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REVIEW

ADDICTION SSA

Associations of cannabis use, tobacco use and co-use with brain volume: A systematic review and meta-analysis

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Abstract

Background and aims: Cannabis is the most widely used illicit drug worldwide and is often co-used with tobacco, the leading cause of preventable death. Although cannabis and tobacco have distinct neurobiological actions, their associations with brain volumes are unclear. We aimed to review studies investigating cannabis use, tobacco use, their co-use and brain volume and triangulate evidence across different study designs.

Methods: A systematic review and meta-analysis preregistered on PROSPERO (CRD42022356982) and reported according to PRISMA 2020 guidelines. We searched SCOPUS, PubMed and PsycINFO up to 5 September 2024 for studies investigating cannabis use, tobacco use, co-use and brain volume. Cross-sectional, longitudinal and Mendelian randomisation studies were included. The outcome was brain volume of global, cortical and subcortical regions. We extracted adjusted and unadjusted estimates. Random effects meta-analyses were stratified by exposure and study design across 33 brain regions. Risk of bias was assessed using a modified version of the Newcastle-Ottawa scale.

Results: Searches yielded 103 studies: 57 investigated cannabis use, 45 investigated tobacco use and one investigated tobacco and cannabis co-use. Seventy-seven studies were included in meta-analysis (n = 72 798), 44 (n = 18 247) in the cross-sectional cannabis analysis, 30 (n = 51 194) for tobacco cross-sectional and four (n = 3357) in the tobacco longitudinal analysis. Meta-analysis of adjusted estimates from cross-sectional studies (k denotes the number of independent studies) indicated smaller amygdala volumes [k = 17, g = 0.13, 95% confidence interval (CI) = 0.03, 0.23)] in people who use cannabis compared with controls. Relative to controls, people who smoked tobacco had smaller volumes in the amygdala (k = 5, g = 0.17, 95% CI = 0.04, 0.31), insula (k = 5, g = 0.17, 95% CI = 0.06, 0.27), pallidum (k = 5, g = 0.17, 95% CI = 0.13, 0.21) and total grey matter volume (TGMV) (k = 7, g = 0.17, 95% CI = 0.04, 0.30). Longitudinal studies

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indicated a larger decrease in TGMV in people who smoke tobacco (k = 5, g = 0.05, 95% CI = 0.01, 0.10) relative to controls.

Conclusions: Cannabis use appears to be associated with smaller volume in the amygdala. Tobacco use appears to be associated with smaller amygdala, insula, pallidum and total grey matter volume.

KEYWORDS
brain volume, cannabis, co-use, meta-analysis, MRI, neuroimaging, systematic review, tobacco

INTRODUCTION

Cannabis and tobacco use are highly prevalent and are associated with negative health outcomes. Cannabis alone was used by approximately 228 million people globally in 2022, representing around 4.4% of the global adult population [1]. Cannabis use is increasing in prevalence and potency [2, 3]. Cannabis products with higher potency carry a greater risk of mental ill health and addiction compared with products of lower potency [4]. Meanwhile, tobacco was used by approximately 1.18 billion people in 2020, representing around 30% of the global population [5]. Over 8 million deaths a year are attributed to tobacco smoking [6, 7]. Tobacco smoking also exacerbates health inequalities, leading to higher levels of harm in more deprived and vulnerable populations [8]. Cannabis can be co-used with tobacco, either separately within the same time period (e.g. same day, with cigarettes and cannabis used separately) or co-administered, where both tobacco and cannabis are delivered together (e.g. through 'spliffs' or 'joints' in European terms) [9].

Tobacco and cannabis act on distinct pathways in the brain. When cannabis is consumed, tetrahydrocannabinol (THC, the primary psychoactive component of cannabis) acts on cannabinoid type one (CB1) receptors, which are found at high levels in the hippocampus, basal ganglia and cerebellum, and at moderate levels in the prefrontal cortex, amygdala and hypothalamus [10, 11]. Nicotine, the main psychoactive component of tobacco, acts on nicotinic acetylcholine receptors (nAChRs) found throughout the brain, including the hippocampus, ventral tegmental area, nucleus accumbens, prefrontal cortex and amygdala [12–14].

Systematic reviews and meta-analyses are important methods to overcome issues arising from small sample sizes, reduced statistical power and limited replicability, which are common in neuroscience studies [15, 16]. Meta-analysis improves precision by combining estimates from multiple studies and creating a larger pooled sample with increased power to detect small effect sizes. Despite high rates of co-use and similar associations with grey matter volume, previous systematic reviews and meta-analyses have focused on brain volume and either cannabis use [17–20] or tobacco use individually [21–24]. A recent umbrella review of meta-analyses of voxel-based morphometry (VBM) tobacco studies found consistently smaller volumes in the prefrontal cortex, insula and cingulate cortex in people who smoke tobacco chronically, compared with controls [25]. Meta-analyses of structural neuroimaging cannabis studies have found smaller volumes of the hippocampus, lateral and medial orbitofrontal cortex (OFC) [17], and cerebellum [19] in people who regularly use cannabis, compared with controls. However, no significant differences were found in adolescents [20]. Only one narrative review has synthesised the evidence on the association between cannabis and tobacco co-use on brain structure [26], and identified one study reporting smaller hippocampal volume for co-users of nicotine and cannabis, compared with controls and users of nicotine only [27].

Systematic reviews to date focus on observational evidence, and include mostly cross-sectional studies, with some longitudinal

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evidence. These study designs are limited by confounding and reverse causation. Mendelian randomisation (MR) is a method increasingly being used to test causal relationships in substance use research where randomised trials are not appropriate. MR uses genetic variation, fixed at conception, that predicts modifiable exposures as instrumental variables (e.g. cannabis or tobacco use), thereby accounting for unobserved confounding and reverse causation, which are present in observational studies [28]. Triangulating evidence across different approaches and comparing results across methods with different sources and directions of bias is recommended to strengthen causal inference and the robustness of conclusions [29, 30]. Therefore, this review aims to triangulate evidence across observational cross-sectional, longitudinal and MR studies. To date, there are no systematic reviews of MR studies examining the associations between tobacco or cannabis use and brain structure, nor any that integrate these findings with evidence from observational studies.

Evidence from both individual studies and reviews generally suggests an association between cannabis and tobacco use and reduced grey matter volume; however, findings regarding specific brain regions remain heterogeneous and inconsistent. Previous reviews focussed only on cross-sectional studies, which reduce the potential for causal inference. Finally, despite high rates of co-use, there is still limited investigation of studies of cannabis and tobacco co-use, or even comparisons of results between cannabis and tobacco studies using similar meta-analysis methods and exposure definitions. Therefore, we present, to our knowledge, the first systematic review and meta-analysis of the associations of cannabis use, tobacco use and/or co-use with brain volume that triangulates evidence across different study designs.

Aims

In this systematic review and meta-analysis, we aimed to synthesise the literature examining brain volumetric differences of people who use cannabis and/or tobacco compared with non-using controls, triangulating evidence across cross-sectional, longitudinal and MR study designs.

METHODS

This review was pre-registered on PROSPERO (CRD42022356982) and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [31] (Appendix S1).

Eligibility criteria

Studies were included if they met the following criteria: (i) journal article, conference abstract or dissertation; (ii) human participants; (iii) measured brain volume using longitudinal T1-weighted structural magnetic resonance imaging (MRI); (iv) exposure group was current tobacco use, cannabis use and/or co-use (as per study definition, e.g. use or use disorder) and a comparator group that was non-exposed (as per study definition); and (v) observational studies (cross-sectional or longitudinal) or instrumental variable studies, such as Mendelian randomisation studies.

Exclusion criteria were: (i) primary substance of use was not cannabis or tobacco (but use of other substances was allowed); (ii) cannabis use defined as pre/post-natal tobacco/cannabis exposure; (iii) studies that reported only voxel-wise results; and (iv) studies where the control group was low frequency of use (as per study definition, e.g. used less than once per month) or absence of cannabis or tobacco abuse, dependence or use disorder. There were no restrictions on date or language, age, psychiatric diagnosis or population type.

Volume can be estimated either by voxel-based techniques [voxel-based morphometry (VBM), analysing voxel-by-voxel differences] or by using an atlas-based region of interest (ROI) approach, with extracted values for the total volume of each region [134]. Here we took the latter approach, including only ROI-level data, and not VBM studies, to minimise methodological heterogeneity and support the meta-analysis.

Information sources and study selection

One author (K.S.) searched SCOPUS, PubMed and PsycINFO on 14 September 2022 for relevant research articles and updated this list on 5 September 2024 (Appendix S1). Further cross-referencing from searching relevant systematic reviews in the field [17, 20] was conducted. Studies in non-English language were translated using Google translate. All title/abstracts and full texts were independently screened by two authors and any discrepancies were resolved by discussion or, if necessary, contacting a third author. K.S. screened all studies, with a second screening performed by A.B., C.B., R.C., C.C., S. Dance, S. Daryan or T.J.

Data extraction

We extracted the following data from studies: exposure/comparator definitions, outcome regions, study design, population group (e.g. general, psychiatric), demographics (e.g. age, sex), frequency of use and MRI parameters. For meta-analysis the following data were extracted: effect size, standard error (or standard deviation/95% CI), *P*-values and *n* per group. Studies that reported on multiple different brain measures were treated as one study with multiple outcomes. Data on all brain regions examined in each study were extracted.

Study characteristics were extracted by one reviewer (K.S., M.S., C.B., S. Dance). Assessment of risk of bias and outcome extraction were completed independently by two reviewers for all studies (first by K.S., M.S., C.B. or S. Dance; then by A.B., M.C.,

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TABLE 1 Studies included in the review.

Study	Title	DOI
Ashtari *et al.* [32]	Medial temporal structures and memory functions in adolescents with heavy cannabis use	10.1016/j.jpsychires.2011.01.004
Austin *et al.* [33]	Association of Brain Volumes and White Matter Injury With Race, Ethnicity, and Cardiovascular Risk Factors: The Multi-Ethnic Study of Atherosclerosis	10.1161/JAHA.121.023159
Batalla *et al.* [34]	The Influence of DAT1, COMT, and BDNF Genetic Polymorphisms on Total and Subregional Hippocampal Volumes in Early Onset Heavy Cannabis Users	10.1089/can.2017.0021
Binnewies *et al.* [35]	Lifestyle-related risk factors and their cumulative associations with hippocampal and total grey matter volume across the adult lifespan: A pooled analysis in the European Lifebrain consortium	10.1016/j.brainresbull.2023.110692
Block *et al.* [36]	Effects of frequent marijuana use on brain tissue volume and composition	10.1097/00001756-200 002 280-00013
Brody *et al.* [37]	Differences between smokers and nonsmokers in regional gray matter volumes and densities	10.1016/S0006-3223(03)00610-3
Buchy *et al.* [38]	Relation between cannabis use and subcortical volumes in people at clinical high risk of psychosis	10.1016/j.pscychresns.2016.06.001
Cahn W *et al.* [39]	Cannabis and brain morphology in recent-onset schizophrenia	10.1016/S0920-9964(03)00003-3
Cardenas *et al.* [40]	Cerebellar Morphometry and Cognition in the Context of Chronic Alcohol Consumption and Cigarette Smoking	10.1111/acer.14222
Chen *et al.* [41]	Effects of cerebrovascular risk factors on gray matter volume in adults aged 60–64 years: A voxel-based morphometric study	10.1016/j.pscychresns.2006.01.009
Chen *et al.* [42]	Sex Difference in Cigarette-Smoking Status and Its Association with Brain Volumes Using Large-Scale Community-Representative Data	10.3390/brainsci13081164
Cho *et al.* [43]	Impact of smoking on neurodegeneration and cerebrovascular disease markers in cognitively normal men	10.1111/ene.12816
Choi *et al.* [44]	Difference between smokers and non-smokers in the corpus callosum volume	10.1016/j.neulet.2010.08.066
Churchwell *et al.* [45]	Altered frontal cortical volume and decision making in adolescent cannabis users	10.3389/fpsyg.2010.00225
Churchwell *et al.* [46]	Abnormal striatal circuitry and intensified novelty seeking among adolescents who abuse methamphetamine and cannabis	10.1159/000337724
Chye *et al.* [47]	Cannabis-related hippocampal volumetric abnormalities specific to subregions in dependent users	10.1007/s00213-017-4620-y
Chye *et al.* [48]	Subcortical surface morphometry in substance dependence: An ENIGMA addiction working group study	10.1111/adb.12830
Cohen *et al.* [49]	Cerebellar grey-matter deficits, cannabis use and first-episode schizophrenia in adolescents and young adults	10.1017/S146114571100068X
D'Souza *et al.* [50]	Preliminary in vivo evidence of lower hippocampal synaptic density in cannabis use disorder	10.1038/s41380-020-00891-4
Durazzo *et al.* [51]	Chronic cigarette smoking and heavy drinking in human immunodeficiency virus: consequences for neurocognition and brain morphology	10.1016/j.alcohol.2007.07.007
Durazzo, Meyerhoff, *et al.* [52]	Interactive effects of chronic cigarette smoking and age on hippocampal volumes	10.1016/j.drugalcdep.2013.08.020
Durazzo, Mon, *et al.* [53]	Chronic cigarette smoking in alcohol dependence: Associations with cortical thickness and N-acetylaspartate levels in the extended brain reward system	10.1111/j.1369-1600.2011.00407.x
Durazzo *et al.* [54]	Cigarette smoking is associated with amplified age-related volume loss in subcortical brain regions	10.1016/j.drugalcdep.2017.04.012
Durhan *et al.* [55]	Assessment of the effect of cigarette smoking on regional brain volumes and lesion load in patients with clinically isolated syndrome	10.3109/00207454.2015.1073727
Duriez *et al.* [56]	Sex-related and tissue-specific effects of tobacco smoking on brain atrophy: Assessment in a large longitudinal cohort of healthy elderly	10.3389/fnagi.2014.00299
Elbejjani *et al.* [57]	Cigarette smoking and gray matter brain volumes in middle age adults: the CARDIA Brain MRI sub-study	10.1038/s41398-019-0401-1

