mental disorders, proposed by Borsboom[18], characterises mental disorders, including depression, as symptoms (shown as network nodes) that are causally related (via network edges) to other symptoms. Stable disorder states arise from strongly activated symptoms keeping each other activated by feedback relations, creating a self-sustaining network. The model includes external factors that can activate one or more symptoms and be part of creating or maintaining stable disorder states.

In part, network theory has arisen from increasingly sophisticated statistical methodology[52], and from how representing mental illnesses graphically as a network allows us to understand their complexity in a way that is hard to achieve otherwise[53].

Likely, the most controversial aspect of the model is that it rejects the notion that mental disorders arise from a common cause, proposing instead that a disorder *is* the causal interactions between symptoms[18]. However, with network theory methodology it is possible to accept a mixture of these two models cooperating. For example, a common cause may activate a cluster of core symptoms that interact with others to create the full disorder profile[52].

What could network theory offer the study of nutrition and depression?

Firstly, a network approach would permit studying the causal relationships between a range of nutritional variables and individual components of depression (i.e. symptoms, or even parts of symptoms (e.g. as described by Bentall[54])). An example network is shown in Fig. 1(a). The strength of causal interactions (edges) between variables (network nodes) is depicted by the thickness of arrows. It is important to recognise that one pitfall of models that study multiple interactions is that they are at risk of overfitting data to the study population and reducing generalisability and replicability of findings. This can be controlled for, however, with statistical methods that reduce false-positive rates – such as reducing all small coefficients to zero, or to give up on weighted comparisons (i.e. identifying the strength of interactions) and instead settle for binary (present/absent) associations[52]. An example binary network model is shown in Fig. 1(b). In either case, a more granular understanding of the nutrition–depression relationship is revealed while avoiding the problematic assumption that nutrition is a central determinant in depression (as was outlined above).

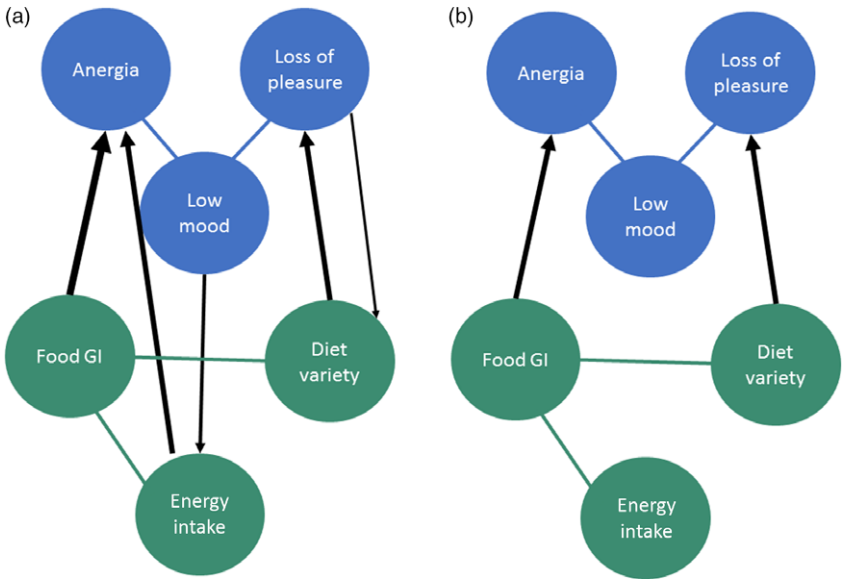

Fig. 1. (a) Nutritional components (food GI, energy intake and diet variety) and depression symptoms (anergia, low mood and loss of pleasure) are depicted as network nodes. Within these two categories, straight lines identify where nodes within each category are likely to co-occur. Arrows depict causal interactions between nutritional components and depression symptoms. The thickness of arrows depicts the strength of interactions. (b) The same network as in (1a) is shown. Here, however, causal interactions between nutritional components and depression symptoms have been reduced to present/absent interactions in a simplified, binary network. GI, glycaemic index.

