

## Original Article

**Cite this article:** Burke C, Freeman TP, Sallis H, Wootton RE, Burnley A, Lange J, Lees R, Sawyer K, Taylor GMJ (2024). Associations of cannabis use, tobacco use, and incident anxiety, mood, and psychotic disorders: a systematic review and meta-analysis. *Psychological Medicine* 1–15. <https://doi.org/10.1017/S0033291724002587>

Received: 30 January 2024

Revised: 25 September 2024

Accepted: 30 September 2024

**Keywords:**

anxiety disorders; cannabis; causal inference; confounding; epidemiology; mood disorders; psychotic disorders; systematic review; tobacco










**Abbreviations:**

95% CI: 95% confidence interval; MR: Mendelian randomization; NOS: Newcastle–Ottawa Scale; OR: odds ratio; PI: prediction interval; RR: risk ratio

**Corresponding author:**

Chloe Burke;  
Email: [cb692@bath.ac.uk](mailto:cb692@bath.ac.uk)

# Associations of cannabis use, tobacco use, and incident anxiety, mood, and psychotic disorders: a systematic review and meta-analysis

Chloe Burke<sup>1</sup> , Tom P. Freeman<sup>1</sup> , Hannah Sallis<sup>2,3</sup> , Robyn E. Wootton<sup>2,4</sup> , Annabel Burnley<sup>1</sup> , Jonas Lange<sup>1</sup> , Rachel Lees<sup>1</sup> , Katherine Sawyer<sup>1</sup>  and Gemma M. J. Taylor<sup>1</sup> 

<sup>1</sup>Department of Psychology, University of Bath, Bath, UK; <sup>2</sup>School of Psychological Science, University of Bristol, Bristol, UK; <sup>3</sup>Centre for Academic Mental Health, Population Health Services, Bristol Medical School, University of Bristol, Bristol, UK and <sup>4</sup>Nic Waals Institute, Lovinsenberga Diagonal Hospital, Oslo, Norway

**Abstract**

**Background.** Observational studies consistently report associations between tobacco use, cannabis use and mental illness. However, the extent to which this association reflects an increased risk of new-onset mental illness is unclear and may be biased by unmeasured confounding.

**Methods.** A systematic review and meta-analysis (CRD42021243903). Electronic databases were searched until November 2022. Longitudinal studies in general population samples assessing tobacco and/or cannabis use and reporting the association (e.g. risk ratio [RR]) with incident anxiety, mood, or psychotic disorders were included. Estimates were combined using random-effects meta-analyses. Bias was explored using a modified Newcastle–Ottawa Scale, confounder matrix, *E*-values, and Doi plots.

**Results.** Seventy-five studies were included. Tobacco use was associated with mood disorders ( $K = 43$ ; RR: 1.39, 95% confidence interval [CI] 1.30–1.47), but not anxiety disorders ( $K = 7$ ; RR: 1.21, 95% CI 0.87–1.68) and evidence for psychotic disorders was influenced by treatment of outliers ( $K = 4$ , RR: 3.45, 95% CI 2.63–4.53;  $K = 5$ , RR: 2.06, 95% CI 0.98–4.29). Cannabis use was associated with psychotic disorders ( $K = 4$ ; RR: 3.19, 95% CI 2.07–4.90), but not mood ( $K = 7$ ; RR: 1.31, 95% CI 0.92–1.86) or anxiety disorders ( $K = 7$ ; RR: 1.10, 95% CI 0.99–1.22). Confounder matrices and *E*-values suggested potential overestimation of effects. Only 27% of studies were rated as high quality.

**Conclusions.** Both substances were associated with psychotic disorders and tobacco use was associated with mood disorders. There was no clear evidence of an association between cannabis use and mood or anxiety disorders. Limited high-quality studies underscore the need for future research using robust causal inference approaches (e.g. evidence triangulation).

**Introduction**

Tobacco and cannabis are two of the most commonly used recreational drugs worldwide. In 2019, approximately 1.14 billion adults globally had smoked tobacco regularly and an estimated 200 million people used cannabis in the last year (UNODC, 2021). Existing observational evidence demonstrates prospective associations between cannabis use, tobacco use, and mental illness; including depression, anxiety, and psychosis (e.g. Arango et al., 2021; Chaiton, Cohen, O’Loughlin, & Rehm, 2009; Chaplin et al., 2023; Esmaealzadeh, Moraros, Thorpe, & Bird, 2018; Farooqui et al., 2022; Fluharty, Taylor, Grabski, & Munafò, 2017; Garey et al., 2020; Gobbi et al., 2019; Gurillo, Jauhar, Murray, & MacCabe, 2015; Hunter, Murray, Asher, & Leonardi-Bee, 2020; Lev-Ran et al., 2014; Luger, Suls, & Vander Weg, 2014; Marconi, Di Forti, Lewis, Murray, & Vassos, 2016; Moore et al., 2007; Myles et al., 2012; Robinson et al., 2023; Stevenson, Miller, Martin, Mohammadi, & Lawn, 2022; Zimmermann, Chong, Vechiu, & Papa, 2020). However, it remains unclear if the associations in question are causal or if they result from observational data biases (e.g. confounding, reverse causality; Hammerton & Munafò, 2021).

Confounding bias occurs when the effects of an exposure under study on a given outcome are ‘mixed in’ with effects of an additional factor, or set of factors, associated with the target exposure and outcome that results in a distortion of the true effect (Skelly, Dettori, & Brodt, 2012). Confounding bias can be reduced if appropriate controls are implemented (e.g. multivariable regression), but in practice it is difficult to measure all confounders and without error (Fewell, Davey Smith, & Sterne, 2007). Numerous reviews of these substances and mental

© The Author(s), 2024. Published by Cambridge University Press. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted re-use, distribution and reproduction, provided the original article is properly cited.

illness highlight confounding bias as a key limitation (Chaplin et al., 2023; Garey et al., 2020; Gobbi et al., 2019; Gurillo et al., 2015; Hunter et al., 2020; Lev-Ran et al., 2014). However, no comprehensive assessment of the strength of potential confounding bias has been conducted.

In this review, confounding bias is evaluated using the confounder matrix (Petersen et al., 2022) and *E*-values (VanderWeele & Ding, 2017). The confounder matrix is an approach for defining and summarizing adequate confounding control in systematic reviews (Petersen et al., 2022). *E*-values are a quantitative approach to evaluate the sensitivity of estimates from an observational study to unmeasured confounding (D'Agostino McGowan, 2022; VanderWeele & Ding, 2017). Briefly, the *E*-value of an estimate represents the minimum strength of an association, on a risk ratio (RR) scale, that an unmeasured confounder would need to have with both the exposure and the outcome to reduce an observed effect estimate to the null (i.e. RR = 1), conditional on measured covariates (VanderWeele & Ding, 2017). Employed together, these tools provide a complementary and in-depth assessment of confounding bias.

A further difficulty is that co-use of cannabis and tobacco is highly common (Agrawal, Budney, & Lynskey, 2012; Gravely et al., 2020; Hindocha & McClure, 2020). Cannabis-tobacco co-use comprises concurrent use (i.e. use of both products in a pre-defined time period) and co-administration (i.e. simultaneous use within the same delivery method; Hindocha & McClure, 2020). Considering the high co-occurrence and associations with mental illness, there has been debate as to which, if any, has a more important role to play in the development of subsequent mental illness (Fergusson, Hall, Boden, & Horwood, 2015; Gage & Munafò, 2015). To our knowledge, few reviews examining psychological outcomes have considered evidence for *both* substances independently (Esmaelzadeh et al., 2018) or jointly (Peters, Budney, & Carroll, 2012; Ramo, Liu, & Prochaska, 2012; Sabe, Zhao, & Kaiser, 2020). These reviews have limitations such as synthesizing predominantly cross-sectional studies (Peters et al., 2012; Ramo et al., 2012), focusing on specific geographic regions or clinical populations (Esmaelzadeh et al., 2018; Sabe et al., 2020) and lack of quality and confounding assessment (Peters et al., 2012; Sabe et al., 2020).

As such, we aimed to synthesize longitudinal studies examining the association of cannabis and tobacco use with incident mental illness, with a focus on critically assessing biases that limit causal interpretation.

## Methods

We pre-registered our protocol on PROSPERO (CRD42021243903) and the Open Science Framework (<https://osf.io/5t2pu/>). We have followed PRISMA (Page et al., 2021) and MOOSE (Brooke, Schwartz, & Pawlik, 2021) reporting guidelines (online Supplementary eMethods 1), and described protocol changes in the online Supplementary materials (eMethods 2).

### Search strategy

We searched CINAHL, Embase, MEDLINE, PsycINFO, and ProQuest Dissertation and Theses from inception to November 2022. Searches were conducted using MeSH headings and text words relating to exposures, outcomes, and study design (online Supplementary eMethods 3). Supplementary searches were performed via forward and backward citation chasing, using the package *citationchaser* (Haddaway, Grainger, & Gray, 2021),

and contact with experts for unpublished data. Screening was completed independently by two authors (CB and AB/RL/KS). Discrepancies were resolved through discussion among the reviewers, or a third reviewer where necessary (GT).

### Eligibility criteria

We included prospective longitudinal studies that (1) measured cannabis, tobacco, or co-use as an exposure, (2) used a 'non-exposed' comparator group, and (3) reported a relevant effect estimate (e.g. RR) and its variance, or necessary raw data. There were no restrictions on publication status, article language, or publication date. To minimize reverse causation bias we only included studies where participants with current indications (i.e. total incidence) and/or history (i.e. first incidence) of the outcome were excluded at baseline. Studies were also excluded if participants were selected on a specific health status (e.g. pregnancy), or other highly selected characteristics (e.g. incarcerated persons). Corresponding authors were contacted, where possible, to request missing effect estimates or information relating to study inclusion. Full details are given in Table 1.

### Data extraction

Standardized forms were used to extract study information by two independent reviewers (CB and JL). A modified Newcastle-Ottawa Scale (NOS) was used to evaluate study quality (Wells et al., 2013). The NOS evaluates studies across selection of study groups, comparability, and outcome ascertainment, awarding a total of nine stars. Studies were rated as 'high' quality if scoring: (i) maximum on items relating to comparability (i.e. confounding bias); (ii) maximum on items relating to attrition (i.e. selection bias); and (iii) only scoring less than one star on all other items (online Supplementary eMethods 4). A standardized assessment sheet was used (CB) and calibrated with a second-rater (JL) for ~20% of the included studies, and disagreements raised with a third reviewer (GT). If studies reported multiple estimates the following estimates were extracted: (i) longest follow-up length; (ii) highest frequency of use; and (iii) adjusted for most confounding variables.

### Data synthesis

We used the RR and the corresponding 95% confidence intervals (95% CIs) as the summary estimate. Included studies presented varied effect estimates and approach for conversion to RR is described in the online Supplementary materials (eMethods 5). Adjusted and unadjusted/minimally adjusted (i.e. age and sex) effect estimates were pooled separately. Considering study heterogeneity, random-effects meta-analysis using generic inverse variance approach was conducted. Between-study heterogeneity was explored through visual inspection of forest plots and tau-squared ( $\tau^2$ ), and statistical inconsistency quantified using the  $I^2$  statistics (Higgins et al., 2020). Prediction Intervals (PIs) were also calculated, i.e. 95% range of true effect estimates to be expected in exchangeable studies (IntHout, Ioannidis, Rovers, & Goeman, 2016). Meta-analyses were conducted in R (v 4.4.1), using the 'meta' package (Schwarzer, 2022). Data and R scripts are available on GitHub (<https://github.com/chloeburke/tobcanmeta>).

**Table 1.** PECOS inclusion/exclusion criteria

|              |   |
|--------------|---|
| Population   | <ul style="list-style-type: none"> <li>• Broadly representative of general population</li> <li>• Can be selected on basic demographics (e.g. age, sex, ethnicity, occupation), but not eligible if comprised of persons with particular health characteristics (e.g. chronic condition) or other clinically relevant factors (e.g. pregnancy, incarcerated adults, 'high-risk')</li> </ul>  |
| Exposure     | <ul style="list-style-type: none"> <li>• Any measure of tobacco product use (e.g. current smoking, cigarettes per day [CPD]); excluding products not containing tobacco leaf (e.g. e-cigarettes)</li> <li>• Any measure of recreational cannabis use (e.g. current use, ever use, lifetime frequency)</li> <li>• Any measure of cannabis–tobacco co-use (e.g. concurrent use, co-administration)</li> </ul>   |
| Comparator   | <ul style="list-style-type: none"> <li>• Eligible comparators are: (1) 'non-exposed' (e.g. never use, non-use, past year non-use, non-regular use); (2) other eligible exposures (e.g. <i>exp</i> = co-use, <i>ref</i> = tobacco use)</li> <li>• Comparators of only lower frequency use groups (e.g. <math>\geq 20</math> CPD <i>v.</i> <math>\geq 10</math> CPD) or absence of problematic use (e.g. Cannabis Use Disorder [CUD] <i>v.</i> no CUD) are not eligible</li> </ul>  |
| Outcome      | <ul style="list-style-type: none"> <li>• Can be any mood, anxiety, or psychotic disorder except for substance-induced disorders (e.g. cannabis-induced psychotic disorder) and outcomes that <i>only</i> measure Obsessive Compulsive Disorder (OCD) or Post Traumatic Stress Disorder (PTSD)</li> <li>• Can be composite measures (e.g. 'any mood disorder') or specific conditions (e.g. depressive symptoms), but not eligible if combined across disorder groups (e.g. 'any mental illness')</li> <li>• Must be a binary measure of an <i>incident</i> condition (i.e. analysis/study excluded participants with a current/lifetime history of condition)</li> <li>• No limit on outcome measurement type, examples may include: self-rated scales, registry codes, interviews, self-reported diagnoses</li> <li>• Must have raw data necessary for meta-analysis or pre-calculated effect estimate (e.g. odds ratio, risk ratio, hazard ratio, incident rate ratio)</li> </ul> |
| Study design | <ul style="list-style-type: none"> <li>• Longitudinal design (cohort or nested case-control) and must collect and assess the exposure/outcome across multiple timepoints (i.e. retrospective recall not eligible)</li> <li>• Studies without original data (e.g. systematic reviews, commentaries) are excluded, and case-reports, case-series, interventional studies, qualitative studies, animal studies, and in-vitro studies are excluded</li> </ul>   |
| Other        | <ul style="list-style-type: none"> <li>• No limits on article publication status, year of publication, or language</li> </ul>   |

### Subgroup and sensitivity analyses

A combination of approaches was used to explore the impact of bias due to unmeasured confounding. The *E*-value represents the minimum strength of association, on an RR scale, an unmeasured confounder would need to have to fully explain a specific exposure–outcome association (i.e. fully reducing an RR to 1; VanderWeele & Ding, 2017). *E*-value calculation is described in the online Supplementary materials (eMethods 6). If the strength of suspected unmeasured confounding is weaker than indicated by the *E*-value, this suggests the exposure–outcome association is robust to unmeasured confounding (VanderWeele & Ding, 2017; VanderWeele, Ding, & Mathur, 2019). To assess the level of uncertainty associated with the effect, the *E*-value was also calculated for the CI closest to the null. There are no cut-offs for what constitutes a small or large *E*-value as it is context dependent, relative to the exposure, outcome, and measured covariates (VanderWeele et al., 2019). Therefore, we used a 'confounder matrix' assessment to establish measured covariates.

