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A review of the effects of mushrooms on mood and neurocognitive health across the lifespan

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ABSTRACT

Mushrooms contain bioactive compounds with documented antioxidant and anti-inflammatory actions. Here, we present a systematic evaluation of epidemiological and clinical studies that investigate the role of mushrooms, either as a separate or integral dietary component, on neurocognition and mood. Following a search of four databases, a total of 34 human studies examining the effect of different mushrooms across varying age cohorts and health statuses were selected for inclusion. Epidemiological studies included in this review (n = 24) revealed a significant benefit of dietary patterns that included mushrooms of any species on cognition and mood in both healthy and compromised populations. However, the results obtained from intervention studies (n = 10) were mixed. Studies mainly investigated Lion's Mane *(Hericium erinaceus)*, showing some enhancement of mood and cognitive function in middle-aged and older adults. Further acute and chronic human intervention studies are needed, using adequate sample sizes, employing appropriately sensitive neurocognitive tests, and investigating a range of dietary mushrooms, to confirm the effects of mushroom supplementation on neurocognition and mood in humans.

1. Introduction

The ageing global population has caused a rise in the occurrence of neurodegenerative and mood-related diseases (Rahman et al., 2016; Valiengo et al., 2016). These disorders are multifactorial and are characterised by alterations in cognitive functions that underpin memory, executive skills, motor ability, behaviour, and mood (Tiwari et al., 2019). Dietary factors, including the adoption of plant-based diets, have been acknowledged to reduce inflammation and oxidative stress, which are both pathogenic features of neurodegenerative and mood-related diseases (Trovato Salinaro et al., 2018; Gregory et al., 2021; Liuzzi et al., 2023). The integration of mushrooms into the diet has gained recent popularity as part of a sustainable and flexitarian plant-based diet, but given the variation in mushroom intake among populations, differences in nutrient composition between species, and individual differences in bioavailability, further investigation is required to fully understand the potential benefits of mushrooms to cognitive health.

Evidence from *in vitro* studies has demonstrated that edible mushroom species (Table 1) contain high levels of bioactive compounds such as vitamins, β-glucans, terpenoids, diterpenoids, polyphenols and sterols that may confer neuroprotection either directly or indirectly (Phan et al., 2017). The most widely studied mushroom bioactives include ergosterols from white button mushrooms, erinacines and hericenones from Lion's Mane mushrooms, ganoderic acids from Reishi mushrooms, β-glucans from Shiitake mushrooms, and ergothioneine from Oyster mushroom species (Yadav et al., 2020; Rai et al., 2021).

The bioactive substances present in different mushroom species have been ascribed to both direct and indirect mechanisms of influence on neurocognition. Four possible "direct" mechanisms have been described that may underlie the beneficial effects of mushrooms on neurocognition (Phan et al., 2015; Anusiya et al., 2021). These are: 1) a decrease in pro-inflammatory markers such as reactive oxygen species (ROS, COX), tumour necrosis factor-a (TNF-a) and interleukins (ILs); 2) an increase in antioxidant enzymes such as glutathione peroxidase (GSH, GPx) and superoxide dismutase (SOD); 3) an increase in neurite outgrowth factors such as neuronal growth factors (BDNF, NGF), cyclic adenosine monophosphate (cAMP), phosphoinositide 3-kinase (PI3K), and nuclear factor- kappa B (NF-κB); and 4) a decrease in factors involved in neurotoxicity such as amyloid precursor protein (APP), amyloid β protein (Aβ), and acetylcholinesterase (AchE). In addition, mushroom bioactives may play a role in upregulation of the vitagene system including NF-E2-related factor 2 (Nrf2), which are thought to be downregulated in

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Table 1
Summary table of the genus, species and common names of edible mushrooms referred to in this review.

Genus family	Species name (abbreviation)	Common name
Agaricus	*Agaricus bisporus or Agaricus blazei (AB)*	White button mushroom
Armillaria	*Armillaria mellea (AM)*	Honey mushroom
Auricularia	*Auricularia auricula (AA)*	Cloud ear mushroom
	Auricularia polytricha (AP)	Wood ear mushroom
Cordyceps	*Cordyceps sinensis (CS)*	Caterpillar mushroom
Ganoderma	*Ganoderma lucidum (GL)*	Reishi (Lingzhi) mushroom
Grifola	*Grifola frondosa (GF)*	Maitake mushroom
Hericium	*Hericium erinaceus (HE)*	Lion's Mane mushroom
Inonotus	*Inonotus obliquus (IO)*	Chaga mushroom
Lentinus	*Lentinula edodes (LE)*	Shiitake mushroom
Pleurotus	*Pleurotus eryngii (PE)*	King Oyster mushroom
	Pleurotus florida (PF)	Oyster mushroom
	Pleurotus ostreatus (PO)	
Polypore	*Coriolus versicolor (CV)*	Turkey tail mushroom

Modified from Anusiya et al. (2021).

neurodegenerative disease (for example, Calabrese et al., 2016). Indeed, this pathway has been identified for similar food bioactives such as curcumin (Concetta Scuto et al., 2019). As has been well-documented, oxidative stress plays a crucial factor in the pathogenesis and progression of neurodegenerative disease, and so the rich anti-inflammatory and antioxidant bioactive profile of mushrooms may mitigate chronic oxidative stress and offer protection from neurodegeneration (Venturella et al., 2021).

