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Mendelian Randomization for Nutritional Psychiatry

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SUMMARY

Nutritional psychiatry is a growing area of research, with several nutritional factors implicated in the aetiology of psychiatric ill health. However, nutritional research is highly complex, with multiple potential factors involved, highly confounded exposures and small individual effect sizes. This paper considers whether Mendelian randomization provides a solution to these difficulties, by investigating causality in a low risk and low-cost way. Current studies using MR in nutritional psychiatry are reviewed, along with the potential opportunities and challenges of using this approach for investigating the causal effects of nutritional exposures. Several studies have identified potentially causal nutritional exposures using Mendelian randomisation in psychiatry, offering opportunities for further mechanistic research, intervention development, and replication. Using Mendelian randomisation as a foundation for intervention development allows the best use of resources in an emerging discipline in which opportunities are rich, but resources are often poor.

Key words

Mendelian randomization, nutritional psychiatry, causality

INTRODUCTION

The founding of the International Society for Nutritional Psychiatry Research[1] reflects an increasing recognition of nutrition as a modifiable risk factor for mental ill-health, and the need for good quality research in this area. Whilst the adverse psychological effects of severe nutritional deficiency are well established,[2] the extent to which subtle nutritional factors might have on cognitive and affective processes, or on the increasing burden of psychological ill health at the population level remains unclear. As wholefood diets have been replaced by processed foods - high in sugar and low in essential fats, vitamins and minerals - many argue that subtle malnutrition may exist even in the presence of calorie-abundance,[3, 4] with unclear repercussions for population mental health. [5, 6] Several meta-analyses of prospective studies suggest that a high-quality diet can reduce the risk of mental illness,[5, 6] warranting further investigation of specific nutritional factors and mechanisms. Conventional epidemiological associations between nutritional intake or status and psychiatric outcomes are highly prone to confounding by lifestyle and correlated dietary factors.[7] Furthermore, as many aspects of nutrition are affected by mental ill-health,[8] it is likely that reverse causality, or at least a bi-directional relationship, explains some of these associations. Finally, as individual nutrients have small effect sizes, large sample sizes are required to explore such associations with adequate statistical power, in which accurate dietary measurement is difficult. Despite the best efforts of researchers to control for these limitations, nutritional epidemiology is limited by issues of residual confounding, biological complexities and limited power.

Interventional research in nutritional psychiatry is a potential solution to these limitations, as good quality randomized controlled trials (RCTs) eliminate issues of confounding and reverse causality. There are a growing number of RCTs in nutritional psychiatry. Although many studies have focused on individual nutritional supplements - probably reflecting the parallels with a pharmacological research model,[9-11] there are few supplements that have been robustly identified as beneficial in psychiatry.[11] Results are often inconsistent, and it is unclear which interventions are worth further investment. Given the complexities and inter-relatedness of dietary composition, a

more comprehensive nutritional approach may be preferable. Combination micronutrient supplement interventions[12-14] and interventions focused on making broader changes to dietary patterns might be advantageous.[15, 16] Dietary pattern interventions offer a potential solution to this complexity, with supporting meta-analytical evidence in both observational[5] and interventional research[17]. However, selecting the right intervention and participants, and accounting for behaviour change and attrition, make the planning and evaluation of such trials complex and costly. With a multitude of potential nutritional interventions, it can be difficult to prioritise the most likely to be effective. False negatives from underpowered designs or minor aberrations in a complex intervention, might hinder the development of potentially beneficial interventions. Conversely, false positives due to biased designs, compounded by publication bias, lead to wasted expenditure and potential harm in repeated trials. Further evidence to establish likely causality for specific nutritional factors to underpin nutritional interventions and identify the most likely beneficial components would prevent wasted time and expenditure.

This paper considers whether 'Mendelian randomization' is a viable method to inform intervention development in nutritional psychiatry, in a low-cost and low-risk way. We review existing Mendelian randomization studies in nutritional psychiatry, the challenges faced, and opportunities for further research.

MENDELIAN RANDOMIZATION

Mendelian randomization (MR) is a method that is increasingly used to infer causality in epidemiological research. MR uses genetic markers that are robustly associated with a particular potentially modifiable exposure as 'instrumental variables' in assessing the relationship between an exposure and an outcome.[18, 19] As genetic markers (or 'alleles') are randomly allocated at conception, many have compared MR to a natural RCT, in which variant alleles rather than interventions, are randomized (figure 1a). The individual variations in genetic alleles are referred to

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as single nucleotide polymorphisms (SNPs). MR exploits this natural genetic variation to circumvent the problem of confounding and reverse causality (figure 1a).

The concept of MR relies on key assumptions for validity (figure 1b). Whilst a comprehensive review of MR is beyond the scope of this review, some key terms used to describe aspects of MR studies relevant to this review are explained in Table 1. For more detail, see Zheng et al 2017[20] and the MR Dictionary.[21]

There are potential benefits to applying MR methodology to nutritional psychiatry, as a cheap and powerful method for attributing causality to putative exposures, and it enables the exploration of multiple avenues for intervention development in a low-cost and low-risk way. This is particularly true with the development of two-sample MR, in which exposures and outcomes need not be measured in the same sample (figure 1c). Two-sample MR takes estimates of the SNP-exposure association from a one population (for example a genome-wide association study (GWAS) of a nutritional exposure), and the SNP-outcome association from another (for example, a GWAS of a given psychiatric outcome). This allows for the possibility of utilising the increasing sample sizes provided by large psychiatric genetic consortia, without the need to access individual-level data on specific nutritional measures. Given the relatively small effect sizes, and modest genetic contribution to nutritional exposures, a two-sample MR methodology using large outcome samples should provide adequate power to investigate them.

One advantage of MR is that, providing appropriate genetic instruments are available, it is theoretically possible to model the results of certain randomised trials, thereby reducing unnecessary potential harms and expenditure. One example in the context of nutritional epidemiology was given by a recent MR study to model the Selenium and Vitamin E Cancer Prevention Trial (SELECT) for prostate cancer, which was based on extensive epidemiological evidence at that time. The SELECT trial, randomised 35,533 men to use selenium supplementation, to investigate whether increasing selenium levels might prevent prostate cancer.[22] The $114 million trial ended prematurely as results showed that selenium supplementation not only failed to reduce

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prostate cancer risk, it was likely to increase the risk of advanced prostate cancer and type 2 diabetes mellitus. These results were replicated by MR, using genetic instruments for circulating selenium in the PRACTICAL consortium.[23] Although retrospective, the MR study took a fraction of the financial and time burden of a trial, and more importantly avoided any potential harm to participants.[23]

A comparison between MR and a naturalised RCT, has its limitations. Firstly, as genetic variants reflect lifetime exposures rather than short durations of therapeutic intervention, MR may produce a stronger effect than in the best approximation of a time-limited intervention. Conversely, individual adaptation to genotype may reduce the effect of the SNP on the exposure and so may underestimate the effect (also known as canalization (see table 1)). Rather than a replacement for RCTs, MR might be viewed as a foundation from which interventions for further development can be identified, in combination with epidemiology and basic science, also referred to as triangulation[24] (figure 2).

MR may be particularly useful for a field such as nutritional psychiatry, in which many of the interventional trials have small to modest sample sizes. A well-powered MR study can be used to verify results in a potentially underpowered study, as well as to inform future studies. MR studies showing no evidence for a causal effect need careful consideration about whether it is possible to rule out a clinically significant effect based on the available parameters, and whether replication using updated background literature would be beneficial at a future date. This includes whether the methods and instruments are valid, power is adequate, and whether biological complexity might complicate results. This is particularly relevant in psychiatry, where diagnostic categorisation is yet to account for the diversity of symptoms and presentations categorized by a single 'disorder'. Studies showing strong evidence for an effect need equal consideration before intervention development is considered, - such as how to increase the nutritional exposure in the desired way, whether participants are selected based on deficiency states, and whether supplementation might have potential adverse effects.

MENDELIAN RANDOMIZATION STUDIES IN NUTRITIONAL PSYCHIATRY

We identified 26 studies using MR to investigate causality in nutritional psychiatry (Table 2). Many have investigated a single exposure or outcome, but some have investigated multiple exposures and outcomes within the same paper. The studies are broadly grouped into three main psychiatric outcomes - cognitive impairment and dementia, schizophrenia, and mood disorders.

Dementia and Cognition

We identified 17 studies using MR to investigate the causality of nutritional factors on dementia and cognitive outcomes. Evidence suggesting a protective effect of 25-hydroxyvitamin D (25(OH)D) in Alzheimer's disease has been shown in two studies in the International Genomics of Alzheimer's Project (IGAP) Cohort (OR 0·86 per SD increase in vitamin D, 95% CI 0·78 to 0·94),[25, 26] but not replicated in the Uppsala Longitudinal Study (Hazard ratio per allele 1.04, 95% CI 0.91 to 1.19).[27] Studies investigating 25(OH)D as a causal factor in cognitive function have found no evidence for an association.[27-29] It may be that vitamin D is particularly relevant to Alzheimer's pathology, or that larger sample size or stronger genetic instruments are required to identify the effects in non-clinical population samples. Furthermore, a possible non-linear observational association between vitamin D and cognition, with both deficiency and excess associated with poor cognition, was noted by Maddock et al 2017.[29] This raises important considerations about the ability of traditional MR techniques to detect causality for cognitive outcomes,[29] as well as other associations in which a similar relationship has been noted.[30] Novel methods are being developed to manage non-linearity in MR,[31] but are not commonly employed.

Studies investigating the causal role for B vitamin pathways in dementia have had mixed results. A study looking at multiple exposures using the IGAP cohort did not provide evidence for folate (OR 0·98 per SD, 95% CI 0·72 to 1·33), homocysteine (OR 0·99 per SD, 95% CI 0·88 to 1·11) or vitamin B12 (OR 1·11 per SD, 95% CI 0·95 to 1·30) in Alzheimer's disease.[32] However, previous

studies looking at homocysteine using a single SNP in the methylenetetrahydrofolate reductase

(*MTHFR*) gene have suggested strong evidence of causality.[33] The *MTHFR* gene produces an enzyme

which activates folate to metabolise homocysteine, and SNPs in this gene have been identified in

GWAS of both homocysteine and circulating folate levels. However, some have suggested caution in

the use of the *MTHFR* gene for MR due to a complex interaction with folate intake, in which the

same polymorphism leading to reduced enzymatic activity in low-intake states (and therefore low

blood folate and high homocysteine), may not have any effect on blood folate or high homocysteine

in high-intake states.[34] Several MR studies of homocysteine using a single SNP relating to *MTHFR*

have failed to replicate using instruments containing more SNPs and explaining a greater variation in

homocysteine levels, suggesting that this SNP may be acting via a different mechanistic pathway. A

meta-analysis of the results for homocysteine in Alzheimer's disease using the different instruments

suggests some causal evidence for homocysteine (pooled effect 1.34 per SD, 95% CI 1.03 to 1.66),

but in light of the complex biology, this may be misleading. Another study investigating vascular

dementia using the same single SNP in the *MTHFR* gene also showed strong causal evidence for

homocysteine (OR 4·29 per SD log(homocysteine), 95% CI 1·11 to 16·57).[35] However, the same

caveats apply.

A single identified study has investigated amino acids in psychiatric disease, suggesting a

potential causal role for isoleucine in Alzheimer's disease (OR 1·35 per SD, 95% CI 1.08 to 1.69),

though not for other branched chain amino acids such as valine and leucine.[36]

The established link between *APOE* genotype and Alzheimer's has been corroborated using

MR studies (OR 1.41 per mg/dL of APOE, 95% CI 1.27 to 1.57).[37] Further exploration of the role of

lipids in dementia have not shown evidence for a causal role for any specific lipid faction when the

APOE SNPs are excluded from analysis.[38, 39] MR studies investigating fasting glucose (OR 1·12 per SD,

95% CI 0·97 to 1·30),[40] and vitamin E levels (OR 0·96 per SD, 95% CI 0·47 to 1·94),[41] have not found

any evidence for a causal association. A single study investigating minerals using several psychiatric

outcomes including Alzheimer's disease found no causal evidence for magnesium (0.43 per SD, 95% CI 0.08 to 2.44), calcium (Ca 0·74 per SD, 95% CI 0·45 to 1·22), Iron (1·02 per SD, 95% CI 0·94 to 1·14) or zinc (0·99 per SD, 95% CI 0·85 to 1·14), with weak evidence for low copper (0·87 per SD, 95% CI 0·75 to 1·00).[42]

Schizophrenia

We identified six studies that have investigated nutritional exposures in schizophrenia using MR. There was weak causal evidence for vitamin B6 (OR 0·99 per SD log(B6), 95% CI 0·65 to 1·51),[43] and for serum minerals (Calcium, Serum Magnesium, Copper, Iron and Zinc, see Table 2) in schizophrenia.[42] Two studies have identified an association between homocysteine and schizophrenia, in European (2·15 per SD, 95% CI 1·39 to 3·32)[44] and Japanese populations (1.14 per SD, 95% CI 1.03 to 1.27);[45] however, both used a single SNP related to the *MTHFR* gene, with the aforementioned limitations. A study looking at the causal role of glucose and insulin related traits found some evidence for fasting glucose (OR 0·84 per SD, 95% CI 0·71 to 0·99), but strong evidence for fasting insulin levels (OR 2·33 per SD, 95% CI 1·40 to 3·90).[46] Given the discrepancy with the strength of effect of fasting glucose in the same study, it is likely that insulin partially acts through an independent pathway to glucose, possibly related to a direct action as a 'neuropeptide', involved in neuroplasticity and modulation.

