

Est.  
1841

YORK  
ST JOHN  
UNIVERSITY

Firth, Joseph, Solmi, Marco, Wootton, Robyn E, Vancampfort, Davy, Schuch, Felipe B, Hoare, Erin, Gilbody, Simon, Torous, John, Teasdale, Scott B, Jackson, Sarah E, Smith, Lee, Eaton, Melissa, Jacka, Felice N, Veronese, Nicola, Marx, Wolfgang, Ashdown-Franks, Garcia ORCID logo ORCID: <https://orcid.org/0000-0002-5032-0171>, Siskind, Dan, Sarris, Jerome, Rosenbaum, Simon, Carvalho, André F and Stubbs, Brendon (2020) A meta-review of "lifestyle psychiatry": the role of exercise, smoking, diet and sleep in the prevention and treatment of mental disorders. *World psychiatry : official journal of the World Psychiatric Association (WPA)*, 19 (3). pp. 360-380.

Downloaded from: <https://ray.yorks.ac.uk/id/eprint/10755/>

The version presented here may differ from the published version or version of record. If you intend to cite from the work you are advised to consult the publisher's version:

<https://doi.org/10.1002/wps.20773>

Research at York St John (RaY) is an institutional repository. It supports the principles of open access by making the research outputs of the University available in digital form. Copyright of the items stored in RaY reside with the authors and/or other copyright owners. Users may access full text items free of charge, and may download a copy for private study or non-commercial research. For further reuse terms, see licence terms governing individual outputs. [Institutional Repository Policy Statement](#)

# RaY

Research at the University of York St John

For more information please contact RaY at [ray@yorks.ac.uk](mailto:ray@yorks.ac.uk)

## **A meta-review of “lifestyle psychiatry”: the role of exercise, smoking, diet and sleep in the prevention and treatment of mental disorders**

Joseph Firth<sup>1,2</sup>, Marco Solmi<sup>3</sup>, Robyn E. Wootton<sup>4</sup>, Davy Vancampfort<sup>5,6</sup>, Felipe B. Schuch<sup>7</sup>, Erin Hoare<sup>8,16</sup>, Simon Gilbody<sup>9</sup>, John Torous<sup>10</sup>, Scott B. Teasdale<sup>11</sup>, Sarah E. Jackson<sup>12</sup>, Lee Smith<sup>13</sup>, Melissa Eaton<sup>2</sup>, Felice N. Jacka<sup>14</sup>, Nicola Veronese<sup>15</sup>, Wolfgang Marx<sup>16</sup>, Garcia Ashdown-Franks<sup>16-18</sup>, Dan Siskind<sup>19,20</sup>, Jerome Sarris<sup>2,21</sup>, Simon Rosenbaum<sup>11</sup>, André F. Carvalho<sup>22,23</sup>, Brendon Stubbs<sup>17,18</sup>

<sup>1</sup>Division of Psychology and Mental Health, Faculty of Biology, Medicine & Health, University of Manchester, Manchester, UK; <sup>2</sup>NICM Health Research Institute, Western Sydney University, Westmead, NSW, Australia; <sup>3</sup>Department of Neurosciences, University of Padua, Padua, Italy; <sup>4</sup>MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK; <sup>5</sup>KU Leuven Department of Rehabilitation Sciences, Leuven, Belgium; <sup>6</sup>University Psychiatric Centre KU Leuven, Kortenberg, Belgium; <sup>7</sup>Department of Sports Methods and Techniques, Federal University of Santa Maria, Santa Maria, Brazil; <sup>8</sup>UKCRC Centre for Diet and Activity Research (CEDAR) and MRC Epidemiology Unit, University of Cambridge, Cambridge, UK; <sup>9</sup>Mental Health and Addictions Research Group, Department of Health Sciences, University of York, York, UK; <sup>10</sup>Department of Psychiatry, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; <sup>11</sup>School of Psychiatry, Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia; <sup>12</sup>Department of Behavioural Science and Health, University College London, London, UK; <sup>13</sup>Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge, UK; <sup>14</sup>Deakin University, Food & Mood Centre, IMPACT – the Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Barwon Health, Geelong, Australia; <sup>15</sup>Geriatric Unit, Department of Internal Medicine and Geriatrics, University of Palermo, Palermo, Italy; <sup>16</sup>Department of Exercise Sciences, University of Toronto, Toronto, ON, Canada; <sup>17</sup>South London and Maudsley NHS Foundation Trust, London, UK; <sup>18</sup>Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; <sup>19</sup>Metro South Addiction and Mental Health Service, Brisbane, Australia; <sup>20</sup>School of Medicine, University of Queensland, Brisbane, QLD, Australia; <sup>21</sup>Department of Psychiatry, University of Melbourne, The Melbourne Clinic, Melbourne, VIC, Australia; <sup>22</sup>Centre for Addiction & Mental Health, Toronto, ON, Canada; <sup>23</sup>Department of Psychiatry, University of Toronto, Toronto, ON, Canada

There is increasing academic and clinical interest in how “lifestyle factors” traditionally associated with physical health may also relate to mental health and psychological well-being. In response, international and national health bodies are producing guidelines to address health behaviors in the prevention and treatment of mental illness. However, the current evidence for the causal role of lifestyle factors in the onset and prognosis of mental disorders is unclear. We performed a systematic meta-review of the top-tier evidence examining how physical activity, sleep, dietary patterns and tobacco smoking impact on the risk and treatment outcomes across a range of mental disorders. Results from 29 meta-analyses of prospective/cohort studies, 12 Mendelian randomization studies, and 2 meta-reviews, and 2 meta-analyses of randomized controlled trials were synthesized to generate overviews of the evidence for targeting each of the specific lifestyle factors in the prevention and treatment of depression, anxiety and stress-related disorders, schizophrenia, bipolar disorder, and attention-deficit/hyperactivity disorder. Standout findings include: a) convergent evidence indicating the use of physical activity in primary prevention and clinical treatment across a spectrum of mental disorders; b) emerging evidence implicating tobacco smoking as a causal factor in onset of both common and severe mental illness; c) the need to clearly establish causal relations between dietary patterns and risk of mental illness, and how diet should be best addressed within mental health care; and d) poor sleep as a risk factor for mental illness, although with further research required to understand the complex, bidirectional relations and the benefits of non-pharmacological sleep-focused interventions. The potentially shared neurobiological pathways between multiple lifestyle factors and mental health are discussed, along with directions for future research, and recommendations for the implementation of these findings at public health and clinical service levels.

**Key words:** Lifestyle factors, mental disorders, psychological well-being, physical activity, sedentary behavior, tobacco smoking, dietary patterns, sleep, depression, anxiety disorders, bipolar disorder, schizophrenia

Mental disorders affect almost 30% of individuals across the lifespan<sup>1</sup>, and are among the largest contributors to the global burden of disease, accounting for 32% of all years lived with disability, and 13% of disability-adjusted life years<sup>2</sup>. Despite many advances in psychotherapies and pharmacological treatments for a range of psychiatric conditions, there remains a substantial proportion of individuals who do not achieve full remission from standard treatment<sup>3,4</sup>. Additionally, a large portion of the global population do not have access to traditional mental health care, due to the scarcity of psychiatric services available, particularly in many low- and middle-income countries<sup>3,5</sup>. There has also been little improvement in primary prevention of mental illness, with clear gaps in both the evidence and implementation for such interventions<sup>6</sup>. Indeed, rates of common mental disorders (i.e., depression and anxiety) appear to even be increasing among the younger generations<sup>7</sup>. Thus, new approaches towards the prevention and treatment of mental illness, which can be delivered alongside or in the absence of traditional mental health care, are needed to reduce the global and growing burden of these conditions.

An emerging body of research has linked both the onset and symptoms of various mental disorders to “lifestyle factors”, a term referring to health behaviors such as physical activity, diet, tobacco smoking and sleep<sup>8</sup>. For instance, a mass of cross-sectional evidence<sup>9</sup> shows that a range of psychiatric conditions (including schizophrenia, bipolar disorder, depression, and anxiety and stress-related disorders) are associated with adverse health behaviors, such as poorer dietary and sleeping patterns, low levels of physical activity, and higher rates of tobacco smoking, compared to healthy controls. Additionally, recent findings from population-scale studies document that the relationships between many of these lifestyle risk factors and mental illness also persist in low- and middle-income countries<sup>10-12</sup>.

Although useful, this expansive body of cross-sectional research does not uncover the causality of the observed relationships. Therefore, the evidence for which lifestyle factors should be addressed when aiming to prevent the onset of mental illness, or reduce symptoms in those with established conditions, is currently very limited.

Nonetheless, a number of national health policy documents and clinical guidelines are now beginning to address the role of specific lifestyle factors in the prevention and treatment of mental illness. For instance, both the US Physical Activity Guidelines for Americans<sup>13</sup> and the UK Chief Medical Officers' Physical Activity Guidelines<sup>14</sup> recommend attaining at least 150 min of moderate-to-vigorous physical activity per week for reducing the risk of depression (including postnatal depression).

In order to preserve both overall mental health and cognitive functioning, both Canada's<sup>15</sup> and Australia's<sup>16</sup> 24-Hour Movement Guidelines have adopted a “whole day time-use” paradigm for young people, recommending that each day should include at least 60 min of

moderate-to-vigorous exercise, several hours of light physical activity, no more than two hours of sedentary leisure activities, and 8-11 hours of uninterrupted sleep. The UK Royal College of Psychiatrist's position statement on public mental health<sup>6</sup> also describes how the clustering of health-risk behaviours (which include smoking, lack of exercise, and unhealthy eating) increases lifetime risk of mental illness.

Along with this surge of recognition from public health perspectives, the role of behavioral factors is also becoming a topic of increasing interest in psychiatric research and mental health services. Notably, the European Psychiatric Association's guidelines<sup>17</sup> on physical activity in mental illness put forth that there is sufficient evidence to recommend structured exercise training as an effective first-line treatment option for moderate depression, and as an adjunctive intervention for improving symptomatic recovery in severe mental illness. Additionally, the Royal Australian and New Zealand College of Psychiatrists' clinical practice guidelines for mood disorders<sup>18</sup> list exercise, smoking, diet and sleep as "step zero" targets, to be addressed before implementation of pharmacotherapy and/or psychotherapy.

There are a large number of individual clinical trials, epidemiological studies, and meta-analyses investigating the impact of other health behaviors in various psychiatric conditions. However, existing guidelines predominantly focus on physical activity, and typically only in relation to depression or schizophrenia. The broader role of lifestyle factors, across the spectrum of mental disorders, has yet to be established.

This meta-review aimed to establish the current evidence on causal relations between key modifiable health behaviors (physical activity, dietary food intake, tobacco smoking, and sleep) with the incidence and outcomes of major mental disorders, including depression, anxiety and stress-related disorders, attention-deficit/hyperactivity disorder (ADHD), bipolar disorder, schizophrenia and related psychotic disorders. We sought to present an empirical overview of the field of lifestyle medicine for mental illness, and produce evidence-based recommendations for targeting modifiable health behavior factors in the prevention and treatment of these conditions, while also identifying key evidential gaps to inform future research.

## **METHODS**

This meta-review aimed to systematically aggregate the most recent, top-tier evidence for the role of "lifestyle factors" in the prevention and treatment of mental disorders, following the PRISMA statement to ensure comprehensive and transparent reporting<sup>19</sup>. The systematic searches were conducted on February 3, 2020 of the following databases: Allied and Complementary Medicine (AMED), PsycINFO, Ovid MEDLINE, Health Management

Information Consortium, EMBASE and the NHS Economic Evaluation and Health Technology Assessment databases.

The following PICOS search algorithm was used: Participants ['mental health or psychological well-being or psychological outcomes or mental well-being or psychiat\* or mental illness\* or mental disorder\* or depress\* or mood disorder\* or affective disorder\* or anxiety\* or panic or obsessive compulsive or OCD or ADHD or attention deficit or attentional deficit or phobi\* or bipolar type or bipolar disorder\* or psychosis or psychotic or schizophr\* or schizoaffective or antipsychotic\* or post traumatic\* or personality disorder\* or stress disorder\* or dissociative disorder or antidepress\* or antipsychotic\*.ti]; Interventions/Exposures [physical activity or exercis\* or sport\* or walking or intensity activity or resistance training or muscle or sedentary or screen time or screentime or aerobic or fitness or diet\* or nutri\* or food\* or vegan or vege\* or meat or carbohy\* or fibre or sugar\* or adipos\* or vitamin\* or fruit\* or sleep\* or insomn\* or circad\* or smoke\* or smoking or tobacco or nicotine or healthy or obes\* or weight or bodyweight or body mass or BMI or health behav\* or behavior change or behavior change or lifestyle\*.ti]; Outcomes ['meta-analy\* or metaanaly\* or meta reg\* or metareg\* or systematic review\* or Mendel\* or meta-review or reviews or umbrella review or updated review\*.ti]; Study design ['prospective or protect\* or inciden\* or onset or prevent\* or cohort or predict\* or risk or longitudinal or randomized or randomised or mendel\* or bidirectional or controlled or trial\* or causal'].

Separate searches of the Cochrane Database of Systematic Reviews and Google Scholar were also conducted to identify additional articles.

## **Eligibility criteria**

The lifestyle factors examined were those pertaining to physical activity, diet, sleep and smoking.

“Physical activity” was considered in the broadest sense, including overall physical activity levels, structured exercise training interventions, and also studies examining the absence of physical activity, i.e. sedentary behavior. “Diet” focused on dietary food intake/interventions, and did not include studies evaluating specific nutrient treatments (as these have been already reviewed extensively in this journal<sup>20</sup>) or those examining blood levels of individual vitamins/minerals/fatty acids (as blood levels of these nutrients are influenced by many genetic and environmental factors, independent from dietary intake<sup>21,22</sup>). “Sleep” was examined as general sleep patterns, quality or quantity, along with studies examining either the impact of sleep disorders (i.e., insomnia) on risk of mental illnesses, or the efficacy of non-pharmacological interventions directly targeting sleep to improve psychiatric symptoms. The term “smoking” was used only in reference to tobacco consumption, from personal usage or

passive exposure, rather than illicit drugs, as the known psychoactive effects of these latter substances have been reviewed extensively in this journal<sup>23</sup>.

Mental disorders eligible to be included in this meta-review were mood disorders (moderate or severe depression, or bipolar disorder), psychotic disorders (including schizophrenia and related conditions), anxiety and stress-related disorders, dissociative disorders, personality disorders, and ADHD. We excluded psychiatric conditions which are directly characterized by adverse health behaviors (i.e., eating disorders and alcohol or substance use disorders) along with other neurodevelopmental disorders (e.g., autism, intellectual disability) and neurodegenerative disorders (e.g., dementia), as these were considered beyond the scope of this review.

Protective factors were examined using two sources of data. First, we searched for meta-analyses of longitudinal data that examined relationships between the various lifestyle factors and prospective risk/onset of mental illness. Eligible meta-analyses were those presenting suitable quantitative data - as adjusted or raw odds ratios (ORs), risk ratios (RRs) or hazard ratios (HRs) – on how baseline status of behavioral variables influences the prospective risk of mental illness, including diagnosed psychiatric conditions, clinically significant symptoms (using established cut-offs on validated screening instruments), or based on percentile cut-offs of psychiatric symptom scores.