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TABLE 1 (Continued)

Study	Title	DOI
Filbey *et al.* [27]	Combined effects of marijuana and nicotine on memory performance and hippocampal volume	10.1016/j.bbr.2015.07.029
Garimella *et al.* [58]	Marijuana and the hippocampus: A longitudinal study on the effects of marijuana on hippocampal subfields	10.1016/j.pnpbp.2020.109897
Gazdzinski *et al.* [59]	Quantitative brain MRI in alcohol dependence: Preliminary evidence for effects of concurrent chronic cigarette smoking on regional brain volumes	10.1097/01.alc.0000175018.72488.61
Gilman *et al.* [60]	Cannabis use is quantitatively associated with nucleus accumbens and amygdala abnormalities in young adult recreational users	10.1523/JNEUROSCI.4745-13.2014
Hoogendam *et al.* [61]	Determinants of cerebellar and cerebral volume in the general elderly population	10.1016/j.neurobiolaging.2012.02.012
James *et al.* [62]	Greater white and grey matter changes associated with early cannabis use in adolescent-onset schizophrenia (AOS)	10.1016/j.schres.2011.02.014
Janowitz *et al.* [63]	Genetic, psychosocial and clinical factors associated with hippocampal volume in the general population	10.1038/tp.2014.102
Jha *et al.* [64]	Smoking status links habenular volume to glycated hemoglobin: Findings from the Human Connectome Project-Young Adult	10.1016/j.psyneuen.2021.105321
Kim *et al.* [65]	Lifestyle-dependent brain change: a longitudinal cohort MRI study	10.1016/j.neurobiolaging.2018.04.017
Knodt *et al.* [66]	Diminished Structural Brain Integrity in Long-term Cannabis Users Reflects a History of Polysubstance Use	10.1016/j.biopsych.2022.06.018
Koenders *et al.* [67]	Brain volume in male patients with recent onset schizophrenia with and without cannabis use disorders	10.1503/jpn.140081
Koenders *et al.* [68]	Longitudinal study of hippocampal volumes in heavy cannabis users	10.1177/0269881117718380
Koenis *et al.* [69]	Associations of cannabis use disorder with cognition, brain structure, and brain function in African Americans	10.1002/hbm.25324
Kumra *et al.* [70]	Parietal lobe volume deficits in adolescents with schizophrenia and adolescents with cannabis use disorders	10.1016/j.jaac.2011.11.001
Launer *et al.* [71]	Vascular factors and multiple measures of early brain health: CARDIA brain MRI study	10.1371/journal.pone.0122138
Levar *et al.* [72]	Verbal Memory Performance and Reduced Cortical Thickness of Brain Regions Along the Uncinate Fasciculus in Young Adult Cannabis Users	10.1089/can.2017.0030
Li *et al.* [73]	Reduced frontal cortical thickness and increased caudate volume within fronto-striatal circuits in young adult smokers	10.1016/j.drugalcdep.2015.03.023
Liang *et al.* [74]	Contributions of chronic tobacco smoking to HIV-associated brain atrophy and cognitive deficits	10.1097/QAD.0000000000003138
Lie *et al.* [75]	The Effect of Smoking on Long-term Gray Matter Atrophy and Clinical Disability in Patients with Relapsing–Remitting Multiple Sclerosis	10.1212/NXI.0000000000200008
Lin *et al.* [76]	Region-Specific Changes of Insular Cortical Thickness in Heavy Smokers	10.3389/fnhum.2019.00265
Lin *et al.* [77]	Sex-specific effects of cigarette smoking on caudate and amygdala volume and resting-state functional connectivity	10.1007/s11682-019-00227-z
Lin *et al.* [78]	Association of smoking with brain gray and white matter volume: a Mendelian randomization study	10.1007/s10072-023-06854-1
Linli *et al.* [79]	Smoking is associated with lower brain volume and cognitive differences: A large population analysis based on the UK Biobank	10.1016/j.pnpbp.2022.110698
Lisdahl *et al.* [80]	The impact of ADHD persistence, recent cannabis use, and age of regular cannabis use onset on subcortical volume and cortical thickness in young adults	10.1016/j.drugalcdep.2016.01.032
Logtenberg *et al.* [81]	Investigating the causal nature of the relationship of subcortical brain volume with smoking and alcohol use	10.1192/bjp.2021.81
Lopez-Larson *et al.* [82]	Altered prefrontal and insular cortical thickness in adolescent marijuana users	10.1016/j.bbr.2011.02.001
Lorenzetti *et al.* [83]	Neuroanatomical alterations in people with high and low cannabis dependence	10.1177/0004867419859077

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TABLE 1 (Continued)

Study	Title	DOI
Lorenzetti *et al.* [84]	Cannabis Dependence is Associated with Reduced Hippocampal Subregion Volumes Independently of Sex: Findings from an ENIGMA Addiction Working Group Multi-Country Study	10.1089/can.2023.0204
Luhar *et al.* [85]	Brain volumes and neuropsychological performance are related to current smoking and alcoholism history	10.2147/NDT.S52298
Luo *et al.* [86]	Alcohol and cannabis co-use and longitudinal gray matter volumetric changes in early and late adolescence	10.1111/adb.13208
Maple *et al.* [87]	Anterior cingulate volume reductions in abstinent adolescent and young adult cannabis users: Association with affective processing deficits	10.1016/j.pscychresns.2019.04.011
Mashhoon *et al.* [88]	Cortical thinness and volume differences associated with marijuana abuse in emerging adults	10.1016/j.drugalcdep.2015.06.016
Mata *et al.* [89]	Gyrification brain abnormalities associated with adolescence and early-adulthood cannabis use	10.1016/j.brainres.2009.12.069
McQueeny *et al.* [90]	Gender effects on amygdala morphometry in adolescent marijuana users	10.1016/j.bbr.2011.05.031
Medina, Nagel, *et al.* [91]	Depressive symptoms in adolescents: Associations with white matter volume and marijuana use	10.1111/j.1469-7610.2007.01728.x
Medina, Schweinsburg, *et al.* [92]	Effects of alcohol and combined marijuana and alcohol use during adolescence on hippocampal volume and asymmetry	10.1016/j.ntt.2006.10.010
Medina *et al.* [93]	Prefrontal cortex morphometry in abstinent adolescent marijuana users: Subtle gender effects	10.1111/j.1369-1600.2009.00166.x
Medina *et al.* [94]	Abnormal cerebellar morphometry in abstinent adolescent marijuana users	10.1016/j.pscychresns.2009.12.004
Meier *et al.* [95]	Associations between adolescent cannabis use frequency and adult brain structure: A prospective study of boys followed to adulthood	10.1016/j.drugalcdep.2019.05.012
Meier *et al.* [96]	Long-Term Cannabis Use and Cognitive Reserves and Hippocampal Volume in Midlife	10.1176/appi.ajp.2021.21060664
Moreno-Alcázar *et al.* [97]	Larger gray matter volume in the basal ganglia of heavy cannabis users detected by voxel-based morphometry and subcortical volumetric analysis	10.3389/fpsyt.2018.00175
Navarri *et al.* [98]	How do substance use disorders compare to other psychiatric conditions on structural brain abnormalities? A cross-disorder meta-analytic comparison using the ENIGMA consortium findings	10.1002/hbm.25114
Otsuka *et al.* [99]	Basic lifestyle habits and volume change in total gray matter among community dwelling middle-aged and older Japanese adults	10.1016/j.ypmed.2022.107149
Owens *et al.* [100]	Recent cannabis use is associated with smaller hippocampus volume: High-resolution segmentation of structural subfields in a large non-clinical sample	10.1111/adb.12874
Paul *et al.* [101]	Chronic cigarette smoking and the microstructural integrity of white matter in healthy adults: A diffusion tensor imaging study	10.1080/14622200701767829
Pennington 2015 [102]	Alcohol use disorder with and without stimulant use: Brain morphometry and its associations with cigarette smoking, cognition, and inhibitory control	10.1371/journal.pone.0122505
Price *et al.* [103]	Effects of marijuana use on prefrontal and parietal volumes and cognition in emerging adults	10.1007/s00213-015-3931-0
Radoman *et al.* [104]	Marijuana use and major depressive disorder are additively associated with reduced verbal learning and altered cortical thickness	10.3758/s13415-019-00704-4
Rais *et al.* [105]	Excessive brain volume loss over time in cannabis-using first-episode schizophrenia patients	10.1176/appi.ajp.2007.07071110
Rapp *et al.* [106]	Cannabis use and brain structural alterations of the cingulate cortex in early psychosis	10.1016/j.pscychresns.2013.06.006
Ringin *et al.* [107]	The impact of smoking status on cognition and brain morphology in schizophrenia spectrum disorders	10.1017/S0033291720005152
Romero *et al.* [108]	Multiple sclerosis, cannabis, and cognition: A structural MRI study	10.1016/j.nicl.2015.04.006
Rossetti *et al.* [109]	Sex and dependence related neuroanatomical differences in regular cannabis users: findings from the ENIGMA Addiction Working Group	10.1038/s41398-021-01382-y

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TABLE 1 (Continued)

Study	Title	DOI
Schacht *et al.* [110]	Associations between cannabinoid receptor-1 (CNR1) variation and hippocampus and amygdala volumes in heavy cannabis users	10.1038/npp.2012.92
Scheffler *et al.* [111]	Cannabis use and hippocampal subfield volumes in males with a first episode of a schizophrenia spectrum disorder and healthy controls	10.1016/j.schres.2021.02.017
Scott *et al.* [112]	Cannabis use in youth is associated with limited alterations in brain structure	10.1038/s41386-019-0347-2
Shang *et al.* [113]	Association of greenspace and natural environment with brain volumes mediated by lifestyle and biomarkers among urban residents	10.1016/j.archger.2024.105546
Shen *et al.* [114]	Altered function but not structure of the amygdala in nicotine-dependent individuals	10.1016/j.neuropsychologia.2017.11.003
Szeszko *et al.* [115]	Anterior cingulate grey-matter deficits and cannabis use in first-episode schizophrenia	10.1192/bjp.bp.106.024521
Thayer *et al.* [116]	Preliminary results from a pilot study examining brain structure in older adult cannabis users and nonusers	10.1016/j.pscychresns.2019.02.001
Thayer, [117]	Marijuana use in an aging population: Global brain structure and cognitive function	
Tzilos *et al.* [118]	Lack of hippocampal volume change in long-term heavy cannabis users	10.1080/10550490590899862
Valsdóttir *et al.* [119]	Cognition and brain health among older adults in Iceland: the AGES-Reykjavik study	10.1007/s11357-022-00642-z
Van Haren *et al.* [120]	Cigarette smoking and progressive brain volume loss in schizophrenia	10.1016/j.euroneuro.2010.02.009
Verde, [121]	Structural abnormalities within the episodic prospection and decision making circuitry in cigarette smokers: A DTI and sMRI analysis	
Vered *et al.* [122]	The association between cannabis use and neuroimaging measures in older adults: findings from the UK biobank	10.1093/ageing/afae068
Wallace *et al.* [123]	Amygdala volume and depression symptoms in young adolescents who use cannabis	10.1016/j.bbr.2024.115150
C. Wang *et al.* [124]	Gray matter volumes of insular subregions are not correlated with smoking cessation outcomes but negatively correlated with nicotine dependence severity in chronic smokers	10.1016/j.neulet.2018.12.013
C. Wang *et al.* [125]	Increased thalamic volume and decreased thalamo-precuneus functional connectivity are associated with smoking relapse	10.1016/j.nicl.2020.102451
Y. Wang *et al.* [126]	Reduction in hippocampal volumes subsequent to heavy cannabis use: a 3-year longitudinal study	10.1016/j.psychres.2020.113588
Weiland *et al.* [127]	Daily Marijuana Use Is Not Associated with Brain Morphometric Measures in Adolescents or Adults	10.1523/JNEUROSCI.2946-14.2015
Welch *et al.* [128]	Impact of cannabis use on thalamic volume in people at familial high risk of schizophrenia	10.1192/bjp.bp.110.090175
Xu *et al.* [129]	Aberrant hippocampal shape development in young adults with heavy cannabis use: Evidence from a longitudinal study	10.1016/j.jpsychires.2022.06.037
Yip *et al.* [130]	Pretreatment measures of brain structure and reward-processing brain function in cannabis dependence: An exploratory study of relationships with abstinence during behavioral treatment	10.1016/j.drugalcdep.2014.03.031
Yu *et al.* [131]	Reduced thalamus volume may reflect nicotine severity in young male smokers	10.1093/ntr/ntx146
Yuan *et al.* [132]	The implication of frontostriatal circuits in young smokers: A resting-state study	10.1002/hbm.23153
Zhao *et al.* [133]	Age-Related Differences in Brain Morphology and the Modifiers in Middle-Aged and Older Adults	10.1093/cercor/bhy300

C.C., S. Daryan, S.H. or V.L.). K.S. checked for consistency and discrepancies were resolved by discussion or contacting a third reviewer. Where there was limited information to determine study inclusion, data extraction or synthesis, the authors of the study were contacted for further information. For more information on data extraction, see Appendix S1.