Alternative mechanisms targeting gut health have been proposed that suggest a more "indirect" effect of mushrooms on neurocognition. Evidence has shown that following a vegetable-rich diet (of which mushrooms are an integral component) microbial diversity is significantly enhanced, and the abundance of specific types of beneficial bacteria such as *Clostridium*, *E. rectale*, *F. prausnitzii*, *Lactobacillus*, *Prevotella*, and *Ruminococcus* is increased, while harmful species such as *Bacteroides* are decreased (Xiao et al., 2022). This increase in beneficial gut microbiota species has been shown to be critical for neuronal homeostasis and regulation of monoamine neurotransmitters such as serotonin (5-HT), norepinephrine (NE), and dopamine (DA) (Jamar et al., 2020). In turn, these actions may lead to better cognitive outcomes (Canipe et al., 2021). Furthermore, poor microbial diversity or the presence of harmful gut microflora leads to the colonic mucosa becoming vulnerable to infection, leading to systemic inflammation, and negatively affecting cognitive and mental health. In addition to the gut microbiota benefits of a general plant-rich diet, some benefits are specifically attributable to mushrooms. The mushroom cell wall is known to be rich in β-glucan polymers, such as lentinan or grifolan, that have been shown to significantly increase production of short chain fatty acids (SCFAs) from gut microbial metabolism (Valverde et al., 2015). SCFAs produce long-term immunomodulatory benefits and themselves regulate neurotransmitter and hormone levels (Li et al., 2021). Specifically, the β-glucans from mushrooms may act as potent agonists of neurotransmitters (Chong et al., 2019; Cerletti et al., 2021) which, in turn, have been shown to influence the regulation of mood and circadian rhythms. Such physiological functions are usually impaired in neuropsychiatric illnesses (Scriven et al., 2018).

Although several experimental studies have considered cognitive outcomes following mushroom interventions, the heterogeneity of methods makes navigating this literature and interpreting the results challenging. Despite these constraints, the main objective of this review was to systematically describe and evaluate the experimental and epidemiological evidence for the effect of different mushroom species on mood and cognitive health. Overall, this review aims to enhance our understanding of the neurocognitive benefits of mushrooms, and to raise public health awareness of the potential utility of including mushrooms in habitual diets to reduce the risk of neurodegenerative and mood related diseases.

2. Methods

This narrative systematic review was conducted by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021).

2.1. Strategy search

The database search engines of PubMed, Scopus, ResearchGate and Web of Science were used to identify intervention studies (including randomised human control trials (RCTs) and pre-post studies), and epidemiological (cross-sectional, case-control, and prospective cohort) studies published before July 2023, investigating the effect of mushroom intake on neurocognitive health and mood, either relating to improvements in memory, executive function, attention, visuospatial imagery, processing speed, problem solving or reduction in depression, anxiety and sleep disturbance symptoms. For the PubMed and Web of Science databases, the following Medical Subject Heading (MeSH) were employed: (edible mushroom **OR** *Pleurotus ostreatus* **OR** oyster mushroom **OR** *Hericium erinaceus* **OR** Lion's Mane mushroom **OR** shiitake mushroom **OR** portobello mushroom **OR** enoki mushroom **OR** chestnut mushroom **OR** porcine mushroom **OR** *Agaricus bisporus* **OR** white button mushroom) **AND** (cognition **OR** memory **OR** mood **OR** perception **OR** psychomotor function **OR** executive function **OR** neurodegenerative disease **OR** dementia **OR** depression), whilst in the Scopus and ResearchGate databases, the following search keywords were used: mushroom* **AND** (cognition **OR** perception **OR** mood **OR** dementia **OR** depression). It should be noted that this review did not include any studies investigating the effect of "psychedelic" mushroom species on neuronal health.

2.2. Eligibility criteria and selection of records

Using a manual exclusion process, studies that were narrative systematic reviews, *in vitro*/cell-line studies, or *in vivo* animal studies, or publications that were not publicly available were excluded. No restrictions were placed on age, gender, health/diseased status, or the cognitive testing methodologies used. Also, no restriction criteria were placed on the design or quality of the studies such as excluding studies that were lacking a control group or were a pilot. All eligible records retrieved from the search databases were combined using EndNote software and duplicates were removed automatically. A classification template was created to categorise the records as being intervention studies or epidemiological studies and our search terms identified 10 intervention studies (9 RCTs and 1 pre-post) and 24 epidemiological (7 cohort, 1 case-control, and 16 cross-sectional) studies.

2.3. Data extraction and table categorisations

Full texts of the eligible records were downloaded, and tables were created to summarise the information obtained from the intervention studies and epidemiological studies. Specifically, each categorisation contained important details for each individual record regarding the author(s), publication year, the country where the study was conducted, cohort(s) being studied (either human or animal species), methodological design, details of the outcomes measured and findings from the study.