The second source of data used for examining protective factors were any Mendelian randomization (MR) studies of the link between lifestyle factors and mental illness. Briefly, MR is a causal inference method that can be used to estimate the effect of an exposure (X) on an outcome (Y) whilst minimizing bias from confounding and reverse causation<sup>24,25</sup>. Suitable genetic instruments (usually single nucleotide polymorphisms, SNPs) are identified through genome-wide association studies (GWAS). Individuals carrying the effect allele of the variant have higher (or lower) levels of X on average than those without the effect alleles. Following Mendel's laws of segregation and independent assortment, the genetic variants are inherited randomly at conception, and are inherited independently of confounding lifestyle factors<sup>26</sup>. Therefore, MR can be considered somewhat analogous to a randomized controlled trial (RCT) of behavioral factors in the prevention of mental illness, as genetic variants randomly predispose individuals to experience different levels of these factors<sup>26</sup>. As genes also remain unchanged throughout the life course, they are also not altered by the outcome of interest, thus reducing bias from reverse causation<sup>26</sup>. Therefore, while meta-analyses of prospective cohort studies are useful for identifying the overall strength and directionality of associations, the MR analyses were used to further infer the causal nature of the observed relationships.

The evidence for lifestyle interventions in the treatment of people with diagnosed mental disorders was examined using two different sources of data, but both based on meta-analyses of RCTs (typically considered the top-tier of evidence in health intervention research). First,

we searched for existing meta-reviews of meta-analyses of RCTs published in the last five years, for each lifestyle factor, providing quantitative effects of physical activity, diet, smoking cessation or non-pharmacological sleep interventions on psychiatric symptoms in people with mental illness. Second, for the lifestyle factors that were not covered within the existing meta-reviews, we sought out meta-analyses of RCTs examining their impact (using the search strategy above), and synthesized the evidence from the meta-analyses using a methodology derived from a previous meta-review<sup>20</sup>. For meta-analyses with mixed samples, only those in which at least 75% of the sample examined the eligible mental illnesses (as described above) were included.

## **Data extraction**

A systematic tool was applied to each eligible meta-analysis/MR study to extract the relevant data on the association of lifestyle factors with risk of mental illness, or the effects of lifestyle interventions on psychiatric outcomes. Results of eligible meta-reviews were extracted narratively, summarised from their respective articles.

For meta-analyses of longitudinal studies, the strength and direction of the prospective associations between lifestyle factors and mental illness was quantified categorically, and thus extracted as ORs, HRs or RRs, with 95% confidence intervals (CIs).

For meta-analyses of RCTs of lifestyle interventions in mental illness, effect size data were quantified as a continuous variable (i.e., magnitude of effect on psychiatric symptoms) and thus extracted as standardized mean differences (SMDs), Cohen's *d* or Hedges' *g*. These were then classified as small (<0.4), moderate (0.4-0.8), or large (>0.8).

For all meta-analyses, data on the degree of between-study heterogeneity (quantified as  $I^2$  values) were also extracted, where reported.

In cases where multiple eligible meta-analyses examined a specific lifestyle factor in the risk/treatment of the same mental disorder were found, the most recent was used preferentially. Where older meta-analyses featured >25% more studies than the newer versions and contained important, novel findings from unique analyses not captured in the most recent versions, these were also extracted and presented alongside the newer findings. In cases where two MR studies had examined the same lifestyle factor for the same mental health outcome, both studies (regardless of recency or sample size) were included and reviewed.

We also extracted relevant study characteristics where reported, including number of pooled comparisons within meta-analyses (*n*), sample size (*N*), details on the specifics of lifestyle exposure or intervention examined, and sample features. The results of key subgroup/sensitivity analyses showing how different age groups, illnesses or outcomes



examined, or different types of exposure/interventions, modified the effect of the specific lifestyle factor were extracted as well. For the purposes of providing a concise summary of the literature, only the findings from secondary analyses which provided important, unique insights into the evidence were extracted.

### **Quality assessment of included studies**

The National Institutes of Health (NIH)'s Quality Assessment Tool for Systematic Reviews and Meta-Analyses was used to assess the quality of the included meta-analyses. This tool evaluates the quality of meta-analyses rating them for adequacy of the search question, specification of inclusion and exclusion criteria, systematic search, screening of papers, quality assessment and summaries of included studies, and tests for publication bias and heterogeneity. In accordance with previous meta-reviews using the NIH tool<sup>27</sup>, the quality of included meta-analyses was categorized as "good" (7 or 8), "fair" (4-6), or "poor" (0-3).

As no consensus tool exists for determining the quality of MR and meta-review studies, these were omitted from formal quality assessment.

## **RESULTS**

### **Systematic search**

The main search returned a total of 1,811 results, which were reduced to 834 after duplicates were excluded. A total of 92 full text papers were retrieved, from which 41 met full inclusion criteria. Of note, one seemingly eligible study<sup>28</sup> was excluded for invalid findings due to inconsistent coding of effect directionality. Four additional studies were identified from the supplementary searches, and thus 45 studies were included in total. Across the different lifestyle factors, 11 of the eligible papers focused on physical activity/exercise, 15 were on smoking, 12 examined diet, and 10 considered sleep. Some papers covered multiple factors.

The results below synthesize the findings of 29 meta-analyses of prospective/cohort studies, 12 Mendelian randomization studies, and 2 meta-reviews, and 2 meta-analyses of RCTs. Individual details for the prospective meta-analyses and MR studies examining lifestyle risk factors for mental disorders are provided in Tables 1-8.

## **Lifestyle factors in the prevention of mental disorders**

### ***Physical activity and risk of depression***

A meta-analysis of 36 prospective comparisons<sup>29</sup> found that higher levels of physical activity significantly reduced the subsequent risk of incident depression over a mean follow-up time of 7.4 years (OR=0.837, 95% CI: 0.794-0.883), with low heterogeneity between included studies ( $I^2=0\%$ ). Although there was indication of publication bias, adjusting for this did not alter overall findings (OR=0.85, 95% CI: 0.81-0.89). Subgroup analyses found similar results for protective effects of physical activity in studies measuring incidence of depressive symptoms (n=28, OR=0.844, 95% CI: 0.798-0.892) or major depressive disorder (n=10, OR=0.862, 95% CI: 0.757-0.981), and in children/adolescents (n=3, OR=0.907, 95% CI: 0.836-0.985), adults (n=16, OR=0.787, 95% CI: 0.707-0.877) or older adults (n=16, OR=0.794, 95% CI: 0.726-0.868). Adjusting for baseline depressive symptoms, body mass index, smoking status, age, gender and other confounds did not alter the findings.

Prospective associations between sedentary behavior and depression were examined in three meta-analyses<sup>30-32</sup>. The largest analysis examining overall sedentary behavior found that more sedentary individuals were at significantly increased risk of depression over time (determined via diagnostic records or clinical interviews) compared to less sedentary counterparts (n=11, RR=1.14, 95% CI: 1.06-1.21,  $I^2=0\%$ )<sup>32</sup>. However, subsequent meta-analyses examining sedentary behavior specifically as “screen time” found no evidence that this domain significantly increased prospective risk of depressive symptoms in all available samples<sup>30</sup>, or in children and adolescents samples only<sup>31</sup>.

Two MR studies examined the causal relations between physical activity and depression<sup>33,34</sup>. Choi et al<sup>34</sup> applied a factor-wide design to Wray et al's GWAS<sup>35</sup>, corrected for multiple testing and adjusted for potential confounders, to identify a broad spectrum of modifiable risk factors potentially implicated in major depression. MR analysis of the available variables related to physical activity found some evidence that self-reported cycling or swimming may causally decrease depression risk, although only at a nominal level of significance (which did not survive correction for multiple testing). Other self-report variables concerning specific types of physical activity (such as self-reported “part of a gym or club”, “walking for pleasure” or “heavy do-it-yourself, DIY”) had no evidence of causal relations with depression.

A second study conducted a bi-directional two-sample MR to investigate risk of major depression in relation to both self-reported moderate-vigorous physical activity and objectively measured physical activity (with accelerometer data, using mean acceleration over 72

hours)<sup>33</sup>. Physical activity summary data were from Wray et al's GWAS<sup>35</sup>. Initial analyses found no clear evidence that either form of activity causally influenced risk of major depression. However, as these initial analyses identified only two SNPs associated with overall objectively measured activity, a relaxed p value threshold of  $p < 1 \times 10^{-7}$  was used, which instead identified 10 SNPs. Using this genetic instrument, there was strong evidence for objectively measured overall physical activity as a protective factor for major depression: IVW (inverse-variance weighted) OR=0.74, 95% CI: 0.59-0.92,  $p=0.006$ . This was consistent across multiple sensitivity analyses to test for pleiotropy.

### ***Physical activity and risk of anxiety and stress-related disorders***

The relationship between physical activity and incident anxiety was examined across 11 cohorts with a total of 69,037 participants<sup>36</sup>. Over the average follow-up period of 3.5 years, higher levels of physical activity significantly reduced incident anxiety (OR=0.748, 95% CI: 0.629-0.889), with low heterogeneity ( $I^2=23.96\%$ ). There was some indication of publication bias, although significant positive effects of physical activity remained when adjusting for this (OR=0.86, 95% CI: 0.69-0.99). Examination of specific anxiety disorders indicated risk reduction from physical activity for agoraphobia ( $n=2$ , OR=0.43, 95% CI: 0.19-0.99) and post-traumatic stress disorder ( $n=2$ , OR=0.58, 95% CI: 0.39-0.86), with no significant effects observed for other disorders. It should be noted, however, that only small samples were available for these subgroup analyses.

A subsequent meta-analysis<sup>37</sup> examining the longitudinal relations of physical activity with different measures of anxiety indicated protective benefits from high levels of physical activity for each measure, including elevated anxiety symptoms ( $n=9$ , OR=0.874, 95% CI: 0.77-0.99,  $I^2=48.7\%$ ), anxiety disorder diagnosis ( $n=3$ , OR=0.663, 95% CI: 0.53-0.82,  $I^2=62.3\%$ ), and generalized anxiety disorder ( $n=3$ , OR=0.544, 95% CI: 0.32-0.92,  $I^2=0\%$ ), although limitations concerning the low number of studies and the considerable heterogeneity were again noted<sup>37</sup>.

No MR studies examined the relationship between physical activity and the risk of anxiety.

### ***Physical activity and risk of psychotic and bipolar disorders***

One prospective meta-analysis examined prospective associations between physical activity for schizophrenia and related psychotic disorders<sup>38</sup>. Across five prospective comparisons, with 4-32 years of follow-up, higher levels of physical activity significantly reduced risk of incident psychosis (OR=0.728, 95% CI: 0.532-0.995,  $I^2=36.9\%$ ). However, in the two studies ( $N=10,583$ ) that adjusted for confounding factors, overall reductions in

psychosis incidence from physical activity were non-significant (OR=0.59, 95% CI: 0.253-1.383,  $I^2=54.7\%$ ).

The risk of schizophrenia and bipolar disorder in relation to overall physical activity, moderate-intensity activity, and sedentary time was examined in one MR study<sup>39</sup>, using SNPs associated with device-measured physical activity over 72 hours from Stahl et al's<sup>40</sup> and Ruderfer et al's<sup>41</sup> GWAS. There was no strong evidence of causal relations with schizophrenia. However, the two-sample MR did find indication of causal relations between increased overall physical activity and decreased risk for bipolar disorder, equating to a 51% lower risk per 8 milligravity increase in mean acceleration (IVW OR=0.491, 95% CI: 0.314-0.767,  $p=0.002$ ). This estimate was consistent across multiple sensitivity analyses to test for pleiotropy. Associations with specific domains of sedentary behavior or moderate intensity activity were non-significant.

### ***Smoking and risk of common mental disorders***

Longitudinal associations between smoking exposure and subsequent risk of depression were examined in four meta-analyses of 19 studies with a total of 79,729 participants. Among 52,568 adults, from seven studies with 1-6 year follow-ups, smoking significantly increased the prospective risk of depression, measured as either diagnosed depressive disorders or clinically-relevant depressive symptoms on validated scales (OR=1.62, 95% CI: 1.1-2.4,  $I^2=N/R$ )<sup>42</sup>.

A meta-analysis of six studies including 15,333 adolescents aged 13-19 showed that smokers were significantly more likely to develop depression than non-smokers over 1-6 year follow-up (OR=1.73, 95% CI: 1.32-2.4)<sup>43</sup>. There was notable heterogeneity among studies ( $I^2=N/R$ , Q test  $p$  value=0.08).

The impact of "second-hand smoking" in childhood on prospective risk of depression was examined across two cohort studies of 8,092 individuals<sup>44</sup>. Those exposed to second-hand smoking were at non-significantly higher risk of subsequent depressive symptoms (OR=1.51, 95% CI: 0.93-2.09,  $I^2=0\%$ ). Additionally, four prospective studies of 3,736 pregnant women found that prenatal smoking was associated with an almost three-fold increased risk of postpartum depression (OR=2.88, 95% CI: 0.99-8.39), although with high heterogeneity ( $I^2=89.3\%$ ) and effects breaching the threshold for statistical significance ( $p=0.052$ )<sup>45</sup>.

No meta-analyses examined the longitudinal relations between smoking and anxiety.

Four MR studies examined smoking as a risk factor for depression or anxiety<sup>46-49</sup>. They assessed relations with individual SNPs located in the nicotine acetylcholine receptor gene cluster (rs16969968 or rs1051730 in CHRNA5-CHRNA3-CHRNA4 on chromosome 15), a gene cluster closely related with smoking behavior, to the extent that each risk allele increase

is associated with smoking an additional cigarette each day (on average)<sup>50</sup>. Using this genetic instrument, analyses in the Norwegian HUNT study (N=53,601)<sup>46</sup> and the Copenhagen General Population Study and City Heart Study (N=63,296)<sup>47</sup> found no evidence for a causal association between smoking with primary depression or anxiety. No evidence for smoking increasing risk of antenatal depression was found in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort (N=6,294)<sup>48</sup>. A study of the Carta Consortium applied the same genetic instrument for smoking heaviness and found no causal effects on depression or anxiety (N=127,632)<sup>49</sup>.

However, these studies lacked statistical power, due to the use of single genetic variants in the MR analyses. More recently, Wootton et al<sup>51</sup> identified a genetic instrument for “lifetime smoking behavior”, consisting of 126 independent SNPs. This instrument captured smoking duration, heaviness and cessation in both smokers and non-smokers. The results provided evidence that lifetime smoking was causally associated with around a two-fold heightened risk of major depression (IVW OR=1.99, 95% CI: 1.71-2.32, p<0.001). Additionally, there was some, although weaker, evidence that genetic risk for major depression was causally associated with smoking (B=0.091, 95% CI: 0.027-0.155, p=0.005). Similarly, smoking initiation increased risk of major depression (IVW OR=1.54, 95% CI: 1.44-1.64, p<0.01), and major depression influenced smoking initiation (B=0.083, 95% CI: 0.039-0.127). The results were consistent across several more pleiotropy robust methods.

### ***Smoking and risk of psychotic disorders and bipolar disorder***

The prospective risk for incident psychotic disorders in those who engaged in regular tobacco use compared to non-smokers were calculated in two meta-analyses, both using data from over 1.7 million individuals<sup>52,53</sup>. These meta-analyses consistently found a significantly heightened prospective risk of psychotic disorders, of around two-fold for smokers vs. non-smokers, in terms of daily tobacco use (n=6, RR=2.18, 95% CI: 1.23-3.85, I<sup>2</sup>=97.7%)<sup>53</sup> and “personal active smoking” (n=6, RR=1.99, 95% CI: 1.1-3.61, I<sup>2</sup>=97%)<sup>52</sup>. However, significant publication bias was indicated and high levels of statistical heterogeneity were found<sup>52,53</sup>.