In contrast to findings in multiple sclerosis[47] and Alzheimer's Disease,[26, 27] no strong causal evidence has been found for vitamin D in schizophrenia (OR 0·99 per 10% increase in 25(OH)D, 95% CI 0·97 to 1·01).[48] This may suggest that the observational estimate is the result of confounding or reverse causality, but it is also possible that standard MR techniques have been unable to detect a true causal association due to limited power, population stratification, or biological complexities (table 4). Although the power of the study appears more than adequate (example sample sizes based on MR power calculations are shown in table 3), diagnosis of schizophrenia is comparatively

vague, and more subject to symptom interpretation that for an outcome such as multiple sclerosis or Alzheimer's Disease. This heterogeneity may require larger sample sizes to identify causal effects of a similar magnitude. A second limitation is MR results represent the causal impact of a lifetime exposure on an outcome, it is unable to account for exposures that are time-limited or during a sensitive period.

For example, if the sensitive period for vitamin D deficiency is intrauterine, as suggested by the higher prevalence among winter-born individuals,[49] an MR analysis would not reflect this. Finally, standard MR techniques assume a linear relationship between exposure and outcome, which in the case of vitamin D might be a fallacy, as both deficiency and excess states may be harmful.[30] Standard MR techniques assume a linear association between the exposure and outcome, and whilst novel methods are being developed to overcome this limitation, they are not yet standard practice.[31]

Mood Disorders

Several nutritional factors have been investigated using MR in major depression samples, with no strong evidence of effect. Nutritional factors include vitamins B12 and folate,[50] omega 3 fatty acids,[51] and 25-hydroxyvitamin D.[52] The five minerals investigated in Cheng 2019 did not show evidence of causality, though the Psychiatric Genomics Consortium sample used as the outcome is small (N=10,640) in comparison to the latest PGC Major Depression sample (N=807,553).[42] An MR study using the Young Finns study [53] showed an inverse association between fasting glucose and depressive symptoms measured using the Beck Depression Inventory, (−0·43 BDI points per weighted effect allele, 95% CI −0·79 to 0·07), which the authors hypothesise to relate to the cognitive effects of hypoglycaemia. A study in UK Biobank suggested a potentially causal role for elevated triglycerides (but not LDL- or HDL-cholesterol) in the development of lifetime major depression (OR 1.18 per SD (1·09–1·27)).[54]

An MR study looking at multiple minerals identified a potentially causal role for low copper (OR 0·87 per SD, 95% CI 0·79 to 0·97) and for high serum magnesium (OR 8·78 per SD, 95% CI 1·16 to

66·26) in bipolar disorder using the Bipolar Disorder Working Group sample of the Psychiatric

Genomics Consortium. Both findings warrant replication and further investigation. Some

observational literature has suggested higher serum magnesium (though lower intracellular

magnesium) levels in bipolar disorder, and the pathophysiological mechanisms behind this could be

further explored using two-step MR (figure 3a).

OPPORTUNITIES FOR MR IN NUTRITIONAL PSYCHIATRY

Although one of the biggest challenges for MR in nutritional psychiatry to date has been the

lack of appropriate genetic instruments, nutritional genetics is evolving. Instruments for many

nutritional exposures are being utilised in MR studies outside psychiatry or applied to only one of a

multitude of psychiatric outcomes. In addition to biological nutritional markers, GWAS of dietary

intake,[55] dietary patterns,[56] and even gut microbial diversity,[57] may provide useful potential

instruments for future MR studies aiming to assess the impact of nutritional characteristics on

psychiatric ill-health. For example, evidence suggests that gut microbial diversity and abundance is

influenced by human genetics,[57] making MR studies of this exposure possible, with examples of

causal relationships being identified using MR in other areas of medicine.[58] MR studies of the gut

microbiome characterised in different ways may help to explain the association between reduced

gut microbiome diversity and the presence of specific bacterial taxa in psychiatric disease,[59] and the

apparent benefits of probiotics in psychiatry.[60, 61]

MR methods are continually evolving (see table 1), with several techniques relevant to

research in nutritional psychiatry. An example is multivariable MR (see figure 3b), which can be

employed in situations where genetic variants are related to several correlated exposures.

Multivariable MR has been used successfully in untangling the association between high density

lipoprotein cholesterol, low density lipoprotein cholesterol, and triglycerides with cardiovascular

disease[62] and depression.[54] Multivariable MR could similarly be used to unpick potentially complex

associations, such as between omega 3 and 6 fatty acids, or B vitamin pathways, in psychiatry. For

positive findings in nutritional psychiatry, potential off-target adverse effects of nutritional supplementation could be identified using MR phenome-wide association study (MR-PheWAS).[63] An MR-PheWAS uses a hypothesis-free approach to scan many outcomes for a given exposure, and could have potentially pre-empted the increased risk of diabetes with selenium supplementation seen in the SELECT trial.[23] As well as informing intervention development, MR can also be used to investigate biological mechanisms in psychiatry including metabolomic, microbiomic, proteomic and epigenomic intermediates, using two-step MR.[64] Two-step MR is a relatively new method for identifying and quantifying mediating mechanisms between an exposure and outcome using an MR framework (figure 3a). Novel MR methods to analyse gene-environment interactions are also under development, and may be particularly useful in the context of nutritional psychiatry. Finally, using MR of the human proteome in relation to psychiatric outcomes may identify novel drug targets.

Standard MR methods rely on a single exposure-outcome framework, which many consider to be oversimplified when in the context of complex nutritional biology. Many nutritional epidemiologists have moved beyond a single nutrient approach to consider whole dietary patterns, adiposity, and the inherently complex interaction between diet, hormones and physical activity.[65] It is possible that future MR methods could consider interactions between other nutritional exposures, as well as with gene-environment interactions considering nutritional intake or other lifestyle factors. Techniques such as machine learning and data mining using nutritional exposures, genetic data, dietary intake and psychiatric diagnoses and symptoms might be necessary for unpicking complex associations and gene-environment interactions further. Machine learning has already been suggested for augmenting MR, by predicting the most appropriate model to optimise power and detect pleiotropy, and could potentially enhance MR in the complex arena of nutritional psychiatry.[66]

CHALLENGES FOR MR IN NUTRITIONAL PSYCHIATRY

With increasing availability of genetic instruments, genetic samples, and platforms for MR analysis, false results can be obtained quickly. Results need careful consideration as to validity of the methods, samples, and instruments used, irrespective of their strength or direction. Subsequent replication in independent cohorts remains crucial.[19]

Several limitations of traditional MR methods may hinder the application to nutritional psychiatry (see table 4). The lack of valid, robust genetic instruments for many nutritional exposures is arguably one of the most fundamental limitations. GWAS studies identifying SNPs robustly associated with nutritional exposures depend on adequately sized genotyped samples of nutritional factors. Difficulties identifying robust and reliable nutritional biomarkers reflecting nutritional status may underlie this, along with the availability of such nutritional measures in adequately sized genotyped cohorts. Instruments that are only weakly associated with the exposure of interest (e.g. F-statistic <10, see table 2) will bias estimates in different directions depending on whether a one-sample or two-sample methodology is used (table 4).

Nutritional genetic epidemiology is a developing field and the expectation is that good quality, validated instruments for nutritional exposures should emerge and evolve. However, even where genetic instruments appear to exist, some consideration needs to be given to whether they are valid for the specific association being tested with MR analyses, checking as far as possible that the assumptions of MR hold, and by understanding their underlying biological function.

With the increasing development of large psychiatric genomics consortia samples, outcome sample sizes are rapidly increasing. At first glance these appear to provide ample power to detect nutritional exposures, even those with a very small effect (see table 3.)[19] However, as sample sizes increase, it is important to consider the extent to which the genetic heterogeneity of the population has increased, and the validity of the genetic instrument within this new population structure. Furthermore, the risk of overlapping exposure and outcome samples may invalidate some of the assumptions of two-sample MR. The relative benefits of using small samples with precisely

measured nutritional exposures and psychiatric symptomatology, compared to large samples with imprecise measures and heterogenous samples are not always clearly defined.

FUTURE DIRECTIONS

Genetic epidemiology is evolving. Sample sizes, genetic markers and MR techniques are continuing to increase in both number and complexity. Negative early findings need careful consideration, and positive findings warrant replication in independent cohorts. As sample sizes and genetic instruments develop, formal repetition of earlier studies and independent replication remains essential. Given the relative ease with which analyses can be conducted once an instrument is identified, a more systematic and thorough approach to evaluating nutritional factors in psychiatry would be beneficial, perhaps considering individual psychiatric presentations along with a 'cross-disorder' approach. Opportunities for undertaking GWAS of nutritional biomarkers should be sought and validated, to make future MR studies possible. Future MR studies should consider novel MR techniques such as multivariable MR where appropriate, techniques for accounting for non-linear associations, as well as two-step MR to identify causal mechanisms. Further understanding of gene-environment interactions using large biobanks with data on genetics as well as nutritional and lifestyle measures might be useful for triangulating with nutritional MR studies. Finally, as the research landscape evolves, replication of earlier studies using larger samples and improved genetic instruments, continues to be of value.

Beyond genetics, ongoing research from a broad range of disciplines including epidemiology, basic sciences, and clinical trials is needed to identify novel biomarkers of nutritional intake and status, to develop new technologies for accurate dietary assessment, and to apply the results of MR studies to inform and conduct large-scale pragmatic trials.

CONCLUSION

Nutritional psychiatry, nutritional genetic epidemiology and psychiatric genetics are all at relatively early stages in their understanding. MR in nutritional psychiatry sits at the centre of these emerging disciplines, providing a unique way to investigate causality in nutritional psychiatry and understand its mechanisms. Despite some challenges in this area, emerging MR evidence for nutritional factors including vitamin D, folate, serum magnesium, copper, triglycerides, and glucose metabolic pathways on psychiatric outcomes highlight the potential utility of this technique for identifying causal factors in nutritional psychiatry and developing a firm evidence base for the causality of nutritional exposures from which successful interventions can develop.

SEARCH STRATEGY AND SELECTION CRITERIA

References for this review were identified through systematic searches of OVID Medline (1946 to January 2019,) PsycINFO (1808 to January 2019) and EMBASE (1974-2019) database for articles published from by use of the terms "Mendelian randomization", "Psychiatry OR Psychology", and other diagnostic terms (see Appendix 1). All abstracts identified were screened to include any exposure related to nutrition. Exposures were included if they measured any factor that was directly related to nutritional components or nutritional status, including micronutrients (including vitamins and minerals), macronutrients (including glucose homeostatic markers, amino acids and peptides and lipids), and biological markers of nutritional status. These factors were not selected *a priori*, but identified *post-hoc* based on the MR exposures available. Studies using psychiatric diagnosis as an exposure rather than outcome, addressing broader lifestyle exposures such as body mass index, physical activity or alcohol, and considered inter-generational exposures (such as offspring outcomes of pregnancy exposures) were excluded. A full search strategy is given in Appendix 1, with a flowchart of included studies in Appendix 2. No exclusions were made on the basis of language.

RESEARCH IN CONTEXT

Evidence before this study

Nutritional psychiatry is an emerging area of research, but its complexities are numerous. Several nutritional factors have been implicated in psychiatric aetiology, but causal evidence remains scarce. Mendelian randomization (MR) is an epidemiological method that can help investigate causality. Outside of psychiatry, MR has identified likely causal associations between low vitamin D and multiple sclerosis, low serum iron and Parkinson's disease, and low serum magnesium and cardiovascular disease. We searched the OVID Medline database for studies using "Mendelian randomization" with any outcome related to "Psychiatry OR Psychology". We excluded studies in which psychiatric conditions were used as an exposure rather than outcome, which used broader lifestyle exposures such as body mass index, physical activity or alcohol, and for which the exposure and outcome was inter-generational (such as offspring outcomes of pregnancy exposures).

Added value of this study

Several studies have investigated potential causal nutritional factors in psychiatry using MR. This study summarizes the current evidence and explores the opportunities and challenges in using this method to underpin intervention development. This paper also summarises some of the novel methods in MR, and how they might overcome issues with correlated nutritional exposures, non-linear effects, and to identify potential harms of supplementation.

Implications of all the available evidence

Several MR studies have shown evidence for causal nutritional factors in psychiatry . A comprehensive approach to investigating nutritional exposures psychiatry would be beneficial for the current evidence base and would help to inform intervention development in a resource-constrained field. It is important to consider the validity of findings irrespective of the direction or

strength of evidence, and to replicate results as new samples, methods and biological insights become available.