The confounder matrix is an approach to summarizing adequate confounding control in reviews of observational studies (Petersen et al., 2022), conducted in three steps: (1) expert consensus regarding necessary adjustment (e.g. constructs, measurement), (2) production of matrices to depict adjustment in each study, and (3) using assessment to inform quantitative synthesis (e.g. subgroup analyses). Based on a causal diagram (online Supplementary eMethods 7), studies in the primary meta-analyses were assessed on adjustment for seven constructs: co-use, other substance use, psychiatric comorbidity, socioeconomic status, sociodemographic factors, psychological factors, and other lifestyle factors. See online Supplementary eMethods 8 for description of constructs. The 'E-Value' online calculator (<https://www.evalue-calculator.com/>) and *metaconfoundr* package (Barrett, Petersen, & Trinquart, 2022) were used.

Where  $\geq 10$  studies were available, sources of heterogeneity in the primary analyses were explored through pre-planned subgroup analyses and meta-regressions (Higgins et al., 2020). Additional exploratory analyses were conducted through (i) excluding outliers, defined as point estimates where the 95% CI lies outside the 95% CI of the pooled effect, and (ii) subgroup analysis by rating on the confounder matrix assessment.

Potential small-study effects, such as publication bias, were examined using Doi plots and the Luis Furuya-Kanamori (LFK) index (Furuya-Kanamori, Barendregt, & Doi, 2018). Doi plots visualize treatment effects on the *x*-axis and a normal rank-based *Z*-score on the *y*-axis. LFK indices less than  $\pm 1$ , greater than  $\pm 1$  but less than  $\pm 2$ , or greater than  $\pm 2$  were considered to represent no, minor, or major asymmetry, respectively (Furuya-Kanamori et al., 2018).

## Results

### Search results

Of the 27789 records screened, 486 studies were retained for full-text screening (online Supplementary eFig. 1). Studies excluded at full-text stage are available in the online Supplementary materials (eTable 1). We identified 75 studies for inclusion (Albers & Biener, 2002; Almeida et al., 2013; An & Xiang, 2015; Armstrong et al., 2017; Bakhshaie, Zvolensky, & Goodwin, 2015; Beutel et al., 2019; Bolstad et al., 2022; Borges, Benjet, Orozco, & Medina-Mora, 2018; Bots, Tijhuis, Giampaoli, Kromhout, & Nissinen, 2008; Breslau, Peterson, Schultz, Chilcoat, & Andreski, 1998; Brown, Lewinsohn, Seeley, & Wagner, 1996; Cabello et al., 2017; Chang, Pan, Kawachi, & Okereke, 2016; Chin, Wan, Choi, Chan, & Lam, 2016; Chireh & D'Arcy, 2019; Choi, Patten, Gillin, Kaplan, & Pierce, 1997; Clark et al., 2007; Coughle, Hakes, Macatee, Chavarria, & Zvolensky, 2015; Cuijpers, Smit, Ten Have, & De Graaf, 2007; Danielsson, Lundin, Agardh, Allebeck, &

Forsell, 2016; do Nascimento et al., 2015; Feingold, Weiser, Rehm, & Lev-Ran, 2015, 2016; Flensburg-Madsen et al., 2011; Fonseca et al., 2022; Ford et al., 1998; Gage et al., 2015; Gentile, Bianco, Nordström, & Nordström, 2021; Goodman & Capitman, 2000; Goodwin et al., 2013; Groffen et al., 2013; Hahad et al., 2022; Hiles et al., 2015; Hoveling, Liefbroer, Scheweren, Bültmann, & Smidt, 2022; Isensee, Wittchen, Stein, Höfler, & Lieb, 2003; Jackson et al., 2019; Kang & Lee, 2010; Kendler, Lönn, Sundquist, & Sundquist, 2015; Kim, Kim, Lim, & Kim, 2022; King, Jones, Petersen, Hamilton, & Nazareth, 2021; Korhonen, Ranjit, Tuulio-Henriksson, & Kaprio, 2017; Lam et al., 2005; Leung, Gartner, Hall, Lucke, & Dobson, 2012; Luijendijk, Stricker, Hofman, Wittman, & Tiemeier, 2008; Manrique-Garcia, Zammit, Dalman, Hemmingsson, & Allebeck, 2012; Meng et al., 2017; Monroe, McDowell, Kenny, & Herring, 2021; Monshouwer, ten Have, de Graaf, Blankers, & van Laar, 2021; Murphy et al., 2003; Mustonen et al., 2018a, 2018b, 2021; Najafipour et al., 2021; Okkenhaug, Tanem, Myklebust, Gjervan, & Johansen, 2018; Park, 2009; Paton, Kessler, & Kandel, 1977; Raffetti, Donato, Forsell, & Galanti, 2019; Ren et al., 2021; Rognli, Bramness, & von Soest, 2020; Rudaz et al., 2017; Sánchez-Villegas et al., 2021; Storeng, Sund, & Krokstad, 2020; Tanaka, Sasazawa, Suzuki, Nakazawa, & Koyama, 2011; Tomita & Manuel, 2020; Tsai, Chi, & Wang, 2013; Van Laar, Van Dorsselaer, Monshouwer, & De Graaf, 2007; van Os et al., 2002; Weiser et al., 2004; Werneck et al., 2022; Weyerer et al., 2013; Zammit, Allebeck, Andreasson, Lundberg, & Lewis, 2002; Zammit et al., 2003; Zhang, Woud, Becker, & Margraf, 2018; Zimmerman, Mast, Miles, & Markides, 2009; Zvolensky et al., 2008) of which 59 were included in the primary meta-analyses of adjusted estimates. No eligible studies of cannabis-tobacco co-use were identified.

### Study characteristics

Studies included in the primary meta-analyses consisted of 1 733 679 participants at risk of incident outcomes. Follow-up length ranged from 6 months to 63 years. Exposures were measured according to heaviness (e.g. cigarettes per day;  $k=28$ ) or status of use (e.g. current use;  $k=31$ ). Outcomes were assessed using symptom-based scales ( $k=21$ ), interviews ( $k=18$ ), registry codes ( $k=14$ ), self-reported treatment/diagnosis ( $k=2$ ), and composites ( $k=4$ ). Study characteristics are presented in the online Supplementary materials (eTables 2–7).

### Meta-analysis

Tobacco use was associated with incident mood disorders ( $K=43$ ; RR: 1.39, 95% CI 1.30–1.47;  $I^2=61.2\%$ ;  $\tau^2=0.014$ ; PI: 1.08–1.77; Fig. 1) (Albers & Biener, 2002; An & Xiang, 2015; Armstrong et al., 2017; Bakhshaie et al., 2015; Bolstad et al., 2022; Borges et al., 2018; Breslau et al., 1998; Brown et al., 1996; Cabello et al., 2017; Chang et al., 2016; Chin et al., 2016; Chireh & D'Arcy, 2019; Choi et al., 1997; Clark et al., 2007; Cogle et al., 2015; Cuijpers et al., 2007; Flensburg-Madsen et al., 2011; Gage et al., 2015; Gentile et al., 2021; Goodman & Capitman, 2000; Groffen et al., 2013; Hahad et al., 2022; Hiles et al., 2015; Hoveling et al., 2022; Jackson et al., 2019; Kang & Lee, 2010; Korhonen et al., 2017; Leung et al., 2012; Luijendijk et al., 2008; Monroe et al., 2021; Monshouwer et al., 2021; Park, 2009; Raffetti et al., 2019; Ren et al., 2021; Rudaz et al., 2017; Sánchez-Villegas et al., 2021; Storeng et al., 2020; Tanaka et al.,

2011; Tomita & Manuel, 2020; Tsai et al., 2013; Werneck et al., 2022; Weyerer et al., 2013; Zhang et al., 2018).

Exclusion of outliers (An & Xiang, 2015; Flensburg-Madsen et al., 2011; Goodman & Capitman, 2000), produced similar results ( $K=40$ ; RR: 1.38, 95% CI 1.31–1.45). Pooled unadjusted studies yielded a larger estimate ( $K=41$ ; RR: 1.47, 95% CI 1.34–1.60; online Supplementary eFig. 2).

Tobacco use was not associated with incident anxiety disorders ( $K=7$ ; RR: 1.21, 95% CI 0.87–1.68;  $I^2=82.2\%$ ;  $\tau^2=0.143$ ; PI: 0.42–3.50; Fig. 2) (Cogle et al., 2015; Cuijpers et al., 2007; Gage et al., 2015; Hahad et al., 2022; Monroe et al., 2021; Monshouwer et al., 2021; Storeng et al., 2020). There were no identified outliers. Pooled unadjusted studies yielded a larger estimate ( $K=8$ ; RR: 1.60, 95% CI 1.10–2.32; online Supplementary eFig. 3).

Tobacco use was not associated with incident psychotic disorders ( $K=5$ ; RR: 2.06, 95% CI 0.98–4.29;  $I^2=92.3\%$ ;  $\tau^2=0.608$ ; PI: 0.13–32.26 (Kendler et al., 2015; King et al., 2021; Mustonen et al., 2018a; Weiser et al., 2004; Zammit et al., 2003). Exclusion of one outlier (Zammit et al., 2003) yielded a larger pooled estimate with CIs that did not include the null ( $K=4$ ; RR: 3.45, 95% CI 2.63–4.53). As outlier identification was exploratory, pooled results with and without the outlier excluded are presented (Fig. 2). Pooled unadjusted studies yielded a larger estimate ( $K=5$ ; RR: 3.12, 95% CI 1.67–5.81; online Supplementary eFig. 4).

Cannabis use was not associated with incident mood disorders ( $K=7$ ; RR: 1.31, 95% CI 0.92–1.86;  $I^2=77.0\%$ ;  $\tau^2=0.164$ ; PI: 0.42–4.09; Fig. 3) (Danielsson et al., 2016; Feingold et al., 2015; Gage et al., 2015; Manrique-Garcia et al., 2012; Mustonen et al., 2021; Rognli et al., 2020; Van Laar et al., 2007). There were no identified outliers. Pooled unadjusted studies yielded a larger estimate ( $K=7$ ; RR: 1.47, 95% CI 1.19–1.81; online Supplementary eFig. 5).

Cannabis use was not associated with incident anxiety disorders ( $K=7$ ; RR: 1.10, 95% CI 0.99–1.22;  $I^2=4.4\%$ ;  $\tau^2=0.002$ ; PI: 0.93–1.31; Fig. 3) (Danielsson et al., 2016; Feingold, Weiser, Rehm, & Lev-Ran, 2016; Gage et al., 2015; Mustonen et al., 2021; Rognli et al., 2020; Van Laar et al., 2007; Zvolensky et al., 2008). There were no identified outliers. Pooled unadjusted studies yielded a larger estimate ( $K=6$ ; RR: 1.51, 95% CI 1.20–1.89; online Supplementary eFig. 6).

Cannabis use was associated with incident psychotic disorders ( $K=4$ ; RR: 3.19, 95% CI 2.07–4.90;  $I^2=0\%$ ;  $\tau^2=0.00$ ; PI: 1.24–8.20; Fig. 3) (Mustonen et al., 2018b; Rognli et al., 2020; van Os et al., 2002; Zammit et al., 2002). There were no identified outliers. Pooled unadjusted studies yielded a larger estimate ( $K=3$ ; RR: 4.68, 95% CI 3.30–6.64; online Supplementary eFig. 7).

### Quality assessment

Of the 59 studies included in the adjusted meta-analyses, roughly one-quarter of studies (27%) were rated as high quality (i.e. lower risk of bias; online Supplementary eTable 8), with an overall mean score of 7.35 (s.d. 1.01). The proportion of high-quality studies differed by analysis (online Supplementary eTable 9). Many studies (58%) were marked down due to high attrition or insufficient information about loss to follow-up (e.g. differential attrition), and 41% of studies were marked down for 'comparability' (i.e. confounding bias).