Three MR studies investigated the causal influence of smoking on schizophrenia. First, the same SNP in the CHRNA3 gene cluster used in the above studies on depression (rs1051730) was used to examine effects on schizophrenia in a Danish general population sample and the international Psychiatric Genomics Consortium (PGC)<sup>47</sup>. Significant causal effects of smoking in increasing the risk of schizophrenia was found in the PGC (OR=1.60, 95% CI: 0.74-3.47). Although the relationship between smoking and diagnosed schizophrenia in the Danish population fell short of statistical significance (OR=1.22, 95% CI: 0.84-1.79), this could have been due to the small number of cases with schizophrenia in the sample (N=57),

as further analyses examining smoking and odds of lifetime antipsychotic medication use in this sample (N=2,795 cases) found evidence for a significant causal relationship (OR=1.16, 95% CI: 1.02-1.31).

Second, a two-sample MR analysis<sup>55</sup> used a genetic instrument for “smoking initiation” (i.e., ever having smoked, without taking into account heaviness, duration or cessation) identified in the Tobacco and Genetics Consortium, and used it to predict schizophrenia in the PGC. They found no consistent evidence for causal relations between initiation of smoking and schizophrenia diagnosis, in either direction.

Third, the same genetic instrument used for lifetime smoking (capturing lifetime duration, heaviness and cessation of smoking) in the aforementioned MR study of smoking and depression<sup>51</sup> found that lifetime smoking significantly increased the risk for schizophrenia (OR=2.27, 95% CI: 1.67-3.08,  $p<0.001$ ). There was also an indication of schizophrenia increasing lifetime smoking ( $B=0.022$ , 95% CI: 0.005-0.038,  $p=0.009$ ).

This MR study<sup>51</sup> also updated the earlier two-sample MR analysis of smoking initiation<sup>55</sup>, using the more recent GSCAN GWAS instrument (comprising 378 genome-wide significant independent SNPs), and found evidence for an effect of smoking initiation on risk of schizophrenia (IVW OR=1.53, 95% CI: 1.35-1.74,  $p<0.001$ ), but less clear evidence for an effect of schizophrenia on smoking initiation ( $B=0.010$ , 95% CI: 0.000-0.021,  $p=0.04$ ). The effects of smoking on schizophrenia were consistent across multiple sensitivity methods more robust to pleiotropy.

Concerning the relationship between smoking and bipolar disorder, no prospective meta-analysis examined relative odds in smokers vs. non-smokers. However, a two-sample MR study<sup>56</sup> assessed the impact of both smoking initiation and total lifetime smoking (using the same genetic instruments as those described above<sup>51</sup>) on risk of bipolar disorder across 41,653 individuals from the PGC (including 20,129 cases and 21,524 controls), using summary level data. These analyses found evidence suggesting that smoking was a causal risk factor for bipolar disorder (IVW OR=1.46 for smoking initiation, 95% CI: 1.28-1.66,  $p<0.001$ , and IVW OR=1.72 for lifetime smoking, 95% CI: 1.29-2.28,  $p<0.001$ ), consistently across pleiotropy robust sensitivity methods. On the other hand, there was no clear evidence that the diagnosis of bipolar disorder causally affected the risk of smoking-related outcomes<sup>56</sup>.

### ***Smoking and risk of ADHD***

The link between smoking and the incidence of ADHD was examined in one meta-analysis<sup>57</sup> and one MR analysis<sup>58</sup>.

A large-scale meta-analysis of 15 cohort studies including 2,965,933 individuals compared the incidence of ADHD diagnoses in the offspring of smoking vs. non-smoking

mothers<sup>57</sup>. Pooled analyses of ORs adjusted for a range of confounding maternal factors (e.g., mother's age, education and socio-demographic status) and offspring variables (i.e., child's gender and gestational age) showed that maternal smoking significantly heightened the risk of ADHD (OR=1.35, 95% CI: 1.2-1.52, I<sup>2</sup>=59.5%). There was non-significant indication of publication bias, and results were robust even when adjusting for this.

The MR study applied a two-sample MR approach using the most recent GWAS of smoking initiation<sup>58</sup> from the GSCAN consortium and ADHD diagnoses after age 18 years<sup>59</sup>. Bi-directional analyses found that smoking initiation significantly increased risk of ADHD (OR=3.72, p<0.001), while ADHD also affected smoking initiation (B=0.07, p<0.001). However, smoking initiation also predicted ADHD diagnosis before age 13 years, leading the authors to conclude that results could be due to pleiotropy.

### ***Diet and risk of depression***

The association between dietary patterns and longitudinal risk for depression (defined as clinical depression or depressive symptoms) was examined in ten eligible meta-analyses.

A meta-analysis pooling all "healthy dietary patterns" from 17 comparisons (total N=127,973) found that these patterns were associated with significantly reduced prospective risk of depression (OR=0.77, 95% CI: 0.69-0.84, I<sup>2</sup>=88.3%)<sup>60</sup>. Similar effects were observed in a pooled analysis of "healthy food groups" such as fish, vegetables and fruits (n=18, N=147,011, OR=0.89, 95% CI: 0.83-0.95, I<sup>2</sup>=71.3%)<sup>60</sup>. However, pooled analyses for all "unhealthy dietary patterns", "unhealthy food groups" and "neutral food groups" found that none of these categories were significantly associated with the risk of depression<sup>60</sup>.

In a more recent meta-analysis examining specific whole-of-diet patterns, the risk of depression was decreased for those with a high Mediterranean diet score (n=5, N=36,556, OR=0.67, 95% CI: 0.55-0.82, I<sup>2</sup>=33.1%) with low heterogeneity between studies. Prospective associations with the DASH diet score (OR=0.89, 95% CI: 0.6-1.31, I<sup>2</sup>=68.0%) and Healthy Eating Index/Alternative Healthy Eating Index (AHEI) scores (OR=0.76, 95% CI: 0.57-1.02, I<sup>2</sup>=80.7%) had greater heterogeneity and were non-significant<sup>61</sup>. The Mediterranean diet score is typically based on nine items: five regarded as beneficial (fruit, vegetables, legumes, cereals, fish), two as detrimental (meat, dairy), one component on fat, and one on moderate alcohol intake. The DASH (dietary approaches to stop hypertension) diet score considers eight components (negative: sweet beverages, meat, sodium; positive: fruit, vegetables, legumes and nuts, wholegrain, low-fat dairy). The AHEI includes 11 components (vegetables, fruit, nut and soy protein, ratio of white to red meat, cereal fiber, trans fat, polyunsaturated-to-saturated fat ratio, duration of multivitamin use, and alcohol).

A subsequent but smaller meta-analysis of three harmonized datasets, and controlling for depressive symptoms at baseline, found significantly reduced risk of depressive symptoms among those with high Mediterranean diet score (OR=0.88, 95% CI: 0.80-0.96, I<sup>2</sup>=15.4%) or DASH score (OR=0.90, 95% CI: 0.84-0.97, I<sup>2</sup>=0%) with little or zero heterogeneity<sup>62</sup>. Prospective associations with the AHEI were non-significant<sup>62</sup>.

A lower Dietary Inflammatory Index (an index that quantifies the inflammatory potential of a diet based on up to 45 food parameters) was also found to be associated with reduced risk of depression (n=7, N=32,908, OR=0.76, 95% CI: 0.63-0.92, I<sup>2</sup>=55.3%)<sup>61</sup>. Confirming this, a separate meta-analysis examining the opposite direction of effect found that individuals with pro-inflammatory diets at baseline were at significantly greater risk of depression, with low heterogeneity between studies (n=10, N=77,420, OR=1.31, 95% CI: 1.2-1.44, I<sup>2</sup>=5.1%), with equally large risk observed in studies using >10 year or <10 year follow-up periods<sup>63</sup>.

Of note, however, the results of the above meta-analyses were based mostly on self-reported of depressive symptoms. Small subgroup analyses of studies which used clinical diagnoses of depression as the outcome did not find significant associations with dietary patterns<sup>60</sup>.

Eligible data on various individual dietary aspects were presented in seven meta-analyses. Prospective risk of depression (including self-reported depressive symptoms) was significantly lower for those with greater intakes of vegetables (n=7, RR=0.86, 95% CI: 0.75-0.98, I<sup>2</sup>=68.1%)<sup>64</sup>, dietary zinc (n=3, RR=0.73, 95% CI: 0.6-0.9, I<sup>2</sup>=0%)<sup>66</sup>, fish (n=16, 0.86, 95% C.I: 0.78-0.95, I<sup>2</sup>=68.4%)<sup>60</sup>, and dietary eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (n=4, RR=0.74, 95% CI: 0.61-0.89, I<sup>2</sup>=0%)<sup>65</sup>, while associations with dietary omega-3 fatty acids also approached significance (n=7, RR=0.85, 95% CI: 0.73-1.00, I<sup>2</sup>=19%)<sup>65</sup>.

The prospective risk of depression was significantly higher for those with greater consumption of sugar-sweetened beverages (n=4, RR=1.30, 95% CI:1.19-1.41, I<sup>2</sup>=0%)<sup>68</sup>. Although greater fruit intake was prospectively associated with reduced risk (n=6, RR=0.83, 95% CI: 0.71-0.98, I<sup>2</sup>=84.5%)<sup>64</sup> and meat consumption was associated with heightened risk (n=3, RR=1.13, 95% CI: 1.03-1.24, I<sup>2</sup>=19.4%)<sup>67</sup> for depression in meta-analyses focusing specifically on these foods, subgroup analyses within a broader meta-analysis found no significant associations for depression with either fruit intake or meat intake<sup>60</sup>.

No significant prospective associations with depression were found for dietary glycaemic index (n=2, HR=1.05, 95% CI: 0.76-1.44, I<sup>2</sup>=86.1%)<sup>69</sup>, legumes/pulses (n=4, OR=0.93, 95% C.I: 0.79-1.10, I<sup>2</sup>= 43.1%)<sup>60</sup>, or nuts/seeds/soy (n=2, OR=0.92, 95% C.I: 0.84-1.02, I<sup>2</sup>= 0.1%)<sup>60</sup>. It should also be noted that the strength of the findings for individual dietary aspects is reduced by the high levels of heterogeneity, limited comparisons within the meta-analyses, lack of clinical diagnostic outcomes used, and inadequate control for how the individual dietary components related to other dietary factors.



The only MR study to examine causal relations between diet and incident mental illness was the aforementioned analysis of data from Wray et al's GWAS<sup>34</sup>, which also examined multiple dietary factors, including salt intake, lamb intake, inconsistent dietary patterns, multivitamin supplement use, tea intake, and cereal intake. There was no firm evidence that any of these factors influenced the risk of developing depression, apart from an unexpected effect of multivitamin supplementation use on increased risk (OR=1.28, 95% CI: 1.11-1.47, p=0.0006), which however was not consistent across sensitivity methods.

No prospective meta-analyses or MR studies examined the relationships between dietary nutrient intake and the risk for mental disorders other than depression.

### ***Sleeping patterns and risk of mental disorders***

A meta-analysis pooling all "sleep disturbances" (including insomnia, complaints of sleeping difficulties, and general poor sleep quality) found that they significantly increased the prospective risk for clinical depression or significant depressive symptoms (n=11, N=16,108, RR=1.92, 95% CI: 1.60-2.30, I<sup>2</sup>=10.2%), with even greater risk following "persistent" sleep disturbances (n=4, N=3,602, RR=3.90, 95% CI: 2.77-5.48, I<sup>2</sup>=27.1%)<sup>70</sup>. There was little heterogeneity between studies.

Beyond generalized sleep disturbances, a large prospective meta-analysis of data from 172,007 individuals in 34 examinations of "insomnia" (primarily identified from night-time symptoms) found that it significantly increased the risk for future depression (RR=2.27, 95% CI: 1.89-2.71, I<sup>2</sup>=92.6%)<sup>72</sup>. However, there was high heterogeneity and many studies were of short (<12 months) duration. Nonetheless, a subsequent meta-analysis examining the psychiatric outcomes of insomnia from studies with at least 12 months follow-up similarly found heightened risk in pooled analysis for all psychiatric disorders (n=19, N=133,967, OR=2.60, 95% CI: 1.70-3.97, I<sup>2</sup>=96.2%), along with statistically significant relations in all individual conditions examined, including for depression (n=10, OR=2.83, 95% CI: 1.55-5.17, I<sup>2</sup>=93.67%), anxiety (n=6, OR=3.23, 95% CI: 1.52-6.85, I<sup>2</sup>=96.37%) and psychotic disorders (n=1 only, data not shown)<sup>73</sup>.

Concerning sleep duration, individuals with both short (median reference value: ≤6 hours) and long (median reference value: ≥8 hours) average daily sleep duration were at significantly higher risk of depression over the 7.9 year average follow-up, with no heterogeneity between studies (short sleep: n=7, N=25,271, RR=1.31, 95% CI: 1.04-1.64; long sleep: n=5, N=23,663, RR=1.42, 95% CI: 1.04-1.92)<sup>74</sup>. A separate meta-analysis also indicated that short sleep duration increased the prospective risk of ADHD (n=3, N=2,386, RR=2.61, 95% CI: 1.36-5.00, I<sup>2</sup>=83.0%)<sup>75</sup>, although the low number of studies and the lack of control for baseline ADHD symptoms decreases confidence in the findings.

Three MR studies assessed the causal role of sleep-related variables on risk for mental illness. Two of these were from the aforementioned two-sample MR studies of physical activity, which also measured sleep time using self-reported<sup>34</sup> and objective<sup>39</sup> measures. There was no evidence for causal associations between hours of sleep with depression, schizophrenia or bipolar disorder. However, it must be noted that MR can only test linear effects, whereas prospective meta-analyses indicate non-linear relations between sleep duration and mental illness<sup>74</sup>.

For disordered sleeping, a two-sample MR study found evidence that self-reported difficulties in falling or staying asleep increase the risk for bipolar disorder (OR=1.79, 95% CI: 1.40-2.29,  $p < 0.001$ ), an effect which was consistent across multiple sensitivity methods to test for pleiotropy, whereas no evidence was found for depression, ADHD or schizophrenia<sup>76</sup>. However, the study by Choi et al<sup>34</sup> did find evidence for self-reported inadvertent daytime napping as a risk factor for the onset of depression (OR=1.34, 95% CI: 1.17-1.53,  $p = 0.00002$ ), consistent across pleiotropy robust sensitivity methods.

## **Lifestyle interventions in the treatment of mental disorders**

### ***Efficacy of physical activity interventions for mental disorders***

One recent meta-review provided sufficient information on the efficacy of physical activity for the treatment of eligible psychiatric conditions, bringing together the data from 16 meta-analyses of RCTs<sup>77</sup>. The most widely assessed condition was major depression, with four meta-analyses in adult samples finding significant positive effects of exercise interventions in comparison to various control conditions, including waitlist and usual treatment, control interventions of flexibility, stretching/relaxation and meditation, and placebo medications.

The largest and most recent was a meta-analysis showing moderately large benefits of exercise across 35 RCTs in adults with depressive disorders (SMD=-0.66, 95% CI: -0.86 to -0.46,  $I^2 = 81\%$ ). However, only small, non-significant benefits were observed in four trials deemed of “high quality” and comparing exercise to other active control conditions (SMD=-0.11, 95% CI: -0.41 to 0.18,  $I^2 = 62\%$ ).