The human neurocognitive and psychological tests used in each study were summarised using the Cattell-Horn-Carroll (CHC) model, allowing categorisation of each task into the "domain" of the neurocognitive function that it was measuring (Jewsbury et al., 2016). It should be noted that the studies included in this review used a range of cognitive tasks or self-report measures to assess attention, verbal fluency and decision making in the executive function domain, semantic /

episodic / visuospatial / numerical / working memory and psychomotor processing speed in the memory and motor function domains, as well as perception and fluid intelligence in the intelligence quotient (IQ) domain. Studies also examined a range of aspects of mood including general affect, anxiety, stress, and depression, and a few also investigated sleep disturbances as these are often associated with mood disorders.

2.4. Quality and risk of bias assessment for individual records

The Cochrane risk of bias tool (RoB2, Higgins and Altman, 2008) was employed to evaluate the quality of the selected intervention studies. This tool comprises 5 bias domains relating to bias arising from 1) sample randomisation, 2) deviations from interventions, 3) missing outcome data, 4) outcome measurements and 5) selection of the reported result. An overall risk of bias for each study was then calculated from the summation of the bias classifications for each domain, leading to the classification of each study as being at low, medium, or high risk of bias. For cross-sectional and cohort epidemiological studies, the National Institutes for Health (NIH, Ma et al., 2020) quality assessment tool was employed to assess the studies examining potential bias in study design, participant randomisation, methodology employed and reported outcome. The overall quality of each study was then rated as being of "good", "fair" or poor" quality based on the answers to the individual 14 questions. A summary of the risk of bias assessment can found in the supplementary data (Tables S1, S2A, S2B, & S2C).

3. Results

3.1. Study selection

After a thorough literature search, a total of 1146 records were identified from PubMed, Web of Science, Scopus and ResearchGate databases. Following screening, 850 records were removed for not meeting

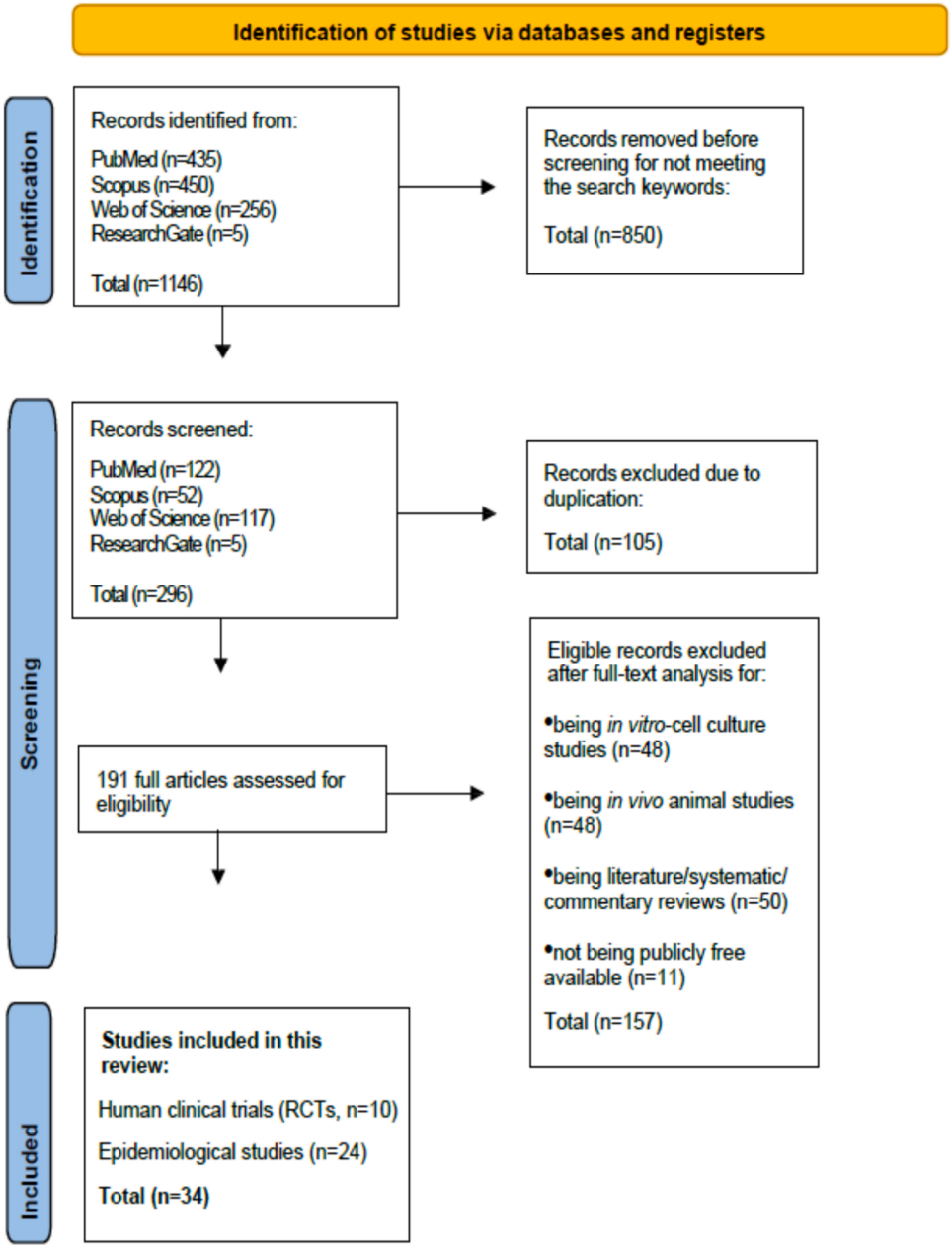

Fig. 1. Flow diagram illustrating the identification of studies for inclusion.