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TABLE 2 Characteristics of cross-sectional cannabis studies included in meta-analysis.

Study ID	Exposure	Comparator	Outcome regions in meta-analysis	Country	Population	Comparator *n* (males)	Comparator age (mean, SD), years	Exposure *n* (males)	Exposure age (mean, SD), years	Risk of bias (%)	Covariates adjusted for in adjusted analysis
Ashtari 2011	CUD	Non-user (< 5 lifetime exposures)	ICV, hippocampus, amygdala	USA	Psychiatric population	14 (14)	18.5 (1.4)	14 (14)	19.3 (0.1)	33.3	TBV, WRAT-111 (reading scores)
Batalla 2018	>14 joints/week for >2 years, positive urine toxicology	Non-user (<15 times, no use in past month, negative urine toxicology)	Hippocampus, Hippocampus CA1, CA2/3, CA4, fimbria, fissure, presubiculum, subiculum	Spain	General	29 (29)	22.4 (3.3)	30 (30)	21.0 (2.3)	66.7	
Block 2000	>7 times/week	Non-using	Cerebellum, hippocampus, ICV	USA	General	13 (6)	22.3 (1.8)	18 (9)	22.6 (2.1)	25.0	ICV by height and sex, cerebellum and hippocampus by ICV and sex
Buchy 2016	Use at baseline (1–4 time/month, 1–4 times/week, almost daily)	Non-using at baseline (abstinent)	Amygdala, hippocampus, thalamus	USA	Psychiatric population	387 (NS)	18.6 (4.2) whole sample	132 (NS)	18.6 (4.2) whole sample	25.0	ICV, scanner site
Cahn 2004	≥ 3 days/week in 3 months before scan	Never used (cannabis-naïve)	TBV, TGMV, TWMV, ICV, cerebellum, caudate	Netherlands	Psychiatric population	20 (17)	27.61 (5.33)	27 (25)	21.13 (3.12)	50.0	Age, ICV/TBV
Churchwell 2010	Abuse/dependence	Non-using (healthy controls)	Lateral OFC, medial OFC, OFC	USA	General	18 (12)	17.2 (0.82)	18 (16)	17.7 (0.94)	25.0	TBV
Churchwell 2012	Abuse/dependence	Non-using (healthy controls)	Accumbens, caudate, putamen	USA/South Africa	Psychiatric population	9 (3)	15.60 (1.43)	8 (3)	16.20 (1.15)	41.7	TBV
Chye 2017b	Dependent users	Non-using (healthy controls)	Hippocampus total, CA1, CA2/3, presubiculum, subiculum, CA4, DG and TGMV	Australia	General	35 (18)	30.37 (11.46)	39 (18)	30.38 (9.99)	75.0	
Cohen 2012	Current cannabis use	Non-using with no history of use	Cerebellum, cerebellar grey matter, cerebellar white matter	Australia	General and Psychiatric population	C: 19 (15) FES: 13 (12)	C: 21.5 (2.3) FES: 20.7 (3.6)	CU C: 17 (15) CU FES: 6 (4)	CU C: 22.7 (2.4) CU FES: 21.8 (1.9)	41.7	

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TABLE 2 (Continued)

Study ID	Exposure	Comparator	Outcome regions in meta-analysis	Country	Population	Comparator *n* (males)	Comparator age (mean, SD), years	Exposure *n* (males)	Exposure age (mean, SD), years	Risk of bias (%)	Covariates adjusted for in adjusted analysis
D'Souza 2021	CUD	Non-using (healthy controls)	ICV, hippocampus	USA	General	12 (7)	27.32 (4.41)	12 (8)	24.24 (3.12)	83.3	ICV
Gilman 2014	Once/week, not dependent	Non-using (not in last year, <5 times/life)	Accumbens, amygdala, caudate, hippocampus, putamen, thalamus, ICV, TBV, TGMV, TWMV	USA	General	20 (9)	20.7 (1.9)	20 (9)	21.3 (1.9)	58.3	Age, sex, alcohol use and cigarette smoking
James 2011	>3 days/week for >6 months	Non-using	TBV, TGMV, TWMV	UK	Psychiatric population	16 (11)	16.2 (1.2)	16 (11)	16.4 (1.1)	66.7	
Knodt 2022	At least weekly in the past year/ were dependent at age 45 years	Non-using (lifelong)	TBV, accumbens, amygdala, brainstem, caudate, cerebellum, hippocampus, pallidum, putamen, thalamus	New Zealand	General	192 (79)	45	82 (53)	45	58.3	Sex
Koenders 2015	CUD	Non-using (<5 times/life)	Amygdala, caudate, hippocampus, insula, putamen, thalamus, TGMV	Netherlands	Psychiatric population	33 (33)	22.15 (3.04)	80 (80)	22.18 (2.74)	41.7	ICV, age
Koenis 2021	CUD	Non-using	Accumbens, amygdala, caudate, hippocampus, pallidum, putamen, thalamus, cerebellum	USA	General	107 (51)	40 (range 19–70)	45 (22)	37 (range 19–69)	58.3	
Kumra 2012	CUD	Non-using (<5 times/life)	Hippocampus, rostral middle frontal gyrus	USA	General and psychiatric population	C: 51 (25) EOS: 35 (15)	C: 16.2 (2.3) EOS: 16.5 (1.8)	C: 16 (8) EOS: 13 (13)	C: 16.6 (1.7) EOS: 17.5 (1.5)	50.0	Age, sex, WRAT reading scores, ICV
Levar 2018	>1/week	Non-using (<5 times/life, no use past 6 months)	Accumbens, amygdala, caudate, hippocampus, ICV, putamen, thalamus, TGMV, TWMV	USA	General	22 (10)	21.59 (1.94)	19 (8)	20.58 (2.52)	58.3	Alcoholic drinks/ week, gender/ sex, ICV
Lopez-Larson 2011	>100 smokes/ previous year	Non-using (no history of use)	TBV	USA	General	18 (12)	17.3 (0.8)	18 (17)	17.8 (1)	25.0	

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TABLE 2 (Continued)

Study ID	Exposure	Comparator	Outcome regions in meta-analysis	Country	Population	Comparator *n* (males)	Comparator age (mean, SD), years	Exposure *n* (males)	Exposure age (mean, SD), years	Risk of bias (%)	Covariates adjusted for in adjusted analysis
Lorenzetti 2020	High dependence	Non-using	Accumbens, amygdala, caudate, cerebellar grey matter, cerebellar white matter, hippocampus, pallidum, putamen	Australia	General	37 (18)	29.95 (11.29)	25 (12)	31.28 (10.44)	50.0	
Lorenzetti 2024	Cannabis dependence	Non-using (differed by site: site 1, <50 joints/lifetime and no use in last year; site 2, 14–28 joints/week over last 2 years; site 3, <1 times/lifetime and no use in last year)	Amygdala, amygdala basolateral nucleus, amygdala central nucleus, hippocampus, hippocampus CA1, hippocampus CA3, hippocampus subiculum, hippocampus dentate gyrus, ICV	Cross-country, ENIGMA Addiction Working Group	General	98 (65)	M: 24.02 (7.20) F: 25.50 (9.06)	59 (42)	M: 24.91 (8.07) F: 26.46 (9.12)	75.0	Sex, age, IQ, alcohol, tobacco, ICV
Mashhoon 2015	Abuse/dependence, >5/7 days prior to the study visit, positive urine screening	Non-using (<5 times/life)	Thalamus	USA	General	15 (13)	22.3 (3.5)	15 (13)	21.8 (3.6)	66.7	ICV
Mata 2010	Once/week for last 3 years	Non-using	ICV	Spain	General	44 (25)	25.8 (5.8)	30 (23)	25.7 (5.0)	33.3	
McQueeny 2011	Chronic use	Non-using	ICV, amygdala	USA	General	47 (36)	17.7 (0.9)	35 (27)	18.0 (0.9)	41.7	ICV, lifetime drinking occasions, nicotine dependence and lifetime episodes of any drug other than alcohol, nicotine or marijuana

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TABLE 2 (Continued)

Study ID	Exposure	Comparator	Outcome regions in meta-analysis	Country	Population	Comparator *n* (males)	Comparator age (mean, SD), years	Exposure *n* (males)	Exposure age (mean, SD), years	Risk of bias (%)	Covariates adjusted for in adjusted analysis
Medina 2007a	Past 3 months and lifetime use	Non-using (<40 lifetime uses)	ICV, hippocampus	USA	Psychiatric population	16 (11)	16.9 (0.7)	26 (16)	17.6 (0.9)	66.7	ICV
Medina 2007b	Past-month use, >60 lifetime use	Non-using (<5 cannabis uses)	TWMV, hippocampus	USA	General	16 (11)	18.0 (0.9)	16 (12)	18.0 (0.7)	50.0	ICV
Medina 2009	Past-month use, >60 lifetime use	Non-using (none past month, <5 lifetime)	PFC	USA	General	16 (10)	F: 18.5 (0.5) M: 17.7 (1.1)	16 (12)	F: 18.2 (0.6) M: 18.1 (0.8)	50.0	ICV, gender, lifetime alcohol use
Medina 2010	Past-month use, >60 lifetime use	Non-using (<5 cannabis uses)	Cerebellum	USA	General	16 (10)	18.0 (0.7)	16 (12)	18.0 (0.9)	50.0	ICV, gender, lifetime alcohol use, and lifetime other drug use (any drugs besides alcohol, nicotine or marijuana)
Meier 2019	Chronic use (age 13–19 years)	Non-using (infrequent/no use, age 13–19 years)	Accumbens, amygdala, caudate, hippocampus, pallidum, putamen, rostral middle frontal gyrus	USA	General	87 (87)	30–36 whole sample	33 (33) chronic use	30–36 whole sample	75.0	Race, ICV, age, years of violence for ages 11–25 years, conduct problems, childhood SES, and alcohol and tobacco use trajectories
Meier 2022	At least weekly in the past year/ were dependent at age 45 years	Non (life-long non users)	Hippocampus, hippocampus CA1, CA3, CA4, fimbria, fissure, parasubiculum, presubiculum, subiculum, tail	New Zealand	General	202 (82)	45	86 (55)	45	66.7	
Moreno-Alcazar 2018	3 joints/day for last 5 years	Non (no use in last year)	accumbens, amygdala, brainstem, caudate, hippocampus, pallidum, putamen, thalamus	Spain	General	100 (40)	31.3 (6.9)	14 (4)	30.1 (5.2)	58.3	ICV

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TABLE 2 (Continued)