CONFLICT OF INTEREST

CONTRIBUTORS

RC was primary author and undertook the literature search. JZ, KW, HS and HJ provided help and training in MR methodology. All other authors contributed through advice on content and editing drafts. All authors had approval of final draft for submission.

Tables and Figures

Figure 1: Mendelian Randomization: comparisons and assumption.

1a Mendelian Randomization as a 'natural' Randomized Controlled Trial

MR has been compared to a randomized controlled trial, with random allocation of genetic alleles at conception could be considered analogous to random allocation of interventions in a trial.
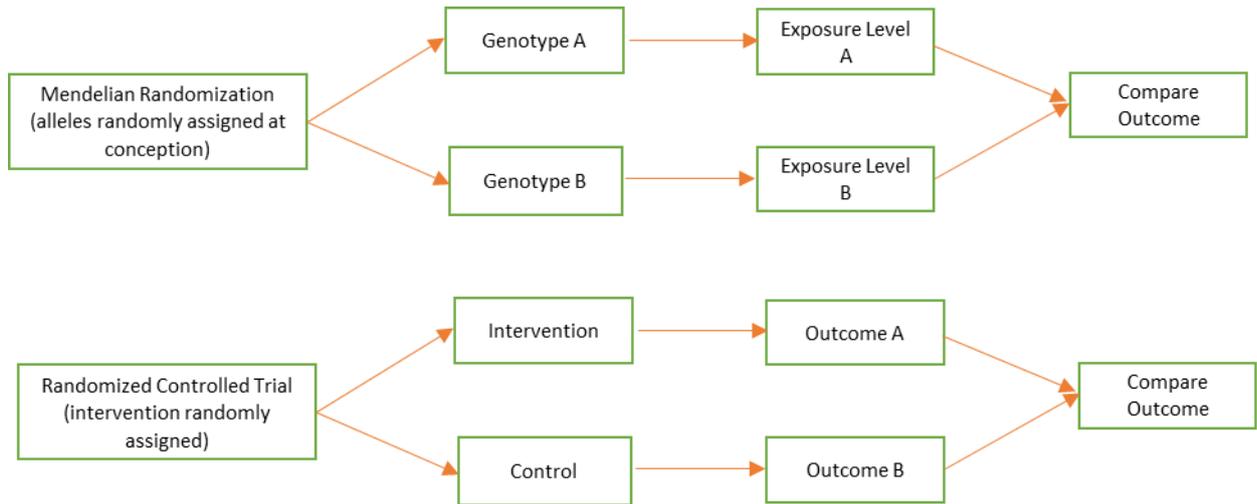
1b Assumptions in Mendelian Randomization

MR assumes that the genetic variants are: a. associated with the exposure of interest; b. not associated with confounders; and c. only associated with the outcome through the exposure
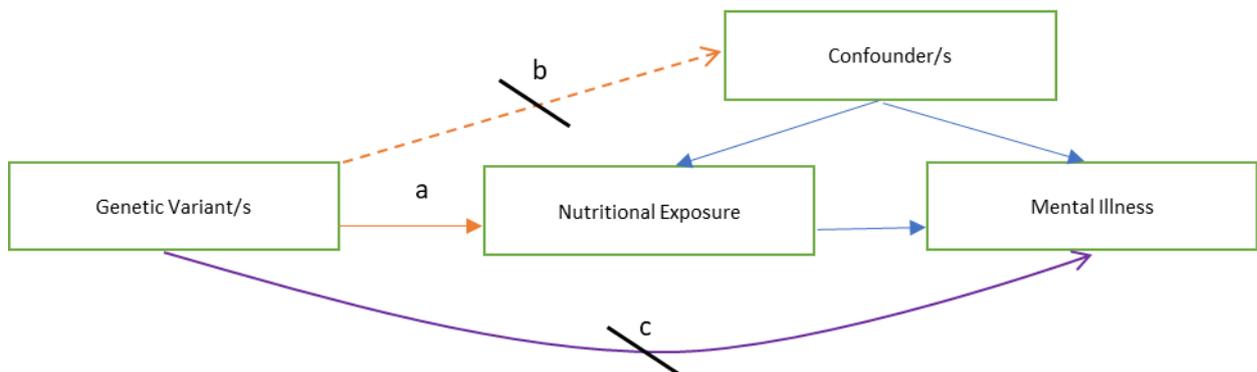
1c Two-sample Mendelian Randomization

Two-sample MR takes estimates of the SNP-exposure association from one population (e.g. a nutritional exposure GWAS) and the SNP-outcome association from a separate sample (e.g. a psychiatric outcome GWAS).

First Sample is used to estimate the SNP-exposure association (i.e. genetic contribution to nutritional status)

Second Sample is used to estimate the SNP-outcome association (i.e. genetic contribution of the exposure SNP(s) on the outcome)
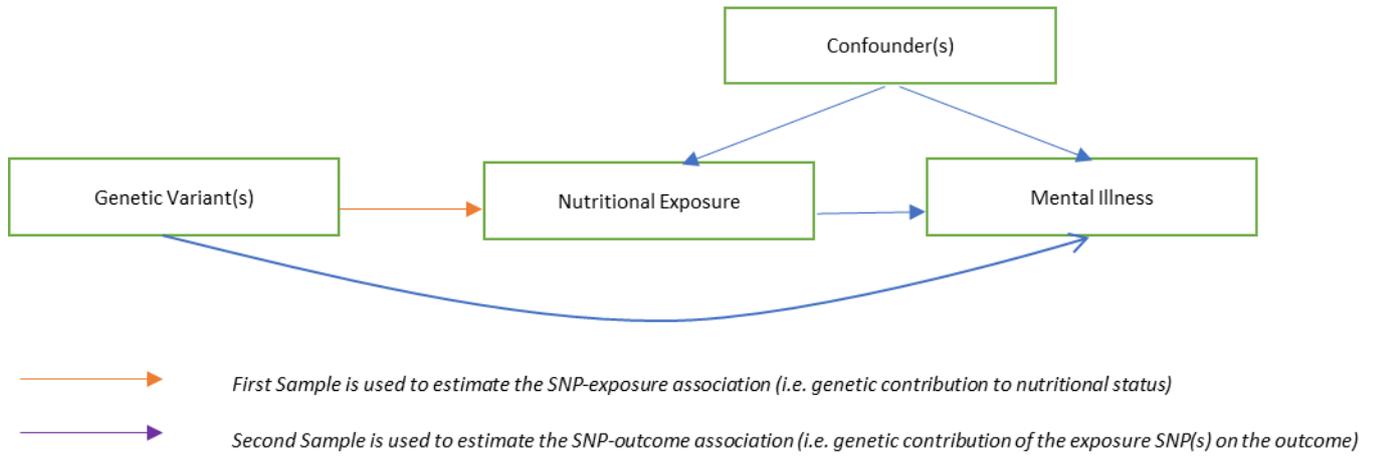
Figure 2: A theoretical pipeline for the use of MR studies in intervention development

Whilst many have compared MR to 'nature's RCT', it may be more realistic to see MR studies as an interim step in intervention development.
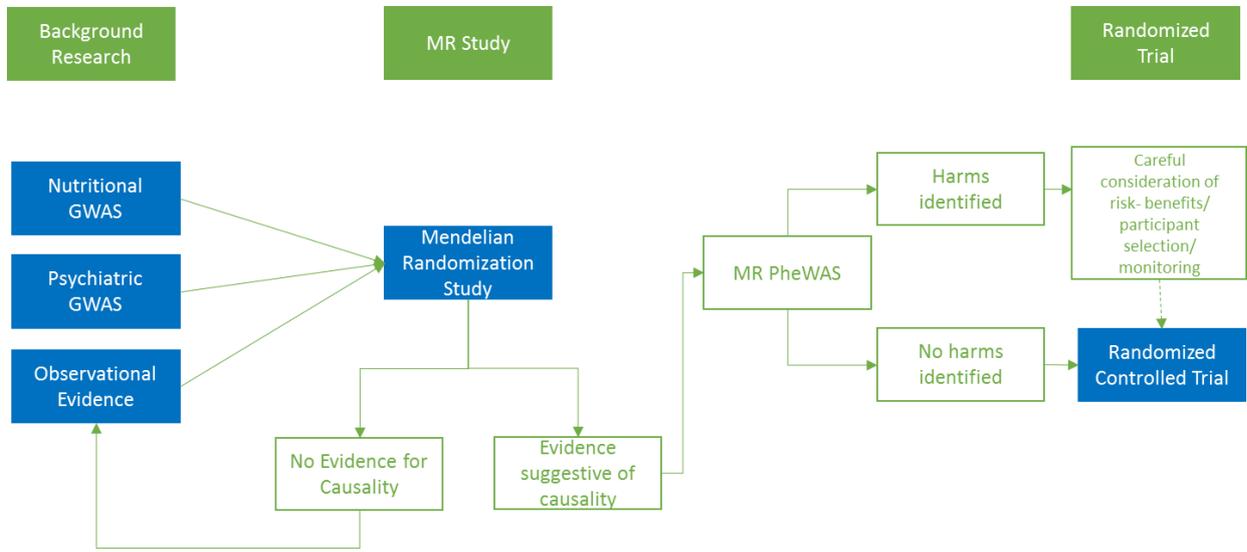
Figure 3: Advanced MR methodologies

3a Two-step Mendelian Randomization

Two-step MR can be used to identify mediating mechanisms between an exposure and outcome using separate MR analyses which are combined in a traditional mediation analysis.
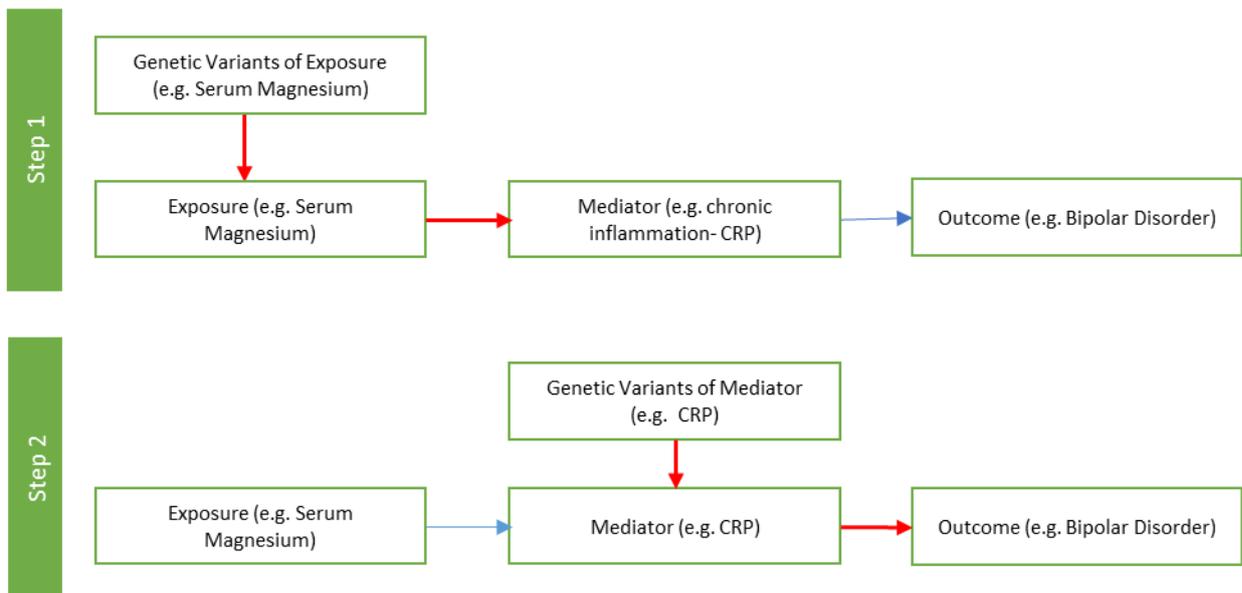
3b Multivariable Mendelian Randomization

Multivariable MR can be used where genetic variants are related to multiple correlated exposures. For example, a SNP for one lipid will often be correlated with others. This technique could be used to untangle potentially opposing associations between omega 3 (EPA/ DHA) and omega 6 fatty acids.
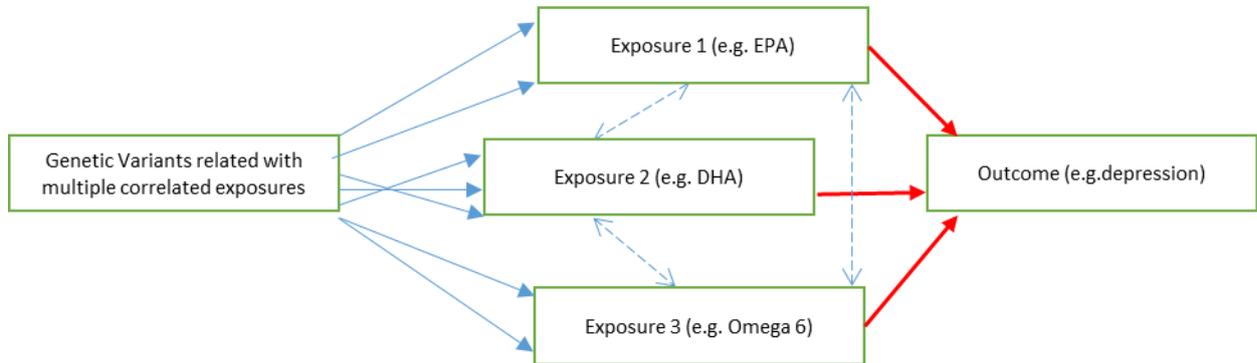
Table 1: Glossary of MR Terms and potential uses in nutritional psychiatry [20] For more information about other terms and the