the search criteria, either because they related to non-cognitive effects, or they investigated physicochemical properties of mushrooms. From the 296 eligible records, 105 were excluded for being duplicates and a further 157 were excluded for being exclusively *in vitro*-cell culture studies (n = 48), *in vivo* animal studies (n = 48), reviews (n = 50), or not publicly available (n = 11). A total of 34 reports appeared to be eligible for this review, with the breakdown as shown in Fig. 1, which summarises the PRISMA-flow diagram for this systematic review.

3.2. Characteristics of the selected studies and their outcome measurements

3.2.1. Epidemiological studies

The 24 eligible epidemiological studies were either cross-sectional (n = 16) or case-control (n = 1) with data being collected at a single timepoint without any follow-up, or they were prospective cohort studies (n = 7). Most studies (n = 20) recruited an Asian population from either Japan (n = 9), China (n = 6), Korea (n = 4) or Singapore (n = 1), while the rest were conducted in the USA (n = 3) or Norway (n = 1). The studies typically recruited a wide range of ages, with the majority only targeting older participants (n = 13). Importantly, most studies (n = 17) treated mushrooms as an integral part of a vegetable diet, thereby categorising participants based on adherence to a "mushroom containing dietary pattern". These studies broadly categorised diets as "healthy" or "Westernised", mostly based on dietary information collected from food frequency questionnaires (FFQ). Specifically, the "healthy" dietary pattern (also described as plant-based, protein and grain-rich, or Japanese traditional), included high intakes of vegetables, fruits, legumes, fish, poultry, rice, wholegrains, oats, soya, green tea and dairy products, whilst in contrast the "Westernised" dietary pattern (also described as low grain or starch rich) was characterised by high intakes of processed foods and meat, carbohydrates, high-fat and sugary foods. A minority of studies (n = 7) specifically investigated frequency of mushroom intake itself (Nurk et al., 2010; Zhang et al., 2017; Feng et al., 2019; Ba et al., 2021a; 2021b; 2022; Park et al., 2022). Of the 17 epidemiological studies (including case-control) that examined mushroom intake as part of a dietary pattern, just over half (n = 9) involved only healthy populations, while the remainder (n = 8) included both healthy and diseased participants. The 7 remaining cohort studies involved either a wide age range cohort (n = 2) or only older-aged (n = 5) healthy participants. Importantly, all 24 epidemiological studies applied logistic regression analyses to examine possible associations between mushroom intake (either measured directly or indirectly through a "vegetable-rich" dietary pattern) and behavioural outcome(s) with strict control over potential covariates such as other aspects of diet and disease history.

The eligible epidemiological studies employed a total of 24 neuropsychiatric tests with MMSE being the most common broad measure of cognitive function relating to neurodegeneration (n = 6). Other similar general measures included the Modified Telephone Interview for Cognitive Status (TICS-M; n = 2), the Montreal Cognitive Assessment – Japan (MoCA-J; n = 1), the Clinical Dementia Rating (CDR; n = 2), the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; n = 1), the Short Form of the Health Related Quality of Life Questionnaire (SF-8; n = 1), and the Alzheimer's disease assessment scale (ADAS-cog; n = 1). Mood measures included the Beck Depression Inventory (BDI; n = 1), Geriatric Depression Scale (GDS; n = 2), the Centre for Epidemiological Studies Depression Scale (CES-D; n = 4), the Edinburgh Postnatal Depression Scale (EPDS-10; n = 1), the Hospital Anxiety and Depression Scale (HADS; n = 1), the Hamilton Depression Rating Scale (HDRS-K; n = 1), and the Patient Health Questionnaire (PHQ-9; n = 3) to assess anxiety, stress, and depression, while the Pittsburgh Sleep Quality Index (PSQI; n = 1) along with bespoke self-report sleep questionnaires (n = 3) were employed to examine participants' sleep quality. Memory was assessed using the Wechsler Logical Memory Scale (LM-WMSR; n = 1), and the Kendrick Object Learning Test (KOLT; n = 1). Verbal skills were assessed using the Animal Fluency test AF; (n = 1), and the access to Sematic memory task (S-task; n = 1), while visuospatial skills and psychomotor function were assessed using the Block Design test (m-BD; n = 1), Trail Making Test (TST; n = 1), and Digit Symbol Substitution Task (DSST; n = 1). Importantly patient health records were also accessed to collect information on neuropsychiatric disease onset and dementia mortality rates. In terms of quality assessment, all studies (n = 24) were rated to be of fair quality due to possible concerns over one or more of the following assessment criteria: sample size justification, the order in which outcomes were measured, the use of clearly defined dietary measures, blinding of outcome assessors, failure to repeat dietary measurements or report follow-up rates in cohort designs, use of appropriate statistical analyses.