Study ID	Exposure	Comparator	Outcome regions in meta-analysis	Country	Population	Comparator *n* (males)	Comparator age (mean, SD), years	Exposure *n* (males)	Exposure age (mean, SD), years	Risk of bias (%)	Covariates adjusted for in adjusted analysis
Navarri 2022	CUD	Non (no SUD)	Accumbens, amygdala, caudate, hippocampus, pallodum, putamen, thalamus	Cross-country, ENIGMA Consortium	General	247 (175)	24.88	200 (139)	23.8	58.3	Age, sex, ICV
Owens 2021	Recent use, positive urine toxicology screen for THC	Non-using (negative urine toxicology for THC)	Amygdala, hippocampus, CA1, CA2/3, CA4, fimbria, fissure, parasubiculum, presubiculum, subiculum, tail, ICV	USA	General	961 (411)	28.93 (3.65)	119 (80)	28.02 (3.82)	75.0	ICV, age, gender, income, education, twin status, drinks/week, tobacco use days/week, other illicit drugs use
Price 2015	>25 past-year joints, >50 joints in lifetime	Non-using (<5 past year joints, <50 lifetime joints)	Lateral OFC, medial OFC, PFC	USA	General	32 (14)	21.1 (2.3)	27 (15)	21.4 (2.2)	66.7	ICV, gender, WRAT-4 reading score, BMI, past year alcohol, nicotine and hallucinogen use
Radoman 2019	Weekly use	Non-users (<5 times/life)	Hippocampus	USA	Psychiatric population	C: 48 (23) MDD: 52 (12)	C: 21.5 (2.0) MDD: 22.1 (2.5)	CU: 46 (24) CU MDD: 24 (11)	CU: 20.3 (2.1) CU MDD: 21.3 (2.4)	58.3	Age, gender, ICV
Romero 2015	2–7 days/week, positive urine toxicology	Never-users	TGMV, TWMV	Canada	Physical health	19 (13)	43.89 (9.085)	20 (14)	41.3 (11.28)	41.7	
Rosetti 2021	Regular use/dependence	Non-using	Accumbens, amygdala, cerebellar grey matter, cerebellar white matter, hippocampus, insula, lateral OFC, medial OFC	Cross-country, ENIGMA Consortium	General	114 (81)	26.19 (9.10)	129 (91)	27.54 (10.12)	75.0	ICV, age, IQ, monthly standard drinks, monthly cigarettes
Schacht 2012	4 times/week in past 6 months	never used regularly in last 6 months	Amygdala, hippocampus, ICV	USA	General	37 (14)	27.8 (8.7)	37 (14)	27.3 (7.9)	58.3	ICV, CPD

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TABLE 2 (Continued)

Study ID	Exposure	Comparator	Outcome regions in meta-analysis	Country	Population	Comparator *n* (males)	Comparator age (mean, SD), years	Exposure *n* (males)	Exposure age (mean, SD), years	Risk of bias (%)	Covariates adjusted for in adjusted analysis
Scheffler 2021	Past 3-months use	No use in past 3 months	Hippocampus:CA1, CA3, CA4, fimbria, fissure, presubiculum, parasubiculum, subiculum, tail	South Africa	Psychiatric population	FES: 45(45) C: 42(42)	FES: 25.9 (7.1) C: NS	FES: 18 (18) C: 16 (16)	FES: 21.2 (4.03) C: NS	41.7	
Thayer 2019a	Weekly use	Never-users	Accumbens, amygdala, brainstem, caudate, hippocampus, pallidum, putamen, thalamus, TGMV, TWMV	USA	General	28 (11)	69.79 (5.71)	28 (18)	66.79 (5.28)	50.0	Age, ethnicity, sex
Tzilos 2005	Smoked >5000 separate occasions	Non (no history of use)	Hippocampus, TGMV, TWMV, TBV	USA	General	26 (19)	29.5 (8.5)	22 (16)	38.1 (6.2)	33.3	Age, ethnicity, sex
Wallace 2024	Cannabis use (positive toxicology test)	Non-use ('denied' use and no positive toxicological test)	Amygdala	USA	General	112 (57)	14.3 (0.7)	112 (56)	14.3 (0.7)	58.3	TBV, scanner
Vered 2024	Current cannabis use (last use within 1 year before MRI exam)	No-use	TBV, TWMV, TGMV, peripheral cortical grey matter volume, hippocampus	UK	General	16 132 (7524)	68.4 (5.1)	67 (NS)	68.0 (5.0)	66.7	Age, age-squared, sex, tobacco smoking, alcohol use, socio-economic status, obesity, physical activity and history of ischaemic heart disease, hypertension, diabetes and mood disorders
Weiland 2015	Daily users	Non (no use in last 60 days)	Accumbens, amygdala, cerebellum, hippocampus, ICV, TBV, TGMW, TWMV,	USA	General	Adults: 29 (16) Adolescents: 50(36)	Adults: 27.5 (6.8) Adolescents: 16.8 (1.0)	Adults: 29 (16) Adolescents: 50(41)	Adults: 27.4 (7.1) Adolescents: 16.7 (1.1)	58.3	ICV

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TABLE 2 (Continued)

Study ID	Exposure	Comparator	Outcome regions in meta-analysis	Country	Population	Comparator *n* (males)	Comparator age (mean, SD), years	Exposure *n* (males)	Exposure age (mean, SD), years	Risk of bias (%)	Covariates adjusted for in adjusted analysis
Yip 2014	CUD	Non (no SUD except nicotine)	Putamen	USA	General	20 (20)	29.2 (SE 2.3)	20 (20)	26.7 (SE 2.2)	33.3	TBV

Abbreviations: ABCD study = Adolescent Brain Cognitive Development Study; BMI = body mass index; C = Controls; CA1 = cornu Ammonis 1; CA2/3 = cornu Ammonis 2/3; CA4 = cornu Ammonis 4; CPD = cigarettes per day; CU = cannabis using group; CUD = cannabis use disorder; DG = dentate gyrus; ENIGMA = Enhancing Neuro Imaging Genetics Through Meta Analysis; EOS = early onset schizophrenia; F = female; FES = first episode schizophrenia; ICV = intracranial volume; IQ = intelligence quotient; M = male; MDD = major depressive disorder; MRI = magnetic resonance imaging; NS = not stated; OFC = orbitofrontal cortex; PFC = prefrontal cortex; SUD = substance use disorder; TBV = total brain volume; TGMV = total grey matter volume; THC = tetrahydrocannabinol; TWMV = total white matter volume; WRAT = Wide Range Achievement Test.

Risk of bias assessment

Risk of bias (ROB) was assessed using an adapted version of the Newcastle–Ottawa Scale (NOS), split by cross-sectional and longitudinal study designs [135]. The NOS assesses studies on ascertainment of exposure, comparability and outcome assessment. The adapted version used in this review is outlined in Appendix S1. Studies were given one or two stars if they presented a low ROB in these categories and the number of stars was then summed to give an overall score. Owing to cannabis studies having one extra ROB criterion, scores were standardised as percentages to aid interpretation, where higher scores indicate a lower ROB.

The quality of MR studies was assessed using a quality assessment framework undertaken in a previous review of MR studies in addiction [136]. The system gives each study a total score of '−', '−/+' or '+', based on key factors important in the validity of MR studies (phenotype measurement, instrument strength, sample size and analytical methods) [136]. For a study to be scored as sufficient (−/+) the study must have sufficient sample size and analytical methods (e.g. instrument strength, temporality and harmonisation, same ethnic group, sample overlap reported, analyses addressing horizontal pleiotropy) [136].

Meta-analysis of brain volume

Specific brain regions were included in the meta-analysis if they were examined by at least three studies. Analysis was organised by study exposure and methodology (cross sectional, longitudinal) for each outcome region. For each region we calculated Hedges' *g* for differences between user and non-user groups in individual studies, using the *esc* package in R [137, 138]. Hedges' *g* represents the effect size of the standardised mean difference [139], and was used to allow for variation in outcome measures and small sample bias (common to neuroimaging studies) [139]. Where necessary, Hedges' *g* values were aggregated across left and right hemispheres (for more information, see Appendix S1). Individual Hedges' *g* estimates were then synthesised using generic inverse variance random effects meta-analysis for each exposure comparison in distinct brain regions, using the *meta* and *metafor* packages in R [137, 140, 141]. Random-effects models were used to account for heterogeneity across studies.

Meta-analyses were split into adjusted and unadjusted estimates for each outcome. Adjusted analyses included studies where the comparison of group differences was statistically adjusted for potential confounding factors, or means adjusted, for example by intracranial volume (ICV) or total brain volume (TBV; either in the MRI pipeline or statistically). Unadjusted analysis included studies that only matched groups on key confounding factors (e.g. age and/or sex) or reported raw volumes (i.e. not adjusted by ICV or any other variable in either the MRI pipeline or statistically). If a study reported both adjusted and unadjusted data, it was included in both the adjusted and unadjusted analyses.

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TABLE 3 Characteristics of cross-sectional tobacco studies included in meta-analysis.

Study ID	Exposure	Comparator	Outcome regions in meta-analysis	Country	Population	Comparator *n* (males)	Comparator age (mean, SD), years	Exposure *n* (males)	Exposure age (mean, SD), years	Risk of bias (%)	Covariates adjusted for in adjusted analysis
Austin 2022	Current smokers	Never smokers	TBV, TGMV, TWMV	USA	Physical health	493 (NS)	72 (8) whole sample	60 (NS)	72 (8) whole sample	63.6	Age, sex and MESA site; total intracranial volume, BMI, smoking status, systolic and diastolic blood pressure, use of hypertension medication, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, diabetes status and estimated glomerular filtration rate
Binnewies 2023	Smoking (current smoking)	No current smoking	Hippocampus, TGMV	Europe cross-country, European Lifebrain Consortium	General	2727 (1425)	NS	333 (160)	NS	54.5	Age, sex, education, scanner and ICV
Brody 2004	>20 CPD and DSM nicotine dependence	<5 cig inlifetime	Thalamus	USA	General	17 (10)	37.9 (12.9)	19 (11)	39.5 (10.3)	72.7	Age, gender
Cardenas 2020	>10 CPD, past 5 years	Never or <40 cig in lifetime	Cerebellum, ICV	USA	Psychiatric population	C: 17(14) ALC: 21(16)	C: 48(12) ALC: 51(12)	C: 31(27) ALC: 23(21)	C: 49(9) ALC: 49(7)	63.6	
Chen 2023	Active smoking in last 2 weeks	Never or <100 cigs/ life	Amygdala, insula, hippocampus, thalamus, caudate, putamen, pallidum, nucleus accumbens, ICV	USA	General	1106 (387)	F: 48.91 (10.97) M: 48.64 (10.19)	402 (188)	F: 49.20 (9.33) M: 48.08 (9.95)	54.5	Age, annual alcohol consumption, ICV
Cho 2016	Current smokers	Never smoker	ICV	Korea	General	270 (270)	66.1 (7.1)	128 (128)	62.7 (7.3)	27.3	
Choi 2010	Currently smoking (yes/no)	Not currently smoking (yes/no)	Corpus callosum, ICV	Korea	General	28 (28)	35.49 (13.11)	30 (30)	32.82 (14.12)	36.4	

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TABLE 3 (Continued)

Study ID	Exposure	Comparator	Outcome regions in meta-analysis	Country	Population	Comparator *n* (males)	Comparator age (mean, SD), years	Exposure *n* (males)	Exposure age (mean, SD), years	Risk of bias (%)	Covariates adjusted for in adjusted analysis
Chye 2020	Nicotine dependence	Non-smokers/ do not use nicotine	ICV	Cross-country, ENIGMA Consortium	General	918 (561)	29.7 (9.6)	565 (325)	31.1 (9.9)	81.8	
Durazzo 2007a	Smoking every day or at least once/day for 6 months prior to study	No use 6 months prior to enrolment	Frontal GM, parietal GM, temporal GM	USA	Physical health	17 (14.96)	44.4 (4.9)	27 (24.03)	43.8 (5.4)	36.4	Age
Durazzo 2013a	Chronic smoking, at least 10 CPD for 5 years or more	Never smoked, or <40 lifetimes cigarettes, with no use in 10 years prior to study	Hippocampus, CA1, CA2/3, CA4-DG, subiculum	USA	General	43 (35)	46.5 (11)	39 (33)	43.3 (12.6)	72.7	ICV, education, average lifetime drinks/month
Durazzo 2013b	'Smokers' undefined	Lifetime non-smoking	ICV	USA	Psychiatric population	33 (NS)	52.0 (9.7)	43 (NS)	50.1 (8.9)	45.5	
Durazzo 2017	10 CPD, past 5 years	Never or <40 cig in lifetime	Cerebellar cortex, thalamus	USA	General	43 (34.83)	43 (13)	40 (34.80)	47 (11)	72.7	BDI, average lifetime drinks/month
Durhan 2016	Current smokers (undefined)	<5 cig in lifetime	Cerebellar cortex, thalamus, ICV	Turkey	Physical health	C: 14 (4) CIS: 17 (4)	C: 29.8 (7.9) CIS: 29.7 (6.9)	C: 13 (7) CIS: 16 (8)	C: 33.7 (7.4) CIS: 34.3 (8.9)	18.2	
Duriez 2014 - cross-sectional	Current smoker	Never smoker	Hippocampus, ICV, TBV, TGMV, TWMV	France	General	920 (162)	M: 72.3 (4) F: 72.7 (4.06) whole sample	83 (49)	M: 72.3 (4) F: 72.7 (4.06) whole sample	54.5	
Elbejjani 2019	>5 cigs/ week almost every week, for at least 3 months	Never regular use	Accumbens, amygdala, caudate, frontal GM, hippocampus, parietal GM, putamen, temporal GM, thalamus, TBV, TGMV, TWMV	USA	General	362 (173)	50.18 (3.61)	117 (60)	49.63 (3.57)	81.8	Age, race, educational attainment, total ICV, study centre, substance use and psychological composite factor