Term	Explanation
F-Statistic	The F-statistic measures the strength of genetic instruments. F<10 is suggestive of weak instrument bias.
Multivariable MR	Multivariable MR is a technique to account for pleiotropy due to multiple correlated exposures.
MR-PheWAS (MR Phenome Wide Association Study)	MR PheWAS is a method using a hypothesis-free approach to scan many outcomes for a given exposure using MR methodology. Such approaches could be used to test for and identify any potential adverse off-target effects of dietary supplementation, providing genetic instruments exist.
Pleiotropy	Horizontal Pleiotropy is where the SNP or SNPs related to the exposure are associated with the outcome through a pathway independent of the exposure (i.e. a violation of assumption c in figure 1b). Pleiotropy can be demonstrated by several methods, including Cochran's Q statistic testing heterogeneity in causal estimates from each SNP, MR-Egger intercept, and leave-one-out analysis to identify influential outliers
Population Stratification	Spurious associations may arise in MR where the genetic variant and the outcome are associated with ancestral background in a mixed or stratified sample. Using genetic associations from within homogenous populations, or checking that the GWAS has controlled for population substructure in the analysis is important.
One-sample MR	Conventional one-sample MR uses a single sample in which exposure, outcome and genetic instrument are measured within the same population. One-sample MR may have power issues due to inadequate

|	
	sample sizes of studies that are required to have genotype, exposure and outcome data.
Two-Sample MR	The estimates of the SNP-exposure and SNP-outcome associations used in MR analyses are identified in independent studies (usually genome-wide association studies)
Two-Step/ Mediation MR	Two-step MR can be used to identify mediating mechanisms between an exposure and outcome using two steps- the first to assess the causal effect of the exposure on the potential mediator, and the second to assess the causal effect of the mediator on the outcome

Table 2: Studies using Mendelian randomization in nutritional psychiatry

Table summarizes current MR studies in nutritional psychiatry. Discrepancies exist between disorders, and the applicability of existing instruments to other outcomes, or to a combined 'cross disorder' cohort may be fruitful. Results are given as odds ratios per standard deviation change in the exposure unless otherwise specified. Abbreviations: IGAP (International Genomics of Alzheimer's), Psychiatric Genomics Consortium (PGC). For further details of instrument rsids, genes and beta coefficients please refer to the original publication.

	Exposure	Study	Measure	Sample	N	MR Method	SNPs	Results Reported OR / beta/ Hazard ratio/ Risk difference (95% confidence intervals) p-value
VITAMINS	Vitamin D	Maddock 2017 [29]	Global Cognitive tests	Cross cohort	172,349	Two-sample	2	β 0.00 points per 25(OH)D decreasing allele (0.01, 0.01) p>0.99
			Memory tests					β 0.00 points per 25(OH)D decreasing allele (-0.01, 0.01) p=0.6
		Jorde 2015 [28]	Cognitive Tests	Tromso Study	5,980	One-sample	4	No overall association
		Mokry 2016 [25]	Alzheimer's Diagnosis	IGAP[1]	54,162	Two-sample	4	OR 0.8 per SD (0.97, 0.66) p=0.021
		Olsson 2017 [27]	Dementia Diagnosis	Uppsala Longitudinal Study	1,087	One-sample	2	HR 1.04 points per effect allele (0.91, 1.19)
			Cognitive Impairment (MMSE)		408	One-sample	2	OR 1.03 per effect allele (0.80, 1.34)
		Larsson 2018 [26]	Alzheimer's Diagnosis	IGAP	54,162	Two-sample	7	OR 0.86 per SD (0.78, 0.94) p = 0.002
		Taylor 2016 [48]	Schizophrenia Diagnosis	PGC[2]	79,845	Two-sample	4	OR 0.99 per 10% increase (0.97, 1.0)
		Michaelsson 2018 [52]	Major Depression Diagnosis	PGC	173,005	Two-sample	6	OR 1.02 per SD (0.97, 1.08) p = 0·44

[1] IGAP International Genomics of Alzheimer's Project
[2] PGC Psychiatric Genomics Consortium

Vitamin E	Liu 2018 [41]	Alzheimer's Diagnosis	IGAP	54,162	Two-sample	3	OR 0·96 per SD (0·47,1·94) p =0·936
Vitamin B6	Tomioka 2018 [43]	Schizophrenia Diagnosis	Tokushima University Hospital	10,689	One-sample	1	OR 0·99 per SD log(B6) (0·65, 1·51) p= 0·96
Folate	Larsson 2017 [32]	Alzheimer's Diagnosis	IGAP	54,162	Two-sample	2	OR 0·98 per SD (0·72, 1·33) p=0·89
	Mollehave 2017 [50]	Depression (SLCR90_r[3])	Health 2006 & Inter 99	4,126	One-sample	2	OR 1·18 per effect allele (0·18, 7·66), P=0·86
Homocysteine	Hu 2016 [33]	Alzheimer's Diagnosis	34 studies	9,397	Two-Sample	1	OR 3·37 per SD (1·90, 5·95) p = 2·9×10-5
	Larsson 2017 [32]	Alzheimer's Diagnosis	IGAP	54,162	Two-sample	18	OR 0·99 per SD (0·88, 1·11) 0·86
	Roostaei 2018 [67]	Alzheimer's Diagnosis	IGAP	54,162	Two-sample	13	OR 1·01 per SD (0·89, 1·15), p=0·84
	Numata 2015 [44]	Schizophrenia Diagnosis	36 Studies	25,599	Two-sample	1	OR 2·15 per SD (1·39, 3·32) p=5·3x10^{-4}
	Kinoshita 2015[45]	Schizophrenia Diagnosis	Meta-analysis	10,378	One-sample	1	OR 1.14 per SD (1.03-1.27), p=1.6x10^{-2}
	Wu 2017[35]	Vascular Dementia Diagnosis	Meta-analysis	1,880	Two-sample	1	OR 4·29 per SD log (hcy) (1·11,16·57) P = 0·03

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[3] SLCR90_r diagnosis depression…

	B12	Mollehave 2017 [50]	Depression (SLCR90_r[4])	Health 2006 & Inter 99	4,126	One-sample	12	0·96 (0·52,1·79), P=0·91
		Larsson 2018 [32]	Alzheimer's Diagnosis	IGAP	54,162	Two-sample	7	OR 1·11 per SD (0·95, 1·30) p=0·18
MINERALS	Calcium	Cheng 2019[42]	Alzheimer's Diagnosis	IGAP	54,162	Two-sample	6	OR 0·74 per SD (0·45, 1·22) p=0·23
			Major Depression Diagnosis	PGC	10,640	Two-sample	6	OR 0·92 per SD (0·67, 1·28) p=0·63
			Bipolar Disorder Diagnosis	PGC	41,653	Two-sample	7	OR 1·85 per SD (0·74, 4·65) p=0·19
			Schizophrenia Diagnosis	PGC	65,967	Two-sample	7	OR 1·85 per SD (0·74, 4·65) p=0·19
	Copper	Cheng 2019[42]	Alzheimer's Diagnosis	IGAP	54,162	Two-sample	2	OR 0·87 per SD (0·75, 1·00) p=0·05
			Bipolar Disorder Diagnosis	PGC	41,653	Two-sample	2	OR 0·87 per SD (0·79, 0·97) p=0·01
			Schizophrenia Diagnosis	PGC	65,967	Two-sample	2	OR 0·96 per SD (0·85, 1·08) p=0·47

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[4] SLCR90_r diagnosis depression…

Magnesium	Cheng 2019[42]	Alzheimer's Diagnosis	IGAP	54,162	Two-sample	4	OR 0·43 per SD (0·08-2·44) p=0·34
		Major Depression Diagnosis	PGC	10,640	Two-sample	3	OR 1·19 per SD (0·22, 6·61) p=0·84
		Bipolar Disorder Diagnosis	PGC	41,653	Two-sample	4	OR 8·78 per SD (1·16, 66·26) p=0·04
		Schizophrenia Diagnosis	PGC	65,967	Two-sample	4	OR 0·87 per SD (0·24, 3·19) p=0·83
Iron	Cheng 2019[42]	Alzheimer's Diagnosis	IGAP	54,162	Two-sample	11	OR 1·02 per SD (0·94, 1·14) p=0·48
		Major Depression Diagnosis	PGC	10,640	Two-sample	9	OR 0·98 per SD (0·91, 1·05) p=0·60
		Bipolar Disorder Diagnosis	PGC	41,653	Two-sample	11	OR 1·17 per SD (0·89, 1·29) p=0·45
		Schizophrenia Diagnosis	PGC	65,967	Two-sample	10	OR 1·04 per SD (0·92, 1·18) p=0·55

	Zinc	Cheng 2019[42]	Alzheimer's Diagnosis	IGAP	54,162	Two-sample	2	OR 0·99 per SD (0·85, 1·14) p=0·85
			Major Depression Diagnosis	PGC	10,640	Two-sample	2	OR 0·99 per SD (0·95, 1·03) p=0·66
			Bipolar Disorder Diagnosis	PGC	41,653	Two-sample	2	OR 1·02 per SD (0·91, 1·14) p=0·70
			Schizophrenia Diagnosis	PGC	65,967	Two-sample	2	OR 0·94 per SD (0·86, 1·02) p=0·11
LIPID FAT AND GLUCOSE HOMEOSTASIS	Isoleucine	Larsson 2017 [36]	Alzheimer's Diagnosis	IGAP	54,162	Two-sample	4	OR 1·35 per SD (1·08,1·69) p=0·007
	Leucine						1	OR 1·16 per SD (95% CI, 0·78–1·72) p=0·46
	Valine						1	OR 1·13 per SD (95% CI, 0·82–1·57 p=0·46
	Fasting Glucose	Weslowska 2017 [53]	Depression (BDI)	Young Finns Study	1,217	One-Sample	35	-0·43 (-0·79, -0·07) p=0·02
		Li 2018 [46]	Schizophrenia Diagnosis	PGC	77,096	Two-sample	30	OR 0·84 per SD, (0·71,0·99) p=0·038
				BIO-X	26,026		14	OR 1·04 per SD (0·84,1·27) p=0·737
		Ostegaard 2015[40]	Alzheimer's Diagnosis	IGAP	54,162	Two-sample	36	OR 1·12 per SD (0·97, 1·30) p=0·112

Fasting insulin and insulin sensitivity	Ostegaard 2015[40]	Alzheimer's Diagnosis	IGAP	54,162	Two-sample	10	OR 1·32 per SD (0·88, 1·98) p=0.18
	Walter 2016 [68]	Alzheimer's Diagnosis	IGAP	54,162	Two-sample	9	OR 1·17 per unit (1·02,1·34) p=0.02
	Li 2018 [46]	Schizophrenia Diagnosis	PGC	77,096	Two-sample	13	OR 2·33 per SD (1·40, 3·90) p=0.001
DHA (Omega 3)	Sallis 2014 [51]	Perinatal Depression (EPDS)	ALSPAC mothers	2,378	One-sample	4	RD 0·08 (-0·05, 0·22) p=0·21
Plasma APOE	Rasmussen[37]	Alzheimer's Diagnosis	Copenhagen General Population Study and Copenhagen City Heart Study	106,562	One-sample	5	OR 1.41 per mg/dL (1.27, 1.57)
		All Dementia					OR 1.33 per mg/dL (1.25, 1.43)
Cholesterol & Triglycerides	Proitsi 2014 [39]	Alzheimer's Diagnosis	Cross Cohort	10,578	Two-Sample	70	OR 0·95 per unit (0·76,1·21) p=0·69 Total Cholesterol
						40	OR 1·10 per unit (0·89,1·37) p=0·36 Triglycerides
						69	1·01 per unit (0·82,1·24) p=0·96 HDL-c
						55	0·90 per unit (0·65,1·25) p=0·53 LDL-c

Ostergaard 2015[40]	Alzheimer's Diagnosis	IGAP	54,162	Two-sample	73	OR 1·94 per SD (1·79-2·10) p=3·1x10^{-56} Total Cholesterol
					39	OR 0·96 per SD (0·87,1·07) p=0·48 Triglycerides
					71	OR 0·75 per SD (0·69, 0·82) p=1x10^{-11} HDL-c
					57	OR 2·31 per SD (2·12, 2·50) p=3x10^{-87} LDL-c
Benn 2017[38]	Alzheimer's Diagnosis	Copenhagen General Population Study and Copenhagen City Heart Study	111,194	One-sample	380	OR 0·57 per mmolL^{-1} (0·27, 1·17) LDL-c
	Vascular Dementia					OR 0·81 per mmolL^{-1} (0·34, 1·89) LDL-c
	All Dementia					OR 0·66 per mmolL^{-1} (0·34, 1·26) LDL-c
Khandaker 2019[54]	Major Depression	UK Biobank	367,703	Two-sample	76	OR 1.02 per SD (0.91–1.14) LDL-c
					86	OR 0.97 per SD (0.91–1.03) HDL-c
					51	OR 1.18 per SD (1.09–1.27) Triglycerides

Table 3: A rough guide to sample size requirements for MR studies

An illustration of minimum sample sizes required for MR studies, taken from the online calculator available at http://cnsgenomics.com/shiny/mRnd/ [69] Results shown are for a binary outcome, assuming 25% cases in study, 0.8 power and alpha 0.05.