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Secondly, having identified which are the strongest edges between network nodes, further study can be directed towards areas that will generate the most clinical gain. What form this further study takes is not mandated by network methodology, while network edges describe a causal relationship, they are otherwise theory free. This is attractive as the nutrition–depression interaction is characterised by several contributing research fields. One could envisage, for example, in Fig. 1(b), the edge between food glycaemic index and anergia being most easily described by biochemical mechanisms, whereas the edge between diet variety and loss of pleasure being most easily described by psychological mechanisms. The process of selecting important edges within a network to study further, by default, gives any theoretical or laboratory-level study of those edges more ecological validity and, consequently, better translational potential.

As well as addressing some of the limitations of previous research, a network approach offers further benefits that are of note. Networks are either constructed at a group level (partial correlation networks dubbed Pairwise Markov Random Fields) at a single time point, or at an intra-individual level (vector autoregressive model) where networks interrogate how symptoms relate to each other/external variables over time. The opportunity to study, with intra-individual level networks, how depression symptoms relate to nutrition over time is particularly appealing as the impact of nutrition on health is a prolonged process. As an example of such a study, Yang *et al.*[55] examined, over the course of a year, how social interactions affected mood. Across the year, participants measured their mood and related parameters after every interaction during three intense 21-d bursts, using smartphones. This allowed researchers to generate detailed conclusions of how mood and social dynamics influence each other over time. A similar protocol would generate understanding of how depression symptoms relate to food behaviour over a prolonged time course. Indeed, a problem faced in studying nutrition–depression interactions is that of reverse causality – it is a known phenomenon that people suffering from depression tend towards high-energy, nutrient-poor diets [5,56]. Although Jacka *et al.*[5] have shown that this tendency does not explain away the nutrition–depression link, intra-individual network modelling would tease out whether a bidirectional relationship or feedback exists between nutrition and depression over time.

Lastly, RCT are a costly way of carrying out research. Generating enough 'it works here' claims through RCT to be able to make confident 'when it will work' claims would be a costly process in both time and money. The number of interactions that can be interrogated in a single network theory study would provide an important shortcut[57]. Given the amount of nutrition–depression research already undertaken, it is possible that data already exist that could be analysed afresh, using a network approach, to gain new insights at a minimal cost.

Changes in nutrition research are relevant to mental health research

Nutrition research has broadened since its inception to incorporate social and environmental factors, and this has bearing on how we research nutrition in depression.

Developments in nutritional science

While nutrition has historically been a biologically driven research field, it is now argued 'nutrition in principle and practice should be a biological and also an environmental and social science' – this is the viewpoint of 'the New Nutrition Science project' (NNS)[19].

This change is a reaction to the rise in non-communicable ill health (e.g. obesity and diabetes) and the 'double burden of malnutrition' (rising obesity and undernutrition)[4]. Public health guidance, based on an early biomedical understanding of nutrition, has not succeeded in curbing these trends. While the biological effects of food in the body are important, public health policy falls short when it is confined to dietary advice. Many complex social and environmental factors are central in determining the food that people have access to and eat on a daily basis[58].

An example of New Nutrition Science in action is shown by Patel *et al.*[59]. In a nutritional intervention in rural Malawi, researchers sought to improve child malnutrition by addressing the distribution of household work between sexes. Men were encouraged to be more involved in the preparation and cooking of food through cultural events and 'recipe days'; children in those communities that adopted the scheme showed improved growth measurements across a 7-year period. Here, one cause of malnutrition, sex inequality, was identified and targeted as a specific cultural determinant of malnutrition. Clearly, this cause of malnutrition could not be identified and addressed through a purely biological understanding of nutrition.

Relevance of New Nutrition Science to researching the depression–nutrition interaction

New Nutrition Science is relevant to researching the nutrition–depression relationship. Given that social determinants have bearing on nutrition, understanding the nutrition–depression link requires accounting for social factors. There are two ways in which we can characterise how social determinants might be relevant.

Firstly, we could examine how a nutritional intervention in depression is dependent on social context: social factors may be effect modifiers of the depression–nutrition interaction. There are a number of ways that a measured effect modifier (socio-economic factors) can be causally related to the effect of one variable (nutrition) on another (depression)[60] to outline a helpful classification). For example, Pourmotabbed *et al.*[36] in systematic review showed that food insecurity increases depression risk (adjusting for other social variables - age, sex, race/ethnicity, income, education, living arrangement, etc.); one could imagine that the impact of a nutritional intervention on depression would vary across the degree of food insecurity at baseline. This would be an example of direct effect modification[60]. Alternatively, Logan[44] advances the idea that urban environments cause unfavourable shifts in gut bacteria (gut dysbiosis) - which is attributed to increasing depression risk (see above). Here, urban environments would be an indirect effect modifier, acting through gut dysbiosis, to modify the effect of a nutritional intervention (say, probiotics) on depression[60].