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TABLE 3 (Continued)

Study ID	Exposure	Comparator	Outcome regions in meta-analysis	Country	Population	Comparator *n* (males)	Comparator age (mean, SD), years	Exposure *n* (males)	Exposure age (mean, SD), years	Risk of bias (%)	Covariates adjusted for in adjusted analysis
Gazdzinksi 2005	<1/2 times/ week in the past 6 months	No use for at least 1 year before enrolment	Caudate, cerebellum, frontal GM, parietal GM, temporal GM, thalamus, ICV	USA	Psychiatric population	nsLD: 23 (23) nsALC: 13 (13)	nsLD: 47.5 (6.0); nsALC: 49.8 (9.7)	sLD: 7 (7); sALC: 24 (24)	sLD: 38.1 (8.7) sALC: 49.4 (8.3)	63.6	Age
Janowitz 2014	>15 CPD	Never smokers	Hippocampus	Germany	General	991 (NS)	NS	235 (NS)	NS	63.6	Gender, age, height, education, alcohol consumption, depression, physical activity, waist circumference, HbA1c, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, diastolic blood pressure, antidepressants, antidiabetics, lipid-lowering drugs, antihypertensive medication
Launer 2015	Current smokers (undefined)	Never-smokers	TBV	USA	General	412 (NS)	50.3 (3.50) whole sample	107 (NS)	50.3 (3.50) whole sample	45.5	Age, sex, race, ICV
Li 2015	DSM nicotine dependence	<5 cigs/life, none past 10 years	Accumbens, caudate, putamen	China	General	22 (22)	19.3 (2.6)	27 (27)	19.7 (2.0)	72.7	Age, ICV
Liang 2022	Current past 6 months, >10 CPD for 2+ years	Lifetime <2 pack years, not smoked for past 2 years	Caudate, hippocampus, putamen, thalamus	USA	Physical health	SN: 43 (41) PWH: 106 (89)	SN: 47.2 (13.6) PWH: 51.0 (9.5)	SN: 65 (51) PWH: 40 (37)	SN: 43.7 (12.4) PWH: 48 (10.1)	63.6	Age, sex, ICV, cannabis use duration
Lie 2022	>85 nmol/l serum cotinine level, self-reported smoked regularly past 10 years	Serum cotinine levels ≤85 nmol/ L, did not report regular smoking, only snuff use	Thalamus, TGMV, TWMV	Norway	Physical health	37 (15)	37.5 (6.8)	47 (15)	37.9 (9.7)	63.6	Age, sex, vascular disease, ICV, BL EDSS, time from diagnosis

(Continues)

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TABLE 3 (Continued)

Study ID	Exposure	Comparator	Outcome regions in meta-analysis	Country	Population	Comparator *n* (males)	Comparator age (mean, SD), years	Exposure *n* (males)	Exposure age (mean, SD), years	Risk of bias (%)	Covariates adjusted for in adjusted analysis
Lin 2021	>10 CPD, last year	<5 cig in lifetime	Accumbens, amygdala, caudate, hippocampus, ICV, pallidum, putamen, thalamus	USA	General	67 (39)	M: 22.54 (3.09) F: 24.44 (3.29)	60 (35)	M: 22.54 (2.62) F: 22.50 (2.89)	54.5	
Linli 2023	Currently smoke on most or all days	Never smoker	ICV, TGMV, 166 cortical and subcortical regions	UK	General	14 667 (6418)	63.12 (7.52)	1254 (644)	61.84 (7.29)	63.6	Age, sex, handedness, ethnicity, BMI, alcohol status, imaging site, and ICV
Luhar 2013	Current smoker (undefined)	Non-smoker (undefined)	Pallidum	USA	Psychiatric population	NALC: 7 (4) ALC: 7 (4)	NALC: 50.4 (9.8) ALC: 52.7 (11.2)	NALC: 6 (66.7%) ALC: 7 (57.1%)	NALC: 47.0 (7.8) ALC: 51.1 (11.2)	54.5	
Ringin 2022	Current smoker (currently smoke cigarettes daily)	Non-smoker (responded no to have you ever smoked cigarettes etc., regularly)	Thalamus, hippocampus, amygdala, caudal anterior cingulate, rostral anterior cingulate, posterior cingulate, pars opercularis, pars orbitalis, pars triangularis, rostral middle frontal, lateral orbitofrontal, medial orbitofrontal, superior temporal, insula	Australia	Psychiatric population	125 (63)	C: 37.2 (14.7) S: 38.1 (9.4)	158 (119)	C: 40.9 (12.8) S: 37.2 (10.0)	54.5	Age, gender, site
Shang 2024	Current smoker	Never smoker	TBV, TGMV, TWMV	UK Biobank	General	20 997 (NS)	NS	2183 (NS)	NS	54.5	Age, gender
Shen 2017	>10 CPD in last year, DSM nicotine dependence	<20 cig in lifetime, none in past 10 years	Amygdala	China	General	41 (41)	38.46 (8.60)	84 (84)	38.23 (6.85)	27.3	
Wang 2020	>10 CPD in last year, DSM nicotine dependence	<20 cig in lifetime, none in past 10 years	ICV, thalamus	China	General	41 (41)	38.5 (8.6)	84 (84)	38.2 (6.8)	81.8	

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TABLE 3 (Continued)

Study ID	Exposure	Comparator	Outcome regions in meta-analysis	Country	Population	Comparator *n* (males)	Comparator age (mean, SD), years	Exposure *n* (males)	Exposure age (mean, SD), years	Risk of bias (%)	Covariates adjusted for in adjusted analysis
Yu 2018	DSM-V nicotine dependence, >10 cigs/day, CO > 6 ppm	<5 cigs/life, CO < 4 ppm	ICV, thalamus	China	General	36 (36)	20.1 (1.2)	36 (36)	20.8 (1.8)	72.7	ICV
Yuan 2016	Tobacco	Non-smoker	Accumbens, caudate, putamen	China	General	60 (52)	19.95 (1.8)	60 (53)	20.0 (1.7)	45.5	ICV

Abbreviations: ALC = alcohol drinking/dependent sample; BDI = Beck's depression inventory; BL EDSS = baseline expanded disability status scale; C = controls; cig = cigarette; CIS = clinically isolated syndrome; CPD = cigarettes per day; DG = dentate gyrus; DSM = Diagnostic Statistical Manual; ENGIMA = Enhancing Neuro Imaging Genetics Through Meta Analysis; F = female; GM = grey matter; ICV = intracranial volume; M = male; NALC = non-alcoholic participants; NS = not stated; nsALC = non-smoking alcohol-dependent individuals; nsLD = non-smoking light drinkers; PWH = people with human immunodeficiency virus (HIV); S = schizophrenia spectrum disorders; SALC = smoking alcohol-dependent individuals; SLD = smoking light drinkers; SN = seronegative for human immunodeficiency virus (HIV); TBV = total brain volume; TGMV = total grey matter volume; TWMV = total white matter volume.

Statistical heterogeneity was quantified using I^2 (the percentage of variability in effect estimates arising from heterogeneity). As I^2 values between 50% and 75% indicate substantial heterogeneity, values in this range or above were considered problematic and the associated meta-analysis results should be treated with caution [139]. Small study bias was assessed using funnel plots, for evidence of asymmetry, and Egger's test. If there was evidence for bias, then Egger's trim and fill was conducted for that outcome [142].

All analyses were conducted using R 4.4.2. The R script and data are available on the Open Science Framework (DOI: 10.17605/OSF.IO/SFPK2). Studies were summarised narratively where a study met the inclusion criteria but there was not enough information for inclusion in any meta-analysis. Potential subgroup analyses proposed in the study protocol were not feasible owing to data availability. For meta-analyses that had I^2 values above 50%, sensitivity analyses (which were not registered) were conducted, where studies were removed to reduce heterogeneity. Studies were removed for high ROB, outlying effect sizes, large variance estimates, population characteristics or exposure definitions. Some regions could not be included in the sensitivity analysis as excluding a study would reduce the number of included studies to fewer than three.

RESULTS

The search identified 24 809 records. Further cross-referencing from searching relevant systematic reviews in the field [17, 20] identified an additional two records, totalling 24 811. Removal of duplicates resulted in 18 294 studies for title/abstract screening. Of these studies, 17 920 were excluded for not meeting the eligibility criteria. The full texts of 374 studies were screened. Of those studies, 271 were excluded (for a list of studies excluded with reasons for the exclusion, see Appendix S1), leaving 103 independent studies included in the review and 77 included in the meta-analysis (for a list of studies excluded along with reasons for exclusion, see Table 1) (for the PRISMA flowchart, see Appendix S1).

Overview of sample characteristics

Study characteristics are reported in Tables 2–7. For studies included in the cross-sectional meta-analysis of cannabis use, the overall sample comprised 18 247 (58% male) participants, aged between 14 and 70 years, of which 1965 (62% male) were people who use cannabis and 16 282 (57% male) were controls. In the cross-sectional tobacco analysis, the overall sample comprised 51 194 (24% male) participants, aged between 19 and 73 years, of which 6453 (36% male) were people who smoked tobacco and 44 741 (22% male) were controls. For the longitudinal tobacco analysis, the overall sample comprised 3357 (36% male) participants, aged between 59 and 72 years, of which 469 (66% male) were people who smoked tobacco and 2888 (30% male) were controls. The average time for follow-up was 3.78 years (range = 2–5 years). MRI data acquisition and processing varied among studies (Appendix S1).

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TABLE 4 Characteristics of cross-sectional co-use study.

Study ID	Exposure	Comparator	Outcome regions in meta-analysis	Country	Population	Comparator *n* (males)	Comparator age (mean, SD), years	Exposure *n* (males)	Exposure age (mean, SD), years	Risk of bias (%)	Covariates adjusted for in adjusted analysis
Filbey 2015	Co-use: cannabis and nicotine users	Non-using	Hippocampus	USA	General	16 (5)	26.88 (6.89)	19 (14)	23.26 (7.32)	75.0	IQ, gender, no. drinks/occasion, ADHD symptoms, age

Abbreviations: ADHD = attention deficit hyperactivity disorder; IQ = intelligence quotient.

Risk of bias assessments

Detailed ROB assessment results can be found in Appendix S1. Summary scores are reported in Tables 2–7. For cross-sectional studies, the average NOS ROB score was 53.8% (25.0%–83.3%) for cannabis and 54.3% (18.2%–81.8%) for tobacco, suggesting a moderate–substantial ROB.

For longitudinal studies, the average NOS ROB score was 60.7% (43.8%–68.8%) for cannabis and 60.7% (43.8%–68.8%) for tobacco, again suggesting a moderate–substantial ROB.

For the two MR studies, the quality rating was '+' for both [78, 143]. It is important to note that both studies used summary level data from the same data sets to obtain their genetic estimates, for both the exposures and the outcomes. Therefore, studies scored similarly on phenotype measurement and instrument strength, with both studies having good instrument strength. Both studies used extensive additional sensitivity methods, resulting in scores of '+' (see Appendix S1).

Cross-sectional studies: meta-analysis results

Cannabis versus control

Fifty cross-sectional studies were identified, 44 of which were included in the meta-analysis (*k* denotes the number of independent studies). A summary of the meta-analysis results is displayed in Figures 1–4 and Appendix S1. Forest plots of the analysis for each individual region are provided in Appendix S2. Narrative results are provided in Appendix S1.

In the adjusted analysis, there was a difference in amygdala volume between people who use cannabis and controls, with people who use cannabis having smaller amygdala volume compared with controls, with a small effect size (k = 17; Hedges' g = 0.13; 95% CI = 0.03, 0.23; P = 0.016; I^2 = 22.90%). There was no evidence of differences for any other region investigated in the adjusted analysis. Egger's test suggested asymmetry in the literature for ICV but implementing Egger's trim and fill did not change these results. The I^2 heterogeneity estimates varied across regions, but were generally moderate–substantial, with highest heterogeneity for the hippocampus CA1, hippocampus dentate gyrus (DG), medial OFC, pallidum, putamen and rostral middle frontal gyrus. Sensitivity analyses to reduce heterogeneity did not significantly change the results (Appendix S1).