Within the meta-review, two meta-analyses of RCTs examined exercise in youth with depressive disorders, and both found significant effects. The most recent observed a large, positive benefit of exercise compared to both waitlist and attention-matched control conditions ( $n = 4$ ,  $N = 100$ , SMD=-0.95, 95% CI: -1.37 to -0.53,  $p < 0.001$ ,  $I^2 = 0\%$ ). Only two trials examined the impact of exercise in older people with a diagnosis of major depressive disorder and did not find a significant effect (SMD=-1.883, 95% CI: -4.21 to 0.44,  $p = 0.11$ ,  $I^2 = 93\%$ ), although exercise did significantly reduce depression in older adults with high levels of depression

symptoms (n=8, N=267, SMD=-0.90, 95% CI: -1.51 to -0.29, p=0.004). The cognitive benefits of exercise in major depression were examined in eight trials, showing no overall benefits.

Concerning the treatment of anxiety and stress-related disorders, the most recent meta-analyses found exercise reduced symptoms significantly more than control conditions in pooled analyses of RCTs in patients with panic disorder, generalized anxiety disorder, post-traumatic stress disorder and social phobia (n=6, N=262, SMD=-0.581, 95% CI: -1.09 to -0.076, I<sup>2</sup>=66%) and in people receiving treatment for anxiety in primary care (n=4, SMD=-0.32, 95% CI: -0.62 to -0.01). However, an earlier meta-analysis found inconsistent evidence for significant benefits, with the effects of exercise on anxiety disorders varying with regards to the type of control condition used<sup>77</sup>.

In schizophrenia and non-affective psychotic disorders, physical activity interventions across 8 RCTs did not significantly reduce total symptoms. However, RCTs of exercise interventions which used at least 90 min of moderate to vigorous activity per week did significantly reduce total symptoms (SMD=-0.72, 95% CI: -1.14 to -0.29), positive symptoms (SMD=-0.54, 95% CI: -0.95 to -0.13) and negative symptoms (SMD=-0.44, 95% CI: -0.78 to -0.09) more than control conditions<sup>77</sup>. Exercise was also found to significantly improve global cognition in schizophrenia (n=7, SMD=0.412, 95% CI: 0.19 to 0.64). Earlier meta-analyses examining the effects of aerobic exercise on comorbid symptoms of depression and anxiety in schizophrenia populations found no significant effects.

The effects of exercise in bipolar disorder were not investigated in any meta-analyses of RCTs. A meta-analysis of RCTs in children with ADHD found moderately large, statistically significant effects of aerobic exercise for various outcomes, including attention, hyperactivity, impulsivity, anxiety and executive functions<sup>77</sup>.

### ***Efficacy of smoking cessation interventions for mental disorders***

The impact of non-pharmacological smoking interventions on psychiatric symptoms in populations with mental disorders was not reported in any meta-analyses of RCTs.

### ***Efficacy of dietary interventions for mental disorders***

One eligible meta-review examined dietary interventions in the treatment of a mental disorder, specifically the effects of food exclusion diets in children with ADHD<sup>78</sup>. Four relevant meta-analyses were included, two on “artificial food colouring (AFC) elimination” (i.e.,

removing all foods from the diet which contain AFCs), and two on “few-foods diets” (i.e., eliminating many potentially symptom-triggering foods, to include only a limited selection of natural foods in the diet).

The results from meta-analyses of placebo-controlled trials indicated a non-significant trend towards improvement in symptoms of ADHD from AFC elimination across parent-rated measures (n=11, SMD=0.21, 95% CI: -0.02 to 0.43, I<sup>2</sup>=68%, p=0.07), with no effects for teacher-rated measures (n=6, SMD=0.08, 95% CI: -0.07 to 0.24, I<sup>2</sup>=0%) and observed-rated measures (n=4, SMD=0.11, 95% CI: -0.13 to 0.34, I<sup>2</sup>=12%)<sup>78</sup>.

The few-foods diets were found to have significant positive effects on ADHD symptoms. The recalculated meta-analyses found moderately large effect sizes in RCTs of the few-foods diets for any-rater measures (n=5, SMD=0.75, 95% CI: 0.31-1.19, I<sup>2</sup>=58.6%) and parent/ward observation measures (n=5, SMD=0.78, 95% CI: 0.42-1.14, I<sup>2</sup>=48.5%) of ADHD symptoms<sup>78</sup>. The few-food diets were broadly described as “lamb, chicken, potatoes, rice, banana, apple and brassica”, although noting that this could be customized to child/parent preference while maintaining the core “few-foods” concept of avoiding artificially sweetened and highly refined foods which could provoke symptomatic response.

No meta-analyses of dietary interventions in the treatment of other mental disorders were identified.

### ***Efficacy of sleep interventions for mental disorders***

The efficacy of sleep interventions in the treatment of psychiatric conditions was investigated in two independent meta-analyses. In a pooled analysis of seven RCTs across a mixed psychiatric sample with anxiety, depression or PTSD, non-pharmacological sleep interventions – predominantly based on cognitive behavior therapy (CBT) – produced a large and significant reduction in depressive symptoms in comparison to control conditions (NIH=6, SMD=0.81, 95% CI: 0.49-1.13, I<sup>2</sup>=27%)<sup>79</sup>. While heterogeneity was low, there was some indication of publication bias, with larger effects observed in smaller studies in the meta-analysis<sup>79</sup>. Large, significant reductions in depressive symptoms were also found from continuous positive airway pressure in people with depression and comorbid obstructive sleep apnoea (NIH=6, SMD=2.00, 95% CI: 1.39-2.62, I<sup>2</sup>=12%)<sup>80</sup>, but included data from only two RCTs for in the psychiatric samples, and thus no strong conclusions can be drawn.

## DISCUSSION

This meta-review provides a systematic and comprehensive appraisal of the current evidence concerning the role of the key modifiable “lifestyle factors” of physical activity, smoking, diet and sleep in the prevention and treatment of mental disorders.

From the literature to date, physical activity emerges as the most widely researched lifestyle factor. There is substantial evidence from multiple meta-analyses of longitudinal data and MR studies that physical activity has a protective role in reducing risk for common mental disorders. Furthermore, while further replication in high-quality RCTs is needed, meta-analyses of RCTs have found exercise interventions may provide effective adjunctive treatment for depression, anxiety and stress-related disorders, psychotic disorders and ADHD.

In public health guidelines, 150 min of moderate activity or 75 min of vigorous activity per week (or some combination of these) are recommended for reducing risk of various health conditions in adults<sup>13,14</sup>. However, it is important to keep in mind that, unlike chronic physical diseases, most mental disorders first arise in young people<sup>6,82</sup>. Simply advising young people to be more active is unlikely to have a substantial impact on behavior change. Instead, realizing the protective role of physical activity will likely require systemic integration of the evidence presented here within environmental modification alongside mental and physical health promotion initiatives for young people<sup>83</sup>, which can be feasibly delivered through school settings<sup>84</sup> and as part of cross-sectoral public health strategies. For treatment of diagnosed mental illness, supervised exercise interventions are recommended, incorporating moderate-to-vigorous activity, and delivered by trained exercise professionals either working within mental health services or made available through referral to community-based schemes<sup>9,17</sup>.

Current recommendations pertain largely to aerobic activity and cardiorespiratory fitness as the focus of exercise interventions, as the majority of observational and interventional research in this area has focused on overall physical activity levels. While this is well-supported by the literature (with growing evidence of cardiorespiratory fitness itself reducing risk of psychiatric disorders<sup>85-87</sup>), it should also be noted that there is now some evidence that muscular strength and resistance training also are protective against mental illness, even independently of general physical activity<sup>88-90</sup>. Furthermore, strength training interventions can significantly improve mental health<sup>91,92</sup>, with effects that may persist over and above those of aerobic exercise alone<sup>93</sup>. Thus, future research and guidelines on physical activity should afford further consideration to the efficacy and feasibility of resistance training interventions, in both the prevention and treatment of mental illness.

There is a significant body of evidence that poor sleep is another key modifiable lifestyle factor, with large-scale meta-analyses of showing prospective links with various psychiatric disorders, and supportive findings from MR studies suggesting a causal role in bipolar

disorder. Alongside this, sleep disturbances have been found to significantly heighten the risk of suicidal behaviour in people living with mental illness<sup>71</sup>.

Furthermore, meta-analyses of RCTs also support the efficacy of sleep interventions in reducing symptoms of depression. Of note, whereas many trials have shown the alleviation of subclinical depressive symptoms following sleep interventions, the available evidence suggests that even larger effects of sleep therapies on depression are observed in those with mental illness<sup>79-81,94</sup>. Additionally, a role of poor sleep in severe mental disorders is suggested by a recent RCT showing that cognitive behavioral therapy for insomnia (CBT-I) significantly reduces the severity of hallucinations and paranoia in youth experiencing symptoms of psychosis<sup>95</sup>.

Overall, poor sleep appears to play an important part in the onset and aggravation of mental illness, and CBT-I may provide an attractive non-pharmacological option (which can also be delivered digitally) for improving sleep and other aspects of mental health<sup>94-96</sup>. Establishing the feasibility and effectiveness of CBT-I in people with psychotic disorders is a priority for future research.

The evidence that tobacco use is a significant and modifiable risk factor for a range of psychiatric conditions is becoming increasingly strong. Whereas early MR studies found inconsistent effects, the most recent GWAS studies have improved statistical power to provide strong indications for smoking as a causal factor in the onset of major depression, bipolar disorder and schizophrenia. These findings are in line with multiple meta-analyses showing that smoking is associated with a heightened prospective risk of mental disorders, earlier age of onset, and adverse outcomes in those living with mental illness<sup>53,54</sup>.

Collectively, these findings provide additional evidence for public health bodies to justify tobacco control initiatives which can effectively reach vulnerable, deprived or marginalized groups. In fact, people with mental illness have so far not clearly benefitted from the recent reductions in tobacco smoking rates observed in the general population across Western societies<sup>97</sup>.

Although we did not identify any meta-analyses of RCTs for smoking cessation reducing symptoms of psychiatric disorders, a consistent body of work shows that stopping smoking does not cause deterioration in mental health among those with mental illness (an assumption which can sometimes be a barrier towards implementation in clinical settings)<sup>98</sup>, and in fact appears to improve psychological well-being<sup>99</sup>, including in those living with mental illness. Furthermore, the critical need for such interventions in mental health care settings is already acknowledged on the basis of physical health risks – as smoking is a leading cause of the 15 to 30 year premature mortality associated with severe mental illness<sup>100</sup>. Lastly, the role of tobacco use as a cause of psychiatric disorders, and source of health inequalities, warrants further research into the potential benefits of harm reduction strategies such as e-cigarettes.

The causal effects of diet on common and severe mental illnesses are less clear. Several meta-analyses have shown that healthy dietary patterns are associated with a significantly reduced risk of depressive symptoms. However, prospective links with diagnosed depression or other mental disorders were not established. There was also an absence of MR evidence to support causal roles of dietary patterns in the onset of any mental illness.

Furthermore, a recent four-arm RCT examined nutrition-based interventions for the prevention of depressive episodes in 1,025 participants with subclinical depressive symptoms, and found no significant benefits from the behavioral activation intervention promoting healthy eating<sup>101</sup>. However, the null effects may be due to poor intervention adherence, given the very marginal improvements in diet quality reported. Interestingly, the other “active” arm of this RCT provided daily multinutrient supplementation, observing significantly worsened outcomes for depressive symptoms compared to placebo<sup>101</sup>. Although seemingly paradoxical, these counterintuitive findings align with results from the MR study by Choi et al<sup>34</sup>, in which the only dietary nutrition factor with evidence for causal relations was multivitamin supplement use relating to increased depression risk.

Clearly, further research is needed to establish how nutrition impacts on mental health. Nonetheless, for those living with current mental illness, a number of existing clinical trials have already suggested that dietary interventions may be used alongside standard care to improve outcomes. Along with the preliminary evidence for specific dietary interventions in ADHD presented above, several recent RCTs (not captured in our meta-review) have reported significant improvements in clinical depression from Mediterranean diet interventions, observing moderately large positive effects<sup>102-104</sup>. While further replication of these findings is still required to determine effects on mental health, the high levels of dietary risk factors and associated cardiometabolic diseases associated with mental illness<sup>6,105</sup> already provides a basis for considering dietary factors within multidisciplinary healthcare for people with mental illness<sup>106</sup>.

Further research is also required to explore the neurobiological pathways through which various lifestyle factors impact mental health, as mechanistic evidence from intervention trials is currently sparse. One potentially shared biological mechanism by which multiple adverse health behaviors could increase risk of mental illness is through inflammation, which has been linked with a broad range of psychiatric disorders<sup>112</sup>. As previous research has indicated anti-inflammatory effects from exercise<sup>113</sup>, Mediterranean diet<sup>114</sup>, improved sleep<sup>115</sup> and smoking cessation<sup>116</sup>, this may partially explain the effects of lifestyle interventions on improving mental health.

Further mechanistic insights are available from studies inducing an adverse health behavior in otherwise healthy samples, and then observing the potentially detrimental effects on mental health. For instance, some experimental evidence indicates that administration of

“unhealthy” meals (e.g., high in glycaemic index or saturated fats) can increase depressive symptoms and inflammatory markers in healthy human subjects<sup>69,108,109</sup>. Whereas less direct experimental evidence exists for smoking or poor sleep, both of these factors have also been shown to have pro-inflammatory effects in humans<sup>110,111</sup>. However, a recent systematic review of induced exercise cessation in previously active adults found that although exercise cessation did significantly increase in depressive symptoms within 2 weeks, this was not accompanied by increases in inflammatory markers<sup>107</sup>, suggesting other mechanisms must explain these effects.

The role of the gut microbiome in mental health is currently receiving considerable research interest<sup>117</sup>. Since the microbiome appears to be influenced by exercise<sup>118</sup> and diet<sup>119</sup>, this could be considered as another potential pathway through which modifiable health behaviors could impact on mental health. However, scientific understanding in this area is still in its infancy, and even the nature of a “healthy microbiome” has yet to be established<sup>120</sup>. Therefore, triangulating the causal relations between lifestyle, mental health and the gut microbiome is currently speculative, although represents an intriguing avenue for future rigorous research.

Besides these possible direct mechanisms, it is also important to consider how the downstream consequences of adverse health behaviors may link lifestyle factors to mental disorders. For instance, insufficient exercise, poor diet, and even sleep disturbances can be contributing factors towards the development of metabolic diseases and obesity, which themselves may adversely impact mental health<sup>121-123</sup>, and have been linked to the recent rise of mental illness in young people<sup>7</sup>.

The biological, social and psychological pathways through which physical health conditions such as obesity, diabetes and even cardiovascular diseases affect mental health have yet to be fully determined. Nonetheless, the emerging field of “lifestyle psychiatry” must not neglect the body of evidence around previously established health-related and social determinants of psychological well-being, and their interaction with lifestyle factors<sup>6,9</sup>, in the development of prevention and treatment initiatives for mental illness.

Additionally, as the field moves forward, further consideration of the role of “newer” lifestyle factors is warranted. Specifically, the widespread use of digital technologies is gaining increasing attention from the public, researchers and clinicians with regards to potential influence on psychological well-being. A growing body of research has identified multiple pathways through which constant Internet usage may be affecting our cognitive and social processes, along with mental health and brain functioning<sup>124</sup>. On the other hand, there is also a rapidly growing body of research examining the potential for using digital technologies in the prevention and treatment of mental illness. Recent meta-analyses of RCTs have shown that psychological interventions for common mental disorders, such as anxiety and depression,



can be delivered remotely via smartphone apps<sup>125</sup>, with a smaller but emerging evidence base also for psychotic disorders<sup>126</sup>.