### Subgroup and sensitivity analyses

Using the confounder matrix, most studies had multiple confounding constructs rated as inadequately adjusted for (Table 2, online

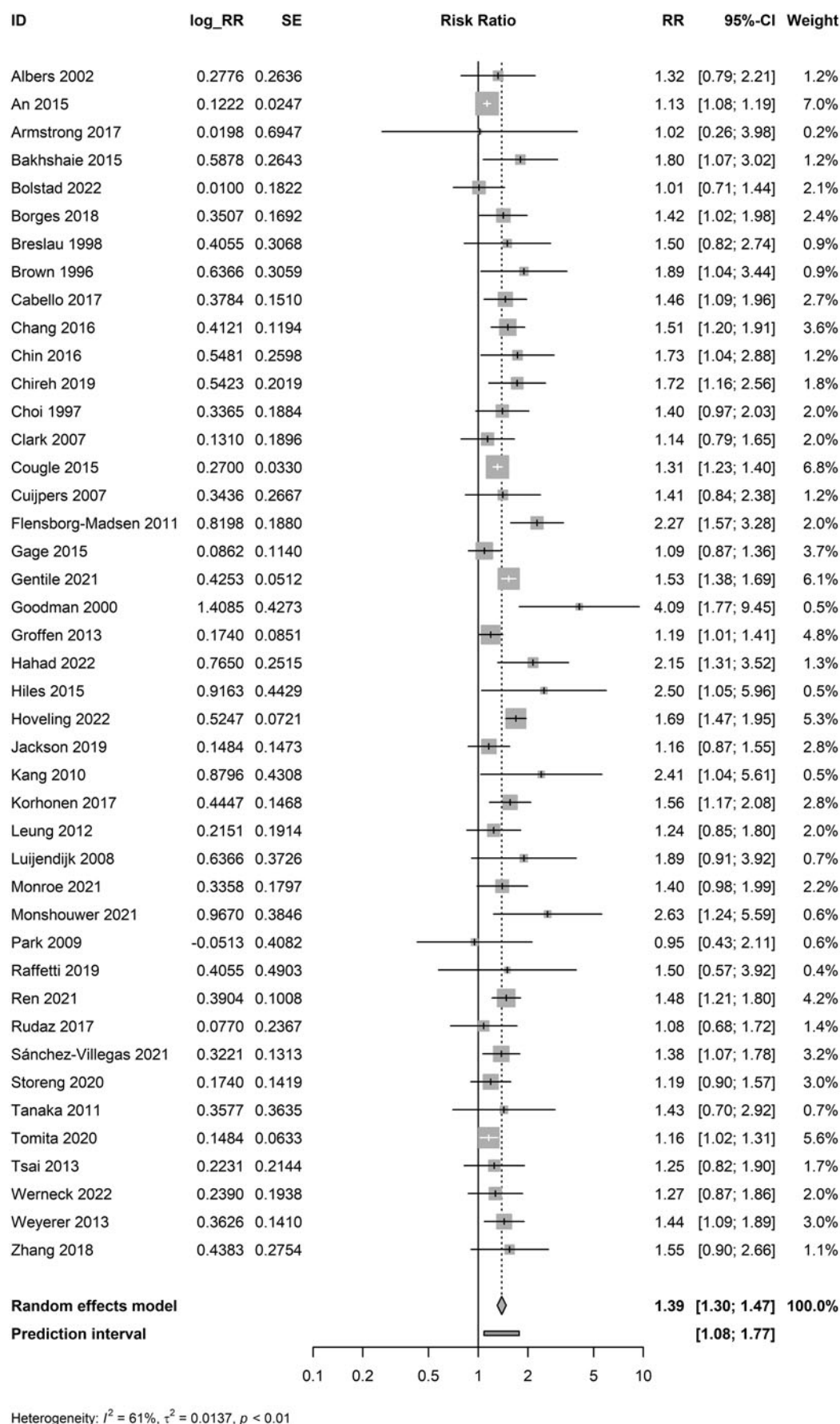
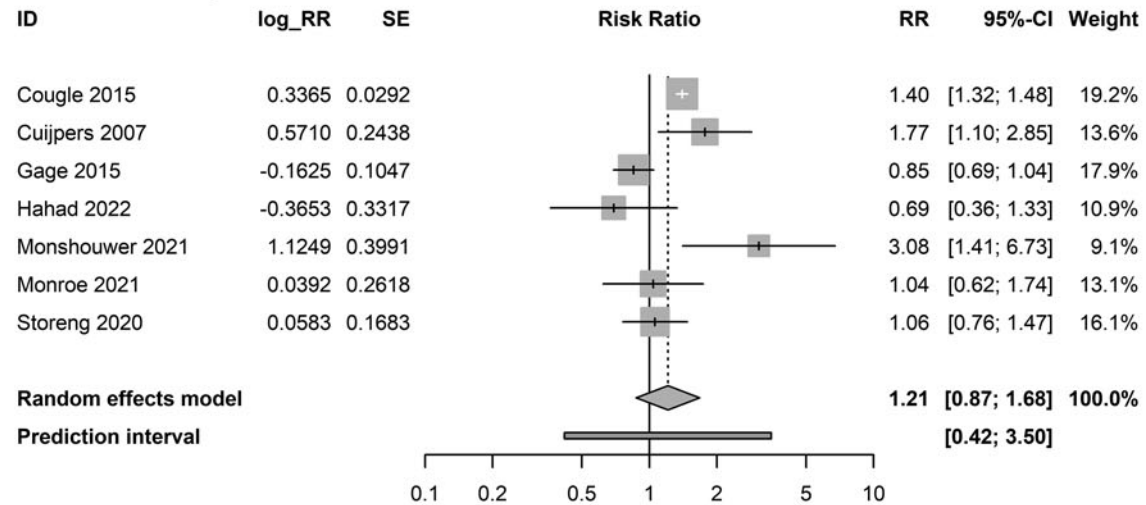


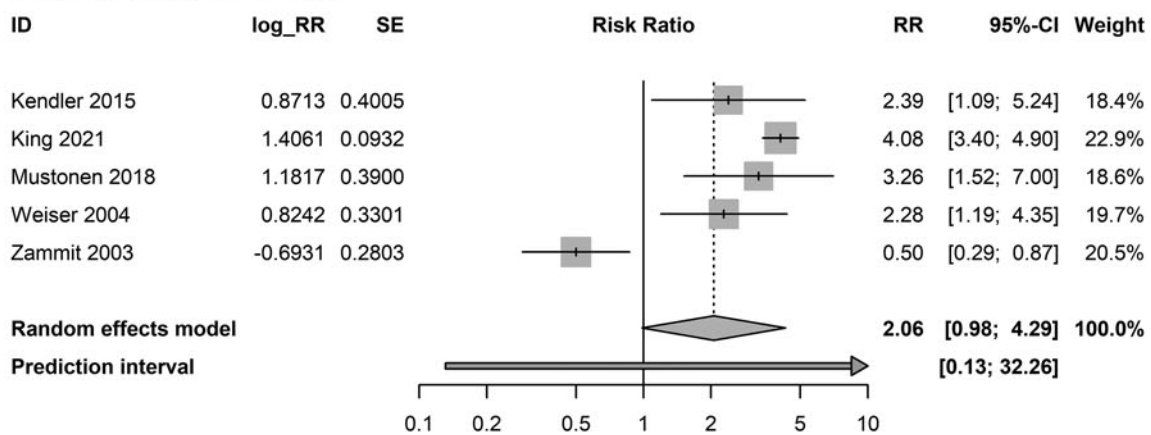
Figure 1. Meta-analysis of adjusted associations of tobacco use and mood disorders.

**Tobacco and Anxiety Disorders**



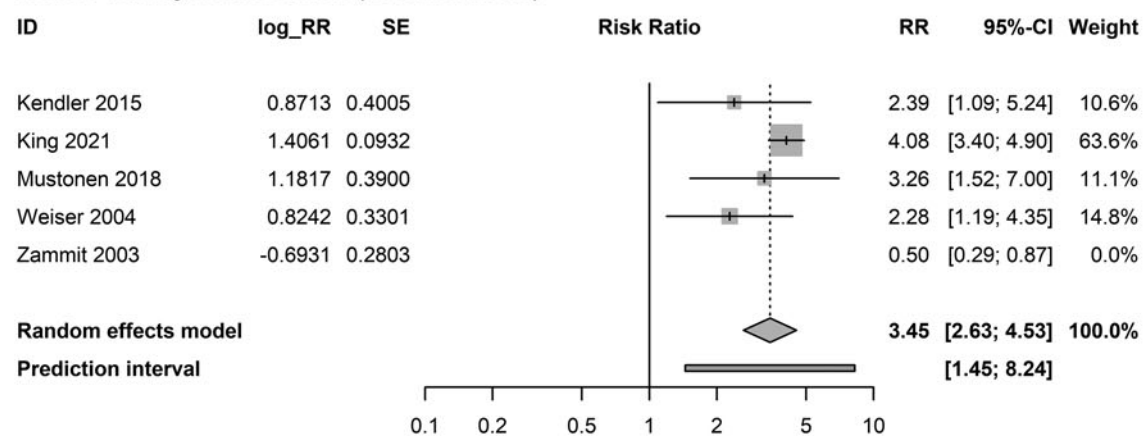
Heterogeneity:  $I^2 = 82\%$ ,  $\tau^2 = 0.1427$ ,  $p < 0.01$

**Tobacco and Psychotic Disorders**



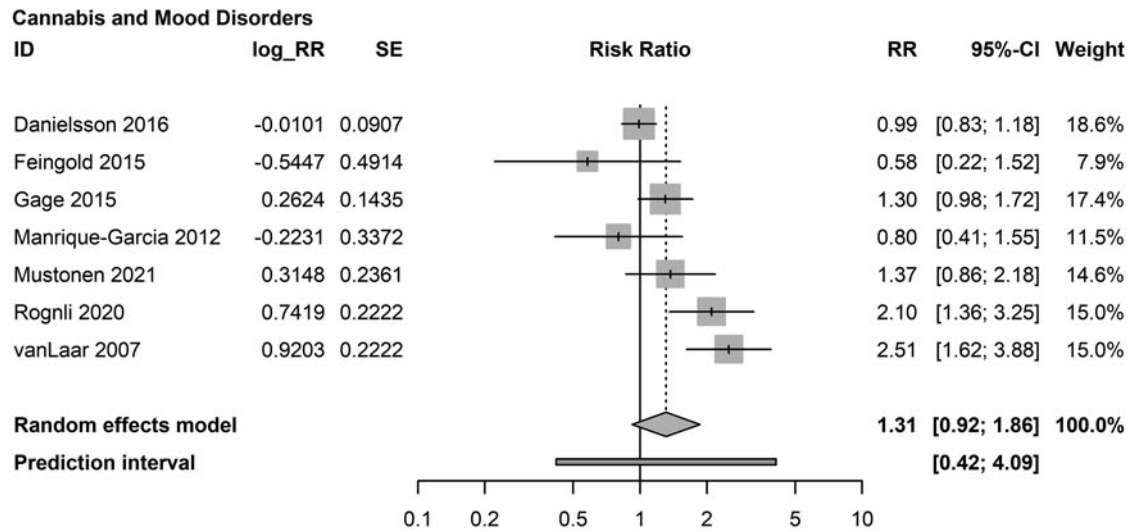
Heterogeneity:  $I^2 = 92\%$ ,  $\tau^2 = 0.6076$ ,  $p < 0.01$

**Tobacco and Psychotic Disorders (Outlier Removed)**

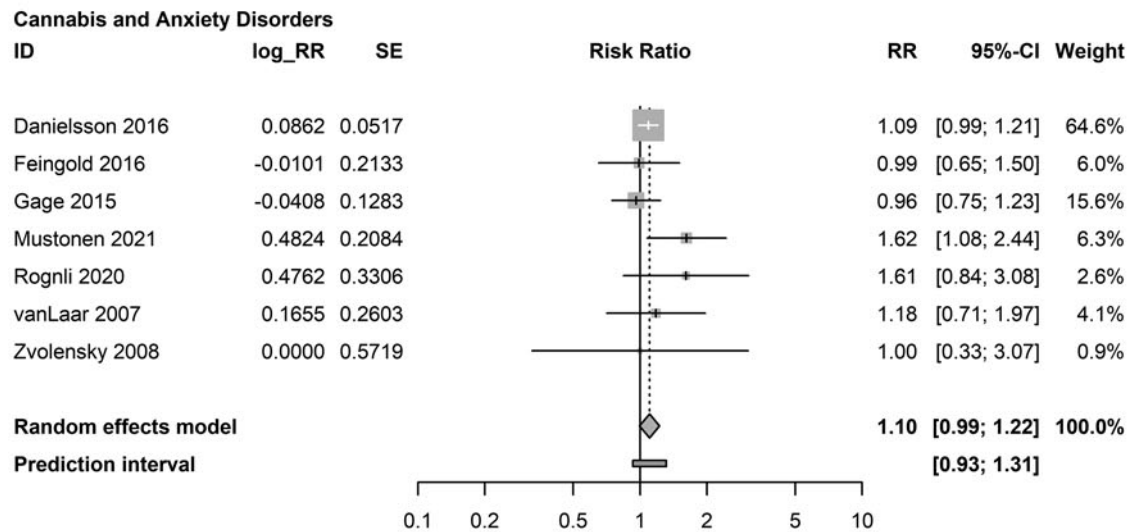


Heterogeneity:  $I^2 = 33\%$ ,  $\tau^2 = 0.0216$ ,  $p = 0.21$

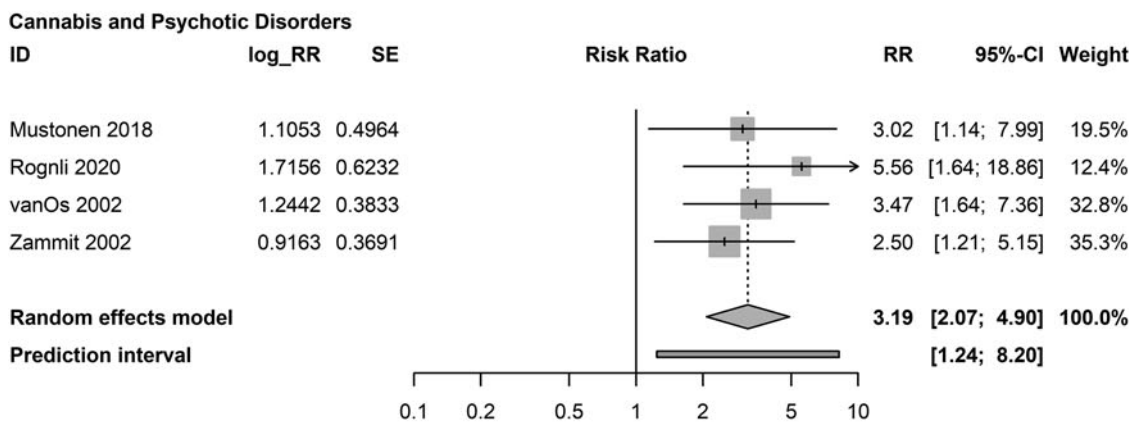
**Figure 2.** Meta-analyses of adjusted associations of tobacco use and anxiety and psychotic disorders.