In the unadjusted analysis there were differences in the volumes of the hippocampus and hippocampus fissure between people who use cannabis and controls. People who use cannabis had a smaller hippocampus than controls (k = 15; g = 0.28; 95% CI = 0.09, 0.47; P = 0.008; I^2 = 53.50%), but a larger fissure than controls (k = 4; g = −0.13; 95% CI = −0.23, −0.03; P = 0.026; I^2 = 0%). However, Egger's test suggested asymmetry in the unadjusted hippocampus analysis, and once Egger's trim and fill was implemented, differences in hippocampus volume between users and controls were no longer present (k = 19; g = 0.13; 95% CI = −0.12, 0.38; P = 0.279; I^2 = 68.70%). I^2

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TABLE 5 Characteristics of longitudinal cannabis studies.

Study ID	Exposure	Comparator	Outcome regions in meta-analysis	Country	Population	Comparator *n* (males)	Comparator age (mean, SD), years	Exposure *n* (males)	Exposure age (mean, SD), years	Risk of bias (%)	Covariates adjusted for in adjusted analysis
Garimella 2020	>10 days/ month for at least 2 years, no treatment for CUD	<50 times in life, not used in past year	Hippocampal tail, subiculum, CA1, presubiculum, parasubiculum, CA3, CA4, fimbria, whole hippocampus, hippocampal fissure, molecular layer, GC-ML-DG (molecular layer, dentate gryus), HATA (hippocampus–amygdala transition area)	Netherlands	General	17 (11)	21.5 (2.67)	17 (14)	20.7 (2.2)	68.8	
Koenders 2017	>10 uses/ month at least 2 years, smoked joints	<50 lifetime occasions	Hippocampus	Netherlands	General	23 (13)	21.79 (2.6)	20 (14)	20.64 (2.23)	68.8	
Luo 2022	Use at baseline	Non-use at baseline	Superior temporal sulcus, caudal anterior cingulate cortex, caudal middle frontal cortex, cuneus cortex, entorhinal cortex, fusiform gyrus, inferior parietal cortex, inferior temporal gyrus, isthmus-cingulate cortex, lateral occipital cortex, lateral orbital frontal cortex, lingual gyrus, medial orbital frontal cortex, middle temporal gyrus, parahippocampal gyrus, paracentral lobule, IFG pars opercularis, IFG pars orbitalis, IFG pars triangularis, pericalcarine cortex, postcentral gyrus, posterior-cingulate cortex, precentral gyrus, precuneus cortex, rostral anterior cingulate cortex, rostral middle frontal gyrus, superior frontal gyrus, superior parietal cortex, superior temporal gyrus, supramarginal gyrus, frontal pole, temporal pole, transverse temporal cortex, insula	USA	General	510 (NS)	16.02 (2.45) whole sample	17 (NS)	16.02 (2.45) whole sample	68.8	
Rais 2008	Self-reported cannabis use at baseline	No lifetime use	ICV, TBV, cerebral grey matter, cerebral white matter	Netherlands	Psychiatric population	C: 31 (25) FES: 32 (26)	C: 24.72 (6.66) FES: 23.28 (5.10)	FES: 19 (19)	FES: 21.83 (3.91)	43.8	
Wang 2021	>10 days/ month for at least 2 years, no treatment for CUD	<30 lifetime uses	Hippocampus, CA1, CA2/CA3, CA4/DG, SR/SL/SM, subiculum	Netherlands	General	22 (14)	21.56 (2.45)	20 (15)	20.53 (2.11)	56.3	
Welch 2011	Use in 2-year follow-up period	No use in 2-year follow up	Thalamus	Scotland	Psychiatric population	32 (15)	21.11 (2.87)	25 (15)	21.76 (2.52)	62.5	

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TABLE 5 (Continued)

Study ID	Exposure	Comparator	Outcome regions in meta-analysis	Country	Population	Comparator *n* (males)	Comparator age (mean, SD), years	Exposure *n* (males)	Exposure age (mean, SD), years	Risk of bias (%)	Covariates adjusted for in adjusted analysis
Xu 2022	>10 days/ month for at least 2 years, no treatment for CUD	Non-using (less than 30 time in life, not used in past year)	Accumbens, amygdala, caudate, pallidum, putamen, TGMV, thalamus TWMV	Netherlands	General	22 (14)	21.56 (2.45)	20 (15)	20.53 (2.11)	56.3	

Abbreviations: C = controls; CA1 = cornu Ammonis 1; CA3 = cornu Ammonis 3; CA4 = cornu Ammonis 4; CUD = cannabis use disorder; FES = first episode of schizophrenia; GC-ML-DG = hippocampus molecular layer dentate gyrus; HATA = hippocampus–amygdala transition area; ICV = Intracranial Volume; IFG = inferior frontal gyrus; NS = not stated; SR/SL/SM = stratum radiatum/stratum lacunosum/stratum moleculare; TBV = total brain volume; TGMV = total grey matter volume; TWMV = total white matter volume.

heterogeneity estimates varied across regions, but were generally moderate to substantial, with highest heterogeneity estimates for the hippocampus, hippocampus CA4, fimbria, parasubiculum and subiculum, putamen, accumbens and cerebellum. Sensitivity analyses to reduce heterogeneity did not significantly change the results, except for the accumbens, where the result was now significant (k = 5; g = −0.34; 95% CI = −0.60, −0.08; P = 0.022; I^2 = 0) (Appendix S1).

Tobacco versus control

Forty cross-sectional studies were identified for inclusion, 30 of which were included in the meta-analysis. A summary of the meta-analysis results is presented in Figures 1, 2, 5 and 6 and in Appendix S1. Forest plots of the analysis for each individual region are provided in Appendix S2; narrative results are provided in Appendix S1.

In the adjusted analysis, there were volumetric differences between people who smoke tobacco and controls in the amygdala, insula, pallidum, total grey matter volume (TGMV) and the hippocampus. There were no differences for any other region investigated in the adjusted analysis. People who smoke tobacco had smaller volume in the amygdala (k = 5; g = 0.17; 95% CI = 0.04, 0.31; P = 0.025; I^2 = 55.90%), insula (k = 5; g = 0.17; 95% CI = 0.06, 0.27; P = 0.011; I^2 = 31.20%), pallidum (k = 5; g = 0.17; 95% CI = 0.13, 0.21; $P \leq 0.0001$; I^2 = 0%) and TGMV (k = 7; g = 0.17; 95% CI = 0.04, 0.30; P = 0.020; I^2 = 93.70). There was weak evidence for smaller hippocampus volume in people who smoke tobacco, compared with controls (k = 10; g = 0.12; 95% CI = 0.00, 0.24; P = 0.049; I^2 = 62.30%). Egger's test suggested asymmetry in the caudate, insula, parietal grey matter and putamen analyses, but implementing Egger's trim and fill did not change the conclusions for these regions. Across regions, I^2 heterogeneity estimates varied, and were generally either low (with scores of <0.0001) or moderate–substantial, with the highest heterogeneity estimates for TGMV. Sensitivity analyses to reduce heterogeneity did not significantly change the results; for some regions heterogeneity remained moderate (Appendix S1).

In the unadjusted analysis, there were no differences in volume between people who smoke tobacco and controls for any brain region (Figure 6). There was no evidence of asymmetry for any regions. I^2 heterogeneity estimates varied across regions but were mostly either substantial or low–moderate, with the highest heterogeneity estimates found for thalamus and caudate. Sensitivity analyses to reduce heterogeneity did not significantly change the results; for some regions heterogeneity remained moderate (Appendix S1).

Co-use of cannabis and tobacco versus control

One eligible cross-sectional study investigated the co-use of cannabis and tobacco [27]. Filbey *et al.* [27] compared bilateral hippocampal volumes across groups with combined use of cannabis and nicotine, use of cannabis only, use of nicotine only and non-use. The authors found a main effect of group for the volume of the right hippocampus [*F*

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TABLE 6 Characteristics of longitudinal tobacco studies.

Study ID	Exposure	Comparator	Outcome regions in meta-analysis	Country	Population	Comparator *n* (males)	Comparator age (mean, SD), years	Exposure *n* (males)	Exposure age (mean, SD), years	Risk of bias (%)	Covariates adjusted for in adjusted analysis
Duriez 2014 – longitudinal	Current smoker	Never smoker	TBV, TGMV	France	General	714 (118)	M: 72.0 (3.93) F: 72.3 (3.93) whole sample	63 (37)	M: 72.0 (3.93) F: 72.3 (3.93) whole sample	53.3	ICV, age, educational level, MMSE score, BMI, CES-D score, SBP, DBP, fasting blood glucose, cholesterolemia, alcohol consumption, WML and Apo-ε4 charge
Kim 2018	Heavy smoker >23 pack years	Non-smokers	TBV	Korea	General	603 (101)	M: 59.8 (2.27) F: 59.2 (7.0) whole sample	103 (95)	M: 59.8 (2.27) F: 59.2 (7.0) whole sample	53.3	ICV, age, sex, baseline volume, waist-to-hip ratio, hypertension and diabetes mellitus
Otsuka 2022	Self-reported current smokers	Self-reported never smoker	TGMV	Japan	General	1451 (674)	M: 60.24 (11.72) F: 59.21 (11.87) whole sample	214 (175)	M: 60.24 (11.72) F: 59.21 (11.87) whole sample	60.0	Age, TGMV at baseline, education, family income, living alone, depressive symptoms and history of stroke, dyslipidemia, diabetes, hypertension or heart disease
Van Haren 2010	Self-reported current smokers	Self-reported non-smoker	Cerebellum	Netherlands	Psychiatric	C: 78 (NS) S: 42 (NS)	NS	C: 35 (NS) S: 54 (NS)	NS	53.3	

Abbreviations: BMI = body mass index; C = controls; CES-D = Centre for Epidemiologic Studies depression scale; DBP = diastolic blood pressure; F = female; ICV = intracranial volume; M = male; MMSE = mini-mental scale examination; NS = not stated; S = schizophrenia patients; SBP = systolic blood pressure; TBV = total brain volume; TGMV = total grey matter volume; WML = white matter lesions.

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TABLE 7 Characteristics of Mendelian randomisation (MR) tobacco studies.

Study ID	Exposure	Comparator	Outcome regions in meta-analysis	Country	Population	Comparator *n* (males)	Comparator age (mean, SD), years	Exposure *n* (males)	Exposure age (mean, SD), years	Risk of bias score
Logtenberg 2022	Smoking initiation, CPD (ever being a regular smoker, >100 lifetime cigarettes, every day for ≥ 1 month)	Never regularly smoked	Nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, thalamus	Europe	General	848 460 exposure GWAS, 50 290 outcome GWAS. Never smokers: 22 555, ever smokers: 14 564	N/A	N/A	N/A	+
Lin 2023	Smoking initiation (ever being a regular smoker), lifetime smoking	Never regularly smoked	TGMV, TWMV	Europe	General	462 690 outcome GWAS	N/A	N/A	N/A	+

Abbreviations: CPD = cigarettes per day; GWAS = genome-wide association study; TGMV = total grey matter volume; TWMV = total white matter volume.

FIGURE 1 Subcortical differences from adjusted analysis between people who use cannabis or tobacco and people who do not.

(3,77) = 4.36; P = 0.007], but not the left hippocampus [F(3,77) = 1.576; P = 0.202], whilst controlling for alcoholic drinks, IQ, gender and age. *Post hoc* pairwise comparisons suggest that people who used only cannabis had smaller right hippocampus volumes compared with the control [F(1,43) = 9.23; P = 0.004] and nicotine only [F(1,45) = 5.79; P = 0.02] groups, but for the group who co-used cannabis and nicotine there were no differences compared with the control [F(1,27) = 2.96; p = 0.09] and nicotine only [F(1,39) = 2.75; P = 0.11] groups.