Variance explained	Estimated Effect Size (OR)	Minimum Sample size
1%	1.01	42,069,473
	1.1	439,015
	1.5	20,408
	2	5,756
5%	1.01	8,413,895
	1.1	87,803
	1.5	4,082
	2	1,152

Table 4: Limitations of MR [20]

Limitation	Description	Relevance to Nutritional Psychiatry	Potential Solution
Lack of Available Instruments	Genetic instruments are unavailable for certain exposures	Lack of GWAS for certain nutritional exposures· Also due to poor measurement of particular nutritional exposures (e·g· serum versus intracellular magnesium).	Choose a proxy exposure for which data is available. Continue to review instruments as nutritional GWAS are published.
Weak instrument Bias	Genetic variants that are weakly associated with an exposure (e.g. F-statistic <10) will bias estimates towards the observational estimate in one-	Weak instruments for nutritional exposures often result from limited sample sizes of pre-existing GWAS, as well as having	Increase sample sizes (e·g· through publicly available GWAS datasets and consortia). Explain more variation in the exposure using allele scores.

	sample MR, and to the null in Two-sample MR	a small proportion of variance explained by genetic variation.	
Low Power	May be caused by small sample size, low variance explained in the exposure by the SNP, confounding and type 1 error rate.	Inadequate power may result in null results and hinder important further research.	Increase sample size or instrument strength where possible Power for one-sample MR can be calculated using free web application at http://cnsgenomics.com/shiny/mRnd/ [69]
Horizontal Pleiotropy	The association between the genetic variant and the outcome of interest goes through an alternative pathway to the exposure.	Violates a core assumption of MR (figure 1c).	Understand underlying biological function of genetic variants. Use variants directly coding for exposure of interest where possible. Use MR-Egger estimation.
Linkage Disequilibrium	Non-random allocation of alleles in close	Confounding can be introduced by using an allele	Omit alleles in close genetic proximity to others.

	proximity during meiosis.	close to another allele, which affects the outcome of interest through another pathway.	Utilise genetic alleles on separate chromosomes Use homogeneous populations where LD structures will be similar
Developmental Compensation (Canalization)	Individual adaptation to a genetic change, which reduces the phenotypic effect of the genetic change·	MR may produce causal estimates that are below the effect achieved by modifying the exposure.	The extent of the impact of canalization on MR is currently unclear.
Population Stratification	Spurious results may result from using mixed populations in which the genetic variant and outcome are associated with a particular genetic background.	Possible limitation of vitamin D in schizophrenia.	Use genetic associations derived from within homogenous populations only· Use summary results statistics that have adequately controlled for population substructure through e.g. principal components analysis or linear mixed models.
Biological Complexity	MR may give misleading results	Several studies have suggested a	Improved understanding of biological pathways.

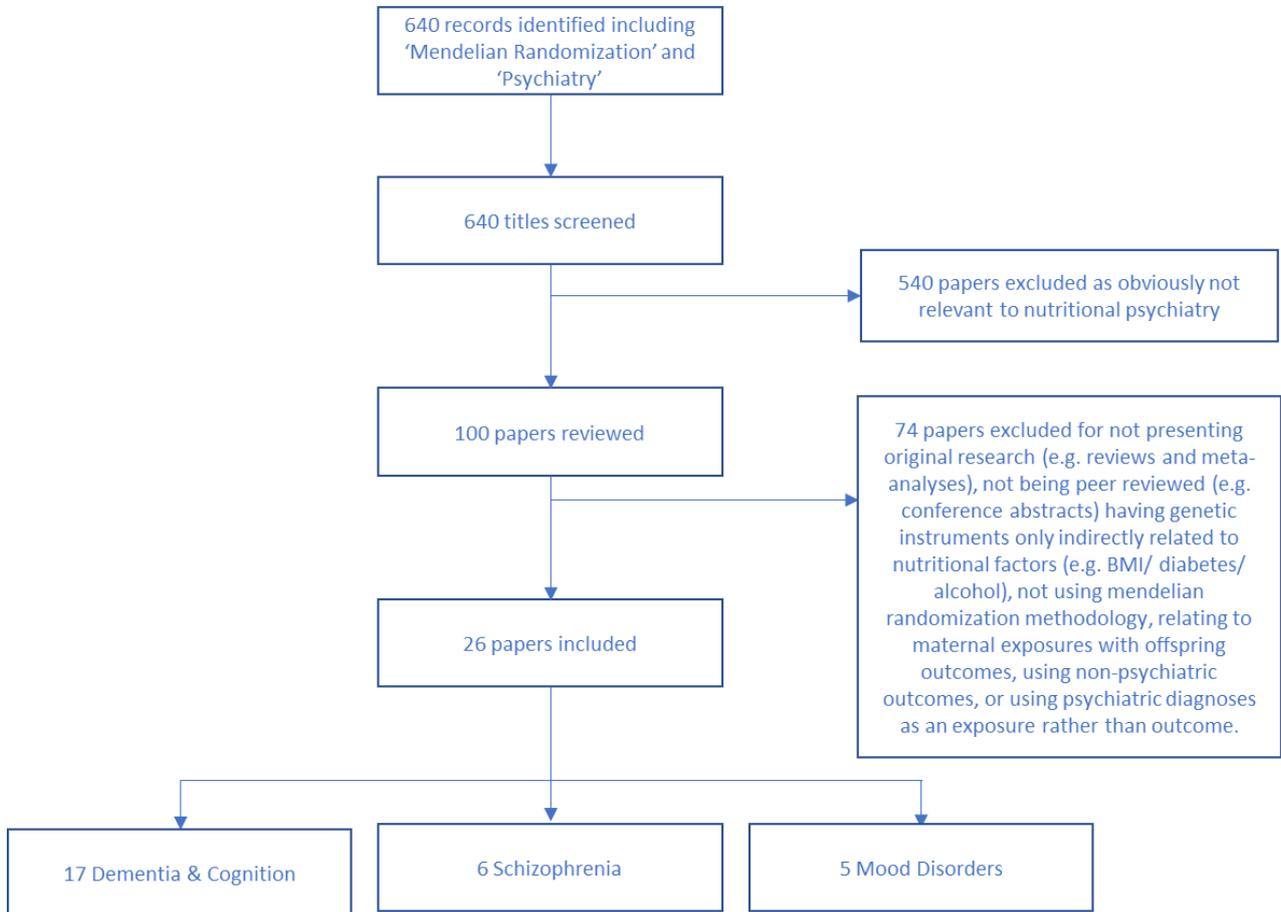|		
	due to overly simplistic interpretation of complex biological pathways.	non-linear association between vitamin D and various outcomes, but standard MR techniques are not able to detect this. Likewise, MR is unable to account for time-limited exposures or sensitive periods, such as intrauterine exposures and psychiatric outcomes.	Use of novel methods to account for non-linear associations.

Appendix 1: Search Strategy

Papers included in this review were identified using the following search strategy (adapted from the Cochrane Mental disorders search strategy at https://cmd·cochrane·org/search-strategies-identification-studies), executed on 5th May 2019. Modified MeSH terms were used for EMBASE/ PsychINFO databases·

1. EATING DISORDERS/ or ANOREXIA NERVOSA/ or BINGE-EATING DISORDER/ or BULIMIA NERVOSA/ or FEMALE ATHLETE TRIAD SYNDROME/ or PICA/
2. HYPERPHAGIA/ or BULIMIA/
3. SELF-INJURIOUS BEHAVIOR/ or SELF MUTILATION/ or SUICIDE/ or SUICIDAL IDEATION/ or SUICIDE, ATTEMPTED/
4. MOOD DISORDERS/ or AFFECTIVE DISORDERS, PSYCHOTIC/ or BIPOLAR DISORDER/ or CYCLOTHYMIC DISORDER/ or DEPRESSIVE DISORDER/ or DEPRESSION, POSTPARTUM/ or DEPRESSIVE DISORDER, MAJOR/ or DEPRESSIVE DISORDER, TREATMENT-RESISTANT/ or DYSTHYMIC DISORDER/ or SEASONAL AFFECTIVE DISORDER/
5. NEUROTIC DISORDERS/
6. DEPRESSION/
7. ADJUSTMENT DISORDERS/
8. exp ANTIDEPRESSIVE AGENTS/
9. ANXIETY DISORDERS/ or AGORAPHOBIA/ or NEUROCIRCULATORY ASTHENIA/ or OBSESSIVE-COMPULSIVE DISORDER/ or OBSESSIVE HOARDING/ or PANIC DISORDER/ or PHOBIC DISORDERS/ or STRESS DISORDERS, TRAUMATIC/ or COMBAT DISORDERS/ or STRESS DISORDERS, POST-TRAUMATIC/ or STRESS DISORDERS, TRAUMATIC, ACUTE/
10. ANXIETY/ or ANXIETY, CASTRATION/ or KORO/
11. ANXIETY, SEPARATION/
12. PANIC/
13. exp ANTI-ANXIETY AGENTS/
14. SOMATOFORM DISORDERS/ or BODY DYSMORPHIC DISORDERS/ or CONVERSION DISORDER/ or HYPOCHONDRIASIS/ or NEURASTHENIA/
15. HYSTERIA/
16. MUNCHAUSEN SYNDROME BY PROXY/ or MUNCHAUSEN SYNDROME/
17. FATIGUE SYNDROME, CHRONIC/
18. OBSESSIVE BEHAVIOR/
19. COMPULSIVE BEHAVIOR/ or BEHAVIOR, ADDICTIVE/
20. IMPULSE CONTROL DISORDERS/ or FIRESETTING BEHAVIOR/ or GAMBLING/ or TRICHOTILLOMANIA/
21. STRESS, PSYCHOLOGICAL/ or BURNOUT, PROFESSIONAL/
22. SEXUAL DYSFUNCTIONS, PSYCHOLOGICAL/ or VAGINISMUS/
23. ANHEDONIA/
24. AFFECTIVE SYMPTOMS/
25. *MENTAL DISORDERS/
26. (eating disorder* or anorexia nervosa or bulimi* or binge eat* or (self adj (injur* or mutilat*)) or suicide* or suicidal or parasuicid* or mood disorder* or affective disorder* or bipolar i or bipolar ii or (bipolar and (affective or disorder*)) or mania or manic or cyclothymic* or depression or depressive or dysthymi* or neurotic or neurosis or adjustment disorder* or antidepress* or anxiety disorder* or agoraphobia or obsess* or compulsi* or panic or phobi* or ptsd or posttrauma* or post trauma* or combat or

somatoform or somati#ation or medical* unexplained or body dysmorphi* or conversion disorder or hypochondria* or neurastheni* or hysteria or munchausen or chronic fatigue* or gambling or trichotillomania or vaginismus or anhedoni* or affective symptoms or mental disorder* or mental health)·ti·

27. Schizophrenia/ or schizophrenia·mp·
28. depression·mp· or Depression/
29. major depressive disorder·mp· or Depressive Disorder, Major/
30. dementia·mp· or Dementia/ or Frontotemporal Dementia/ or Dementia, Vascular/ or Dementia, Multi-Infarct/
31. autism·mp· or Autistic Disorder/
32. eating disorder·mp· or "Feeding and Eating Disorders"/
33. Borderline Personality Disorder/ or Mental Disorders/ or borderline personality·mp· or Personality Disorders/
34. psychosis·mp· or Psychotic Disorders/
35. exp "psychiatry and psychology (non mesh)"/ or psychiatry/
36. Attention Deficit Disorder with Hyperactivity/ or ADHD.mp./ or "attention deficit and disruptive behavior disorders"/ or child behavior disorders/
37. neurodevelopmental disorder.mp. or Neurodevelopmental Disorders/
38. communication disorders/ or language disorders/ or dyslexia/ or language development disorders/ or speech disorders/ or learning disorders/ or intellectual disability/
39. Developmental Disabilities/ or Motor Skills Disorders/ or motor delay.mp.
40. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39
41. mendelian adj2 random*
42. Mendelian Randomization Analysis/ or mendelian randomization·mp·
43. instrumental adj2 variable
44. 41 OR 42OR 43
45. 40 AND 44

Appendix 2: Flow chart for identification and inclusion of studies. (Numbers for inclusion do not

add up to 26 as some studies investigated multiple outcomes.)