Heterogeneity:  $I^2 = 77\%$ ,  $\tau^2 = 0.1641$ ,  $p < 0.01$



Heterogeneity:  $I^2 = 4\%$ ,  $\tau^2 = 0.0017$ ,  $p = 0.39$



Heterogeneity:  $I^2 = 0\%$ ,  $\tau^2 = 0$ ,  $p = 0.73$

Figure 3. Meta-analyses of adjusted associations of cannabis use and mood, anxiety and psychotic disorders.

Supplementary eTables 10–15, eFigs 8–13). Sociodemographic factors (e.g. age, sex) were generally well-adjusted for across all analyses. Psychological factors (e.g. loneliness, adverse childhood experiences [ACEs]) and psychiatric comorbidity were generally insufficiently controlled for with lower rates of adequate adjustment, particularly in tobacco and mood studies. There were differences in adjustment patterns across analyses, for example a higher proportion of cannabis studies (e.g. 100% of cannabis and mood studies) were rated as adequately adjusting for other substance use (i.e. alcohol use, illicit drug use), whereas co-use was more comprehensively adjusted for in tobacco studies as none of the included cannabis studies adjusted for confounding via co-administration of tobacco. Adjustment for other substance use by subconstructs (i.e. alcohol use, illicit drug use) is available in online Supplementary eTables 10–15. All cannabis studies were rated as inadequate adjustment for other lifestyle factors (e.g. physical activity, diet), with evidence of more adjustment in studies of tobacco and mood and anxiety disorders. Percentages of studies by adjustment rating for the different constructs are reported in Table 2, alongside median *E*-values for study point estimates and CIs. Median *E*-values for the point estimate ranged from 1.40 to 5.95.

As an example, the median *E*-value of the point estimate of the association of tobacco use and incident mood disorders was 2.21. This suggests if an omitted set of unmeasured confounders had an RR of 2.21 on both tobacco use and mood disorders, conditional on measured covariates, the association between tobacco use and mood disorders may be reduced to the null in half the studies. The same approach applies to the median *E*-value of the CI, i.e. if an omitted set of unmeasured confounders had an RR of 1.16 on both tobacco use and mood disorders, conditional on measured covariates, the association between tobacco use and mood disorders may be reduced to the null in half the studies.

Doi plots and LFK indices (online Supplementary eFigs 14–19) indicated major asymmetry in tobacco use and mood (LFK = 4.12) and psychotic disorders (LFK = -3.86). The remaining exposure–outcome analyses were indicated to have minor asymmetry (LFK = -1.68 to 1.89; Table 3), except for cannabis use and mood disorders (LFK = -0.59).

Subgroup and meta-regression analyses were only performed for tobacco use and mood disorders due to low study numbers ( $K < 10$ ) in other meta-analyses. Results were examined across age groups, follow-up length, sample size, study quality, confounding adjustment, and exposure/outcome types. The analyses did not support evidence of subgroup effects (online Supplementary eTables 16 and 17), including analyses by adequate adjustment for co-use and overall confounding adjustment. However, a far smaller number of studies contributed to some subgroups and there is substantial heterogeneity across the included studies, meaning results should be interpreted with caution (Richardson, Garner, & Donegan, 2019).

## Discussion

To our knowledge, this is the first systematic review and meta-analysis examining the association of tobacco use, cannabis use, and incident mental illness that has undertaken a comprehensive assessment of the influence of confounding bias. We found evidence for associations of tobacco and incident mood and psychotic disorders, and for cannabis and incident psychotic disorders. Our review includes the first meta-analysis of the longitudinal

association between tobacco use and incident anxiety disorders and addresses limitations of previous reviews which have considered evidence for both substances and psychological outcomes.

Accurately understanding the causal effects of substance use on mental illness is crucial to informing effective evidence-based public health policies (Taylor & Treur, 2023). Results from this review are based on observational evidence and cannot in isolation be considered proof of causality. However, this study contributes toward a wider, growing body of evidence across multiple study designs (e.g. Mendelian randomization [MR], smoking cessation trials) that these substances have a causal role in development of psychotic disorders, and tobacco use in mood disorders (Firth, Wootton, Sawyer, & Taylor, 2023; Ganesh & D'Souza, 2022; Munafò, 2022).

We did not find compelling evidence to suggest tobacco use is associated with incident anxiety disorders. Previous narrative syntheses report mixed evidence of associations between tobacco use and later anxiety (Fluharty et al., 2017; Stevenson et al., 2022). The effect size observed in the analysis of tobacco use and mood disorders is consistent with previous meta-analyses (Chaiton et al., 2009; Chaplin et al., 2023; Esmaelzadeh et al., 2018; Luger et al., 2014). Although there was considerable methodological heterogeneity present across studies, tests for subgroup differences did not indicate any significant differences. Importantly, non-significant subgroup tests do not automatically imply equivalent results. If there is substantial between-study heterogeneity within the subgroup this will decrease the precision of the pooled effect, and mean CIs are more likely to overlap such that specific subgroup effects may be affected by other sources of heterogeneity across the review (Harrer, Cuijpers, Furukawa, & Ebert, 2021; Richardson et al., 2019).

Our analyses of cannabis use and subsequent mood and anxiety disorders did not support evidence of an increased risk in the cannabis use *v.* non-use groups. Several previous meta-analyses have reported mixed evidence of associations between cannabis use and anxiety symptoms or disorder (Hall, Leung, & Lynskey, 2020), and multiple meta-analyses of prospective studies report a modest association between cannabis use and depressive symptoms or disorder (Hall et al., 2020). Three previous meta-analyses of prospective studies, adjusting for baseline depression, report modest associations (odds ratio [OR] range: 1.17–1.37; Esmaelzadeh et al., 2018; Gobbi et al., 2019; Lev-Ran et al., 2014) between cannabis use and subsequent depression. It is possible that examining incident outcomes (*v.* statistical adjustment) could explain the discrepancy in findings, but may also relate to other differences in review content (e.g. adolescents only, more studies). Recent reviews focusing on studies of cannabis frequency and potency suggest that more frequent use (Robinson et al., 2023) and higher-potency cannabis (Petrilli et al., 2022) poses greater risk. However, due to limited study numbers and measurements, it was not possible to investigate this.

In line with other meta-analyses, this study reported evidence of a strong association between both substances and psychotic disorders (Gurillo et al., 2015; Hunter et al., 2020; Marconi et al., 2016; Moore et al., 2007; Myles et al., 2012; Robinson et al., 2023). Considerable uncertainty regarding the size of the association was indicated by CIs and PIs. 'Noisy' effect estimates are common in the case of rare outcomes, due to lower statistical power. Pooling these effects in a meta-analysis can yield more precise estimates, but this review included few studies. This is likely related to the exclusion of traditional case-control designs. Although well suited to the study of rare outcomes, they are at



**Table 2.** E-value and confounder matrix summary

|  | Confounder summary matrix <sup>a</sup> |                     |                         |                           |                       |                       |                         | Median E-value <sup>b</sup> |      |
|--|--|---------------------|-------------------------|---------------------------|-----------------------|-----------------------|-------------------------|-----------------------------|------|
|  | Co-use                                 | Other substance use | Psychiatric comorbidity | Socio-demographic factors | Socio-economic status | Psychological factors | Other lifestyle factors | Point estimate              | CI   |
| Tobacco and mood ( <i>K</i> = 43)      |  |                     |                         |                           |                       |                       |                         |                             |      |
| Adequate                               | 63%                                    | 49%                 | 7%                      | 65%                       | 47%                   | 26%                   | 44%                     | 2.21                        | 1.16 |
| Concerns                               | 0%                                     | 23%                 | 19%                     | 30%                       | 33%                   | 30%                   | 21%                     |                             |      |
| Inadequate                             | 37%                                    | 28%                 | 74%                     | 5%                        | 21%                   | 44%                   | 35%                     |                             |      |
| Tobacco and anxiety ( <i>K</i> = 7)    |  |                     |                         |                           |                       |                       |                         |                             |      |
| Adequate                               | 86%                                    | 57%                 | 29%                     | 86%                       | 57%                   | 43%                   | 57%                     | 2.15                        | 1.00 |
| Concerns                               | 0%                                     | 14%                 | 43%                     | 14%                       | 43%                   | 29%                   | 14%                     |                             |      |
| Inadequate                             | 14%                                    | 29%                 | 29%                     | 0%                        | 0%                    | 29%                   | 29%                     |                             |      |
| Tobacco and psychosis ( <i>K</i> = 5)  |  |                     |                         |                           |                       |                       |                         |                             |      |
| Adequate                               | 60%                                    | 20%                 | 40%                     | 20%                       | 80%                   | 40%                   | 0%                      | 4.21                        | 1.67 |
| Concerns                               | 0%                                     | 40%                 | 0%                      | 40%                       | 0%                    | 20%                   | 0%                      |                             |      |
| Inadequate                             | 40%                                    | 40%                 | 60%                     | 40%                       | 20%                   | 40%                   | 100%                    |                             |      |
| Cannabis and mood ( <i>K</i> = 7)      |  |                     |                         |                           |                       |                       |                         |                             |      |
| Adequate                               | 0%                                     | 100%                | 43%                     | 86%                       | 43%                   | 57%                   | 0%                      | 2.08                        | 1.00 |
| Concerns                               | 57%                                    | 0%                  | 57%                     | 14%                       | 43%                   | 29%                   | 0%                      |                             |      |
| Inadequate                             | 43%                                    | 0%                  | 0%                      | 0%                        | 14%                   | 14%                   | 100%                    |                             |      |
| Cannabis and anxiety ( <i>K</i> = 7)   |  |                     |                         |                           |                       |                       |                         |                             |      |
| Adequate                               | 0%                                     | 86%                 | 43%                     | 71%                       | 43%                   | 43%                   | 0%                      | 1.40                        | 1.00 |
| Concerns                               | 57%                                    | 14%                 | 43%                     | 14%                       | 29%                   | 29%                   | 0%                      |                             |      |
| Inadequate                             | 43%                                    | 0%                  | 14%                     | 14%                       | 29%                   | 29%                   | 100%                    |                             |      |
| Cannabis and psychosis ( <i>K</i> = 4) |  |                     |                         |                           |                       |                       |                         |                             |      |
| Adequate                               | 0%                                     | 50%                 | 50%                     | 75%                       | 0%                    | 25%                   | 0%                      | 5.95                        | 1.20 |
| Concerns                               | 75%                                    | 25%                 | 0%                      | 0%                        | 50%                   | 75%                   | 0%                      |                             |      |
| Inadequate                             | 25%                                    | 25%                 | 50%                     | 25%                       | 50%                   | 0%                    | 100%                    |                             |      |

Note. <sup>a</sup>Percentages denote the proportion of studies in the adjusted meta-analyses that were rated as 'adequate', 'some concerns', or 'inadequate' for the different constructs and assessment criteria for different constructs is detailed in online Supplementary eMethods 8; briefly: co-use (i.e. adjustment for cannabis/tobacco use); other substance use (i.e. adjustment for alcohol use and illicit drug use); psychiatric comorbidity (i.e. adjustment for other mental health condition(s) at baseline); sociodemographic factors (i.e. adjustment for age, sex and ethnicity, urbanicity, or marital status); socioeconomic status (i.e. adjustment for combination of indicators like education and income, or index of socioeconomic status); psychological factors (i.e. adjustment for two factors from varied list including loneliness, adverse childhood experiences, IQ, and stressful life events); other lifestyle factors (i.e. adjustment for two factors from physical activity, health conditions, adiposity, and diet). <sup>b</sup>The E-value represents the minimum strength of association, on the RR scale, that an unmeasured confounder would need to have with both the exposure and the outcome to fully explain away a specific exposure–outcome association, conditional on the measured covariates. This interpretation applies to the point estimate and the lower CI. Generally, a larger E-value implies that considerable unmeasured confounding would be needed to explain away an effect estimate. Generally, a smaller E-value implies little unmeasured confounding would be needed to explain away an effect estimate. For more information see online Supplementary eMethods 6.