Despite these recent increases in the amount of empirical research on the interaction between digital technologies and mental health, there is still a need for further large-scale and interventional research to determine what types and quantities of usage impact on mental health, and how this interacts with other lifestyle factors, such as sedentary behavior and diet.

In conclusion, health behaviours may play an important role in prevention and treatment of mental illness. The converging lines of supportive evidence for the roles exercise, smoking, diet and sleep are summarized in Figure 1 (with further details on quality and consistency of evidence displayed in Tables 1-8). At the public health level, further research is still required to improve evidence-based implementation of health promotion initiatives, and to determine their impact on risk of mental illness. Nonetheless, the positive mental health findings from system-wide approaches to health promotion in children and adolescents<sup>83,84</sup> reinforces the assertion that effectively addressing multiple lifestyle factors in young people presents a promising approach towards tackling the rates of mental illness across the population<sup>6,7,83,84</sup>.

For clinical settings, the findings presented above add to the growing rationale for broad-scale provision of lifestyle interventions within primary and secondary care services for people with mental disorders<sup>6,9,17,18</sup>. These should aim to capture all “core principles” of evidence-based lifestyle interventions for mental illness, which briefly can be summarized as: a) using behavior change techniques with specific, measurable behavioral goals and self-monitoring; b) involving dedicated “physical health” staff, such as professionals in specific aspects of health behavior change, delivering supervised sessions for service users; c) training mental health staff in the importance and goals of lifestyle interventions; and d) facilitating peer-support to improve uptake and adherence<sup>9</sup>.

Further research is required to address the existing barriers towards implementation and dissemination of lifestyle interventions. For instance, harnessing the reach of digital technologies may present a new option for wide-scale delivery of lifestyle-based prevention and management strategies for mental illness, which may be particularly useful for low- and middle-income settings, where traditional mental health care services are often unavailable. However, further investigation into how certain aspects of digital technologies may pose a new “lifestyle risk factor” for mental health is also required.

Finally, as the field progresses, it must always be considered that the etiology of mental disorders is of course multifactorial, and cases will often occur (and persist) independently of lifestyle factors. Thus, attributing an individual’s condition to his/her health behaviors would often be ill-founded, stigmatizing and unhelpful. Instead, the onus to act is on policy makers, public health bodies, and clinical services to properly address adverse health environments and behaviors, in order to reduce risks and improve outcomes of mental disorders.

## ACKNOWLEDGEMENTS

J. Firth is supported by a UK Research and Innovation Future Leaders Fellowship (MR/T021780/1). S. Rosenbaum is funded by a fellowship from the Australian National Health and Medical Research Council (NHMRC) (APP1123336). G. Ashdown-Franks is funded by a Canadian Institutes of Health Research (CIHR) doctoral fellowship. B. Stubbs is supported by a Clinical Lectureship (ICA-CL-2017-03-001) jointly funded by Health Education England and the National Institute for Health Research (NIHR), and by the NIHR Biomedical Research Centre at South London and Maudsley NHS Foundation Trust. F. Schuch is funded by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES). The views expressed in this paper are those of the authors and not necessarily those of the funding organizations.

## REFERENCES

1. Kessler RC, Demler O, Frank RG et al. Prevalence and treatment of mental disorders, 1990 to 2003. *N Engl J Med* 2005;352:2515-23.
2. Vigo D, Thornicroft G, Atun R. Estimating the true global burden of mental illness. *Lancet Psychiatry* 2016;3:171-8.
3. Patel V, Saxena S, Lund C et al. The Lancet Commission on global mental health and sustainable development. *Lancet* 2018;392:1553-1598.
4. Correll CU, Rubio JM, Kane JM. What is the risk-benefit ratio of long-term antipsychotic treatment in people with schizophrenia? *World Psychiatry* 2018;17:49-60.
5. Singla DR, Raviola G, Patel V. Scaling up psychological treatments for common mental disorders: a call to action. *World Psychiatry* 2018;17:226-7.
6. Royal College of Psychiatrists. No health without public mental health: the case for action (PS04/2010). [https://www.rcpsych.ac.uk/pdf/PS04\\_2010.pdf](https://www.rcpsych.ac.uk/pdf/PS04_2010.pdf).
7. Patalay P, Gage SH. Changes in millennial adolescent mental health and health-related behaviours over 10 years: a population cohort comparison study. *Int J Epidemiol* 2019;48:1650-64.
8. Lianov L, Johnson M. Physician competencies for prescribing lifestyle medicine. *JAMA* 2010;304:202-3.
9. Firth J, Siddiqi N, Koyanagi A et al. The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. *Lancet Psychiatry* 2019;6:675-712.
10. Stubbs B, Koyanagi A, Hallgren M et al. Physical activity and anxiety: a perspective from the World Health Survey. *J Affect Disord* 2017;208:545-52.
11. Stubbs B, Vancampfort D, Firth J et al. Association between depression and smoking: a global perspective from 48 low-and middle-income countries. *J Psychiatr Res* 2018;103:142-9.
12. Vancampfort D, Van Damme T, Stubbs B et al. Sedentary behavior and anxiety-induced sleep disturbance among 181,093 adolescents from 67 countries: a global perspective. *Sleep Med* 2019;58:19-26.
13. Piercy KL, Troiano RP, Ballard RM et al. The physical activity guidelines for Americans. *JAMA* 2018;320:2020-8.
14. Department of Health and Social Care. UK Chief Medical Officers' Physical Activity Guidelines. [www.gov.uk/government/news/new-physical-activity-guidelines](http://www.gov.uk/government/news/new-physical-activity-guidelines).
15. Tremblay MS, Carson V, Chaput J-P et al. Canadian 24-hour movement guidelines for children and youth: an integration of physical activity, sedentary behaviour, and sleep. *Appl Physiol Nutr Metab* 2016;41:S311-27.

16. Australian Department of Health. Australia's Physical Activity and Sedentary Behaviour Guidelines and the Australian 24-Hour Movement Guidelines. [www1.health.gov.au/internet/main/publishing.nsf/Content/health-pubhlth-strateg-phys-act-guidelines](http://www1.health.gov.au/internet/main/publishing.nsf/Content/health-pubhlth-strateg-phys-act-guidelines)
17. Stubbs B, Vancampfort D, Hallgren M et al. EPA guidance on physical activity as a treatment for severe mental illness: a meta-review of the evidence and position statement from the European Psychiatric Association (EPA), supported by the International Organization of Physical Therapists in Mental Health (IOPTMH). *Eur Psychiatry* 2018;54:124-44.
18. Malhi GS, Bassett D, Boyce P et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Aust N Z J Psychiatry* 2015;49:1087-206.
19. Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
20. Firth J, Teasdale S, Allot K et al. The efficacy and safety of nutrient supplements in the treatment of mental disorders: a meta-review of meta-analyses of randomized controlled trials. *World Psychiatry* 2019;18:308-24.
21. Webb AR. Who, what, where and when – influences on cutaneous vitamin D synthesis. *Prog Biophys Mol Biol* 2006;92:17-25.
22. Friso S, Choi S-W, Girelli D et al. A common mutation in the 5,10-methylenetetrahydrofolate reductase gene affects genomic DNA methylation through an interaction with folate status. *Proc Natl Acad Sci USA* 2002;99:5606-11.
23. Murray RM, Quigley H, Quattrone D et al. Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. *World Psychiatry* 2016;15:195-204.
24. Smith GD, Ebrahim S. What can Mendelian randomisation tell us about modifiable behavioural and environmental exposures? *BMJ* 2005;330:1076-9.
25. Smith GD, Ebrahim S. Mendelian randomization: prospects, potentials, and limitations. *Int J Epidemiol* 2004;33:30-42.
26. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. *Hum Mol Genet* 2014;23:R89-98.
27. Biddle SJ, Ciaccioni S, Thomas G et al. Physical activity and mental health in children and adolescents: an updated review of reviews and an analysis of causality. *Psychol Sport Exerc Sep* (in press).
28. Shafiei F, Salari-Moghaddam A, Larijani B et al. Adherence to the Mediterranean diet and risk of depression: A systematic review and updated meta-analysis of observational studies. *Nutrition reviews*. 2019;77:230-9.
29. Schuch FB, Vancampfort D, Firth J et al. Physical activity and incident depression: a meta-analysis of prospective cohort studies. *Am J Psychiatry* 2018;175:631-48.
30. Wang X, Li Y, Fan H. The associations between screen time-based sedentary behavior and depression: a systematic review and meta-analysis. *BMC Public Health* 2019;19:1524.
31. Liu M, Wu L, Yao S. Dose-response association of screen time-based sedentary behaviour in children and adolescents and depression: a meta-analysis of observational studies. *Br J Sports Med* 2016;50:1252-58.
32. Zhai L, Zhang Y, Zhang D. Sedentary behaviour and the risk of depression: a meta-analysis. *Br J Sports Med* 2015;49:705-9.
33. Choi KW, Chen C-Y, Stein MB et al. Assessment of bidirectional relationships between physical activity and depression among adults: a 2-sample Mendelian randomization study. *JAMA Psychiatry* 2019;76:399-408.
34. Choi KW, Stein MB, Nishimi K et al. A two-stage approach to identifying and validating modifiable factors for the prevention of depression. *bioRxiv* 2019:759753.
35. Wray NR, Ripke S, Mattheisen M et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat Genet* 2018;50:668-81.
36. Schuch FB, Stubbs B, Meyer J et al. Physical activity protects from incident anxiety: a meta-analysis of prospective cohort studies. *Depress Anxiety* 2019;36:846-58.
37. McDowell CP, Dishman RK, Gordon BR et al. Physical activity and anxiety: a systematic review and meta-analysis of prospective cohort studies. *Am J Prev Med* 2019;57:545-56.
38. Brokmeier L, Firth J, Vancampfort D et al. Does physical activity reduce the risk of psychosis? A systematic review and meta-analysis of prospective studies. *Psychiatry Res* (in press).

39. Sun H, Gao X, Que X et al. The causal relationships of device-measured physical activity with bipolar disorder and schizophrenia in adults: a 2-sample Mendelian randomization study. *J Affect Disord* 2019;263:598-604.
40. Stahl EA, Breen G, Forstner AJ et al. Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nat Genet* 2019;51:793-803.
41. Ruderfer DM, Ripke S, McQuillin A et al. Genomic dissection of bipolar disorder and schizophrenia, including 28 subphenotypes. *Cell* 2018;173:1705-15.
42. Luger TM, Suls J, Vander Weg MW. How robust is the association between smoking and depression in adults? A meta-analysis using linear mixed-effects models. *Addict Behav* 2014;39:1418-29.
43. Chaiton MO, Cohen JE, O'Loughlin J et al. A systematic review of longitudinal studies on the association between depression and smoking in adolescents. *BMC Public Health* 2009;9:356.
44. Han C, Liu Y, Gong X et al. Relationship between secondhand smoke exposure and depressive symptoms: A systematic review and dose-response meta-analysis. *Int J Environ Res Public Health* 2019;16:8.
45. Chen HL, Cai JY, Zha ML et al. Prenatal smoking and postpartum depression: a meta-analysis. *J Psychosom Obstet Gynecol* 2019;40:97-105.
46. Bjorngaard JH, Gunnell D, Elvestad MB et al. The causal role of smoking in anxiety and depression: a Mendelian randomization analysis of the HUNT study. *Psychol Med* 2013;43:711-9.
47. Wium-Andersen MK, Orsted DD, Nordestgaard BG. Tobacco smoking is causally associated with antipsychotic medication use and schizophrenia, but not with antidepressant medication use or depression. *Int J Epidemiol* 2015;44:566-77.
48. Lewis SJ, Araya R, Smith GD et al. Smoking is associated with, but does not cause, depressed mood in pregnancy – a Mendelian randomization study. *PLoS One* 2011;6:e21689.
49. Taylor AE, Fluharty ME, Bjorngaard JH et al. Investigating the possible causal association of smoking with depression and anxiety using Mendelian randomisation meta-analysis: the CARTA consortium. *BMJ Open* 2014;4:e006141.
50. Ware JJ, van den Bree MB, Munafò MR. Association of the CHRNA5-A3-B4 gene cluster with heaviness of smoking: a meta-analysis. *Nicotine Tob Res* 2011;13:1167-75.
51. Wootton RE, Richmond RC, Stuijzand BG et al. Evidence for causal effects of lifetime smoking on risk for depression and schizophrenia: a Mendelian randomisation study. *Psychol Med* 2019;1-9.
52. Hunter A, Murray R, Asher L et al. The effects of tobacco smoking, and prenatal tobacco smoke exposure, on risk of schizophrenia: a systematic review and meta-analysis. *Nicotine Tob Res* 2020;22:3-10.
53. Gurillo P, Jauhar S, Murray RM et al. Does tobacco use cause psychosis? Systematic review and meta-analysis. *Lancet Psychiatry* 2015;2:718-25.
54. Sankaranarayanan A, Mancuso S, Wilding H et al. Smoking, suicidality and psychosis: a systematic meta-analysis. *PLoS One* 2015;10:e0138147..
55. Gage SH, Jones HJ, Taylor AE et al. Investigating causality in associations between smoking initiation and schizophrenia using Mendelian randomization. *Sci Rep* 2017;7:40653.
56. Vermeulen JM, Wootton RE, Treur JL et al. Smoking and the risk for bipolar disorder: evidence from a bidirectional Mendelian randomisation study. *Br J Psychiatry* (in press).
57. Huang L, Wang Y, Zhang L et al. Maternal smoking and attention-deficit/hyperactivity disorder in offspring: a meta-analysis. *Pediatrics* 2018;141(1).
58. Treur J, Demontis D, Davey Smith G et al. Investigating causality between liability to ADHD and substance use, and liability to substance use and ADHD risk, using Mendelian randomization. *Addict Biol* 2020:e12849.
59. Demontis D, Walters RK, Martin J et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet* 2019;51:63-75.
60. Molendijk M, Molero P, Ortuno Sanchez-Pedreno F et al. Diet quality and depression risk: a systematic review and dose-response meta-analysis of prospective studies. *J Affect Disord* 2018;226:346-54.
61. Lassale C, Batty GD, Baghdadli A et al. Healthy dietary indices and risk of depressive outcomes: a systematic review and meta-analysis of observational studies. *Mol Psychiatry* 2019;24:965-86.
62. Nicolaou M, Colpo M, Vermeulen E et al. Association of a priori dietary patterns with depressive symptoms: a harmonised meta-analysis of observational studies. *Psychol Med* (in press).