Table 2 summarises the main characteristics of the epidemiological studies and will be briefly discussed here. Cross-sectional studies involving participants aged 18–65 years old showed that those participants who adhered most strongly to a "healthy/vegetable rich" dietary pattern (which included mushrooms) exhibited lower incidence of depressive symptoms (Nanri et al., 2010; Miki et al., 2015; Park et al., 2019; Kim et al., 2020), although this finding was not supported in all studies (*e.g.*, Toyomaki et al., 2017). Nevertheless, the Miki et al. (2015) finding was also maintained in an extension to the study where participants were followed-up after a 3-year period (Miki et al., 2018). The case-control study by Yoon et al. (2023) also observed that depressed 19–39-year-old males consumed fewer mushrooms compared to healthy males of the same age, although it should be noted that no significant difference in mushroom intake was evident between the healthy and depressed females of the same age. Zhao et al. (2022) observed a higher prevalence of postpartum depression symptoms in 20–45-year-old lactating women that followed a dietary pattern rich in meat and eggs but low in vegetables, mushrooms, and nuts. In a further study involving an older age group (65–97 years), significantly fewer depression symptoms were observed in those following a dietary pattern with a high intake of vegetables, mushrooms, soyabeans, potatoes, fish, seaweeds, fruits, and green tea compared with those that did not adhere to this dietary pattern (Yokoyama et al., 2019). For sleep measures, studies have shown mixed findings. "Vegetable rich" dietary patterns that included mushrooms have been linked with lower prevalence of difficulty in initiating sleep in healthy young and middle-aged adults (Kurotani et al., 2015). However, no significant association between a fruit and vegetable-rich diet and overall sleep (PSQI score) was seen for healthy participants aged 39–81 years old (Toyomaki et al., 2017). Shang et al. (2021) observed that when healthy 55–89-year-olds followed a dietary pattern that included beans and edible mushrooms, their average sleep duration, and cognitive outcomes over a 7-year follow-up period were better than for their counterparts that did not consume a similarly healthy diet.

Regarding cognitive outcomes, evidence from the SONIC cohort demonstrated that a "plant foods and fish" based dietary pattern diet (including mushrooms) was positively associated with MoCA-J performance (Okubo et al., 2017). Yu et al. (2018) observed that following a Westernised diet (without mushrooms) was associated with a higher risk of cognitive impairment. In the CHNS cohort, following a "protein rich" dietary pattern that contained mushrooms was associated with better outcomes in global cognition and verbal memory, as shown by high TICS-M scores (Xu et al., 2018). Similarly, Wei et al. (2022) observed that cognitively healthy older adults from the CLHLS cohort consumed significantly more mushrooms and algae than cognitively impaired participants across the 3-year cohort study. The Gerontological Investigation of Microbiome (Gimlet) study also observed significantly lower dementia incidence and higher LM-WMSR score for participants with a high Japanese dietary index (JDI_{12}, indicative of a diet rich in mushrooms), when compared with participants with a low JDI_{12} (Saji et al., 2022), although there were no significant differences in GDS, ADAS-cog or MMSE between the two groups. Sun et al. (2018) did however observe that a healthy diet including mushrooms and algae was associated with

Table 2
Characteristics of the eligible epidemiological studies investigating the effect of mushroom intake on neurocognitive and psychological well-being, based on cohort age and chronological order (*).