**Table 3.** LFK index and asymmetry rating for primary meta-analyses

| Exposure | Outcome   | K  | LFK index score | Asymmetry rating <sup>a</sup> |
|----------|-----------|----|-----------------|-------------------------------|
| Tobacco  | Mood      | 43 | 4.12            | Major                         |
| Tobacco  | Anxiety   | 7  | -1.68           | Minor                         |
| Tobacco  | Psychosis | 5  | -3.86           | Major                         |
| Cannabis | Mood      | 7  | -0.59           | No asymmetry                  |
| Cannabis | Anxiety   | 7  | 1.89            | Minor                         |
| Cannabis | Psychosis | 4  | 1.73            | Minor                         |

Note. K, number of studies included in meta-analysis.

<sup>a</sup>LFK index scores of  $\pm 1$ , between  $\pm 1$  and  $\pm 2$ , or  $\pm 2$  indicate 'no asymmetry', 'minor asymmetry', and 'major asymmetry' respectively.

increased risk of recall bias and reverse causation (Rothman, Lash, VanderWeele, & Haneuse, 2021). Lack of prospective research in this area has been highlighted (Quigley & MacCabe, 2019; Sideli, Quigley, La Cascia, & Murray, 2020).

We did not identify any eligible studies of cannabis–tobacco co-use. Assuming causality, dual use may place consumers at a higher risk of developing a mental health condition than independent use of either substance. There is a handful of cross-sectional studies which indicate people who co-use have a higher prevalence of mental health disorders (Hindocha, Brose, Walsh, & Cheeseman, 2020; Peters, Schwartz, Wang, O'Grady, & Blanco, 2014) and levels of psychological distress (Wang, Yao, Sung, & Max, 2022). Some longitudinal evidence suggests co-use is associated with greater mental health symptoms (Tucker et al., 2019), but prospective evidence is lacking.

While adjustment for other substance use (i.e. alcohol use, illicit drug use) was often applied, adjustment for co-use was mixed and none of the included cannabis use studies measured or adjusted for tobacco co-administration. Although degree of confounding bias will differ at a population-level across countries due to international differences in co-administration prevalence (e.g. Europe v. America; Hindocha, Freeman, Ferris, Lynskey, & Winstock, 2016), this remains an important source of information to collect and adjust for within individual cohorts as people who co-administer cannabis with tobacco (e.g. blunts, spliffs) will frequently self-report to be non-smokers (Hindocha & McClure, 2020).

Analyses of small-study effects suggested possible risk of publication bias, with evidence of asymmetry for most meta-analyses. As such, pooled estimates may misrepresent the 'true' association. However, asymmetry can be driven by multiple factors (e.g. methodological heterogeneity) and may not represent publication bias (Sterne & Harbord, 2004). Furthermore, although Doi plots have advantages over traditional funnel plots in detecting asymmetry with few studies ( $K < 10$ ), they may still misrepresent asymmetry (Furuya-Kanamori et al., 2018).

E-values and confounder matrix assessment suggested that many studies were at risk of confounding bias. Studies often inadequately adjusted for key confounding variables (e.g. ACEs). Previous reviews of these exposures have demonstrated moderate-strong adjusted associations with substance use and mental health outcomes (e.g. ACEs:  $OR_{Smoking}$  2.82,  $OR_{Depression}$  4.40; Hughes et al., 2017). Furthermore, none of the study estimates adjusted for genetic vulnerability which alternative study designs (e.g. familial-based designs) suggest may play a substantial role in the

observed associations (Barkhuizen, Taylor, Freeman, & Ronald, 2019; Ranjit et al., 2019; Schaefer et al., 2021). E-values must be interpreted considering some key assumptions and limitations (VanderWeele, 2022; VanderWeele et al., 2019). Importantly, adjustment for some measured covariates (e.g. socioeconomic status) likely reduces bias from some unmeasured confounding (e.g. ACEs) due to associations between these constructs. The E-value is also conservative (i.e. overestimates bias), insofar as it assumes the distribution of the unmeasured confounder(s) is as unfavorable as possible (VanderWeele et al., 2019). Nonetheless, the smaller E-values observed for some estimates (i.e. tobacco/mood) in the presence of multiple unmeasured confounders suggests that the pooled estimates likely overestimate the effect size.

Although unmeasured confounding was a focus of this review, many studies were also limited by inadequate description of attrition or individual-level missing data and few used methods to account for this (e.g. multiple imputation). This contradicts recommendations by relevant reporting guidelines (e.g. STROBE; Vandenbroucke et al., 2007), and hinders assessment of selection bias. Future studies aiming to explore causal effects must provide more detailed descriptions of missing data and apply appropriate methods to reduce bias (VanderWeele, 2021). Furthermore, although we focused on incident outcomes in prospective studies this does not exclude risk of bias from reverse causation. Many mental disorders do not have discrete onsets, and there are challenges to accurately defining incidence including subthreshold or prodromal symptoms at baseline (Patten, 2021) and diagnostic lag (e.g. in studies using registry data). As such, to support the identification of causal effects, there is the need for further research focusing on addressing and exploring the biases that arise in conventional observational studies.

MR is one such method, which uses genetic variation as an instrumental variable for an exposure to estimate causal effects that are more robust to reverse causality and confounding bias (Davies, Holmes, & Smith, 2018). Reviews of MR studies investigating substance use and mental health suggest evidence to support a bi-directional, increasing relationship between smoking and depression, bipolar disorder and schizophrenia (Treur, Munafò, Logtenberg, Wiers, & Verweij, 2021). Evidence regarding cannabis use and mental health is less conclusive, which may relate to historical lack of frequency instruments (Hines, Treur, Jones, Sallis, & Munafò, 2020; Treur et al., 2021). However, MR is 'far from a silver bullet' (Wootton, Jones, & Sallis, 2022) with limitations to be addressed through more advanced methods (e.g. multivariable MR), additional sensitivity tests (e.g. residual population stratification), and incorporation into planned triangulation frameworks (Hammerton & Munafò, 2021), including triangulation with carefully planned longitudinal cohort analyses (Hammerton & Munafò, 2021; Treur et al., 2021). Widespread adoption of DAGs when selecting secondary data sources may yield insights as to whether research questions are feasibly explored within datasets (VanderWeele et al., 2019). Alongside the need for well-controlled longitudinal studies, more evidence using alternative study designs is required as meta-analyses of the same study design may amplify inherent biases.

### Limitations

Several important limitations need to be considered. All studies used self-report to define exposure status. This is not unusual in large, population-based cohort studies but will result in measurement error that can bias effect estimates in the case of both

differential and non-differential misclassification. Similarly, we included studies which used symptom-based scales, self-reported diagnosis, and resource access (e.g. medication) which will introduce further measurement error. Most studies were based in high-income countries and to reduce sources of heterogeneity we restricted the review to include a specific type of study design (i.e. prospective, incident outcomes) conducted in general population samples. This does not capture all evidence regarding the link between substance use and mental illness, such as evidence that cannabis and tobacco use may impair treatment outcomes in people with mental health conditions (Asharani & Subramaniam, 2022; Reid & Bhattacharyya, 2019; Sideli et al., 2020; Tourjman et al., 2023) and increased risk in people with underlying risk factors (e.g. ultra-high risk for psychosis; Andreou et al., 2023). Understanding the causal effect of these substances on mental health in vulnerable groups is essential for designing targeted interventions and addressing existing health inequalities. The number of studies included in most meta-analyses was low and prevented planned explorations of heterogeneity, which is recommended for syntheses of non-randomized studies (Egger, Higgins, & Smith, 2022). Finally, analyzing overarching diagnostic groups (e.g. mood disorders) may overlook relevant differences for individual disorders (e.g. bipolar disorder) which will be important to consider in exploring possible causal mechanisms (e.g. neuroadaptations in nicotinic pathways; Firth et al., 2023).

## Conclusion

This review and meta-analysis presents evidence for longitudinal associations between both substances and incident psychotic disorders, and tobacco use and incident mood disorders. In contrast to previous meta-analyses, there was no clear evidence to support an association between cannabis use and incident mood or anxiety disorders. Existing evidence across all outcomes was limited by inadequate adjustment for potential confounders. Future research should prioritize approaches supporting stronger causal inference, such as evidence triangulation.

**Supplementary material.** The supplementary material for this article can be found at <https://doi.org/10.1017/S0033291724002587>.

**Data availability statement.** Data and R code for the analyses included in this study have been provided online at <https://github.com/chloeoburke/tobcanmeta>.

**Acknowledgments.** We thank the patient and public involvement (PPI) members that were involved in providing helpful feedback on the draft study protocol. The authors wish to thank J. Hartmann-Boyce for assistance provided in developing the study protocol.

**Author contributions.** C. B., T. P. F., H. S., R. E. W., and G. M. J. T. formulated the review protocol and search strategy. C. B. performed the database and supplementary searches. C. B., A. B., K. S., and R. L. independently screened and selected studies. C. B. and G. M. J. T. resolved any outstanding disagreements about eligibility of studies or study information. C. B. and J. L. independently performed data extraction, including risk of bias. C. B. drafted the manuscript, performed statistical analysis, and prepared figures and tables. C. B. and G. M. J. T. reviewed all data and statistical analyses. All authors reviewed the study findings, read, and approved the final version of the manuscript, and had the responsibility for the decision to submit the manuscript for publication.

**Funding statement.** This work was supported by a Ph.D. studentship awarded to C. B. by the Society for the Study of Addiction. The funder of the

study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit the article for publication.

**Competing interests.** G. M. J. T. has previously received funding from Grand (Pfizer) for work not related to this project. C. B., H. S., and R. E. W. have completed paid consultancy work for Action on Smoking and Health (ASH) for work related to this project. The remaining authors have no relevant competing interests to declare.

**Ethical standards.** As this was a review paper, no ethical approval was required.

## References

- Agrawal, A., Budney, A. J., & Lynskey, M. T. (2012). The co-occurring use and misuse of cannabis and tobacco: A review. *Addiction*, 107(7), 1221–1233. doi:10.1111/j.1360-0443.2012.03837.x
- Albers, A. B., & Biener, L. (2002). The role of smoking and rebelliousness in the development of depressive symptoms among a cohort of Massachusetts adolescents. *Preventive Medicine*, 34(6), 625–631. doi:10.1006/pmed.2002.1029
- Almeida, O. P., Hankey, G. J., Yeap, B. B., Golledge, J., McCaul, K., & Flicker, L. (2013). A risk table to assist health practitioners assess and prevent the onset of depression in later life. *Preventive Medicine*, 57(6), 878–882. doi:10.1016/j.ypmed.2013.09.021
- An, R., & Xiang, X. (2015). Smoking, heavy drinking, and depression among U.S. middle-aged and older adults. *Preventive Medicine*, 81, 295–302. doi:10.1016/j.ypmed.2015.09.026
- Andreou, C., Eickhoff, S., Heide, M., de Bock, R., Obleser, J., & Borgwardt, S. (2023). Predictors of transition in patients with clinical high risk for psychosis: An umbrella review. *Translational Psychiatry*, 13(1), 1–11. doi:10.1038/s41398-023-02586-0
- Arango, C., Dragioti, E., Solmi, M., Cortese, S., Domschke, K., Murray, R. M., ... Fusar-Poli, P. (2021). Risk and protective factors for mental disorders beyond genetics: An evidence-based atlas. *World Psychiatry*, 20(3), 417–436. doi:10.1002/wps.20894
- Armstrong, N. M., Meoni, L. A., Carlson, M. C., Xue, Q.-L., Bandeen-Roche, K., Gallo, J. J., & Gross, A. L. (2017). Cardiovascular risk factors and risk of incident depression throughout adulthood among men: The Johns Hopkins Precursors Study. *Journal of Affective Disorders*, 214, 60–66. doi:10.1016/j.jad.2017.03.004
- Asharani, P. V., & Subramaniam, M. (2022). Mental illness and tobacco usage. In V. B. Patel & V. R. Preedy (Eds.), *Handbook of substance misuse and addictions: From biology to public health* (pp. 775–800). Cham: Springer International Publishing. doi:10.1007/978-3-030-92392-1\_41
- Bakhshaie, J., Zvolensky, M. J., & Goodwin, R. D. (2015). Cigarette smoking and the onset and persistence of depression among adults in the United States: 1994–2005. *Comprehensive Psychiatry*, 60, 142–148. doi:10.1016/j.comppsy.2014.10.012
- Barkhuizen, W., Taylor, M. J., Freeman, D., & Ronald, A. (2019). A twin study on the association between psychotic experiences and tobacco use during adolescence. *Journal of the American Academy of Child & Adolescent Psychiatry*, 58(2), 267–276.e8. doi:10.1016/j.jaac.2018.06.037
- Barrett, M., Petersen, J. M., & Trinquart, L. (2022). metaconfounder: Visualize ‘Confounder’ Control in Meta-Analyses. Retrieved from <https://CRAN.R-project.org/package=metaconfounder>
- Beutel, M. E., Brähler, E., Wiltink, J., Kerahrodi, J. G., Burghardt, J., Michal, M., ... Tibubos, A. N. (2019). New onset of depression in aging women and men: Contributions of social, psychological, behavioral, and somatic predictors in the community. *Psychological Medicine*, 49(7), 1148–1155. doi:10.1017/S0033291718001848
- Bolstad, I., Alakokkare, A.-E., Bramness, J. G., Rognli, E. B., Levola, J., Mustonen, A., ... Niemelä, S. (2022). The relationships between use of alcohol, tobacco and coffee in adolescence and mood disorders in adulthood. *Acta Psychiatrica Scandinavica*, 146(6), 594–603. doi:10.1111/acps.13506
- Borges, G., Benjet, C., Orozco, R., & Medina-Mora, M. E. (2018). A longitudinal study of reciprocal risk between mental and substance use disorders