63. Tolkien K, Bradburn S, Murgatroyd C. An anti-inflammatory diet as a potential intervention for depressive disorders: a systematic review and meta-analysis. *Clin Nutr* 2019;38:2045-52.
64. Saghafian F, Malmir H, Saneei P et al. Fruit and vegetable consumption and risk of depression: accumulative evidence from an updated systematic review and meta-analysis of epidemiological studies. *Br J Nutr* 2018;119:1087-101.
65. Grosso G, Micek A, Marventano S et al. Dietary n-3 PUFA, fish consumption and depression: a systematic review and meta-analysis of observational studies. *J Affect Disord* 2016;205:269-81.
66. Li Z, Li B, Song X et al. Dietary zinc and iron intake and risk of depression: a meta-analysis. *Psychiatry Res* 2017;251:41-7.
67. Zhang Y, Yang Y, Xie MS et al. Is meat consumption associated with depression? A meta-analysis of observational studies. *BMC Psychiatry* 2017;17:409.
68. Hu D, Cheng L, Jiang W. Sugar-sweetened beverages consumption and the risk of depression: a meta-analysis of observational studies. *J Affect Disord* 2019;245:348-55.
69. Salari-Moghaddam A, Saneei P, Larijani B et al. Glycemic index, glycemic load, and depression: a systematic review and meta-analysis. *Eur J Clin Nutr* 2019;73:356-65.
70. Bao YP, Han Y, Ma J et al. Cooccurrence and bidirectional prediction of sleep disturbances and depression in older adults: meta-analysis and systematic review. *Neurosci Biobehav* 2017;75:257-73.
71. Wang X, Cheng S, Xu H. Systematic review and meta-analysis of the relationship between sleep disorders and suicidal behaviour in patients with depression. *BMC Psychiatry* 2019;19:303.
72. Li L, Wu C, Gan Y et al. Insomnia and the risk of depression: a meta-analysis of prospective cohort studies. *BMC Psychiatry* 2016;16:375.
73. Hertenstein E, Feige B, Gmeiner T et al. Insomnia as a predictor of mental disorders: a systematic review and meta-analysis. *Sleep Med Rev* 2019;43:96-105.
74. Zhai L, Zhang H, Zhang D. Sleep duration and depression among adults: a meta-analysis of prospective studies. *Depress Anxiety* 2015;32:664-70.
75. Lee S-H, Kim H-B, Lee K-W. Association between sleep duration and attention-deficit hyperactivity disorder: a systematic review and meta-analysis of observational studies. *J Affect Disord* 2019;256: 62-9.
76. Gao X, Meng LX, Ma KL et al. The bidirectional causal relationships of insomnia with five major psychiatric disorders: a Mendelian randomization study. *Eur Psychiatry* 2019;60:79-85.
77. Ashdown-Franks G, Firth J, Carney R et al. Exercise as medicine for mental and substance use disorders: a meta-review of the benefits for neuropsychiatric and cognitive outcomes. *Sports Med* 2020;50:151-70.
78. Pelsser LM, Frankena K, Toorman J et al. Diet and ADHD, reviewing the evidence: a systematic review of meta-analyses of double-blind placebo-controlled trials evaluating the efficacy of diet interventions on the behavior of children with ADHD. *PLoS One* 2017;12:e0169277.
79. Gee B, Orchard F, Clarke E et al. The effect of non-pharmacological sleep interventions on depression symptoms: a meta-analysis of randomised controlled trials. *Sleep Med Rev* 2019;43:118-28.
80. Povitz M, Bolo CE, Heitman SJ et al. Effect of treatment of obstructive sleep apnea on depressive symptoms: systematic review and meta-analysis. *PLoS Med* 2014;11:e1001762.
81. Gebara MA, Siripong N, DiNapoli EA et al. Effect of insomnia treatments on depression: a systematic review and meta-analysis. *Depress Anxiety* 2018;35:717-31.
82. Kessler RC, Angermeyer M, Anthony JC et al. Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry* 2007;6:168-76.
83. Hoare E, Thorisdóttir IE, Kristjansson AL et al. Lessons from Iceland: developing scalable and sustainable community approaches for the prevention of mental disorders in young Australians. *Mental Health & Prevention* 2019;15:200166.
84. Malakellis M, Hoare E, Sanigorski A et al. School-based systems change for obesity prevention in adolescents: outcomes of the Australian Capital Territory 'It's Your Move!'. *Aust N Z J Public Health* 2017;41:490-6.
85. Kandola A, Ashdown-Franks G, Stubbs B et al. The association between cardiorespiratory fitness and the incidence of common mental health disorders: a systematic review and meta-analysis. *J Affect Disord* 2019;257:748-57.

86. Schuch FB, Vancampfort D, Sui X et al. Are lower levels of cardiorespiratory fitness associated with incident depression? A systematic review of prospective cohort studies. *Prev Med* 2016;93:159-65.
87. Tacchi MJ, Heggelund J, Scott J. Predictive validity of objective measures of physical fitness for the new onset of mental disorders in adolescents and young adults. *Early Interv Psychiatry* 2019;13:1310-8.
88. Ortega FB, Silventoinen K, Tynelius P et al. Muscular strength in male adolescents and premature death: cohort study of one million participants. *BMJ* 2012;345:e7279.
89. Gordon BR, McDowell CP, Lyons M et al. Associations between grip strength and generalized anxiety disorder in older adults: results from the Irish longitudinal study on ageing. *J Affect Disord* 2019;255:136-41.
90. Bennie JA, Teychenne MJ, De Cocker K et al. Associations between aerobic and muscle-strengthening exercise with depressive symptom severity among 17,839 US adults. *Prev Med* 2019;121:121-7.
91. Gordon BR, McDowell CP, Hallgren M et al. Association of efficacy of resistance exercise training with depressive symptoms meta-analysis and meta-regression: analysis of randomized clinical trials. *JAMA Psychiatry* 2018;75:566-76.
92. Gordon BR, McDowell CP, Lyons M et al. The effects of resistance exercise training on anxiety: a meta-analysis and meta-regression analysis of randomized controlled trials. *Sports Med* 2017;47:2521-32.
93. Nebiker L, Lichtenstein E, Minghetti A et al. Moderating effects of exercise duration and intensity in neuromuscular vs. endurance exercise interventions for the treatment of depression: a meta-analytical review. *Front Psychiatry* 2018;9:305.
94. Ye Y-Y, Chen N-K, Chen J et al. Internet-based cognitive-behavioural therapy for insomnia (ICBT-i): a meta-analysis of randomised controlled trials. *BMJ Open* 2016;6:e010707.
95. Freeman D, Sheaves B, Goodwin GM et al. The effects of improving sleep on mental health (OASIS): a randomised controlled trial with mediation analysis. *Lancet Psychiatry* 2017;4:749-58.
96. Krystal AD, Prather AA, Ashbrook LH. The assessment and management of insomnia: an update. *World Psychiatry* 2019;18:337-52.
97. Prochaska JJ, Das S, Young-Wolff KC. Smoking, mental illness, and public health. *Annu Rev Public Health* 2017;38:165-85.
98. Peckham E, Brabyn S, Cook L et al. Smoking cessation in severe mental ill health: What works? An updated systematic review and meta-analysis. *BMC Psychiatry* 2017;17:252.
99. Taylor G, McNeill A, Girling A et al. Change in mental health after smoking cessation: systematic review and meta-analysis. *BMJ* 2014;348:g1151.
100. Gilbody S, Peckham E, Bailey D et al. Smoking cessation for people with severe mental illness (SCIMITAR+): a pragmatic randomised controlled trial. *Lancet Psychiatry* 2019;6: 379-90.
101. Bot M, Brouwer IA, Roca M et al. Effect of multinutrient supplementation and food-related behavioral activation therapy on prevention of major depressive disorder among overweight or obese adults with subsyndromal depressive symptoms: the MoodFOOD randomized clinical trial. *JAMA* 2019;321:858-68.
102. Francis HM, Stevenson RJ, Chambers JR et al. A brief diet intervention can reduce symptoms of depression in young adults – A randomised controlled trial. *PLoS One* 2019;14:10.
103. Jacka FN, O’Neil A, Opie R et al. A randomised controlled trial of dietary improvement for adults with major depression (the ‘SMILES’ trial). *BMC Med* 2017;15:23.
104. Parletta N, Zarnowiecki D, Cho J et al. A Mediterranean-style dietary intervention supplemented with fish oil improves diet quality and mental health in people with depression: a randomized controlled trial (HELFIMED). *Nutr Neurosci* 2019;22:474-87.
105. Firth J, Stubbs B, Teasdale SB et al. Diet as a hot topic in psychiatry: a population-scale study of nutritional intake and inflammatory potential in severe mental illness. *World Psychiatry* 2018;17:365-7.
106. Teasdale S, Firth J. Recommendations for dietetics in mental healthcare. *J Hum Nutr Diet* 2020;33:149-50.
107. Morgan JA, Olagunju AT, Corrigan F et al. Does ceasing exercise induce depressive symptoms? A systematic review of experimental trials including immunological and neurogenic markers. *J Affect Disord* 2018;234:180-92.

108. O'Keefe JH, Gheewala NM, O'Keefe JO. Dietary strategies for improving post-prandial glucose, lipids, inflammation, and cardiovascular health. *J Am Coll Cardiol* 2008;51:249-55.
109. Kiecolt-Glaser JK, Fagundes CP, Andridge R et al. Depression, daily stressors and inflammatory responses to high-fat meals: when stress overrides healthier food choices. *Mol Psychiatry* 2017;22:476-82.
110. Krysta K, Krzystanek M, Bratek A et al. Sleep and inflammatory markers in different psychiatric disorders. *J Neural Transm* 2017;124:179-86.
111. Hamer M, Molloy GJ, de Oliveira C et al. Persistent depressive symptomatology and inflammation: to what extent do health behaviours and weight control mediate this relationship? *Brain Behav Immun* 2009;23:413-8.
112. Yuan N, Chen Y, Xia Y et al. Inflammation-related biomarkers in major psychiatric disorders: a cross-disorder assessment of reproducibility and specificity in 43 meta-analyses. *Transl Psychiatry* 2019;9:1-13.
113. Gleeson M, Bishop NC, Stensel DJ et al. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nature Rev Immunol* 2011;11:607-15.
114. Kastorini C-M, Milionis HJ, Esposito K et al. The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. *J Am Coll Cardiol* 2011;57:1299-313.
115. Chen H-Y, Cheng I-C, Pan Y-J et al. Cognitive-behavioral therapy for sleep disturbance decreases inflammatory cytokines and oxidative stress in hemodialysis patients. *Kidney Int* 2011;80:415-22.
116. Reichert V, Xue X, Bartscherer D et al. A pilot study to examine the effects of smoking cessation on serum markers of inflammation in women at risk for cardiovascular disease. *Chest* 2009;136:212-9.
117. Dinan TG, Cryan JF. Gut microbiota: a missing link in psychiatry. *World Psychiatry* 2020;19:111-2.
118. Mailing LJ, Allen JM, Buford TW et al. Exercise and the gut microbiome: a review of the evidence, potential mechanisms, and implications for human health. *Exerc Sport Sci Rev* 2019;47:75-85.
119. Ghosh T, Rampelli S, Jeffery I. Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: the NU-AGE 1-year dietary intervention across five European countries. *Gut* (in press).
120. Eisenstein M. The hunt for a healthy microbiome. *Nature* 2020;577:S6.
121. Wootton RE, Lawn RB, Millard LA et al. Evaluation of the causal effects between subjective wellbeing and cardiometabolic health: Mendelian randomisation study. *BMJ* 2018;362:k3788.
122. Jebeile H, Gow ML, Baur LA et al. Association of pediatric obesity treatment, including a dietary component, with change in depression and anxiety: a systematic review and meta-analysis. *JAMA Pediatrics* 2019;173:e192841.
123. Salvi V, Hajek T. Brain-metabolic crossroads in severe mental disorders. *Front Psychiatry* 2019;10:492.
124. Firth J, Torous J, Stubbs B et al. The "online brain": how the Internet may be changing our cognition. *World Psychiatry* 2019;18:119-29.
125. Linardon J, Cuijpers P, Carlbring P et al. The efficacy of app-supported smartphone interventions for mental health problems: a meta-analysis of randomized controlled trials. *World Psychiatry* 2019;18:325-36.
126. Bucci S, Lewis S, Ainsworth J et al. Digital interventions in severe mental health problems: lessons from the Actissist development and trial. *World Psychiatry* 2018;17:230-1.

**Table 1** Physical activity and prospective risk of mental disorders in meta analyses

	Outcome	n	Exposure	Main results	Summary
Schuch et al <sup>29</sup> (NIH = 7)	Clinical depression or depressive symptoms	36	Higher physical activity levels	OR=0.837, 95% CI: 0.794-0.883 I <sup>2</sup> =0.00%	Good quality review indicating that high levels of physical activity reduce the risk of depression. Effects persisted across age groups and geographic regions. Although there was evidence of significant publication bias, correcting for this did not alter the indicated protective effects.
Wang et al <sup>30</sup> (NIH = 5)	Clinical depression or depressive symptoms	7	Screen time-based sedentary behavior	OR=1.02, 95% CI: 1.01-1.04 I <sup>2</sup> =3.0%	Fair quality review which concluded screen time-based sedentary behavior did not significantly increase the prospective risk of depression, with low heterogeneity.
Liu et al <sup>31</sup> (NIH = 5)	Depressive symptoms	4	Screen time in children and adolescents	OR=0.88, 95% CI: 0.67-1.14 I <sup>2</sup> =90.4%	Fair quality review finding no prospective associations between screen time and depression. However, there was a lack of large-scale longitudinal studies to determine this.
Zhai et al <sup>32</sup> (NIH = 6)	Clinical depression or depressive symptoms	11	Sedentary behavior	RR=1.14, 95% CI: 1.06-1.21 I <sup>2</sup> =0.00%	Fair quality review showing that higher sedentary behaviour (of all types) at baseline was associated with increased risk of depression at follow-up.
Schuch et al <sup>36</sup> (NIH = 7)	Incident anxiety	11	Higher physical activity levels	OR=0.748, 95% CI: 0.629-0.889 I <sup>2</sup> =23.96%	Good quality review indicating that self-reported physical activity reduces the risk of anxiety. There was evidence of significant publication bias, and correcting for this slightly reduced the protective effects. Subgroup analyses found that physical activity reduces risk of agoraphobia and post-traumatic stress.
McDowell et al <sup>37</sup> (NIH = 7)	Anxiety symptoms	9	Higher physical activity levels	OR=0.874, 95% CI: 0.77-0.99 I <sup>2</sup> =48.7%	Good quality review showing that physical activity is associated with reduced risk of anxiety symptoms and anxiety disorders. The moderate degree of heterogeneity between studies and the limited number of studies using diagnosis outcomes prevents firm conclusions.
	Any anxiety disorder	3		OR=0.663, 95% CI: 0.53-0.82 I <sup>2</sup> =62.3%	
	Diagnosed GAD	3		OR=0.544, 95% CI: 0.32-0.92 I <sup>2</sup> =0.00%	
Brokmeier et al <sup>38</sup> (NIH = 6)	Psychotic disorders	5	Higher physical activity levels	OR=0.728, 95% CI: 0.532-0.995 I <sup>2</sup> =36.9%	Fair quality review showing that higher levels of physical activity are associated with significantly reduced prospective risk of psychosis. However, significant associations were



					not observed in the two studies that sufficiently adjusted for confounding factors, although this may be due to the limited sample size of this subgroup underpowering the analysis.
--	--	--	--	--	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

n – number of comparisons, OR – odds ratio, RR – risk ratio, NIH – quality of the study evaluated by the National Institutes of Health's Quality Assessment Tool for Systematic Reviews and Meta-Analyses (good: 7 or 8; fair: 4-6; poor: 0-3), GAD – generalized anxiety disorder