Author	Cohort characteristics	Covariates	Design method	Results (mushroom-related outcomes)
Nanri et al. (2010)	●521 (healthy (n = 186) & depressed (n = 335)] males & females ●21-67 y old ●Japan	Age, sex, workplace, marital status, BMI, smoking status, physical activity, history of diabetes-hypertension & energy intake.	Cross-sectional study *Dietary assessment:* 56-item FFQ, *Depression assessment:* CES-D.	PCA identified 3 dietary patterns. The "Japanese healthy" diet (containing mushrooms) associated with ↓ risk of depression symptoms. Response rate: 91%.
Miki et al. (2015)	●2006 healthy males & females (Furukawa Nutrition Health, 2012-2013) ●19-69 y old ●Japan	Age, sex, marital & employment status, smoking, physical activity & energy intake.	Cross-sectional study *Dietary assessment:*46-item FFQ. *Depression assessment:* CES-D.	RRR identified diets rich in vegetables (including mushrooms) associated with ↓ risk of depression symptoms. Response rate: 76%.
Miki et al. (2018)	●903 healthy males & females (follow-up from Furukawa Nutrition Health, 2012-2013) ●30-55 y old ●Japan	Age, sex, marital & employment status, smoking history, sleep duration, physical activity, BMI & total energy intake.	Cohort survey at baseline & after 3-y *Dietary assessment:* 46-items FFQ. *Depression assessment:* CES-D.	RRR identified diets rich in vegetables (including) mushrooms associated with ↓ risk of depression symptoms over 3 y. Drop-outs: 30% of cohort.
Yokoyama et al. (2019)	●982 [healthy (n = 849) & depressed (n = 133)] community-dwelling males & females from HCS (2012, n = 576) & KLS (2013, n = 608) ●65-97 y old ●Japan	Age, gender, BMI, energy intake, sleep duration, study area, education, living arrangement, smoking, exercise, chewing ability, mobility limitations, going outdoors frequency, medical history & experience of hospitalisation.	Cross-sectional study *Dietary assessment:* 10-item dietary variety score (DVS) & Brief Diet History Questionnaire (BDHQ). *Depression assessment*: 15-item GDS.	RRR revealed 6 dietary patterns. Higher DVS associated with ↓ depression symptoms. Highest tertile of the dietary pattern containing vegetables, soyabeans, potatoes, fish, mushrooms, seaweeds, fruits & green tea, associated with ↓ depression symptoms. Response rate: n/a.
Park et al. (2019)	●3388 [healthy (n = 2940) & depressed (n = 448)] males & females (2001-2002) from Korean Genome & Epidemiology Study ●40-69 y old ●Korea	Age, sex, BMI, marital status, exercise, alcohol & smoking status, educational level, disease history, sleep quality & total energy intake.	Cross-sectional study *Dietary assessment:* 106-item FFQ. *Depression assessment:* BDI.	Factor analysis identified 2 dietary patterns. The "healthy" pattern (including mushrooms) associated with ↓ risk of depression. "Unhealthy" pattern associated with↑ depression. Response rate: n/a.
Kim et al. (2020)	●2960 males & females from KNHANES Study (2012-2016) ●19-64 y old ●Korea	Age, sex, socioeconomic status, BMI, educational level, smoking status, alcohol intake, physical activity, health status & total energy intake.	Cross-sectional study *Dietary (mainly fiber intake) assessment:* FFQ. *Depression assessment:* PHQ-9 (1st analysis) & self-reported clinical diagnosis by a physician (2nd analysis).	Fibre intake from mushroom inversely associated with depression symptoms (PHQ-9 scores only). Response rate: n/a.
Yoon et al. (2023)	●115 males & females [(healthy controls (n = 76) & depressed cases (n = 39)] ●19-39 y old ●Korea	Age, sex, marital status, education, health behaviours, smoking, exercise, supplement intake.	Case-control study *Dietary assessment*: 127-item 3-d FFQ. *Depression assessment (interview):* K-HDRS. Other measurements: sociodemographic (health, marital & educational status) & anthropometric (BMI).	Depressed male cases consumed ↓ mushrooms than healthy control males. NS in females. Response rate: not reported.
Kurotani et al. (2015)	●2025 healthy males & females (Furukawa Nutrition & Health Study) ●18-70 y old ●Japan	Age, gender, employment & marital status, smoking, alcohol consumption, physical activity & BMI.	Cross-sectional study *Dietary assessment*: 58-item FFQ. *Sleep assessment:* Survey for sleep duration, sleep problems & sleep quality.	PCA identified 3 dietary patterns. The "healthy" diet (containing mushrooms) associated with ↓ risk of difficulty initiating sleep. Response rate: 77%.
Sun et al. (2018)	●339 healthy males & females ●60 + y old ●China	Age, sex, marital status, BMI, socioeconomic status, income & education.	Cross-sectional study *Dietary assessment*: FFQ. *Neurocognitive assessment:* MMSE. *Sleep assessment*: PSQI.	Factor analysis showed higher consumption of meat, fish, fruits, nuts & mushroom/algae associated with ↑ MMSE score. Response rate: not reported.
Toyomaki et al. (2017)	●282 healthy males & females ●39-81 y old ●Japan	Age, gender, BMI & disease history.	Cross-sectional study *Dietary assessment:* 58-item FFQ. *Depression assessment:* PHQ-9. *Sleep assessment:* PSQI. *Impulsive behaviour assessment:* BIS-11. *Physical activity* assessment: GPAQ. Quality of life assessment: SF-8.	Cluster analysis identified 3 dietary patterns. The high fruit and vegetable diet (including mushrooms) associated with: ●↓ BIS-11 scores, ●↑ SF-8 scores, ●NS PHQ-9, PSQI & GPAQ. Response rate: 64%.
Shang et al. (2021)	●2307 healthy males & females from CHNS (1989-2015) ●55-89 y old ●China	Age, gender, region, education, smoking, alcohol consumption, energy intake, physical activity & disease history.	Cohort study (follow-up 7-y: 2004-2011) *Dietary assessment: Weighing method (households) and* 24-h recalls (individuals) for 3-d. *Sleep assessment*: Sleep duration survey. *Neurocognitive assessment*: modified TICS (including immediate, delayed	Factor analysis revealed 5 dietary patterns. Following ''beans and mushrooms'' pattern associated with: ●healthy sleep duration (8 h) & higher global cognitive z-score. ●↑ global cognition, immediate memory & working memory, over the 7-y follow-up.