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┌─────────────────────────────────┐
│ 640 records identified including │
│  'Mendelian Randomization' and   │
│           'Psychiatry'           │
└─────────────────────────────────┘
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                 ▼
┌─────────────────────────────────┐         ┌──────────────────────────────┐
│       640 titles screened       │────────▶│ 540 papers excluded as        │
│                                 │         │ obviously not relevant to     │
│                                 │         │ nutritional psychiatry        │
└─────────────────────────────────┘         └──────────────────────────────┘
                 │
                 ▼
┌─────────────────────────────────┐         ┌──────────────────────────────┐
│       100 papers reviewed       │────────▶│ 74 papers excluded for not    │
│                                 │         │ presenting original research  │
└─────────────────────────────────┘         │ (e.g. reviews and meta-       │
                 │                           │ analyses), not being peer     │
                 │                           │ reviewed (e.g. conference     │
                 │                           │ abstracts) having genetic     │
                 ▼                           │ instruments only indirectly   │
┌─────────────────────────────────┐         │ related to nutritional        │
│       26 papers included         │         │ factors (e.g. BMI/ diabetes/  │
│                                 │         │ alcohol), not using mendelian │
└─────────────────────────────────┘         │ randomization methodology,    │
     │           │            │              │ relating to maternal          │
                                             │ exposures with offspring      │
                                             │ outcomes, using non-psychiatric│
                                             │ outcomes, or using psychiatric │
                                             │ diagnoses as an exposure       │
                                             │ rather than outcome.           │
                                             └──────────────────────────────┘
     │           │            │
     ▼           ▼            ▼
┌──────────┐ ┌──────────┐ ┌──────────────┐
│ 17       │ │ 6        │ │ 5 Mood       │
│ Dementia │ │ Schizo-  │ │ Disorders    │
│ &        │ │ phrenia  │ │              │
│ Cognition│ │          │ │              │
└──────────┘ └──────────┘ └──────────────┘
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Appendix 3: Excluded papers

The following papers were identified in the search strategy as potentially relevant. Reasons for exclusion from the current review is given where appropriate.

	Paper	Justification for exclusion

1	Arafat, S. and C. C. Minica (2018). "Fetal origins of mental disorders? An answer based on Mendelian randomization." <u>Twin Research and Human Genetics</u> **21**(6): 485-494.	Exposure (birth weight)
2	Belbasis, L., et al. (2018). "Risk factors and peripheral biomarkers for schizophrenia spectrum disorders: An umbrella review of meta-analyses." <u>Acta Psychiatrica Scandinavica</u> **137**(2): 88-97.	Review
3	Benn, M., et al. "Low LDL cholesterol, PCSK9 and HMGCR genetic variation, and risk of Alzheimer's disease and Parkinson's disease: Mendelian randomisation study." <u>BMJ</u> **357**: j1648.	Included
4	Benn, M., et al. (2018). "Glucose and risk of Alzheimer's dementia, vascular dementia and unspecified dementia." <u>Circulation. Conference</u> **138**(Supplement 1).	Conference abstract
5	Bjorngaard, J. H., et al. (2015). "Association of body mass index with depression, anxiety and suicide - An instrumental variable analysis of the HUNT study." <u>PLoS ONE</u> **10 (7) (no pagination)**(e0131708).	Exposure (BMI)
6	Bonilla, C., et al. "Maternal and offspring fasting glucose and type 2 diabetes-associated genetic variants and cognitive function at age 8: a Mendelian randomization study in the Avon Longitudinal Study of Parents and Children." <u>BMC Medical Genetics</u> **13**: 90.	Maternal/ Offspring
7	Bonilla, C., et al. "Vitamin B-12 status during pregnancy and child's IQ at age 8: a Mendelian randomization study in the Avon longitudinal study of parents and children." <u>PLoS ONE [Electronic Resource]</u> **7**(12): e51084.	Maternal/ Offspring
8	Byrne, E., et al. (2019). "Investigating Causal Relationships between Major Depressive Disorder and Genetically Correlated Traits Using Mendelian Randomisation." <u>European Neuropsychopharmacology</u> **29 (Supplement 3)**: S791.	Exposure (BMI/ education/ schizophrenia/ coronary heart disease)
9	Byrne, E. M., et al. "Inference in Psychiatry via 2-Sample Mendelian Randomization-From Association to Causal Pathway?" <u>JAMA Psychiatry</u> **74**(12): 1191-1192.	Review
10	Caramaschi, D., et al. "Exploring a causal role of DNA methylation in the relationship between maternal vitamin B12 during pregnancy and child's IQ at age 8, cognitive performance and educational attainment: a two-step Mendelian randomization study." <u>Human Molecular Genetics</u> **26**(15): 3001-3013.	Maternal/ Offspring
11	Chekroud, A. M. (2019). "A Mendelian Randomization Approach for Assessing the Relationship Between Physical Activity and Depression." <u>JAMA Psychiatry</u> **23**: 23.	Exposure (physical activity)
12	Cheng, W. W., et al. (2019). "Mineral Nutrition and the Risk of Chronic Diseases: A Mendelian Randomization Study." <u>Nutrients</u> **11**(2): 12.	Included
13	Choi, K. W., et al. (2019). "Assessment of Bidirectional Relationships Between Physical Activity and Depression Among Adults: A 2-Sample Mendelian Randomization Study." <u>JAMA Psychiatry</u> **23**: 23.	Exposure (physical activity)
14	Clarke, T.-K., et al. (2017). "Investigating shared aetiology between type 2 diabetes and major depressive disorder in a population based cohort." <u>American Journal of Medical Genetics Part B: Neuropsychiatric Genetics</u> **174**(3): 227-234.	Exposure (T2DM)
15	Cornelis, M. C. and M. R. Munafo (2018). "Mendelian Randomization Studies of Coffee and Caffeine Consumption." <u>Nutrients</u> **10**(10): 20.	Review and Exposure (caffeine)

16	Cruchaga, C., et al. (2012). "Cerebrospinal fluid APOE levels: An endophenotype for genetic studies for Alzheimer's disease." Human Molecular Genetics **21**(20): 4558-4571.	Exposure (CSF proteins)
17	Fluegge Ba, K. "Zinc and Copper Metabolism and Risk of Autism: a reply to Sayehmiri et al." Iranian Journal of Child Neurology **11**(3): 66-69.	Methods (not MR)
18	Fluegge, K. (2016). "A reply to Wang T, Shan L, Du L, Feng J, Xu Z, Staal WG, Jia F. Serum concentration of 25-hydroxyvitamin D in autism spectrum disorder: a systematic review and meta-analysis. Eur Child Adolesc Psychiatry. 2015; doi: 10.1007/s00787-015-0786-1." European Child and Adolescent Psychiatry **25**(4): 453-454.	Response
19	Fluegge, K. (2017). "Zinc and copper metabolism and risk of autism: A reply to Sayehmiri et al." Iranian Journal of Child Neurology **11**(3): 66-69.	Response
20	Frangou, S., et al. (2019). "Insulin resistance: Genetic associations with depression and cognition in population based cohorts." Experimental Neurology **06**: 06.	Methods (non-MR)
21	Giltay, E. J., et al. (2009). "Serum cholesterol, apolipoprotein E genotype and depressive symptoms in elderly European men: The FINE study." Journal of Affective Disorders **115**(3): 471-477.	Included
22	Grant, W. B. (2017). "Vitamin D and incident dementia and cognitive impairment." American Journal of Clinical Nutrition **106**(2): 699-700.	Response
23	Hamer, M., et al. (2016). "Depressive symptoms and obesity: Instrumental variable analysis using mother-offspring pairs in the 1970 British Cohort Study." International Journal of Obesity **40**(11): 1789-1793.	Exposure (obesity)
24	Hannon, E., et al. (2019). "Pleiotropic Effects of Genetic Variation Associated with Psychiatric Disorders on DNA Methylation." European Neuropsychopharmacology **29 (Supplement 3)**: S984-S985.	Exposure (DNA methylation)
25	Harbord, R. M., et al. (2010). "Genetically determined adiposity and reduced risk of common mental disorder. the copenhagen general population study with 53,221 participants." American Journal of Epidemiology **11)**: S52.	Exposure (adiposity)
26	Harbord, R. M., et al. (2011). "Using genetic loci to understand the relationship between adiposity and psychological distress: A Mendelian Randomization study in the Copenhagen General Population Study of 53221 adults." Journal of Internal Medicine **269**(5): 525-537.	Exposure (adiposity)
27	Hartwig, F. P., et al. (2016). "Body mass index and psychiatric disorders: a Mendelian randomization study." Scientific Reports **6**: 32730.	Exposure (BMI)
28	Hu, Q., et al. (2016). "Homocysteine and Alzheimer's disease: Evidence for a causal link from Mendelian randomization." Journal of Alzheimer's Disease **52**(2): 747-756.	Included
29	Hung, C. F., et al. (2014). "Relationship between obesity and the risk of clinically significant depression: Mendelian randomisation study." British Journal of Psychiatry **205**(1): 24-28.	Exposure (obesity)
30	Jiang, L., et al. (2019). "Constrained instruments and their application to Mendelian randomization with pleiotropy." Genetic Epidemiology **12**: 12.	Review
31	Jokela, M., et al. (2012). "Body mass index and depressive symptoms: Instrumental-variables regression with genetic risk score." Genes, Brain & Behavior **11**(8): 942-948.	Exposure (BMI)
32	Jorde, R., et al. (2015). "Vitamin D and cognitive function: The Tromso study." Journal of the Neurological Sciences **355**(1-2): 155-161.	Included

33	Khandaker, G. M., et al. (2019). "Shared mechanisms between coronary heart disease and depression: findings from a large UK general population-based cohort." Molecular Psychiatry **19**: 19.	Included
34	Kinoshita, M. (2015). "One-carbon Metabolism and Schizophrenia. [Japanese]." Seishin shinkeigaku zasshi = Psychiatria et neurologia Japonica **117**(5): 362-368.	Included
35	Kivimaki, M., et al. (2011). "Does obesity really protect against psychological distress? Examining the 'fat-jolly' versus 'fat-sad' hypotheses using Mendelian randomization." Journal of Internal Medicine **269**(5): 519-520.	Exposure (obesity)
36	Kivimaki, M., et al. (2011). "Examining Overweight and Obesity as Risk Factors for Common Mental Disorders Using Fat Mass and Obesity-Associated (FTO) Genotype-Instrumented Analysis." American Journal of Epidemiology **173**(4): 421-429.	Exposure (obesity)
37	Koshy, B., et al. (2010). "Genetic deficiency of plasma lipoprotein-associated phospholipase A <inf>2</inf> (PLA2G7 V297F null mutation) and risk of Alzheimer's disease in Japan." Journal of Alzheimer's Disease **21**(3): 775-780.	Exposure (inflammatory marker)
38	Kubzansky, L. D., et al. (2015). "Revisiting mendelian randomization studies of the effect of body mass index on depression." American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics **168**(2): 108-115.	Exposure (BMI)
39	Kumari, M., et al. "Alcohol consumption and cognitive performance: a Mendelian randomization study." Addiction **109**(9): 1462-1471.	Exposure (alcohol)
40	Kunutsor, S. K., et al. "Genetically elevated gamma-glutamyltransferase and Alzheimer's disease." Experimental Gerontology **106**: 61-66.	Exposure (iver enzymes)
41	Kuzma, E., et al. (2017). "A systematic review of mendelian randomization studies investigating causal associations between risk factors and dementia." Alzheimer's and Dementia **13 (7)**: P1180.	Review
42	Kuzma, E., et al. (2018). "Which Risk Factors Causally Influence Dementia? A Systematic Review of Mendelian Randomization Studies." Journal of Alzheimer's Disease **64**(1): 181-193.	Review
43	Kwok, M. K., et al. "Habitual coffee consumption and risk of type 2 diabetes, ischemic heart disease, depression and Alzheimer's disease: a Mendelian randomization study." Scientific Reports **6**: 36500.	Expoure (coffee/ caffeine)
44	Larsson, S. C., et al. "Modifiable pathways in Alzheimer's disease: Mendelian randomisation analysis." BMJ **359**: j5375.	Included
45	Larsson, S. C., et al. (2018). "Serum Parathyroid Hormone, 25-Hydroxyvitamin D, and Risk of Alzheimer's Disease: A Mendelian Randomization Study." Nutrients **10**(9): 06.	Included
46	Lauritzen, L., et al. "Mendelian randomization shows sex-specific associations between long-chain PUFA-related genotypes and cognitive performance in Danish schoolchildren." American Journal of Clinical Nutrition **106**(1): 88-95.	Outcome (non-psychiatric)
47	Lawlor, D. A., et al. "Using genetic loci to understand the relationship between adiposity and psychological distress: a Mendelian Randomization study in the Copenhagen General Population Study of 53,221 adults." Journal of Internal Medicine **269**(5): 525-537.	Exposure (adiposity)
48	Lehmann, D. J. and M. Cortina-Borja (2019). "Genetic influence of plasma homocysteine on Alzheimer's disease." Neurobiology of Aging **76**: 217-218.	Review
49	Lewis, S. J., et al. "Maternal iron levels early in pregnancy are not associated with offspring IQ score at age 8, findings from a Mendelian	Maternal/ Offspring