- among Mexican youth. *Journal of Psychiatric Research*, 105, 45–53. doi:10.1016/j.jpsychires.2018.08.014
- Bots, S., Tjihuis, M., Giampaoli, S., Kromhout, D., & Nissinen, A. (2008). Lifestyle- and diet-related factors in late-life depression – A 5-year follow-up of elderly European men: The FINE study. *International Journal of Geriatric Psychiatry*, 23(5), 478–484. doi:10.1002/gps.1919
- Breslau, N., Peterson, E. L., Schultz, L. R., Chilcoat, H. D., & Andreski, P. (1998). Major depression and stages of smoking: A longitudinal investigation. *Archives of General Psychiatry*, 55(2), 161–166. doi:10.1001/archpsyc.55.2.161
- Brooke, B. S., Schwartz, T. A., & Pawlik, T. M. (2021). MOOSE reporting guidelines for meta-analyses of observational studies. *JAMA Surgery*, 156(8), 787–788. doi:10.1001/jamasurg.2021.0522
- Brown, R. A., Lewinsohn, P. M., Seeley, J. R., & Wagner, E. F. (1996). Cigarette smoking, major depression, and other psychiatric disorders among adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry*, 35(12), 1602–1610. doi:10.1097/00004583-199612000-00011
- Cabello, M., Miret, M., Caballero, F. F., Chatterji, S., Naidoo, N., Kowal, P., ... Ayuso-Mateos, J. L. (2017). The role of unhealthy lifestyles in the incidence and persistence of depression: A longitudinal general population study in four emerging countries. *Globalization and Health*, 13(1), 18. doi:10.1186/s12992-017-0237-5
- Chaiton, M. O., Cohen, J. E., O'Loughlin, J., & Rehm, J. (2009). A systematic review of longitudinal studies on the association between depression and smoking in adolescents. *BMC Public Health*, 9, 356. doi:10.1186/1471-2458-9-356
- Chang, S.-C., Pan, A., Kawachi, I., & Okereke, O. I. (2016). Risk factors for late-life depression: A prospective cohort study among older women. *Preventive Medicine*, 91, 144–151. doi:10.1016/j.ypmed.2016.08.014
- Chaplin, A. B., Daniels, N. F., Ples, D., Anderson, R. Z., Gregory-Jones, A., Jones, P. B., & Khandaker, G. M. (2023). Longitudinal association between cardiovascular risk factors and depression in young people: A systematic review and meta-analysis of cohort studies. *Psychological Medicine*, 53(3), 1049–1059. doi:10.1017/S0033291721002488
- Chin, W.-Y., Wan, E. Y. F., Choi, E. P. H., Chan, K. T. Y., & Lam, C. L. K. (2016). The 12-month incidence and predictors of PHQ-9 – Screened depressive symptoms in Chinese primary care patients. *The Annals of Family Medicine*, 14(1), 47–53. doi:10.1370/afm.1854
- Chireh, B., & D'Arcy, C. (2019). Shared and unique risk factors for depression and diabetes mellitus in a longitudinal study, implications for prevention: An analysis of a longitudinal population sample aged ≥45 years. *Therapeutic Advances in Endocrinology and Metabolism*, 10, 2042018819865828. doi:10.1177/2042018819865828
- Choi, W. S., Patten, C. A., Gillin, J. C., Kaplan, R. M., & Pierce, J. P. (1997). Cigarette smoking predicts development of depressive symptoms among U.S. adolescents. *Annals of Behavioral Medicine*, 19(1), 42–50. doi:10.1007/BF02883426
- Clark, C., Haines, M. M., Head, J., Klineberg, E., Arephin, M., Viner, R., ... Stansfeld, S. A. (2007). Psychological symptoms and physical health and health behaviours in adolescents: A prospective 2-year study in East London. *Addiction*, 102(1), 126–135. doi:10.1111/j.1360-0443.2006.01621.x
- Cogle, J. R., Hakes, J. K., Macatee, R. J., Chavarria, J., & Zvolensky, M. J. (2015). Quality of life and risk of psychiatric disorders among regular users of alcohol, nicotine, and cannabis: An analysis of the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). *Journal of Psychiatric Research*, 66–67, 135–141. doi:10.1016/j.jpsychires.2015.05.004
- Cuijpers, P., Smit, F., Ten Have, M., & De Graaf, R. (2007). Smoking is associated with first-ever incidence of mental disorders: A prospective population-based study. *Addiction*, 102(8), 1303–1309. doi:10.1111/j.1360-0443.2007.01885.x
- D'Agostino McGowan, L. (2022). Sensitivity analyses for unmeasured confounders. *Current Epidemiology Reports*, 9(4), 361–375. doi:10.1007/s40471-022-00308-6
- Danielsson, A.-K., Lundin, A., Agardh, E., Allebeck, P., & Forsell, Y. (2016). Cannabis use, depression and anxiety: A 3-year prospective population-based study. *Journal of Affective Disorders*, 193, 103–108. doi:10.1016/j.jad.2015.12.045
- Davies, N. M., Holmes, M. V., & Smith, G. D. (2018). Reading Mendelian randomisation studies: A guide, glossary, and checklist for clinicians. *BMJ*, 362, k601. doi:10.1136/bmj.k601
- do Nascimento, K. K. F., Pereira, K. S., Firmo, J. O. A., Lima-Costa, M. F., Diniz, B. S., & Castro-Costa, E. (2015). Predictors of incidence of clinically significant depressive symptoms in the elderly: 10-year follow-up study of the Bambui cohort study of aging. *International Journal of Geriatric Psychiatry*, 30(12), 1171–1176. doi:10.1002/gps.4271
- Egger, M., Higgins, J. P. T., & Smith, G. D. (2022). *Systematic reviews in health research: Meta-analysis in context*. Hoboken, NJ, USA: John Wiley & Sons.
- Esmaeelzadeh, S., Moraros, J., Thorpe, L., & Bird, Y. (2018). Examining the association and directionality between mental health disorders and substance use among adolescents and young adults in the U.S. and Canada – A systematic review and meta-analysis. *Journal of Clinical Medicine*, 7(12), 543. doi:10.3390/jcm7120543
- Farooqui, M., Shoaib, S., Afaq, H., Quadri, S., Zaina, F., Baig, A., ... Younus, S. (2022). Bidirectionality of smoking and depression in adolescents: A systematic review. *Trends in Psychiatry and Psychotherapy*, 45, e20210429. doi:10.47626/2237-6089-2021-0429
- Feingold, D., Weiser, M., Rehm, J., & Lev-Ran, S. (2015). The association between cannabis use and mood disorders: A longitudinal study. *Journal of Affective Disorders*, 172, 211–218. doi:10.1016/j.jad.2014.10.006
- Feingold, D., Weiser, M., Rehm, J., & Lev-Ran, S. (2016). The association between cannabis use and anxiety disorders: Results from a population-based representative sample. *European Neuropsychopharmacology*, 26(3), 493–505. doi:10.1016/j.euroneuro.2015.12.037
- Fergusson, D. M., Hall, W., Boden, J. M., & Horwood, L. J. (2015). *Rethinking cigarette smoking, cannabis use, and psychosis*. *The Lancet Psychiatry*, 2(7), 581–582. doi:10.1016/S2215-0366(15)00208-4
- Fewell, Z., Davey Smith, G., & Sterne, J. A. C. (2007). The impact of residual and unmeasured confounding in epidemiologic studies: A simulation study. *American Journal of Epidemiology*, 166(6), 646–655. doi:10.1093/aje/kwm165
- Firth, J., Wootton, R. E., Sawyer, C., & Taylor, G. M. (2023). Clearing the air: Clarifying the causal role of smoking in mental illness. *World Psychiatry*, 22(1), 151–152. doi:10.1002/wps.21023
- Flensburg-Madsen, T., Bay von Scholten, M., Flachs, E. M., Mortensen, E. L., Prescott, E., & Tolstrup, J. S. (2011). Tobacco smoking as a risk factor for depression. A 26-year population-based follow-up study. *Journal of Psychiatric Research*, 45(2), 143–149. doi:10.1016/j.jpsychires.2010.06.006
- Fluharty, M., Taylor, A. E., Grabski, M., & Munafò, M. R. (2017). The association of cigarette smoking with depression and anxiety: A systematic review. *Nicotine & Tobacco Research*, 19(1), 3–13. doi:10.1093/ntr/ntw140
- Fonseca, L. B., Pereira, L. P., Rodrigues, P. R. M., Muraro, A. P., Andrade, A. C. de S., Pereira, R. A., & Ferreira, M. G. (2022). Incidence of depressive symptoms and its association with sociodemographic factors and lifestyle-related behaviors among Brazilian university students. *Psychology, Health & Medicine*, 27(6), 1311–1325. doi:10.1080/13548506.2021.1874432
- Ford, D. E., Mead, L. A., Chang, P. P., Cooper-Patrick, L., Wang, N. Y., & Klag, M. J. (1998). Depression is a risk factor for coronary artery disease in men: The precursors study. *Archives of Internal Medicine*, 158(13), 1422–1426. doi:10.1001/archinte.158.13.1422
- Furuya-Kanamori, L., Barendregt, J. J., & Doi, S. A. R. (2018). A new improved graphical and quantitative method for detecting bias in meta-analysis. *International Journal of Evidence-Based Healthcare*, 16(4), 195–203. doi:10.1097/XEB.0000000000000141
- Gage, S. H., Hickman, M., Heron, J., Munafò, M. R., Lewis, G., Macleod, J., & Zammit, S. (2015). Associations of cannabis and cigarette use with depression and anxiety at age 18: Findings from the Avon longitudinal study of parents and children. *PLoS ONE*, 10(4), e0122896. doi:10.1371/journal.pone.0122896
- Gage, S. H., & Munafò, M. R. (2015). Smoking as a causal risk factor for schizophrenia. *The Lancet Psychiatry*, 2(9), 778–779. doi:10.1016/S2215-0366(15)00333-8
- Ganesh, S., & D'Souza, D. C. (2022). Cannabis and psychosis: Recent epidemiological findings continuing the 'causality debate'. *American Journal of Psychiatry*, 179(1), 8–10. doi:10.1176/appi.ajp.2021.21111126