**Table 2** Causal relations of physical activity and mental disorders in Mendelian randomization studies

	Outcome	Sample	Exposure	Main results	Summary
Choi et al <sup>33</sup>	Major depression	N=143,265 from Wray et al's GWAS <sup>35</sup>	Self-reported moderate-vigorous physical activity (9 SNPs) Objective accelerometer activity (10 SNPs)	Self-reported: IVW OR=1.28, 95% CI: 0.57-3.37, p=0.48 Objective: IVW OR=0.74, 95% CI: 0.59-0.92, p=0.006	This bi-directional analysis found evidence that accelerometer-measured physical activity was protective for depression. Evidence was consistent across multiple pleiotropy robust methods. There was no clear evidence to suggest that depression risk decreased physical activity. Equally, there was no clear evidence that self-reported physical activity was protective for major depression. The analysis was run with a relaxed p value threshold of $p < 1 \times 10^{-7}$ .
Choi et al <sup>34</sup>	Major depression	N=431,394 from Wray et al's GWAS <sup>35</sup>	Self-reported: part of a gym/club; usual walking pace; walking for pleasure; transport by walking; frequency of walking; heavy do-it-yourself (DIY); other exercise (including swimming and cycling)	Gym/club member: IVW OR=0.91, 95% CI: 0.784-1.057, p=0.217 Walking pace: IVW OR=1.038, 95% CI: 0.877-1.228, p=0.666 Walking for pleasure: IVW OR=1.02, 95% CI: 0.918-1.123, p=0.765 Transport by walking: IVW OR=0.983, 95% CI: 0.870-1.111, p=0.782 Frequency of walking: IVW OR=1.024, 95% CI: 0.849-1.234, p=0.807 DIY: IVW OR=0.995, 95% CI: 0.889-1.114, p=0.931 Other: IVW OR=0.90, 95% CI: 0.82-0.99, p=0.033	There was no clear evidence for any of the examined factors being causal. There was a nominal association with other exercise (e.g., swimming and cycling), but this did not survive Bonferroni correction. When testing the effects of depression on these outcomes, none was significant after Bonferroni adjustment.
Sun et al <sup>39</sup>	Bipolar disorder	N=20,352 cases and 31,358 controls from Stahl et al's GWAS <sup>40</sup>	Device measured: overall activity (5 SNPs);	Overall activity: IVW OR=0.491, 95% CI: 0.314-0.767, p=0.002. Sedentary time: IVW OR=0.702, 95% CI: 0.366-1.345, p=0.287 Moderate activity: IVW OR=0.726, 95% CI: 0.255-2.068, p=0.549	Overall physical activity was protective for bipolar disorder and this result was consistent across the more pleiotropy robust methods. No evidence was found for the reverse direction (i.e., bipolar

	Schizophrenia	N=33,426 cases and 32,541 controls from Ruderfer et al's GWAS <sup>41</sup>	sedentary time (5 SNPs); moderate activity (1 SNP)	Overall activity: IVW OR=1.133, 95% CI: 0.636-2.020, p=0.672 Sedentary time: IVW OR=0.707, 95% CI: 0.430-1.161, p=0.170 Moderate activity: IVW OR=0.657, 95% CI: 0.378-2.026, p=0.379	disorder risk did not influence physical activity). There was no evidence for an effect of overall activity on schizophrenia, nor evidence that sedentary behavior or moderate intensity activity were protective for either disorder.
--	---------------	-----------------------------------------------------------------------------	-------------------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

GWAS – genome-wide association study, SNP – single nucleotide polymorphism, IVW OR – inverse-variance weighted odds ratio

**Table 3** Smoking and prospective risk of mental disorders in meta-analyses

	<b>Outcome</b>	<b>n</b>	<b>Exposure</b>	<b>Main results</b>	<b>Summary</b>
Luger et al <sup>42</sup> (NIH = 3)	Major depressive disorder and depressive symptoms	7	Smokers vs. never smokers	OR=1.62, 95% CI: 1.1-2.4, I <sup>2</sup> =NA	Smoking was strongly associated with risk of depression, with effects of 1.5-2 times the risk of non-smoking from a variety of designs, measurements and populations. However, review quality scored low, and the impact of publication bias and study heterogeneity was not determined.
Chaiton et al <sup>43</sup> (NIH = 4)	Adolescent depression (diagnosis or clinical symptoms)	6	Smoking	OR=1.73, 95% CI: 1.32-2.4 I <sup>2</sup> =NA	Fair quality review showing smoking in adolescence is associated with increased risk of future depression. However, clinical measures of depression were more likely to report a bidirectional effect (i.e., depression also predicting smoking).
Han et al <sup>44</sup> (NIH = 6)	Incident depressive symptoms in children	2	Early life second-hand smoking	OR=1.51, 95% CI: 0.93-2.09, I <sup>2</sup> =0%	Fair quality review showing that exposure to second-hand smoking in early life was associated with increased odds of depressive symptoms in cross-sectional studies. However, the effects in the two prospective cohort studies was non-significant.
Chen et al <sup>45</sup> (NIH = 6)	Postpartum depression	4	Prenatal smoking	OR=2.88, 95% CI: 0.99-8.39, I <sup>2</sup> =89.3%	Fair quality review showing that prenatal smoking was strongly associated with postpartum depression in the overall analysis (including retrospective and longitudinal studies), with no indication of publication bias. However, in the subgroup analysis of longitudinal studies, the effect size was similarly large, but fell short of statistical significance.
Hunter et al <sup>52</sup> (NIH = 7)	Incident schizophrenia	6	Personal active smoking	RR=1.99, 95% CI: 1.1-3.61, I <sup>2</sup> =97%	Good quality review showing that smokers had an approximately doubled risk of developing schizophrenia relative to non-smokers. Smaller, but still significant, effects were found for prenatal smoking (although this analysis was based on retrospective reports of prenatal smoke exposure).
Gurillo et al <sup>53</sup> (NIH = 4)	Psychotic disorders	6	Smoking	RR=2.18, 95% CI: 1.23-3.85, I <sup>2</sup> =97.7%	Fair quality review showing that daily tobacco use was associated with a doubled risk of psychosis. Significant risk of publication bias was indicated, and heterogeneity was high.
Huang et al <sup>57</sup> (NIH = 5)	ADHD	15	Prenatal exposure to maternal smoking	OR=1.35, 95% CI: 1.2-1.52, I <sup>2</sup> =59.5	Fair quality review showing that maternal smoking during pregnancy was associated with increased risk of ADHD in offspring. However, familial and genetic factors were not adequately controlled for, and impact of publication bias was not established.

n – number of comparisons, OR – odds ratio, RR – risk ratio, NIH – quality of the study evaluated by the National Institutes of Health's Quality Assessment Tool for Systematic Reviews and Meta-Analyses (good: 7 or 8; fair: 4-6; poor: 0-3), NA – not available, ADHD – attention-deficit/hyperactivity disorder

**Table 4** Causal relations of smoking and mental disorders in Mendelian randomization studies

	Outcome	Sample	Exposure	Main results	Summary
Wootton et al <sup>51</sup>	Major depression	N=135,458 cases and 344,901 controls from Wray et al's GWAS <sup>35</sup>	Lifetime smoking (126 SNPs for combined smoking initiation, duration, heaviness and cessation)	Lifetime smoking: IVW OR=1.99, 95% CI: 1.71-2.32, p<0.001 Smoking initiation: IVW OR=1.54, 95% CI: 1.44-1.64, p<0.01	Strong evidence to suggest causal effects of smoking on risk of both depression and schizophrenia. Results were highly consistent across sensitivity analyses testing for pleiotropy. Bi-directional analyses also showed some evidence for depression and schizophrenia causally increasing odds of smoking behavior. Again this was consistent across more pleiotropy robust methods.
	Schizophrenia	N=36,989 cases and 113,075 controls from Psychiatric Genomics Consortium (PGC)	Smoking initiation (378 SNPs)	Lifetime smoking: IVW OR: 2.27, 95% CI: 1.67-3.08, p<0.001 Smoking initiation: IVW OR=1.53, 95% CI: 1.35-1.74, p<0.01	
Vermeulen et al <sup>56</sup>	Bipolar disorder	N=20,129 cases and 21,524 controls from Stahl et al's GWAS <sup>40</sup>	Smoking initiation (378 SNPs) Lifetime smoking (126 SNPs)	Smoking initiation: IVW OR=1.46, 95% CI: 1.28-1.66, p<0.001 Lifetime smoking: IVW OR=1.72, 95% CI: 1.29-2.28, p<0.001	Evidence to suggest that smoking is a causal factor in increased risk for bipolar disorder. This effect was consistent across multiple sensitivity analyses for pleiotropy. The bi-directional effects were tested, but there was no evidence to suggest that bipolar disorder risk increased smoking initiation, heaviness, cessation or lifetime smoking.
Treur et al <sup>58</sup>	ADHD	N=15,548 cases diagnosed >18 years from Demontis et al's GWAS <sup>59</sup>	Smoking initiation (378 SNPs)	OR=3.72, 95% CI: 3.10-4.44, p<0.001	Evidence to suggest that smoking initiation causally increased risk of ADHD. This was consistent across several more pleiotropy robust methods. However, Steiger filtering did also suggest some reverse causation. Furthermore, smoking initiation also predicted ADHD before age 13 years, when a biological causal effect of own smoking is implausible. This result, along with the Steiger filtering, suggests the instrument could be capturing wider risk-taking and impulsivity. Bi-directional analyses suggested that liability to ADHD increased likelihood of smoking initiation and cigarettes per day.
Gage et al <sup>55</sup>	Schizophrenia	N=36,989 cases and 113,075 controls from PGC	Smoking initiation (4 SNPs)	Genome-wide significant SNPs: IVW OR=1.73, 95% CI: 1.30-2.25, p<0.001 Relaxed p-value threshold: IVW OR=1.03, 95% CI: 0.97-1.09, p=0.32	There were very few SNPs associated with smoking initiation at the time when this GWAS was conducted, and resultantly the four SNPs used were all in the same gene. With a relaxed p-value threshold, there was no evidence for an effect of smoking on schizophrenia. Similarly, no evidence was found for schizophrenia causally increasing smoking.

Wium-Anderson et al <sup>47</sup>	Major depression	Danish Population Registry (N=63,296) comprising the Copenhagen General Population Study (CGPS) and the Copenhagen City Heart Study (CCHS)	Smoking heaviness (ever vs. never smokers) from rs1051730 genotype	Depression: OR=0.85, 95% CI: 0.66-1.10	Evidence that smoking heaviness may be causally associated with prescription of antipsychotic use and could causally influence psychotic conditions. A negative control analysis in never smokers found no effect, suggesting that results were not biased by pleiotropy. There was no evidence for a causal effect of smoking heaviness on depression. However, analysis of the Danish registry was underpowered for the schizophrenia analysis (due to a low number of cases) and replication analysis conducted using PGC data was unable to separate smokers and non-smokers (thus failing to test for pleiotropy).
	Lifetime prescription of antidepressants			Antidepressants: OR=1.02, 95% CI: 0.93-1.13 (for TT allele compared to CC allele in smokers only) No evidence for an interaction	
	Schizophrenia			Schizophrenia: OR=1.60, 95% CI: 0.74-3.47	
	Lifetime use of antipsychotics			Antipsychotics: OR=1.16, 95% CI: 1.02-1.31 (for TT allele compared to CC allele in smokers only) No evidence for an interaction	
Taylor et al <sup>49</sup>	Depression, anxiety and psychological distress assessed by clinical interview, symptom scales or self-reported recall of clinician diagnosis	N=127,632 from CARTA Consortium, comprising 25 studies of European ancestry aged ≥16 years	Smoking heaviness in ever vs. current vs. former vs. never smokers from rs1051730 / rs16969968 genotype	In current smokers (OR per T allele): Depression: OR=1.00, 95% CI: 0.95-1.05 Anxiety: OR=1.02, 95% CI: 0.97-1.07 Psychological distress: OR=1.02, 95% CI : 0.98-1.06	There was no evidence for an effect of rs16969968/ rs1051730 genotype on depression, anxiety or psychological stress.
Bjørngaard et al <sup>46</sup>	Depression and anxiety measured on the Hospital Anxiety and Depression Scale (HADS)	N=53,601 from Norwegian HUNT study	Smoking heaviness in current vs. former vs. never smokers from rs1051730 genotype	In smokers only (OR per T allele): Anxiety: OR=1.03, 95% CI: 0.97-1.09 Depression: OR: 1.02, 95% CI: 0.95-1.09	There was evidence for an effect of rs1051730 genotype on anxiety when combining smokers and non-smokers, but this was not the case in current and former smokers, thus suggesting that smoking is not a cause of anxiety and depression.
Lewis et al <sup>48</sup>	Depressed mood at 18 weeks of pregnancy measured by the Edinburgh Postnatal Depression Scale (EPDS)	N=6,294 from Avon Longitudinal Study of Parents and Children (ALSPAC) cohort	Smoking status before and during pregnancy from rs1051730 genotype Smoking heaviness stratified by pre-pregnancy smoking status from rs1051730 genotype	For TT compared to CC in smokers: Prenatal depression: OR=0.56, 95% CI: 0.37-0.84 Weak evidence for an interaction (p=0.07)	The rs1051730 genotype predicts smoking heaviness during pregnancy and mothers being less likely to quit. However, there was no clear evidence for a causal effect of smoking on prenatal depression, as the results of genotype given continued smoking during pregnancy were consistent with a reduced risk of reporting depressed mood per effect allele rather than an increased risk.

GWAS – genome-wide association study, SNP – single nucleotide polymorphism, IVW OR – inverse-variance weighted odds ratio, OR – odds ratio, ADHD – attention-deficit/hyperactivity disorder

**Table 5** Diet and prospective risk of mental disorders in meta-analyses

	Outcome	n	Exposure	Main results	Summary
Nicolaou et al <sup>62</sup> (NIH = 3)	High depressive symptoms	3	Mediterranean diet	OR=0.88, 95% CI: 0.80-0.96, I <sup>2</sup> =15.4%	This meta-analysis of harmonised studies found that adults following a healthy dietary pattern have significantly lower risk of depressive symptoms overtime, even when controlling for depressive symptoms at baseline. Small but significant positive effects were indicated from adherence to a Mediterranean or DASH diet, whereas the AHEI index was non-significant. Scores were low on review quality, probably due to this study been a meta-analysis of specific studies (not full systematic review).
			Alternative Healthy Eating Index	OR=0.95, 95% CI: 0.84-1.06, I <sup>2</sup> =35%	
			Dietary approaches to stop hypertension (DASH)	OR=0.9, 95% CI: 0.84-0.97, I <sup>2</sup> =0%	
Lassale et al <sup>61</sup> (NIH = 7)	Clinical depression or depressive symptoms	5	Mediterranean diet	OR=0.67, 95% CI: 0.55-0.82, I <sup>2</sup> =33.1	Good quality review of multiple dietary patterns which found that adhering to a Mediterranean diet or low inflammatory diet is associated with reduced depression risk in prospective studies. It should be noted that there was heterogeneity in all analyses, and few studies used diagnosis of depression as the outcome.
		4	Healthy Eating Index/Alternative Healthy Eating Index	OR=0.76, 95% CI: 0.57-1.02, I <sup>2</sup> =80.7	
		4	Dietary approaches to stop hypertension (DASH)	OR=0.89, 95% CI: 0.6-1.31, I <sup>2</sup> =68.0	
		7	Low dietary inflammatory index	OR=0.76, 95% CI: 0.63-0.92, I <sup>2</sup> =55.3	
Tolkien et al <sup>63</sup> (NIH = 5)	Clinical depression or depressive symptoms	10	Pro-inflammatory diet	OR=1.31, 95% CI: 1.2-1.44, I <sup>2</sup> =5.1%	Fair quality review showing that pro-inflammatory diets are associated with significantly increased risk of depression/depressive symptoms, with low heterogeneity between studies.
Molendijk et al <sup>60</sup> (NIH = 7)	Clinical depression or depressive symptoms	17	Healthy dietary pattern	OR=0.77, 95% CI: 0.69-0.84, I <sup>2</sup> =88.3	Good quality review showing that healthy dietary patterns and healthy food groups were associated with a lower prospective risk of depressive symptoms. However, there was no evidence for unhealthy diet patterns or unhealthy food groups increasing depression risk. Additionally, no significant associations between diet and depression were found in subgroup analyses of the few studies which controlled for baseline depression severity, or used diagnosis of depression as the outcome. Subgroup analyses further examined various individual food groups, finding mixed results.
		18	Healthy food groups	OR=0.89, 95% CI: 0.83-0.95, I <sup>2</sup> =71.3	
		10	Unhealthy dietary patterns	OR=1.05, 95% CI: 0.99-1.12, I <sup>2</sup> =45.2	
		7	Unhealthy food groups	OR=1.09, 95% CI: 1.00-1.19, I <sup>2</sup> =26.2	