Longitudinal studies

Longitudinal changes in cannabis versus control groups

Seven longitudinal studies using independent samples were identified for inclusion, none of which were meta-analysed because there were no brain regions with more than two independent samples. A narrative summary can be found in Appendix S1. In brief, most studies found no longitudinal volumetric differences between people who use cannabis and those who do not, including in cortical regions [86], global measures of brain integrity and subcortical regions [129]. No differences were identified in volumes of the hippocampus [58, 68, 126] and hippocampus subfields [58, 126]. Garimella *et al.* [58] found volumetric increases in the right parasubiculum, right fimbria, and the right and left CA3 in people who use cannabis, compared with controls. In contrast, Wang *et al.* [126] identified a faster rate of volume decrease for the right hippocampus in people who use cannabis, compared with controls. In patients with schizophrenia, Rais *et al.* [105] found larger TGMV loss in patients

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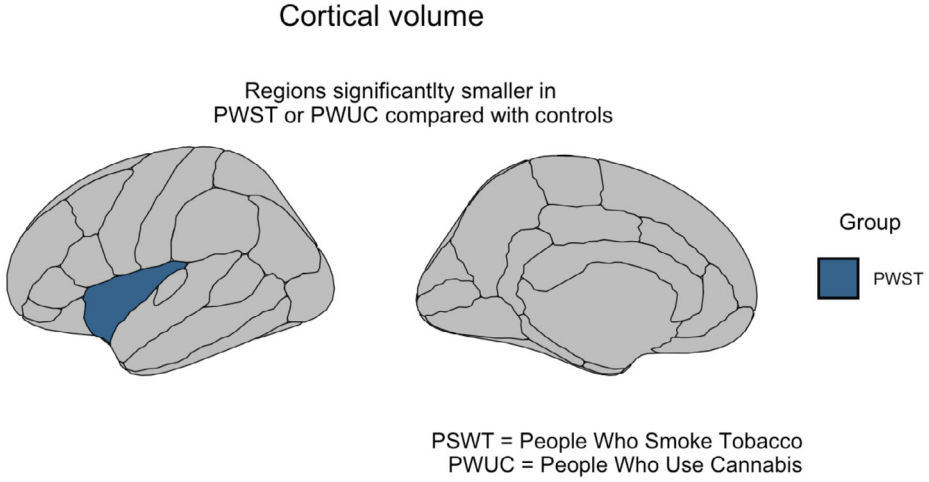

FIGURE 2 Cortical differences between people who use cannabis or tobacco and people who do not.

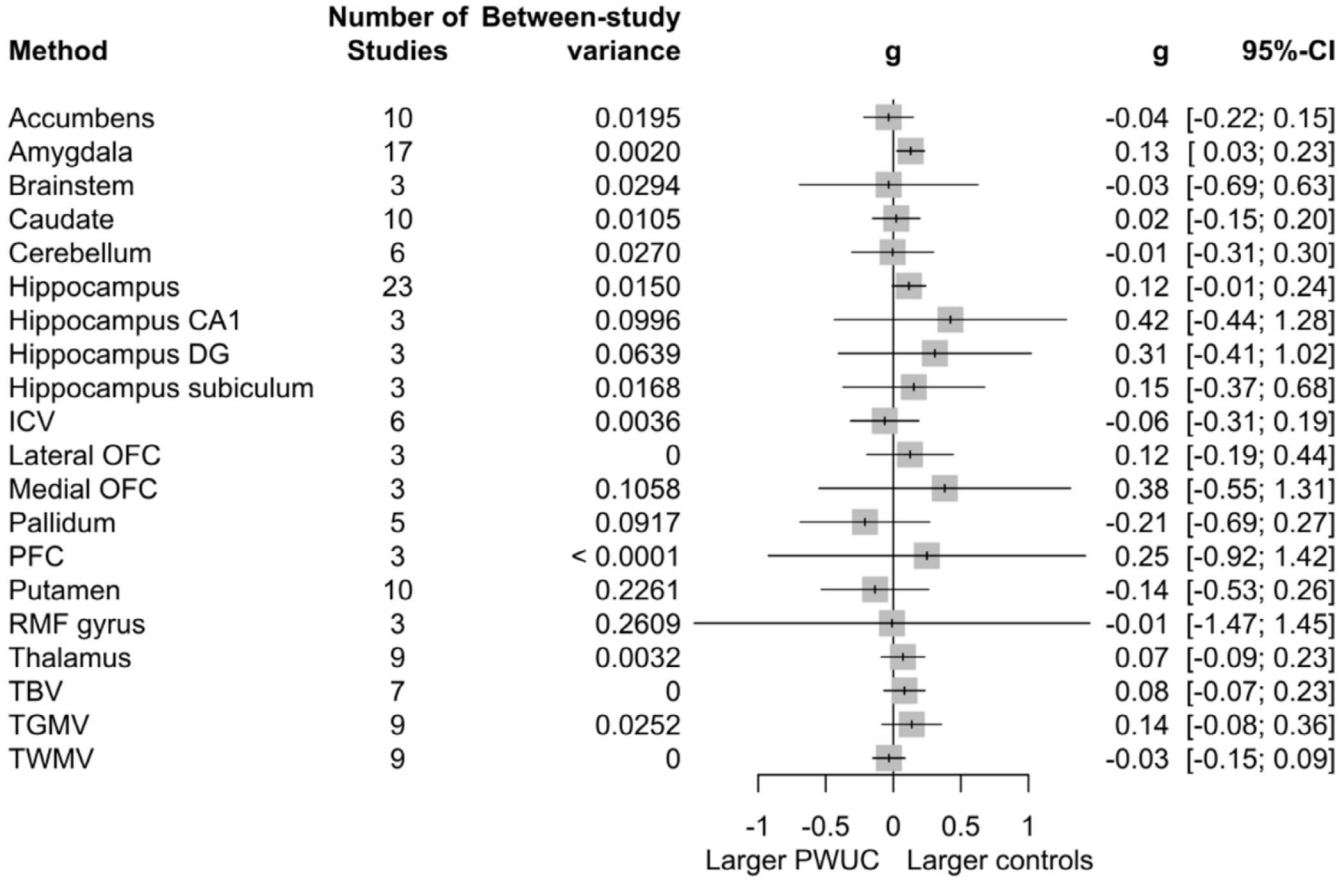

FIGURE 3 Summary forest plot of adjusted cross-sectional meta-analyses of differences in brain volume between people who use Cannabis (PWUC) and controls. Results presented to the nearest four decimal places; 0 refers to <0.0001. CA1 = cornu Ammonis 1; DG = dentate gyrus; ICV = intracranial volume; OFC = orbitofrontal cortex; PFC = prefrontal cortex; RMF = rostral middle frontal; TBV = total brain volume; TGMV = total grey matter volume; TWMV = total white matter volume.

who used cannabis compared with non-using patients and non-using controls. Welch *et al.* [128] reported that in people with familial high risk for schizophrenia, there was greater right thalamic volume loss from baseline to follow-up in people who use cannabis, compared with controls.

Longitudinal changes in tobacco versus control groups

Four unique longitudinal studies were identified for inclusion, three of which were included in the meta-analysis for two outcome regions only. Total brain volume (TBV) and TGMV were the only outcome

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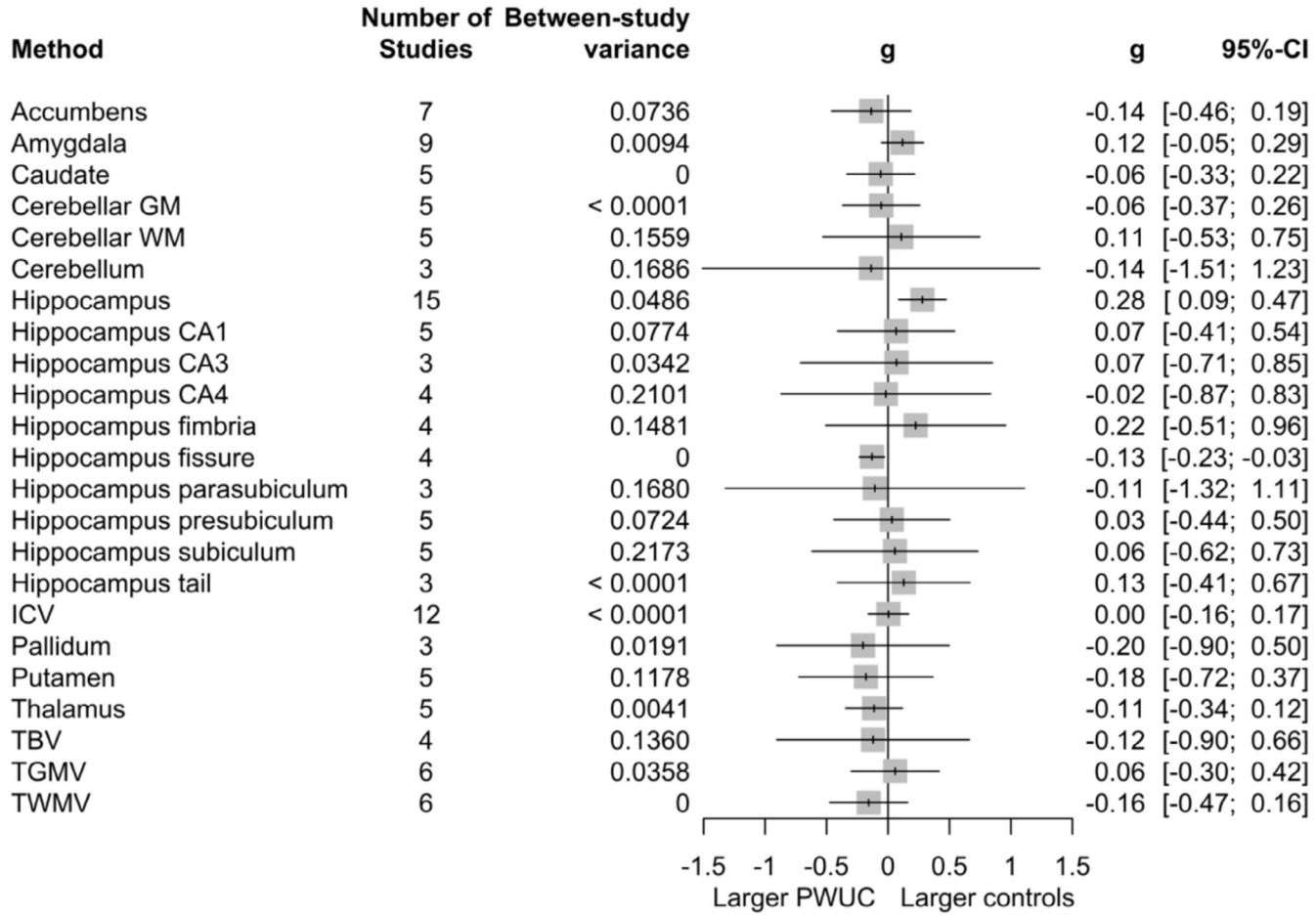

FIGURE 4 Summary forest plot of unadjusted cross-sectional meta-analyses of differences in brain volume between people who use cannabis (PWUC) and controls. Results presented to the nearest four decimal places; 0 refers to <0.0001. CA1 = cornu Ammonis 1; CA3 = cornu Ammonis 3; CA4 = cornu Ammonis 4; GM = grey matter; ICV = intracranial volume; TBV = total brain volume; TGMV = total grey matter volume; TWMV = total white matter volume; WM = white matter.

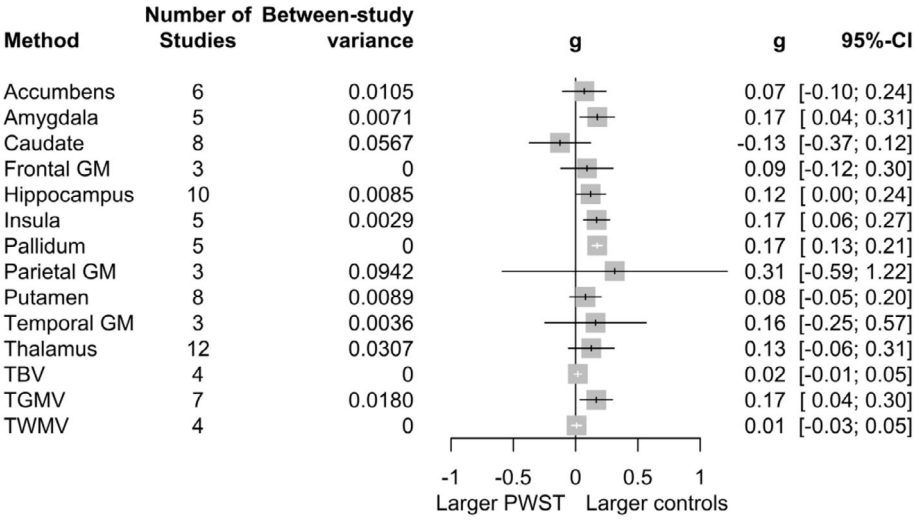

FIGURE 5 Summary forest plot of adjusted cross-sectional meta-analyses of differences in brain volume between people who smoke tobacco (PWST) and controls. Results presented to the nearest four decimal places; 0 refers to <0.0001. GM = grey matter; TBV = total brain volume; TGMV = total grey matter volume; TWMV = total white matter volume.

regions with at least three samples to be meta-analysed (Figure 7). For both TBV and TGMV, all studies reported a decrease in brain volume between baseline and follow-up. For TBV, there was no difference in TBV between people who use tobacco and controls (k = 3; g = 0.11; 95% CI = −0.11, 0.32; P = 0.170; I^2 = 0%). For TGMV, there was a greater decrease in TGMV in people who use

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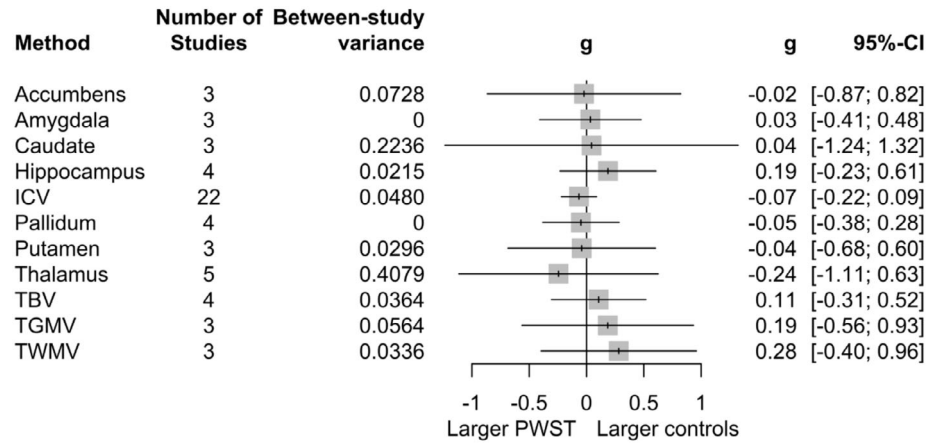

FIGURE 6 Summary forest plot of unadjusted cross-sectional meta-analyses of differences in brain volume between people who smoke tobacco (PWST) and controls. Results presented to the nearest four decimal places; 0 refers to <0.0001. ICV = intracranial volume; TBV = total brain volume; TGMV = total grey matter volume; TWMV = total white matter volume.