- Garey, L., Olofsson, H., Garza, T., Rogers, A. H., Kauffman, B. Y., & Zvolensky, M. J. (2020). Directional effects of anxiety and depressive disorders with substance use: A review of recent prospective research. *Current Addiction Reports*, 7(3), 344–355. doi:10.1007/s40429-020-00321-z
- Gentile, A., Bianco, A., Nordström, A., & Nordström, P. (2021). Use of alcohol, drugs, inhalants, and smoking tobacco and the long-term risk of depression in men: A nationwide Swedish cohort study from 1969–2017. *Drug and Alcohol Dependence*, 221, 108553. doi:10.1016/j.drugalcdep.2021.108553
- Gobbi, G., Atkin, T., Zytynski, T., Wang, S., Askari, S., Boruff, J., ... Mayo, N. (2019). Association of cannabis use in adolescence and risk of depression, anxiety, and suicidality in young adulthood: A systematic review and meta-analysis. *JAMA Psychiatry*, 76(4), 426–434. doi:10.1001/jamapsychiatry.2018.4500
- Goodman, E., & Capitman, J. (2000). Depressive symptoms and cigarette smoking among teens. *Pediatrics*, 106(4), 748–755. doi:10.1542/peds.106.4.748
- Goodwin, R. D., Prescott, M., Tamburrino, M., Calabrese, J. R., Liberzon, I., & Galea, S. (2013). Smoking is a predictor of depression onset among National Guard soldiers. *Psychiatry Research*, 206(2), 321–323. doi:10.1016/j.psychres.2012.11.025
- Gravely, S., Driezen, P., Smith, D. M., Borland, R., Lindblom, E. N., Hammond, D., ... Fong, G. T. (2020). International differences in patterns of cannabis use among adult cigarette smokers: Findings from the 2018 ITC Four Country Smoking and Vaping Survey. *International Journal of Drug Policy*, 79, 102754. doi:10.1016/j.drugpo.2020.102754
- Groffen, D. A. I., Koster, A., Bosma, H., van den Akker, M., Kempen, G. I. J. M., van Eijk, J. T. M., ... Kritchevsky, S. B. (2013). Unhealthy lifestyles do not mediate the relationship between socioeconomic status and incident depressive symptoms: The health ABC study. *The American Journal of Geriatric Psychiatry*, 21(7), 664–674. doi:10.1016/j.jagp.2013.01.004
- Gurillo, P., Jauhar, S., Murray, R. M., & MacCabe, J. H. (2015). Does tobacco use cause psychosis? Systematic review and meta-analysis. *The Lancet Psychiatry*, 2(8), 718–725. doi:10.1016/S2215-0366(15)00152-2
- Haddaway, N. R., Grainger, M. J., & Gray, C. T. (2021). *Citationchaser: An R package and shiny app for forward and backward citations chasing in academic searching*. Zenodo. doi:10.5281/ZENODO.4543513
- Hahad, O., Beutel, M., Gilan, D. A., Michal, M., Schulz, A., Pfeiffer, N., ... Münzel, T. (2022). The association of smoking and smoking cessation with prevalent and incident symptoms of depression, anxiety, and sleep disturbance in the general population. *Journal of Affective Disorders*, 313, 100–109. doi:10.1016/j.jad.2022.06.083
- Hall, W., Leung, J., & Lynskey, M. (2020). The effects of cannabis use on the development of adolescents and young adults. *Annual Review of Developmental Psychology*, 2(1), 461–483. doi:10.1146/annurev-devpsych-040320-084904
- Hammerton, G., & Munafò, M. R. (2021). Causal inference with observational data: The need for triangulation of evidence. *Psychological Medicine*, 51(4), 563–578. doi:10.1017/S0033291720005127
- Harrer, M., Cuijpers, P., Furukawa, T. A., & Ebert, D. D. (2021). Chapter 7: Subgroup analyses. Doing meta-analysis in R. Retrieved from [https://bookdown.org/MathiasHarrer/Doing\\_Meta\\_Analysis\\_in\\_R/subgroup.html](https://bookdown.org/MathiasHarrer/Doing_Meta_Analysis_in_R/subgroup.html)
- Higgins, J., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M., & Welch, V. (2020). *Cochrane handbook for systematic reviews of interventions*. Retrieved from [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook)
- Hiles, S. A., Baker, A. L., de Malmanche, T., McEvoy, M., Boyle, M., & Attia, J. (2015). Unhealthy lifestyle may increase later depression via inflammation in older women but not men. *Journal of Psychiatric Research*, 63, 65–74. doi:10.1016/j.jpsyres.2015.02.010
- Hindocha, C., & McClure, E. A. (2020). Unknown population-level harms of cannabis and tobacco co-use: If you don't measure it, you can't manage it. *Addiction*, 116(7), 1622–1630. doi:10.1111/add.15290
- Hindocha, C., Freeman, T. P., Ferris, J. A., Lynskey, M. T., & Winstock, A. R. (2016). No smoke without tobacco: A global overview of cannabis and tobacco routes of administration and their association with intention to quit. *Frontiers in Psychiatry*, 7, 104. doi:10.3389/fpsy.2016.00104
- Hindocha, C., Brose, L. S., Walsh, H., & Cheeseman, H. (2020). Cannabis use and co-use in tobacco smokers and non-smokers: Prevalence and associations with mental health in a cross-sectional, nationally representative sample of adults in Great Britain, 2020. *Addiction*, 116(8), 2209–2219. doi:10.1111/add.15381
- Hines, L. A., Treur, J. L., Jones, H. J., Sallis, H. M., & Munafò, M. R. (2020). Using genetic information to inform policy on cannabis. *The Lancet Psychiatry*, 7(12), 1002–1003. doi:10.1016/S2215-0366(20)30377-1
- Hoveling, L. A., Liefbroer, A. C., Schwaren, L. J. S., Bültmann, U., & Smidt, N. (2022). Socioeconomic differences in major depressive disorder onset among adults are partially explained by lifestyle factors: A longitudinal analysis of the lifelines cohort study. *Journal of Affective Disorders*, 314, 309–317. doi:10.1016/j.jad.2022.06.018
- Hughes, K., Bellis, M. A., Hardcastle, K. A., Sethi, D., Butchart, A., Mikton, C., ... Dunne, M. P. (2017). The effect of multiple adverse childhood experiences on health: A systematic review and meta-analysis. *The Lancet Public Health*, 2(8), e356–e366. doi:10.1016/S2468-2667(17)30118-4
- Hunter, A., Murray, R., Asher, L., & Leonardi-Bee, J. (2020). The effects of tobacco smoking, and prenatal tobacco smoke exposure, on risk of schizophrenia: A systematic review and meta-analysis. *Nicotine & Tobacco Research*, 22(1), 3–10. doi:10.1093/ntr/nty160
- Int'Hout, J., Ioannidis, J. P. A., Rovers, M. M., & Goeman, J. J. (2016). Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open*, 6(7), e010247. doi:10.1136/bmjopen-2015-010247
- Isensee, B., Wittchen, H.-U., Stein, M. B., Höfler, M., & Lieb, R. (2003). Smoking increases the risk of panic: Findings from a prospective community study. *Archives of General Psychiatry*, 60(7), 692–700. doi:10.1001/archpsyc.60.7.692
- Jackson, S. E., Brown, J., Ussher, M., Shahab, L., Steptoe, A., & Smith, L. (2019). Combined health risks of cigarette smoking and low levels of physical activity: A prospective cohort study in England with 12-year follow-up. *BMJ Open*, 9(11), e032852. doi:10.1136/bmjopen-2019-032852
- Kang, E., & Lee, J. (2010). A longitudinal study on the causal association between smoking and depression. *Journal of Preventive Medicine and Public Health*, 43(3), 193–204. doi:10.3961/jpmp.2010.43.3.193
- Kendler, K. S., Lönn, S. L., Sundquist, J., & Sundquist, K. (2015). Smoking and schizophrenia in population cohorts of Swedish women and men: A prospective co-relative control study. *American Journal of Psychiatry*, 172(11), 1092–1100. doi:10.1176/appi.ajp.2015.15010126
- Kim, G. E., Kim, M., Lim, W.-J., & Kim, S. I. (2022). The effects of smoking habit change on the risk of depression – Analysis of data from the Korean National Health Insurance Service. *Journal of Affective Disorders*, 302, 293–301. doi:10.1016/j.jad.2022.01.095
- King, M., Jones, R., Petersen, I., Hamilton, F., & Nazareth, I. (2021). Cigarette smoking as a risk factor for schizophrenia or all non-affective psychoses. *Psychological Medicine*, 51(8), 1373–1381. doi:10.1017/S0033291720000136
- Korhonen, T., Ranjit, A., Tuulio-Henriksson, A., & Kaprio, J. (2017). Smoking status as a predictor of antidepressant medication use. *Journal of Affective Disorders*, 207, 221–227. doi:10.1016/j.jad.2016.09.035
- Lam, T. H., Stewart, S. M., Ho, S. Y., Lai, M. K., Mak, K. H., Chau, K. V., ... Salili, F. (2005). Depressive symptoms and smoking among Hong Kong Chinese adolescents. *Addiction*, 100(7), 1003–1011. doi:10.1111/j.1360-0443.2005.01092.x
- Leung, J., Gartner, C., Hall, W., Lucke, J., & Dobson, A. (2012). A longitudinal study of the bi-directional relationship between tobacco smoking and psychological distress in a community sample of young Australian women. *Psychological Medicine*, 42(6), 1273–1282. doi:10.1017/S0033291711002261
- Lev-Ran, S., Roerecke, M., Le Foll, B., George, T. P., McKenzie, K., & Rehm, J. (2014). The association between cannabis use and depression: A systematic review and meta-analysis of longitudinal studies. *Psychological Medicine*, 44(4), 797–810. doi:10.1017/S0033291713001438
- Luger, T. M., Suls, J., & Vander Weg, M. W. (2014). How robust is the association between smoking and depression in adults? A meta-analysis using linear mixed-effects models. *Addictive Behaviors*, 39(10), 1418–1429. doi:10.1016/j.addbeh.2014.05.011
- Luijckendijk, H. J., Stricker, B. H., Hofman, A., Witteman, J. C. M., & Tiemeier, H. (2008). Cerebrovascular risk factors and incident depression in community-dwelling elderly. *Acta Psychiatrica Scandinavica*, 118(2), 139–148. doi:10.1111/j.1600-0447.2008.01189.x
- Manrique-García, E., Zammit, S., Dalman, C., Hemmingsson, T., & Allebeck, P. (2012). Cannabis use and depression: A longitudinal study of a national cohort of Swedish conscripts. *BMC Psychiatry*, 12(1), 112. doi:10.1186/1471-244X-12-112

- Marconi, A., Di Forti, M., Lewis, C. M., Murray, R. M., & Vassos, E. (2016). Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophrenia Bulletin*, 42(5), 1262–1269. doi:10.1093/schbul/sbw003
- Meng, X., Brunet, A., Turecki, G., Liu, A., D'Arcy, C., & Caron, J. (2017). Risk factor modifications and depression incidence: A 4-year longitudinal Canadian cohort of the Montreal Catchment Area Study. *BMJ Open*, 7(6), e015156. doi:10.1136/bmjopen-2016-015156
- Monroe, D. C., McDowell, C. P., Kenny, R. A., & Herring, M. P. (2021). Dynamic associations between anxiety, depression, and tobacco use in older adults: Results from The Irish Longitudinal Study on Ageing. *Journal of Psychiatric Research*, 139, 99–105. doi:10.1016/j.jpsychires.2021.05.017
- Monshouwer, K., ten Have, M., de Graaf, R., Blankers, M., & van Laar, M. (2021). Tobacco smoking and the association with first incidence of mood, anxiety, and substance use disorders: A 3-year prospective population-based study. *Clinical Psychological Science*, 9(3), 403–412. doi:10.1177/2167702620959287
- Moore, T. H. M., Zammit, S., Lingford-Hughes, A., Barnes, T. R. E., Jones, P. B., Burke, M., & Lewis, G. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *The Lancet*, 370(9584), 319–328. doi:10.1016/S0140-6736(07)61162-3
- Munafò, M. R. (2022). Growing evidence for a causal role for smoking in mental health. *Nicotine & Tobacco Research*, 24(5), 631–632. doi:10.1093/ntr/ntac027
- Murphy, J. M., Horton, N. J., Monson, R. R., Laird, N. M., Sobol, A. M., & Leighton, A. H. (2003). Cigarette smoking in relation to depression: Historical trends from the Stirling County study. *American Journal of Psychiatry*, 160(9), 1663–1669. doi:10.1176/appi.ajp.160.9.1663
- Mustonen, A., Ahokas, T., Nordström, T., Murray, G. K., Mäki, P., Jääskeläinen, E., ... Niemelä, S. (2018a). Smokin' hot: Adolescent smoking and the risk of psychosis. *Acta Psychiatrica Scandinavica*, 138(1), 5–14. doi:10.1111/acps.12863
- Mustonen, A., Hielscher, E., Miettunen, J., Denissoff, A., Alakokkare, A.-E., Scott, J. G., & Niemelä, S. (2021). Adolescent cannabis use, depression and anxiety disorders in the Northern Finland Birth Cohort 1986. *BJPsych Open*, 7(4), e137. doi:10.1192/bjo.2021.967
- Mustonen, A., Niemelä, S., Nordström, T., Murray, G. K., Mäki, P., Jääskeläinen, E., & Miettunen, J. (2018b). Adolescent cannabis use, baseline prodromal symptoms and the risk of psychosis. *The British Journal of Psychiatry*, 212(4), 227–233. doi:10.1192/bjp.2017.52
- Myles, N., Newall, H. D., Curtis, J., Nielsen, O., Shiers, D., & Large, M. (2012). Tobacco use before, at, and after first-episode psychosis: A systematic meta-analysis. *The Journal of Clinical Psychiatry*, 73(4), 2015. doi:10.4088/JCP.11r07222
- Najafipour, H., Shahrokhbabadi, M. S., Banivaheb, G., Sabahi, A., Shadkam, M., & Mirzazadeh, A. (2021). Trends in the prevalence and incidence of anxiety and depressive symptoms in Iran: Findings from KERCADRS. *Family Medicine and Community Health*, 9(3), e000937. doi:10.1136/fmch-2021-000937
- Okkenhaug, A., Tanem, T., Myklebust, T., Gjervan, B., & Johansen, A. (2018). Self-reported premorbid health in 15 individuals who later developed schizophrenia compared with healthy controls: Prospective data from the Young-HUNT1 Survey (The HUNT Study). *Scandinavian Psychologist*, 5, e8. doi:10.15714/scandpsychol.5.e8
- Page, M. J., Moher, D., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., ... McKenzie, J. E. (2021). PRISMA 2020 explanation and elaboration: Updated guidance and exemplars for reporting systematic reviews. *BMJ*, 372, n160. doi:10.1136/bmj.n160
- Park, S. (2009). The causal association between smoking and depression among south Korean adolescents. *Journal of Addictions Nursing*, 20(2), 93–103. doi:10.1080/10884600902850111
- Paton, S., Kessler, R., & Kandel, D. (1977). Depressive mood and adolescent illicit drug use: A longitudinal analysis. *The Journal of Genetic Psychology*, 131(2), 267–289. doi:10.1080/00221325.1977.10533299
- Patten, S. B. (2021). Cannabis and non-psychotic mental disorders. *Current Opinion in Psychology*, 38, 61–66. doi:10.1016/j.copsyc.2020.09.006
- Peters, E. N., Budney, A. J., & Carroll, K. M. (2012). Clinical correlates of co-occurring cannabis and tobacco use: A systematic review. *Addiction*, 107(8), 1404–1417. doi:10.1111/j.1360-0443.2012.03843.x
- Peters, E. N., Schwartz, R. P., Wang, S., O'Grady, K. E., & Blanco, C. (2014). Psychiatric, psychosocial, and physical health correlates of co-occurring Cannabis use disorders and nicotine dependence. *Drug and Alcohol Dependence*, 134, 228–234. doi:10.1016/j.drugalcdep.2013.10.003
- Petersen, J. M., Barrett, M., Ahrens, K. A., Murray, E. J., Bryant, A. S., Hogue, C. J., ... Trinquart, L. (2022). The confounder matrix: A tool to assess confounding bias in systematic reviews of observational studies of etiology. *Research Synthesis Methods*, 13(2), 242–254. doi:10.1002/jrsm.1544
- Petrilli, K., Ofori, S., Hines, L., Taylor, G., Adams, S., & Freeman, T. P. (2022). Association of cannabis potency with mental ill health and addiction: A systematic review. *The Lancet Psychiatry*, 9(9), 736–750. doi:10.1016/S2215-0366(22)00161-4
- Quigley, H., & MacCabe, J. H. (2019). The relationship between nicotine and psychosis. *Therapeutic Advances in Psychopharmacology*, 9, 2045125319859969. doi:10.1177/2045125319859969
- Raffetti, E., Donato, F., Forsell, Y., & Galanti, M. R. (2019). Longitudinal association between tobacco use and the onset of depressive symptoms among Swedish adolescents: The Kupol cohort study. *European Child & Adolescent Psychiatry*, 28(5), 695–704. doi:10.1007/s00787-018-1237-6
- Ramo, D. E., Liu, H., & Prochaska, J. J. (2012). Tobacco and marijuana use among adolescents and young adults: A systematic review of their co-use. *Clinical Psychology Review*, 32(2), 105–121. doi:10.1016/j.cpr.2011.12.002
- Ranjit, A., Korhonen, T., Buchwald, J., Heikkilä, K., Tuulio-Henriksson, A., Rose, R. J., ... Latvala, A. (2019). Testing the reciprocal association between smoking and depressive symptoms from adolescence to adulthood: A longitudinal twin study. *Drug and Alcohol Dependence*, 200, 64–70. doi:10.1016/j.drugalcdep.2019.03.012
- Reid, S., & Bhattacharyya, S. (2019). Antipsychotic treatment failure in patients with psychosis and co-morbid cannabis use: A systematic review. *Psychiatry Research*, 280, 112523. doi:10.1016/j.psychres.2019.112523
- Ren, X., Wang, S., He, Y., Lian, J., Lu, Q., Gao, Y., & Wang, Y. (2021). Chronic lung diseases and the risk of depressive symptoms based on the China health and retirement longitudinal study: A prospective cohort study. *Frontiers in Psychology*, 12, 585597. doi:10.3389/fpsyg.2021.585597
- Richardson, M., Garner, P., & Donegan, S. (2019). Interpretation of subgroup analyses in systematic reviews: A tutorial. *Clinical Epidemiology and Global Health*, 7(2), 192–198. doi:10.1016/j.cegh.2018.05.005
- Robinson, T., Ali, M. U., Easterbrook, B., Hall, W., Jutras-Aswad, D., & Fischer, B. (2023). Risk-thresholds for the association between frequency of cannabis use and the development of psychosis: A systematic review and meta-analysis. *Psychological Medicine*, 53(9), 3858–3868. doi:10.1017/S0033291722000502
- Rognli, E. B., Bramness, J. G., & von Soest, T. (2020). Cannabis use in early adulthood is prospectively associated with prescriptions of antipsychotics, mood stabilizers, and antidepressants. *Acta Psychiatrica Scandinavica*, 141(2), 149–156. doi:10.1111/acps.13104
- Rothman, K., Lash, T., VanderWeele, T., & Haneuse, S. (2021). *Modern epidemiology* (Vol. 63, 4th ed.). Philadelphia, PA, USA: Wolters Kluwer.
- Rudaz, D. A., Vandeleur, C. L., Gebreab, S. Z., Gholam-Rezaee, M., Strippoli, M.-P. F., Lasserre, A. M., ... Preisig, M. (2017). Partially distinct combinations of psychological, metabolic and inflammatory risk factors are prospectively associated with the onset of the subtypes of major depressive disorder in midlife. *Journal of Affective Disorders*, 222, 195–203. doi:10.1016/j.jad.2017.07.016
- Sabe, M., Zhao, N., & Kaiser, S. (2020). Cannabis, nicotine and the negative symptoms of schizophrenia: Systematic review and meta-analysis of observational studies. *Neuroscience and Biobehavioral Reviews*, 116, 415–425. doi:10.1016/j.neubiorev.2020.07.007
- Sánchez-Villegas, A., Gea, A., Lahortiga-Ramos, F., Martínez-González, J., Molero, P., & Martínez-González, M.Á. (2021). Bidirectional association between tobacco use and depression risk in the SUN cohort study. *Adicciones*, 0(0), 1725. doi:10.20882/adicciones.1725
- Schaefer, J. D., Hamdi, N. R., Malone, S. M., Vrieze, S., Wilson, S., McGue, M., & Iacono, W. G. (2021). Associations between adolescent cannabis use and young-adult functioning in three longitudinal twin studies. *Proceedings of the National Academy of Sciences*, 118(14), e2013180118. doi:10.1073/pnas.2013180118
- Schwarzer, G. (2022). meta: General package for meta-analysis. Retrieved from <https://CRAN.R-project.org/package=meta>