(*continued on next page*)

Table 2 (*continued*)

Author	Cohort characteristics	Covariates	Design method	Results (mushroom-related outcomes)
			recall, counting backward & serial 7 s) used to calculate global cognitive z-score. *Other measurements:* BMI & BP.	● lower risk of MCI Drop-outs: not reported.
Zhao et al. (2022)	●955 lactating females from Young Investigation Study (2019-2020) ●20-45 y old ●China	Age, income, lactation, family size & sleep quality.	Cross-sectional study *Dietary assessment:* 25-item FFQ. *Depression assessment:* 10-item EPDS & *question about postpartum practice*. *Sleep assessment:* Self-report sleep quality.	RRR identified that a dietary pattern high in meat & eggs and low in vegetables, mushrooms & nuts was associated with increased risk of postpartum depression. Response rate: not reported.
Okubo et al. (2017)	●635 healthy males & females (baseline from SONIC, 2010-2012) ●69-71 y old ●Japan	Sex, age, residential area, education level, smoking & drinking alcohol status, BMI & disease history.	Cross-sectional study *Dietary assessment:* FFQ. *Neurocognitive assessment:* MoCA-J (global cognition). *Other measurements:* ApoE in serum & BP	PCA revealed 3 dietary patterns. The "plant foods & fish" diet (including mushrooms) was associated with ↑ MoCA-J scores. Response rate: n/a.
Yu et al. (2018)	●1676 [(healthy (n = 1314) & MCI (n = 362)] males & females ●45-75 y old ●China	Physical activity, smoking status, age, BMI, socioeconomic income & total energy intake.	Cross-sectional study *Dietary assessment:* 85-item FFQ. *Neurocognitive assessment:* MMSE (global cognition).	PCA revealed 3 dietary patterns. ●↑ risk of cognitive impairment for highest quartile of "Westernised" diet (no mushrooms) compared with lowest quartile, ●↓ risk of cognitive impairment for highest quartile of "grains/fruits/vegetables" diet (no mushrooms) compared with lowest quartile, ●NS difference in risk of cognitive impairment between quartiles of "traditional Chinese" diet (including mushrooms & fungi). Response rate: not reported.
Xu et al. (2018)	●4847 healthy males & females (CHNS, 1997-2006) ●55 + y old ●China	Age, gender, sociodemographic characteristics, employment & marital status, education level, smoking & alcohol status, physical activity, BMI & disease history.	Cohort study (follow up across 10-y) *Dietary assessment:* 24-h recalls over 3-d. *Neurocognitive assessment:* TICS-M (global cognitive function & verbal memory). *Other measurements:* BP.	Factor analysis revealed 3 dietary patterns. ●Positive association between "protein rich" pattern (containing fungi) and both global cognition & verbal memory, ● Positive association between "traditional Chinese" pattern (containing fresh vegetables) and global cognition but not verbal memory, ●Negative association between "starch-rich" pattern and both global cognition & verbal memory, ●↑ global cognition & verbal memory in fungi eaters compared with non-eaters. Drop-outs: not reported.
Saji et al. (2022)	●85 [(healthy (n = 62) & with dementia (n = 23)] males & females from Gimlet (2016-2017) ●68-81 y old ●Japan	Age, sex, education level, disease history & lifestyle risk factors.	Cross-sectional study *Dietary assessment:* 12-item FFQ to calculate Japanese Dietary Indices (JDI_9, & JDI_{12}). *Neurocognitive assessment:* ADAS-cog, CDR, GDS, LM-WMSR, MMSE. *Imaging assessment:* MRI. *Gut health:* Fecal samples for gut microbial metabolites.	Compared with those with dementia, healthy subjects exhibited: ●↑ JDI9 & JDI12(including mushrooms), ●↑ mushroom intake. High JDI12 compared with low JDI12: ●↓ dementia incidence & CDR-SB, ●↑ LM-WMSR, ●NS GDS, ADAS-cog & MMSE, ●↓ MRI White matter hyperintensity, ●NS microbial metabolites (except skatole). Response rate: not reported.
Wei et al. (2022)	●14966 [(healthy (n = 10614) & MCI (n = 4322)] community-dwelling males & females from CLHLS (2008-2012) ●65 + y old ●China	Age, gender, race, occupation, marital status, residence, BMI, smoking, alcohol drinking, socioeconomic status, loneliness, living arrangement, living preference, social/leisure activity score, self-rated health, comorbidity & hearing/vision problems.	Cohort study (follow-up 3-y) *Dietary assessment:* FFQ. *Neurocognitive assessment*: MMSE. *Other measurements:* physical exercise survey.	Cognitively healthy participants consumed significantly more mushrooms or algae compared with cognitively impaired participants. Drop-outs: 15.4% of cohort.
Nurk et al. (2010)	●2031 ([healthy (n = 1707) & depressed (n = 172)] males & females (HUSK, 1997-1999) ●70-74 y old ●Norway	Sex, education, dietary supplements, self-reported disease history & education, smoking status.	Cross-sectional study *Dietary assessment:* 169-item FFQ/d-w-m. *Neurocognitive assessment:* KOLT, m-BD, m-DST, m-MMSE, S-task & TMT-A -tasks (executive function, visuospatial & short/long-term memory). *Depression assessment:* HADS.	Dose-dependent association between cognition & fruits/vegetables up to 500 g/d. High mushroom intake *versus* low/no mushrooms showed better performance on all cognitive test scores. Response rate: not reported.