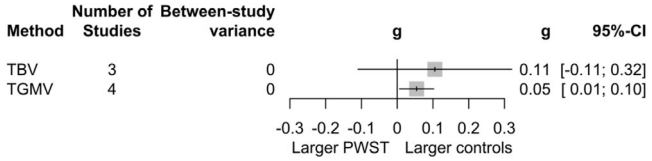

FIGURE 7 Summary forest plot of adjusted longitudinal meta-analyses of differences in brain volume between people who smoke tobacco (PWST) and controls. A positive value indicates a greater reduction in PWST compared with controls. Results presented to the nearest four decimal places; 0 refers to <0.0001. TBV = total brain volume; TGMV = total grey matter volume.

tobacco compared with controls (k = 5; g = 0.05; 95% CI = 0.01, 0.10; P = 0.037; I^2 = 0%). There was no evidence of heterogeneity or asymmetry (Appendixes S1 and S2). A narrative summary can be found in Appendix S1.

Longitudinal changes in co-use versus control groups

There were no longitudinal studies that investigated cannabis and tobacco co-use and brain volume.

Mendelian randomisation studies

Cannabis use

There were no studies that used MR to investigate the causal effect of cannabis on brain volume.

Tobacco use

We identified two tobacco MR studies [78, 143]. Logtenberg *et al*. [143] investigated bidirectional associations between smoking and subcortical brain volume. They found weak evidence that smoking initiation might decrease amygdala volumes (β = −0.05; P = 0.046). There was strong evidence that smoking more cigarettes per day (CPD) might decrease hippocampus volumes (β = −94.73; P = 1.8E-06). Lin *et al*. [78] investigated the links between smoking initiation and grey/white matter volume and found that smoking initiation might decrease TGMV (β − 0.100; 95% CI = −0.156, −0.043; P = 0.000523), but this was attenuated when adjusting for alcohol drinking using multivariable MR (β = −0.056; SE = 0.037; P = 0.122). Lin *et al*. [79] found no effect of smoking initiation on white matter volume (β = −0.004; 95% CI = −0.065, 0.058; P = 0.907).

Co-use

There were no studies that used MR to investigate the causal effect of cannabis and tobacco co-use on brain volume.

DISCUSSION

Overall, this systematic review and meta-analyses demonstrated that cross-sectional evidence suggests people who use cannabis had smaller volumes in the amygdala. There were smaller volumes in the amygdala, insula and pallidum in people who smoke tobacco, compared with non-smokers. The evidence from longitudinal studies is limited, with only seven studies investigating cannabis and four investigating tobacco. For cannabis, narrative synthesis identified limited consistency in evidence for differences in brain volume between groups. For tobacco, meta-analyses showed no differences in TBV, but did identify smaller TGMV in people who smoked tobacco, compared with controls. Evidence from two MR studies suggests that smoking more cigarettes might decrease hippocampus volume, and that smoking initiation might reduce amygdala volume [143] and TGMV [78]. Only one study examined the co-use of cannabis and tobacco, reporting that reductions in right hippocampal volumes were associated with cannabis use, but not cannabis and nicotine co-use or nicotine use alone [27].

The literature assessing cannabis and/or tobacco use and brain volume was mostly cross-sectional, which limits our ability to make

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causal inferences on the effects of these substances on brain structure. Longitudinal study designs should be used as well as methods that allow improved understanding of causality, such as well-designed instrumental variable studies, particularly in a triangulation framework. Furthermore, larger studies powered to detect small effects with consideration of key confounding factors are needed. Clearer reporting of non-significant results and sample overlap is needed to facilitate accurate evidence synthesis.

Our meta-analysis of adjusted estimates identified smaller amygdala volumes, updating earlier findings from previous meta-analyses that reported no significant differences [17, 20, 144]. This discrepancy may be associated with the inclusion of a greater number of studies in the current review, which likely increased the statistical power to detect subtle effects. As a result of our conservative exclusion of samples with fully and partially overlapping participants, this review did not assess all relevant regions, as there were not enough independent studies available for meta-analysis (e.g. the lateral OFC and anterior cingulate cortex, where previous reviews have found reductions in people who use cannabis) [17].

In our review we triangulated evidence across different study designs (cross-sectional, longitudinal and MR), increasing the robustness of our findings and the strength of our conclusions. We found consistent differences in global brain volume between people who smoke and controls across cross-sectional, longitudinal studies and MR methods. There was consistent evidence for amygdala reductions in people who smoke tobacco across cross-sectional and MR methods, suggesting a potential causal effect [143]. Although both MR studies had good instrument strength and included additional sensitivity analysis, horizontal pleiotropy is likely present, whereby genetic variants influence brain volume through pathways other than smoking, or the causal relationship between smoking and amygdala volume may operate via multiple distinct mechanisms, such as risk-taking [143, 145].

Consistent with the most recent umbrella review of VBM reviews examining smoking and grey matter volume [25], we found that the insula was smaller in people who currently smoke tobacco, compared with controls. We identified additional smaller volumes in the amygdala, pallidum and TGMV. Van De Weijer *et al*. [25] also concluded that there was consistent evidence for smaller volumes in the prefrontal cortex and cingulate cortex in people who smoke, compared with controls. The prefrontal cortex and cingulate cortex were not meta-analysed in this review owing to insufficient independent studies that reported extracted volumes for these regions.

The group differences identified in the reviewed literature could be attributable to the primary psychoactive components of each substance. For instance, THC could cause structural changes through reducing the number of synapses [146–148], reducing neuronal density [149] and a reduction in dendritic length [148] or complexity [147]. The anatomically specific effects of THC on the amygdala and hippocampus in our review could result from the high density of CB1 receptors [150–152]. Similarly, nicotine has been associated with cell loss, altered cell size, and reduced dendritic length and complexity. Brain regions associated with tobacco use in this review have a high density of nicotinergic receptors [153–155].

Brain volume changes could also be attributed to harms of combustion. Combustion can cause high concentrations of reactive oxygen species (ROS), which cause oxidative stress and inflammation (with an increase of proinflammatory cytokines), leading to neuronal cell death [156–160]. Tobacco smoke contains thousands of harmful carcinogens and combustion products, so the global effect of tobacco on TGMV in the brain could be attributed to oxidative stress and inflammation arising from combustion products [157]. While cannabis smoke also contains harmful by-products, cannabis also contains cannabidiol (CBD), which has been recognised for antioxidative/anti-inflammatory effects. This could explain why limited differences were found for cannabis use, although evidence for the protective effects of CBD is inconsistent [156] and differences in exposure to CBD or other cannabinoids was not provided in individual studies.

Understanding the neurobiological actions of cannabis, tobacco and co-use could inform public health and individual-level interventions. For example, Vermont department of health have released posters warning young people of the harms of cannabis for brain development [161]. Given that this review found evidence for differences attributed to tobacco, public health campaigns could also include messaging around the potential harms of tobacco use on the brain. Additionally, healthcare professionals could discuss the impact of tobacco and cannabis on the brain when talking to their patients about their use, as well as physical outcomes such as lung cancer. Interventions could also consider the implications of the co-use of cannabis and tobacco and whether supplementing cannabis with tobacco is a technique for harm reduction, or if this increases harm. Considering the limited previous research, future studies should look at the effects of co-use on the brain to better disentangle the effects. The findings of this review could also provide insights into potential mechanisms for associations between smoking and mental health; however, this was not assessed in this review [25, 162, 163].

Strengths and limitations

To our knowledge, this is the most comprehensive synthesis of studies exploring the associations of cannabis use, tobacco use and brain volume to date. The triangulation of evidence across different study designs—cross-sectional, longitudinal and Mendelian randomisation—is a strength. Another strength of this review was the separation of adjusted and unadjusted meta-analyses. However, there were inconsistencies in the adjusted estimates: for example, some studies adjusted for ICV only, whereas others adjusted for multiple confounding variables (e.g. other drug use, alcohol use), which introduced heterogeneity into the analysis. However, by presenting both sets of analyses and considering evidence from adjusted estimates, the results of this meta-analysis may provide stronger evidence for associations with the exposures of interest, and may have minimised confounding by other variables. Owing to the vast extent of the literature reviewed herein, this review focused on binary categorisations of current use or non-use. It is, however, also important to consider the level of severity of use and—for cannabis—the potency of the

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products used, as these could theoretically affect differences in brain volume. Another limitation of this review is the use of cortical volume as the primary structural measure. Because volume reflects the product of cortical thickness and surface area, it may be less sensitive to differences driven by one component over the other. Given that thickness and surface area are driven by distinct biological processes and follow different developmental trajectories, assessing volume alone may obscure thickness/surface area-specific associations and attenuate observed associations [164].

CONCLUSION

This systematic review and meta-analysis, the largest to date, synthesised findings from 103 studies using rigorous methodology and comprehensive inclusion criteria. We found cross-sectional evidence that people who use cannabis had smaller volumes in the amygdala. There were smaller volumes in the amygdala, insula and pallidum associated with tobacco use. There was consistent evidence for reductions in TGMV associated with smoking across cross-sectional, longitudinal and MR studies. Finally, this review highlights significant gaps in the literature, including a lack of studies using longitudinal and causal inference designs, as well as a lack of research on cannabis and tobacco co-use. Addressing these limitations would enhance the quality of evidence in estimating the effects of cannabis and tobacco on the brain.

AUTHOR CONTRIBUTIONS

Katherine Sawyer: Conceptualization; funding acquisition; writing—original draft; investigation; methodology; visualization; writing—review and editing; project administration; formal analysis; data curation; validation; software; resources. **Tom Freeman P:** Conceptualization; writing—review and editing; methodology; supervision; validation; investigation; funding acquisition. **Martine Skumlien:** Supervision; writing—review and editing; methodology; validation; investigation; conceptualization. **Esther Walton:** Supervision; methodology; writing—review and editing. **Thomas Lancaster:** Methodology; writing—review and editing; supervision. **Jorien Treur L:** Methodology; writing—review and editing; supervision. **Valentina Lorenzetti:** Methodology; writing—review and editing; supervision. **Anna Blackwell K M:** Writing—review and editing; investigation. **Chloe Burke:** Writing—review and editing; investigation. **Richie J. Carr:** Writing—review and editing; investigation. **Constantinos Constantinides:** Writing—review and editing; investigation. **Maisie Cox:** Writing—review and editing; investigation. **Sarah Dance:** Writing—review and editing; investigation. **Shadi Daryan:** Writing—review and editing; investigation. **Sorcha Hamilton:** Writing—review and editing; investigation. **Tom Jenkins:** Writing—review and editing; investigation. **Gemma M. J. Taylor:** Conceptualization; methodology; writing—review and editing; supervision; validation; investigation; funding acquisition.

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DECLARATION OF INTERESTS

G.T. previously received funding from Pfizer, who manufacture smoking cessation products, for research unrelated to this study. G.T. previously worked at a health economics consultancy providing statistical and research support for pharmaceutical companies for medicines unrelated to this article. There are no other conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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