- Sideli, L., Quigley, H., La Cascia, C., & Murray, R. M. (2020). Cannabis use and the risk for psychosis and affective disorders. *Journal of Dual Diagnosis*, 16(1), 22–42. doi:10.1080/15504263.2019.1674991
- Skelly, A. C., Dettori, J. R., & Brodt, E. D. (2012). Assessing bias: The importance of considering confounding. *Evidence-Based Spine-Care Journal*, 03(1), 9–12. doi:10.1055/s-0031-1298595
- Sterne, J. A. C., & Harbord, R. M. (2004). Funnel plots in meta-analysis. *The Stata Journal*, 4(2), 127–141. doi:10.1177/1536867X0400400204
- Stevenson, J., Miller, C. L., Martin, K., Mohammadi, L., & Lawn, S. (2022). Investigating the reciprocal temporal relationships between tobacco consumption and psychological disorders for youth: An international review. *BMJ Open*, 12(6), e055499. doi:10.1136/bmjopen-2021-055499
- Storeng, S. H., Sund, E. R., & Krokstad, S. (2020). Prevalence, clustering and combined effects of lifestyle behaviours and their association with health after retirement age in a prospective cohort study, the Nord-Trøndelag Health Study, Norway. *BMC Public Health*, 20(1), 900. doi:10.1186/s12889-020-08993-y
- Tanaka, H., Sasazawa, Y., Suzuki, S., Nakazawa, M., & Koyama, H. (2011). Health status and lifestyle factors as predictors of depression in middle-aged and elderly Japanese adults: A seven-year follow-up of the Komo-Ise cohort study. *BMC Psychiatry*, 11(1), 20. doi:10.1186/1471-244X-11-20
- Taylor, G. M. J., & Treur, J. L. (2023). An application of the stress-diathesis model: A review about the association between smoking tobacco, smoking cessation, and mental health. *International Journal of Clinical and Health Psychology*, 23(1), 100335. doi:10.1016/j.ijchp.2022.100335
- Tomita, A., & Manuel, J. I. (2020). Evidence on the association between cigarette smoking and incident depression from the South African national income dynamics study 2008–2015: Mental health implications for a resource-limited setting. *Nicotine & Tobacco Research*, 22(1), 118–123. doi:10.1093/ntr/nty163
- Tourjman, S. V., Buck, G., Jutras-Aswad, D., Khullar, A., McInerney, S., Saraf, G., ... Beaulieu, S. (2023). Canadian network for mood and anxiety treatments (CANMAT) task force report: A systematic review and recommendations of cannabis use in bipolar disorder and major depressive disorder. *The Canadian Journal of Psychiatry*, 68(5), 299–311. doi:10.1177/07067437221099769
- Treur, J. L., Munafo, M. R., Logtenberg, E., Wiers, R. W., & Verweij, K. J. H. (2021). Using Mendelian randomization analysis to better understand the relationship between mental health and substance use: A systematic review. *Psychological Medicine*, 51(10), 1593–1624. doi:10.1017/S003329172100180X
- Tsai, A. C., Chi, S.-H., & Wang, J.-Y. (2013). Cross-sectional and longitudinal associations of lifestyle factors with depressive symptoms in ≥53-year old Taiwanese – Results of an 8-year cohort study. *Preventive Medicine*, 57(2), 92–97. doi:10.1016/j.ypmed.2013.04.021
- Tucker, J. S., Rodriguez, A., Dunbar, M. S., Pedersen, E. R., Davis, J. P., Shih, R. A., & D'Amico, E. J. (2019). Cannabis and tobacco use and co-use: Trajectories and correlates from early adolescence to emerging adulthood. *Drug and Alcohol Dependence*, 204, 107499. doi:10.1016/j.drugalcdep.2019.06.004
- United Nations Office on Drugs and Crime (UNODC). (2021). *World drug report 2020*. Vienna, Austria: United Nations Publication. Retrieved from <https://wdr.unodc.org/wdr2020/en/index2020.html>
- Vandenbroucke, J. P., von Elm, E., Altman, D. G., Gøtzsche, P. C., Mulrow, C. D., Pocock, S. J., ... Egger, M. (2007). Strengthening the reporting of observational studies in epidemiology (STROBE): Explanation and elaboration. *PLoS Medicine*, 4(10), e297. doi:10.1371/journal.pmed.0040297
- VanderWeele, T. J. (2021). Can sophisticated study designs with regression analyses of observational data provide causal inferences? *JAMA Psychiatry*, 78(3), 244–246. doi:10.1001/jamapsychiatry.2020.2588
- VanderWeele, T. J. (2022). Are Greenland, Ioannidis and Poole opposed to the cornfield conditions? A defence of the E-value. *International Journal of Epidemiology*, 51(2), 364–371. doi:10.1093/ije/dyab218
- VanderWeele, T. J., & Ding, P. (2017). Sensitivity analysis in observational research: Introducing the E-value. *Annals of Internal Medicine*, 167(4), 268–274. doi:10.7326/M16-2607
- VanderWeele, T. J., Ding, P., & Mathur, M. (2019). Technical considerations in the use of the E-value. *Journal of Causal Inference*, 7(2), 20180007. doi:10.1515/jci-2018-0007
- Van Laar, M., Van Dorsselaer, S., Monshouwer, K., & De Graaf, R. (2007). Does cannabis use predict the first incidence of mood and anxiety disorders in the adult population? *Addiction*, 102(8), 1251–1260. doi:10.1111/j.1360-0443.2007.01875.x
- van Os, J., Bak, M., Hanssen, M., Bijl, R. V., de Graaf, R., & Verdoux, H. (2002). Cannabis use and psychosis: A longitudinal population-based study. *American Journal of Epidemiology*, 156(4), 319–327. doi:10.1093/aje/kwf043
- Wang, N., Yao, T., Sung, H.-Y., & Max, W. (2022). The association of cannabis use and cigarette smoking with psychological distress among adults in California. *Substance Use & Misuse*, 57(2), 193–201. doi:10.1080/10826084.2021.1995758
- Weiser, M., Reichenberg, A., Grotto, I., Yasvitzky, R., Rabinowitz, J., Lubin, G., ... Davidson, M. (2004). Higher rates of cigarette smoking in male adolescents before the onset of schizophrenia: A historical-prospective cohort study. *American Journal of Psychiatry*, 161(7), 1219–1223. doi:10.1176/appi.ajp.161.7.1219
- Wells, G., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2013). The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Retrieved from [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)
- Werneck, A. O., Vancampfort, D., Stubbs, B., Silva, D. R., Cucato, G. G., Christofaro, D. G. D., ... Bittencourt, M. S. (2022). Prospective associations between multiple lifestyle behaviors and depressive symptoms. *Journal of Affective Disorders*, 301, 233–239. doi:10.1016/j.jad.2021.12.131
- Weyerer, S., Eifflaender-Gorfer, S., Wiese, B., Lupp, M., Pentzek, M., Bickel, H., ... Riedel-Heller, S. G. (2013). Incidence and predictors of depression in non-demented primary care attenders aged 75 years and older: Results from a 3-year follow-up study. *Age and Ageing*, 42(2), 173–180. doi:10.1093/ageing/afs184
- Wootton, R. E., Jones, H. J., & Sallis, H. M. (2022). Mendelian randomisation for psychiatry: How does it work, and what can it tell us? *Molecular Psychiatry*, 27(1), 53–57. doi:10.1038/s41380-021-01173-3
- Zammit, S., Allebeck, P., Andreasson, S., Lundberg, I., & Lewis, G. (2002). Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: Historical cohort study. *BMJ*, 325(7374), 1199. doi:10.1136/bmj.325.7374.1199
- Zammit, S., Allebeck, P., Dalman, C., Lundberg, I., Hemmingsson, T., & Lewis, G. (2003). Investigating the association between cigarette smoking and schizophrenia in a cohort study. *American Journal of Psychiatry*, 160(12), 2216–2221. doi:10.1176/appi.ajp.160.12.2216
- Zhang, X. C., Woud, M. L., Becker, E. S., & Margraf, J. (2018). Do health-related factors predict major depression? A longitudinal epidemiologic study. *Clinical Psychology & Psychotherapy*, 25(3), 378–387. doi:10.1002/cpp.2171
- Zimmerman, J. A., Mast, B. T., Miles, T., & Markides, K. S. (2009). Vascular risk and depression in the Hispanic established population for the Epidemiologic Study of the Elderly (EPSE). *International Journal of Geriatric Psychiatry*, 24(4), 409–416. doi:10.1002/gps.2136
- Zimmermann, M., Chong, A. K., Vecchiu, C., & Papa, A. (2020). Modifiable risk and protective factors for anxiety disorders among adults: A systematic review. *Psychiatry Research*, 285, 112705. doi:10.1016/j.psychres.2019.112705
- Zvolensky, M. J., Lewinsohn, P., Bernstein, A., Schmidt, N. B., Buckner, J. D., Seeley, J., & Bonn-Miller, M. O. (2008). Prospective associations between cannabis use, abuse, and dependence and panic attacks and disorder. *Journal of Psychiatric Research*, 42(12), 1017–1023. doi:10.1016/j.jpsychires.2007.10.012