		7	Neutral food groups	OR=0.91, 95% CI: 0.84-1.00, I <sup>2</sup> =42.8	
Salari-Moghaddam et al <sup>69</sup> (NIH = 7)	Clinical depression or depressive symptoms	2	High dietary glycaemic index	HR=1.05, 95% CI: 0.76-1.44, I <sup>2</sup> =86.1%	Good quality review which failed to find prospective relationships between dietary glycaemic index and depression in random effect models. However, this was only examined in two longitudinal studies (for which fixed-effects analyses did observe a significant, positive relationship). Thus, the findings overall can neither confirm or rule-out relationships between dietary glycaemic index and depression.
Hu et al <sup>68</sup> (NIH = 6)	Clinical depression or depressive symptoms	4	Sugar-sweetened beverage consumption	RR=1.30, 95% CI: 1.19-1.41, I <sup>2</sup> =0.00%	Fair quality review showing that regular consumption of sugar-sweetened beverages is associated with greater risk of depression. However, there was a low number of prospective studies assessing this association, which also did not adequately control for broader dietary factors.
Saghafian et al <sup>64</sup> (NIH = 5)	Clinical depression or depressive symptoms	6	Fruit intake	RR=0.83, 95% CI: 0.71-0.98, I <sup>2</sup> =84.5%	Fair quality review showing that fruit and vegetable intake is prospectively associated with reduced risk of depression. There was significant heterogeneity among studies. However, the observed associations between fruit and depression are inconsistent with other meta-analyses <sup>60</sup> .
		7	Vegetable intake	RR=0.86, 95% CI: 0.75-0.98, I <sup>2</sup> =68.1%	
Zhang et al <sup>67</sup> (NIH = 6)	Clinical depression or depressive symptoms	3	High meat consumption	RR=1.13, 95% CI: 1.03-1.24, I <sup>2</sup> =19.4%	Fair quality review showing that those with highest levels of meat consumption are at higher risk of depression. However, there was a small number of studies in the pooled analysis, which combined odds ratios from “never vs. any” comparisons of meat consumption with studies of high vs. low levels of meat consumption. A larger analysis from subgroups within another review found no associations for meat and depression <sup>60</sup> .
Li et al <sup>66</sup> (NIH = 6)	Clinical depression or depressive symptoms	3	High dietary zinc intake	RR=0.73, 95% CI: 0.6-0.9, I <sup>2</sup> =0.00%	Fair quality review indicating an inverse association between dietary zinc intake and future risk of depression. However, there was a low number of prospective studies assessing this association, which also did not control for other dietary factors.
Grosso et al <sup>65</sup> (NIH = 4)	Clinical depression or depressive symptoms	7	Dietary n-3 PUFA consumption	RR=0.85, 95% CI: 0.73-1.00, I <sup>2</sup> =19%	Fair quality review supporting the hypothesis that dietary polyunsaturated fatty acids may lower risk of depression. Fish intake was also associated with reduced risk of depression, which is consistent with a subsequent larger analysis <sup>60</sup> .
		4	Dietary EPA + DHA consumption	RR=0.74, 95% CI: 0.61-0.89, I <sup>2</sup> =0.00%	

n – number of comparisons, OR – odds ratio, RR – risk ratio, HR – hazard ratio, NIH – quality of the study evaluated by the National Institutes of Health's Quality Assessment Tool for Systematic Reviews and Meta-Analyses (good: 7 or 8; fair: 4-6; poor: 0-3), NA – not available, ADHD – attention-deficit/hyperactivity disorder, PUFA – polyunsaturated fatty acid, EPA – eicosapentaenoic acid, DHA – docosahexaenoic acid

**Table 6** Causal relations of diet and mental disorders in Mendelian randomization studies

	Outcome	Sample	Exposure	Main results	Summary
Choi et al <sup>34</sup>	Major depression	N=431,394 from Wray et al's GWAS <sup>35</sup>	Multivitamin supplements, tea intake, salt intake, lamb intake, inconsistent diet, cereal intake, vitamin B supplements	Multivitamin: OR=1.28, 95% CI: 1.11-1.47, p=0.0006 Tea intake: OR=0.95, 95% CI: 0.91-0.99, p=0.02 Salt intake: OR=1.10, 95% CI: 1.01-1.19, p=0.03 Lamb intake: OR=1.17, 95% CI: 0.95-1.44, p=0.14 Inconsistent diet: OR=1.15, 95% CI : 0.87-1.53, p=0.34 Cereal intake: OR=0.98, 95% CI: 0.94-1.02, p=0.42 Vitamin B: OR=1.002, 95% CI: 0.95-1.05, p=0.93	There was evidence to suggest that multivitamin intake causally increased risk of major depression at follow-up. This result survived Bonferroni correction for multiple testing. There was also nominal evidence for salt intake as a causal factor for depression (non-significant after correction for multiple testing). The only diet-related factor indicated as causally reducing depression risk was tea drinking. However, this association was non-significant after correcting for multiple testing.

OR – odds ratio, GWAS – genome-wide association study

**Table 7** Sleep activity and prospective risk of mental disorders in meta-analyses

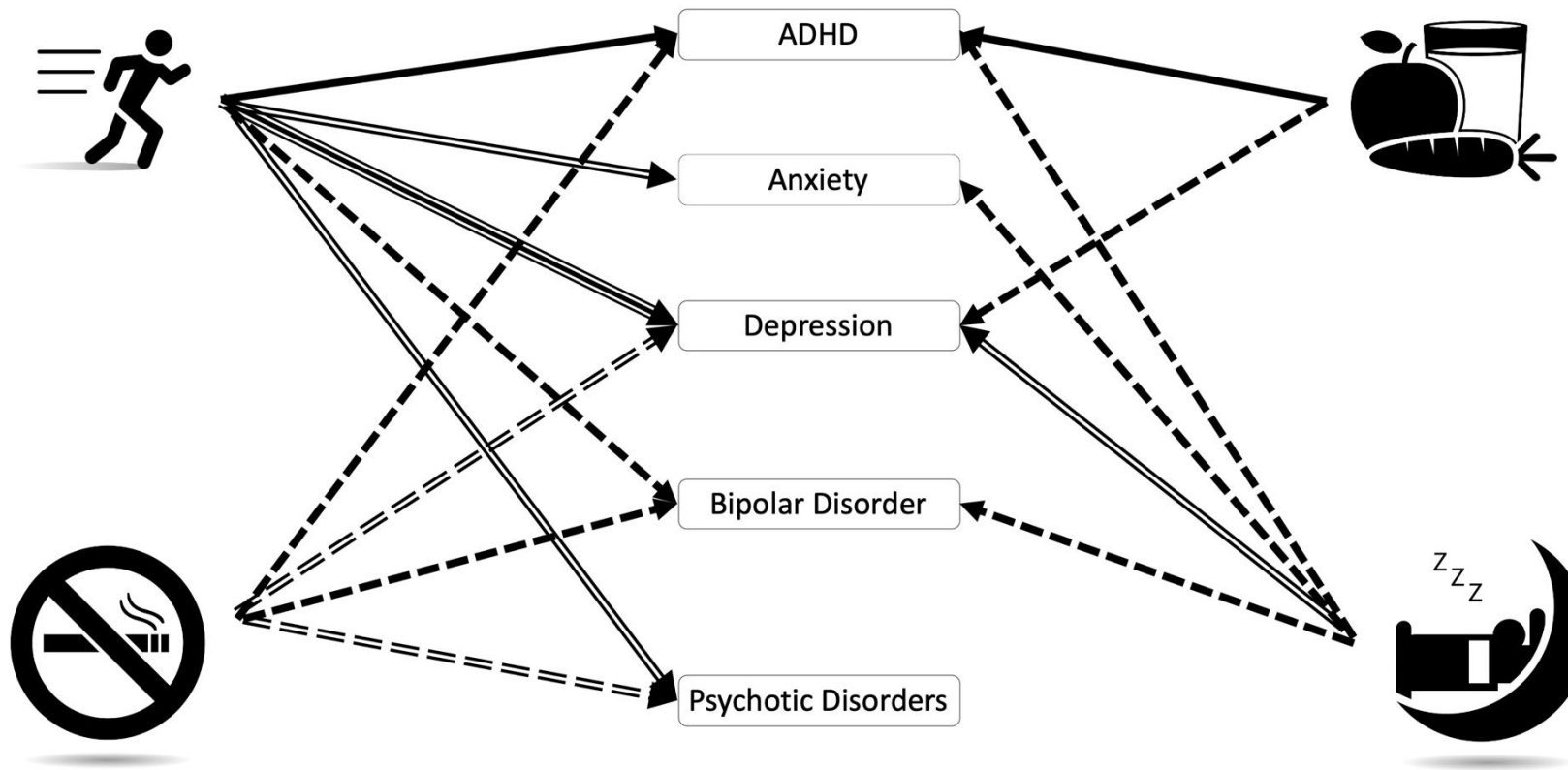
	Outcome	n	Exposure	Main results	Summary
Bao et al <sup>70</sup> (NIH = 5)	Clinical depression or depressive symptoms	11	Sleep disturbances	RR=1.92, 95% CI: 1.6-2.30, I <sup>2</sup> =10.2%	Fair quality review finding that individuals with “sleep disturbances” (including insomnia, complaints of sleeping difficulties and general poor sleep quality) were at significantly heightened risk of developing depression, with low heterogeneity between studies. Sensitivity analyses found associations between depression and sleep disturbances applied to both major depressive disorders and general depressive symptoms.
		4	Persistent sleep disturbances	RR=3.90, 95% CI: 2.77-5.48, I <sup>2</sup> =27.1%	
Zhai et al <sup>74</sup> (NIH = 6)	Clinical depression or depressive symptoms	7	Short sleep duration	RR=1.31, 95% CI: 1.04-1.64, I <sup>2</sup> =0%	Fair quality review indicating that both shorter and longer than average sleep durations are equally associated with significantly increased risk of depression in adults, with no indication of heterogeneity influencing the findings.
		5	Long sleep duration	RR=1.42, 95% CI: 1.04-1.92, I <sup>2</sup> =0%	
Lee et al <sup>75</sup> (NIH = 8)	ADHD or clinically significant ADHD symptoms	3	Short sleep duration	RR=2.61, 95% CI: 1.36-5.00, I <sup>2</sup> =83.0%	Good quality review finding that short sleep duration is associated with significantly greater risk of ADHD overtime, in children and adults. However, there was a low number of total studies/participants and significant heterogeneity among prospective studies.
Li et al <sup>72</sup> (NIH = 7)	Clinical depression or depressive symptoms	34	Insomnia (night-time symptoms)	RR=2.27, 95% CI: 1.89-2.71, I <sup>2</sup> =92.6%	Good quality review showing that insomnia (although primarily identified by night-time symptoms) significantly increases the risk of depression, although with high heterogeneity between studies. There was also some indication of publication bias, but adjusting for this did not alter the overall findings.
Hertenstein et al <sup>73</sup> (NIH = 7)	All psychiatric disorders	19	Insomnia disorders	OR=2.60, 95% CI: 1.70-3.97, I <sup>2</sup> =96.2%	Good quality review of studies with at least 12 months of follow-up reporting that individuals with insomnia (including presence of both day-time and night-time symptoms) are at greatly increased risk of developing psychiatric disorders. Subgroup analyses found that
	Clinical depression or depressive symptoms	10		OR=2.83, 95% CI: 1.55-5.17, I <sup>2</sup> =93.67%	

	Anxiety disorders	6		OR=3.23, 95% CI: 1.52-6.85, I <sup>2</sup> =96.37%	insomnia increased the risk of depression or anxiety disorders by around 3-fold, whereas effects on psychosis risk were weaker (n=1 only, data not shown). There was a substantial degree of heterogeneity between studies, and publication bias may influence effect estimates.
--	-------------------	---	--	----------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

n – number of comparisons, OR – odds ratio, RR – risk ratio, NIH – quality of the study evaluated by the National Institutes of Health’s Quality Assessment Tool for Systematic Reviews and Meta-Analyses (good: 7 or 8; fair: 4-6; poor: 0-3), ADHD – attention-deficit/hyperactivity disorder

<b>Table 8</b> Causal relations of sleep and mental disorders in Mendelian randomization studies					
	<b>Outcome</b>	<b>Sample</b>	<b>Exposure</b>	<b>Main results</b>	<b>Summary</b>
Gao et al <sup>76</sup>	ADHD	N =20,183 cases and 35,191 controls from Demontis et al's GWAS <sup>59</sup>	Night-time symptoms of insomnia (15-23 SNPs)	OR=1.08, 95% CI: 0.88-1.34, p=0.46	There was evidence to suggest that having insomnia increased risk for bipolar disorder. The same trend was observed for more pleiotropy robust sensitivity methods, but the evidence was weaker.
	Major depression	N = 9,240 cases and 9,519 controls from PGC		OR=0.99, 95% CI: 0.69-1.40, p=0.94	
	Schizophrenia	N =33,426 cases and 32,541 controls from PGC		OR=1.14, 95% CI: 0.93-1.39, p=0.20	
	Bipolar disorder	N =20,129 cases and 21,524 controls from PGC		OR=1.79, 95% CI: 1.40-2.29, p<0.001	
Choi et al <sup>34</sup>	Depression	N=431,394 from Wray et al's GWAS <sup>35</sup>	Daytime napping	Daytime napping: OR=1.34, 95% CI: 1.17-1.53, p=0.00002	There was strong evidence for an effect of daytime napping as a risk factor for depression, and this was consistent across sensitivity analyses and survived correction for multiple testing. There was no clear evidence for an effect of hours of sleep on depression risk.
			Hours of sleep	Hours of sleep: OR=1.04, 95% CI: 0.93-1.15, p=0.49	
Sun et al <sup>39</sup>	Bipolar disorder	N =20,352 cases and 31,358 controls from Stahl et al's GWAS <sup>40</sup>	Device measured sleep time (14 SNPs)	OR=1.05, 95% CI: 0.77-1.39, p=0.72	There was no clear evidence for an effect of objectively measured sleep on either bipolar disorder or schizophrenia.
	Schizophrenia	N =33,426 cases and 32,541 controls from Ruderfer et al's GWAS <sup>41</sup>		OR=1.13, 95% CI: 0.95-1.75, p=0.10.	

OR – odds ratio, GWAS – genome-wide association study, SNP – single nucleotide polymorphism, PGC – Psychiatric Genomics Consortium, ADHD – attention-deficit/hyperactivity disorder



**Figure 1** Lifestyle factors in the prevention and treatment of mental illness. The dashed line indicates protective benefit from either prospective meta-analyses (P-MAs) or Mendelian randomization studies (MRs). The double-dashed line indicates protective effects supported by evidence from both prospective P-MAs and MRs. The solid line indicates evidence for efficacy in treatment of mental illness from MAs of randomized controlled trials (RCTs). The double solid line indicates convergent evidence from MRs or P-MAs with MAs of RCTs. The treble solid line indicates convergent evidence from all three (P-MAs + MRs + MAs of RCTs). ADHD – attention-deficit/hyperactivity disorder. Note: quality and consistency of evidence presented elsewhere.