	randomization study." _European Journal of Clinical Nutrition_ **68**(4): 496-502.	
50	Li, Z., et al. (2018). "Glucose and Insulin-Related Traits, Type 2 Diabetes and Risk of Schizophrenia: A Mendelian Randomization Study." _EBioMedicine_ **34**: 182-188.	Included
51	Ligthart, S., et al. "Genome Analyses of >200,000 Individuals Identify 58 Loci for Chronic Inflammation and Highlight Pathways that Link Inflammation and Complex Disorders." _American Journal of Human Genetics_ **103**(5): 691-706.	Exposure (CRP)
52	Liu, G., et al. (2018). "Circulating vitamin E levels and Alzheimer's disease: A Mendelian randomization study." _Neurobiology of Aging_ **72**: 189.	Included
53	Lund, I. O., et al. (2019). "Is the association between maternal alcohol consumption in pregnancy and pre-school child behavioural and emotional problems causal? Multiple approaches for controlling unmeasured confounding." _Addiction_ **08**: 08.	Maternal/ offsping
54	Mack, S., et al. "Evaluating the Causal Relation of ApoA-IV with Disease-Related Traits - A Bidirectional Two-sample Mendelian Randomization Study." _Scientific Reports_ **7**(1): 8734.	Outcomes (lipids, renal function/ adiposity and diabetes)
55	Maddock, J., et al. (2017). "Vitamin D and cognitive function: A Mendelian randomisation study." _Sci Rep_ **7**(1): 13230.	Included
56	Mejia-Guevara, I., et al. (2013). "The causal effect of obesity on anxiety: genetic iv analyses in the hrs study." _American Journal of Epidemiology_ **11)**: S13.	Exposure (obesity)
57	Michaelsson, K., et al. (2018). "Serum 25-Hydroxyvitamin D Concentrations and Major Depression: A Mendelian Randomization Study." _Nutrients_ **10**(12): 15.	Included
58	Mokry, L. E., et al. (2016). "Genetically decreased Vitamin D and risk of Alzheimer disease." _Neurology_ **87**(24): 2567-2574.	Included
59	Mollehave, L. T., et al. (2017). "Association studies of genetic scores of serum vitamin B12 and folate levels with symptoms of depression and anxiety in two danish population studies." _European Journal of Clinical Nutrition_ **71**(9): 1054-1060.	Included
60	Mukherjee, S., et al. (2015). "Genetically predicted body mass index and Alzheimer's disease-related phenotypes in three large samples: Mendelian randomization analyses." _Alzheimer's and Dementia_ **11**(12): 1439-1451.	Exposure (BMI)
61	Murray, J., et al. (2016). "Moderate alcohol drinking in pregnancy increases risk for children's persistent conduct problems: Causal effects in a Mendelian randomisation study." _Journal of Child Psychology and Psychiatry_ **57**(5): 575-584.	Maternal/ Offspring
62	Nigg, J. T., et al. (2016). "Variation in an iron metabolism gene moderates the association between blood lead levels and attention-deficit/hyperactivity disorder in children." _Psychological Science_ **27**(2): 257-269.	Methods (moderation analysis)
63	Nishi, A., et al. (2014). "Meta-analyses of blood homocysteine levels for gender and genetic association studies of the MTHFR C677T polymorphism in schizophrenia." _Schizophrenia Bulletin_ **40**(5): 1154-1163.	Review
64	Nordestgaard, B. G., et al. (2017). "Low LDL cholesterol, PCSK9 and HMGCR genetic variation, and risk of Alzheimer's disease and Parkinson's disease: Mendelian randomisation study." _BMJ (Clinical research ed.)_ **357**: j1648.	Duplicate of Benn 2017 (included)

65	Nordestgaard, L. T., et al. (2017). "Body mass index and risk of Alzheimer's disease: A mendelian randomization study of 399,536 individuals." Journal of Clinical Endocrinology and Metabolism **102**(7): 2310-2320.	Exposure (BMI)
66	Numata, S., et al. "Evaluation of an association between plasma total homocysteine and schizophrenia by a Mendelian randomization analysis." BMC Medical Genetics **16**: 54.	Included
67	Olsson, E., et al. (2017). "Vitamin D is not associated with incident dementia or cognitive impairment: An 18-y follow-up study in community-living old men." American Journal of Clinical Nutrition **105**(4): 936-943.	Included
68	Olsson, E., et al. (2015). "Vitamin D does not predict dementia or cognitive impairment-a 20 year follow up study in community living old men." Clinical Nutrition **1)**: S15.	Conference abstract
69	Ostergaard, S. D., et al. "Associations between Potentially Modifiable Risk Factors and Alzheimer Disease: A Mendelian Randomization Study." PLoS Medicine / Public Library of Science **12**(6): e1001841; discussion e1001841.	Included
70	Pagoni, P., et al. (2019). "Using Mendelian randomisation to assess causality in observational studies." Evidence Based Mental Health **12**: 12.	Exposure (BMI)
71	Peterson, R., et al. (2019). "Investigation of the Genetic Overlap between Major Depressive Disorder and Body Mass Index in Han Chinese Women." European Neuropsychopharmacology **29 (Supplement 3)**: S976.	Exposure (BMI)
72	Peterson, R. E., et al. (2019). "Evidence of causal effect of major depression on alcohol dependence: findings from the psychiatric genomics consortium." Psychological Medicine: 1-9.	Exposure (alcohol)
73	Polimanti, R., et al. (2018). "Genetically determined schizophrenia is not associated with impaired glucose homeostasis." Schizophrenia Research **195**: 286-289.	Schizophrenia used as exposure
74	Polimanti, R., et al. "Evidence of causal effect of major depression on alcohol dependence: findings from the psychiatric genomics consortium." Psychological Medicine: 1-9.	Exposure (alcohol)
75	Proitsi, P., et al. "Genetic predisposition to increased blood cholesterol and triglyceride lipid levels and risk of Alzheimer disease: a Mendelian randomization analysis." PLoS Medicine / Public Library of Science **11**(9): e1001713.	Included
76	Rasmussen, K. L., et al. (2018). "Plasma apolipoprotein E levels and risk of dementia: A Mendelian randomization study of 106,562 individuals." Alzheimer's & Dementia: The Journal of the Alzheimer's Association **14**(1): 71-80.	Included
77	Reed, Z. E., et al. "Assessing the causal role of adiposity on disordered eating in childhood, adolescence, and adulthood: a Mendelian randomization analysis." American Journal of Clinical Nutrition **106**(3): 764-772.	Exposure (adiposity)
78	Romo, M. L. and C. M. Schooling (2017). "Examining the Causal Role of Leptin in Alzheimer Disease: A Mendelian Randomization Study." Neuroendocrinology **105**(2): 182-188.	Exposure
79	Roostaei, T., et al. (2018). "Genetic influence of plasma homocysteine on Alzheimer's disease." Neurobiology of Aging **62**: e7-e14.	Included
80	Ruseski, J. E., et al. "Sport participation and subjective well-being: instrumental variable results from German survey data." Journal of Physical Activity & Health **11**(2): 396-403.	Exposure/ outcome/ methods

81	Sallis, H., et al. (2014). "Perinatal depression and omega-3 fatty acids: A Mendelian randomisation study." Journal of Affective Disorders **166**: 124-131.	Included
82	Smith, A. D. and H. Refsum (2016). "Homocysteine, B Vitamins, and Cognitive Impairment." Annual Review of Nutrition **36**: 211-239.	Review
83	Smulders, Y. M. and H. J. Blom "The homocysteine controversy." Journal of Inherited Metabolic Disease **34**(1): 93-99.	Review
84	So, H. C., et al. "Exploring shared genetic bases and causal relationships of schizophrenia and bipolar disorder with 28 cardiovascular and metabolic traits." Psychological Medicine: 1-13.	Methods (non-MR)
85	Taylor, A. E., et al. (2016). "Investigating causality in the association between 25(OH)D and schizophrenia." Scientific Reports **6**: 26496.	Included
86	Tomioka, Y., et al. (2018). "Decreased serum pyridoxal levels in schizophrenia: Meta-analysis and Mendelian randomization analysis." Journal of Psychiatry & Neuroscience **43**(3): 194-200.	Included
87	Tyrrell, J., et al. (2018). "Using genetics to understand the causal influence of higher BMI on depression." International Journal of Epidemiology **13**: 13.	Exposure (BMI)
88	Vaez, A., et al. (2018). "Genome Analyses of >200,000 Individuals Identify 58 Loci for Chronic Inflammation and Highlight Pathways that Link Inflammation and Complex Disorders." American Journal of Human Genetics **103**(5): 691-706.	Exposure (inflammation)
89	van den Broek, N., et al. "Causal associations between body mass index and mental health: a Mendelian randomisation study." Journal of Epidemiology & Community Health **72**(8): 708-710.	Exposure (BMI)
90	Vaucher, J., et al. "Cannabis use and risk of schizophrenia: a Mendelian randomization study." Molecular Psychiatry **23**(5): 1287-1292.	Exposure (cannabis)
91	Walter, S., et al. (2015). "Do genetic risk scores for body mass index predict risk of phobic anxiety? Evidence for a shared genetic risk factor." Psychological Medicine **45**(1): 181-191.	Exposure (BMI)
92	Walter, S., et al. (2015). "Revisiting Mendelian Randomization studies of the effect of body mass index on depression." American Journal of Medical Genetics Part B: Neuropsychiatric Genetics **168**(2): 108-115.	Exposure (BMI)
93	Walter, S., et al. (2016). "Diabetic phenotypes and late-life dementia risk: A mechanism-specific Mendelian Randomization study." Alzheimer Disease and Associated Disorders **30**(1): 15-20.	Included
94	Walter, S., et al. (2013). "A genetic iv analysis to assess the effect of body mass index on depression in the health and retirement study." American Journal of Epidemiology **11)**: S12.	Exposure (BMI)
95	Wesolowska, K., et al. (2015). "Type-2 diabetes and depressive symptoms: Results of applying a Mendelian randomization in the Cardiovascular Risk in Young Finns Study." Psychotherapy and Psychosomatics **1)**: 77.	Conference abstract
96	Wesolowska, K., et al. (2017). "Fasting glucose and the risk of depressive symptoms: Instrumental-variable regression in the Cardiovascular Risk in Young Finns Study." International Journal of Behavioral Medicine **24**(6): 901-907.	Included
97	Wu, S. P., et al. (2017). "Plasma homocysteine levels and risk of vascular dementia: A Mendelian randomization study." International Journal of Clinical and Experimental Medicine **10**(6): 9142-9151.	Included

| 98 | Xuan, L., et al. (2018). "Type 2 diabetes is causally associated with depression: a Mendelian randomization analysis." <u>Frontiers of medicine</u> **12**(6): 678-687. | Exposure (T2DM) |

References

1.   Sarris J, Logan AC, Akbaraly TN, Paul Amminger G, Balanza-Martinez V, Freeman MP, et al. International Society for Nutritional Psychiatry Research consensus position statement: nutritional medicine in modern psychiatry. World Psychiatry. 2015;14(3):370-1.

2.   Tobey JA. The Biology of Human Starvation. Am J Public Health N. 1951;41(2):236-7.

3.   Monteiro CA, Levy RB, Claro RM, de Castro IRR, Cannon G. Increasing consumption of ultra-processed foods and likely impact on human health: evidence from Brazil. Public Health Nutr. 2011;14(1):5-13.

4.   Sarris J. Nutritional Psychiatry: From Concept to the Clinic. Drugs. 2019;79(9):929-34.

5.   Lassale C, Batty GD, Baghdadli A, Jacka F, Sanchez-Villegas A, Kivimaki M, et al. Healthy dietary indices and risk of depressive outcomes: a systematic review and meta-analysis of observational studies. Mol Psychiatry. 2019;24(7):965-86.

6.   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(4):580-91.

7.   Ioannidis JPA. The Challenge of Reforming Nutritional Epidemiologic Research. Jama-J Am Med Assoc. 2018;320(10):969-70.

8.   Dipasquale S, Pariante CM, Dazzan P, Aguglia E, McGuire P, Mondelli V. The dietary pattern of patients with schizophrenia: A systematic review. J Psychiatr Res. 2013;47(2):197-207.

9.   Shaffer JA, Edmondson D, Wasson LT, Falzon L, Homma K, Ezeokoli N, et al. Vitamin D Supplementation for Depressive Symptoms: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Psychosomatic Medicine. 2014;76(3):190-6.

10.   Bloch MH, Hannestad J. Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis. Mol Psychiatr.17(12):1272-82.

11.   Sarris J, Murphy J, Mischoulon D, Papakostas GI, Fava M, Berk M, et al. Adjunctive Nutraceuticals for Depression: A Systematic Review and Meta-Analyses. Am J Psychiatry. 2016;173(6):575-87.

12.   Rucklidge JJ, Eggleston MJF, Johnstone JM, Darling K, Frampton CM. Vitamin-mineral treatment improves aggression and emotional regulation in children with ADHD: a fully blinded, randomized, placebo-controlled trial. J Child Psychol Psychiatry. 2018;59(3):232-46.