Alternatively, we can describe the relevance of social factors as impacting depression via nutrition. For example, in an

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observational study, one might detect lower rates of depression in poor rural farming communities compared with rates of depression in poor urban environments. Some of the effect of social context on depression could occur via nutrition (e.g. to take from the above example, lower energy intake and unhealthy gut flora in the urban group) as well as by other means (e.g. more violent crime in urban areas).

Jacka *et al.*[56] have already made strides to outline the extent that social factors affect the depression–nutrition interaction. Indeed, they found that 'socioeconomic factors explained 25·2 % of the effect of prudent diet and 66·0 % of the effect of western diet on depression symptom scores'. Future research could help elucidate how to use nutritional interventions clinically in depression by exploring which social factors impact depression via nutrition. In patients from these backgrounds, nutritional interventions would be more strongly indicated.

How then to develop a full and detailed understanding of the complex interaction of nutrition, depression and social factors? Network modelling may again provide a solution. Network modelling has been used to identify the different factors influencing food behaviour[61]. Meanwhile, social network studies have investigated how food behaviour spreads across social networks[62], for example, obesity developing through peer groups in schools[63] and eating disorders developing across friendship groups[64,65]. Furthermore, directed acyclic graphs that are used in epidemiology and to model effect modification[60,66] are also used by the proponents of the network theory of mental disorders[67].

One could imagine either (a) at a population-level study, incorporating social factors (e.g. social isolation) within a network model of the nutrition–depression interaction (see Fig. 2), or (b) at an intra-individual level, studying how food behaviour–depression links are impacted by other individuals in a social network over time. Work of this kind combining 'slow and fast networks' has already been done studying the interaction between background personality and depressive episodes[68]. Similarly, network modelling has been employed to study the interaction between neighbourhood social environment and mental health[69] and the bidirectional relationship between social media use and depressive symptoms[70].

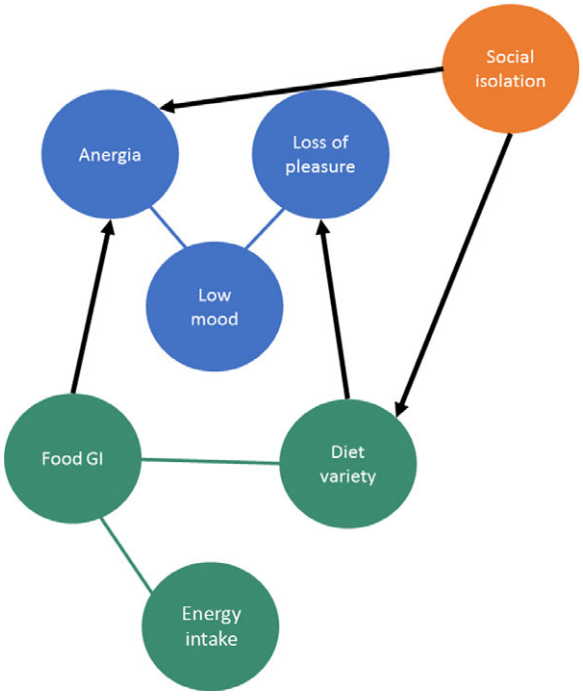

Fig. 2. In the above example, the network node 'social isolation' is causally related via network edge to anergia and diet variety. One can envisage the knock-on effect this would have on loss of pleasure in particular.

Conclusion

Progress has been made in investigating the relationship between depression and nutrition, although problems remain. Population-level research has not revealed the mechanisms that account for the relationship and cannot, therefore, reliably predict when interventions will be effective. Theoretical research has focussed on individual causal pathways, which makes their results hard to generalise to less-controlled contexts. The solution to these problems is to adopt a model of depression, derived from the network theory of mental disorders, and an understanding of nutrition, which incorporates social and environmental factors. These are highly compatible paradigms and, between them, allow the incorporation of multiple causal pathways into a testable mechanistic model. Looking forward, this is the most promising route to determining exactly when and whether dietary interventions can be used to combat depression.

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