13.   Rucklidge JJ, Kaplan BJ. Broad-spectrum micronutrient formulas for the treatment of psychiatric symptoms: a systematic review. Expert Rev Neurother. 2013;13(1):49-73.

14.   Kimball SM, Mirhosseini N, Rucklidge J. Database Analysis of Depression and Anxiety in a Community Sample-Response to a Micronutrient Intervention. Nutrients. 2018;10(2).

15.   Jacka FN, O'Neil A, Opie R, Itsiopoulos C, Cotton S, Mohebbi M, et al. A randomised controlled trial of dietary improvement for adults with major depression (the 'SMILES' trial). Bmc Med. 2017;15.

16.   Roca M, Kohls E, Gili M, Watkins E, Owens M, Hegerl U, et al. Prevention of depression through nutritional strategies in high-risk persons: rationale and design of the MooDFOOD prevention trial. Bmc Psychiatry. 2016;16.

17.   Firth J, Marx W, Dash S, Carney R, Teasdale SB, Solmi M, et al. The Effects of Dietary Improvement on Symptoms of Depression and Anxiety: A Meta-Analysis of Randomized Controlled Trials. Psychosomatic Medicine. 2019;81(3):265-80.

18.   Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. Human Molecular Genetics. 2014;23:R89-R98.

19.   Haycock PC, Burgess S, Wade KH, Bowden J, Relton C, Smith GD. Best (but oft-forgotten) practices: the design, analysis, and interpretation of Mendelian randomization studies. Am J Clin Nutr. 2016;103(4):965-78.

20.   Zheng J, Baird D, Borges MC, Bowden J, Hemani G, Haycock P, et al. Recent Developments in Mendelian Randomization Studies. Curr Epidemiol Rep. 2017;4(4):330-45.

21.   A Lawlor D, Wade K, Borges M, Palmer T, Hartwig F, Hemani G, et al. A Mendelian Randomization dictionary: Useful definitions and descriptions for undertaking, understanding and interpreting Mendelian Randomization studies2019.

22.   Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, et al. Effect of Selenium and Vitamin E on Risk of Prostate Cancer and Other Cancers The Selenium and Vitamin E Cancer Prevention Trial (SELECT). Jama-J Am Med Assoc. 2009;301(1):39-51.

23.   Yarmolinsky J, Bonilla C, Haycock PC, Langdon RJQ, Lotta LA, Langenberg C, et al. Circulating Selenium and Prostate Cancer Risk: A Mendelian Randomization Analysis. J Natl Cancer Inst. 2018;110(9):1035-8.

24.   Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. Int J Epidemiol. 2016;45(6):1866-86.

25.   Mokry LE, Ross S, Morris JA, Manousaki D, Forgetta V, Richards JB. Genetically decreased vitamin D and risk of Alzheimer disease. Neurology.87(24):2567-74.

26.   Larsson SC, Traylor M, Markus HS, Michaelsson K. Serum Parathyroid Hormone, 25-Hydroxyvitamin D, and Risk of Alzheimer's Disease: A Mendelian Randomization Study. Nutrients. 2018;10(9).

27.   Olsson E, Byberg L, Karlstrom B, Cederholm T, Melhus H, Sjogren P, et al. Vitamin D is not associated with incident dementia or cognitive impairment: An 18-y follow-up study in community-living old men. American Journal of Clinical Nutrition. 2017;105(4):936-43.

28.   Jorde R, Mathiesen EB, Rogne S, Wilsgaard T, Kjaergaard M, Grimnes G, et al. Vitamin D and cognitive function: The Tromso Study. Journal of the Neurological Sciences. 2015;355(1-2):155-61.

29.   Maddock J, Zhou A, Cavadino A, Kuzma E, Bao Y, Smart MC, et al. Vitamin D and cognitive function: A Mendelian randomisation study. Sci Rep. 2017;7(1):13230.

30.   McGrath JJ, Eyles DW, Pedersen CB, Anderson C, Ko P, Burne TH, et al. Neonatal Vitamin D Status and Risk of Schizophrenia: A Population-Based Case-Control Study. Schizophrenia Research. 2010;117(2-3):312-.

31.   Staley JR, Burgess S. Semiparametric methods for estimation of a nonlinear exposure-outcome relationship using instrumental variables with application to Mendelian randomization. Genet Epidemiol. 2017;41(4):341-52.

32.   Larsson SC, Traylor M, Malik R, Dichgans M, Burgess S, Markus HS, et al. Modifiable pathways in Alzheimer's disease: Mendelian randomisation analysis. BMJ. 2017;359:j5375.

33.   Hu Q, Teng W, Li J, Hao F, Wang N. Homocysteine and Alzheimer's Disease: Evidence for a Causal Link from Mendelian Randomization. Journal of Alzheimer's Disease. 2016;52(2):747-56.

34.   Schatzkin A, Abnet CC, Cross AJ, Gunter M, Pfeiffer R, Gail M, et al. Mendelian randomization: how it can--and cannot--help confirm causal relations between nutrition and cancer. Cancer Prev Res (Phila). 2009;2(2):104-13.

35.   Wu SP, Ma JJ, Qi YW, Zhang JW. Plasma homocysteine levels and risk of vascular dementia: A Mendelian randomization study. International Journal of Clinical and Experimental Medicine. 2017;10(6):9142-51.

36.   Larsson SC, Markus HS. Branched-chain amino acids and Alzheimer's disease: a Mendelian randomization analysis. Sci Rep-Uk. 2017;7.

37.   Rasmussen KL, Tybjaerg-Hansen A, Nordestgaard BG, Frikke-Schmidt R. Plasma apolipoprotein E levels and risk of dementia: A Mendelian randomization study of 106,562 individuals. Alzheimers Dement. 2018;14(1):71-80.

38.   Benn M, Nordestgaard BG, Frikke-Schmidt R, Tybjaerg-Hansen A. Low LDL cholesterol, PCSK9 and HMGCR genetic variation, and risk of Alzheimer's disease and Parkinson's disease: Mendelian randomisation study. BMJ. 2017;357:j1648.

39.   Proitsi P, Lupton MK, Velayudhan L, Newhouse S, Fogh I, Tsolaki M, et al. Genetic predisposition to increased blood cholesterol and triglyceride lipid levels and risk of Alzheimer disease: a Mendelian randomization analysis. PLoS Medicine / Public Library of Science.11(9):e1001713.

40.   Ostergaard SD, Mukherjee S, Sharp SJ, Proitsi P, Lotta LA, Day F, et al. Associations between Potentially Modifiable Risk Factors and Alzheimer Disease: A Mendelian Randomization Study. PLoS Medicine / Public Library of Science.12(6):e1001841; discussion e.

41.   Liu G, Zhao Y, Jin S, Hu Y, Wang T, Tian R, et al. Circulating vitamin E levels and Alzheimer's disease: A Mendelian randomization study. Neurobiology of Aging. 2018;72:189.

42.   Cheng WW, Zhu Q, Zhang HY. Mineral Nutrition and the Risk of Chronic Diseases: A Mendelian Randomization Study. Nutrients. 2019;11(2):12.

43.   Tomioka Y, Numata S, Kinoshita M, Umehara H, Watanabe S, Nakataki M, et al. Decreased serum pyridoxal levels in schizophrenia: meta-analysis and Mendelian randomization analysis. J Psychiatr Neurosci. 2018;43(3):194-200.

44.   Numata S, Kinoshita M, Tajima A, Nishi A, Imoto I, Ohmori T. Evaluation of an association between plasma total homocysteine and schizophrenia by a Mendelian randomization analysis. BMC Medical Genetics. 2015;16:54.

45.   Kinoshita M. One-carbon Metabolism and Schizophrenia. [Japanese]. Seishin shinkeigaku zasshi = Psychiatria et neurologia Japonica. 2015;117(5):362-8.

46.   Li Z, Chen P, Chen J, Xu Y, Wang Q, Li X, et al. Glucose and Insulin-Related Traits, Type 2 Diabetes and Risk of Schizophrenia: A Mendelian Randomization Study. Ebiomedicine. 2018;34:182-8.

47.   Mokry LE, Ross S, Ahmad OS, Forgetta V, Smith GD, Leong A, et al. Vitamin D and Risk of Multiple Sclerosis: A Mendelian Randomization Study. Plos Med. 2015;12(8).

48.   Taylor AE, Burgess S, Ware JJ, Gage SH, Richards JB, Davey Smith G, et al. Investigating causality in the association between 25(OH)D and schizophrenia. Sci Rep. 2016;6:26496.

49.   Dalen P. Month of Birth and Schizophrenia. Acta Psychiat Scand. 1968;S:55-+.

50.   Mollehave LT, Skaaby T, Simonsen KS, Thuesen BH, Mortensen EL, Sandholt CH, et al. Association studies of genetic scores of serum vitamin B12 and folate levels with symptoms of depression and anxiety in two danish population studies. Eur J Clin Nutr. 2017;71(9):1054-60.

51.   Sallis H, Steer C, Paternoster L, Smith GD, Evans J. Perinatal depression and omega-3 fatty acids: A Mendelian randomisation study. J Affect Disorders. 2014;166:124-31.

52.   Michaelsson K, Melhus H, Larsson SC. Serum 25-Hydroxyvitamin D Concentrations and Major Depression: A Mendelian Randomization Study. Nutrients. 2018;10(12).

53.   Wesolowska K, Elovainio M, Hintsa T, Jokela M, Pulkki-Raback L, Pitkanen N, et al. Fasting Glucose and the Risk of Depressive Symptoms: Instrumental-Variable Regression in the Cardiovascular Risk in Young Finns Study. International Journal of Behavioral Medicine. 2017;24(6):901-7.

54.   Khandaker GM, Zuber V, Rees JMB, Carvalho L, Mason AM, Foley CN, et al. Shared mechanisms between coronary heart disease and depression: findings from a large UK general population-based cohort. Mol Psychiatr. 2019;19:19.

55.   Meddens SFW, Vlaming Rd, Bowers P, Burik CA, Linnér RK, Lee C, et al. Genomic analysis of diet composition finds novel loci and associations with health and lifestyle. bioRxiv. 2018.

56.   Guenard F, Bouchard-Mercier A, Rudkowska I, Lemieux S, Couture P, Vohl MC. Genome-Wide Association Study of Dietary Pattern Scores. Nutrients. 2017;9(7).

57.   Goodrich JK, Waters JL, Poole AC, Sutter JL, Koren O, Blekhman R, et al. Human Genetics Shape the Gut Microbiome. Cell. 2014;159(4):789-99.

58.   Sanna S, van Zuydam NR, Mahajan A, Kurilshikov A, Vila AV, Vosa U, et al. Causal relationships among the gut microbiome, short-chain fatty acids and metabolic diseases. Nature Genetics. 2019;51(4):600-+.

59.   Bastiaanssen TFS, Cowan CSM, Claesson MJ, Dinan TG, Cryan JF. Making Sense of ... the Microbiome in Psychiatry. Int J Neuropsychoph. 2019;22(1):37-52.

60.   Kali A. Psychobiotics: An emerging probiotic in psychiatric practice. Biomed J. 2016;39(3):223-4.

61.   Wallace CJK, Milev R. The effects of probiotics on depressive symptoms in humans: a systematic review (vol 16, 14, 2017). Annals of General Psychiatry. 2017;16.

62.   Burgess S, Freitag DF, Khan H, Gorman DN, Thompson SG. Using Multivariable Mendelian Randomization to Disentangle the Causal Effects of Lipid Fractions. Plos One. 2014;9(10).

63.   Millard LA, Davies NM, Timpson NJ, Tilling K, Flach PA, Davey Smith G. MR-PheWAS: hypothesis prioritization among potential causal effects of body mass index on many outcomes, using Mendelian randomization. Sci Rep-Uk.5:16645.

64.   Relton CL, Davey Smith G. Two-step epigenetic Mendelian randomization: a strategy for establishing the causal role of epigenetic processes in pathways to disease. Int J Epidemiol. 2012;41(1):161-76.

65.   Giovannucci E. Nutritional epidemiology: forest, trees and leaves. Eur J Epidemiol. 2019;34(4):319-25.

66.   Hemani G, Bowden J, Haycock P, Zheng J, Davis O, Flach P, et al. Automating Mendelian randomization through machine learning to construct a putative causal map of the human phenome. bioRxiv. 2017.

67.   Roostaei T, Felsky D, Nazeri A, De Jager PL, Schneider JA, Bennett DA, et al. Genetic influence of plasma homocysteine on Alzheimer's disease. Neurobiology of Aging.62:243.e7-.e14.

68.   Walter S, Marden JR, Kubzansky LD, Mayeda ER, Crane PK, Chang S-C, et al. Diabetic phenotypes and late-life dementia risk: A mechanism-specific Mendelian Randomization study. Alzheimer Disease and Associated Disorders. 2016;30(1):15-20.

69.   Brion MJA, Shakhbazov K, Visscher PM. Calculating statistical power in Mendelian randomization studies. Int J Epidemiol. 2013;42(5):1497-501.