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Table 2 (*continued*)

Author	Cohort characteristics	Covariates	Design method	Results (mushroom-related outcomes)
Zhang et al. (2017)	●13230 [(healthy (n = 12082) & with dementia (n = 1148)] males & females from Ohsaki (2006-2007) ●65-80 y old ●Japan	Age, gender, BMI, alcohol consumption, smoking, education level & psychological stress.	Cohort study (follow-up 6-y) *Mushroom intake assessment:* 68-item FFQ & 3-d food diary. *Neurocognitive assessment:* Dementia incidence.	Significant inverse dose-response association between mushroom intake & dementia incidence. Drop-outs: < 1% of cohort.
Feng et al. (2019)	●663 [(healthy (n = 573) & MCI (n = 90)] males & females from DaHA (2011-2017) ●60-75 y old ●Singapore	Age, gender, education level, smoking & alcohol status, disease history & physical activity.	Cross-sectional study *Dietary assessment* : 6 item mushroom questionnaire. *Neurocognitive assessment: SM*-MMSE, CDR, and structured assessment battery MCI diagnosis	Participants who consumed > 2 mushroom portions/ w ↓ odds of MCI. Response rate: not reported.
Ba et al. (2021a)	●15546 healthy males & females from NHANES III (1988-1994) ●18 + y old ●USA	Age, total energy intake, alcohol & smoking status, education level, ethnicity-race, sex, physical activity, BMI & total energy intake.	Cohort study (follow-up 20-y) *Dietary assessment:* 24-h dietary recall using the USDA survey nutrient database system for nutrient quantification. *Health assessment:* All-cause and specific mortality risk from death certificates (including AD deaths).	Mushroom consumers compared with non-consumers: ●↓ risk of all-cause mortality (inverse dose-response relationship), ●NS risk of cause-specific mortality (including AD). Nutritional substitution model: ●↓ all-cause mortality risk for dietary replacement of 100 g/d red meat with 70 g/d mushroom. Drop-outs: not reported.
Ba et al. (2021b)	●24699 [(healthy (n = 23042) & depressed (n = 1657)] males & females from NHANES (2005-2016) ●18 + y old ●USA	Age, sex, ethnicity, education level, marital status, smoking, disease history, BMI & total energy intake.	Cross-sectional study *Dietary assessment:* 2 × 24-h dietary recall using the USDA survey nutrient database system for nutrient quantification. *Depression assessment:* PHQ-9.	Mushroom consumers compared with non-consumers: ●↓ depression odds (but no dose-response relationship). Nutritional substitution model: ●NS depression odds for dietary replacement of 100 g/d red meat with 70 g/day mushroom. Response rate: n/a.
Ba et al. (2022)	●2840 healthy males & females from NHANES (2011-2014) ●> 60 y old ●USA	Age, sex, ethnicity, education level, lifestyle, smoking, disease history, diet, BMI & total energy intake.	Cross-sectional study *Dietary assessment:* 2 × 24-h dietary recalls. *Neurocognitive assessment:* AF, CERAD-DR, CERAD-WL & DSST (executive function, word recall, learning & motor speed).	Highest consumers of mushrooms compared with lowest: ●↑ CERAD-WL & DSST, ●NS AF & CERAD-DR. Response rate: n/a.
Park et al. (2022)	●87822 [(healthy (n = 74897) & depressed (n = 12925)] males & females from KSHS (2011-2018) ●18-87 y old ●Korea	Age, gender, BMI, alcohol intake, hypertension, diabetes, smoking, marital status, education, total calorie intake.	Cohort study (follow-up 6-y) *Dietary assessment:* FFQ for mushroom intake (oyster mushroom and other mushrooms). *Depression assessment*: 20-item CES-D (2011-2012). *Other measurements:* sociodemographic (lifestyle factors, income, education) & biochemical measurements (BMI, BP, hemoglobin A1c, uric acid, glucose).	Proportion of participants with intake of ≥ 1 serving/week mushroom was higher in females (51.2%) than males (38.4%). Intake of ≥ 1 serving/month had ↓ risk of depression symptoms compared to rare/never intake. Stratified by age: Participants ≥ 40 y old consuming ≥ 1 serving/month mushroom showed ↓ risk of depression symptoms compared with rare/never intake. Marginal significance for participants< 40. Drop-outs: not reported.

higher MMSE scores. Combined, these studies provide some evidence for an association between mood, cognition, and dietary mushroom intake, but not as a separately quantifiable component of habitual diet.

However, a few epidemiological studies (n = 7) have directly quantified the relationships between mushroom consumption and neurocognition or mood. Specifically, older participants from the Hordaland Health cohort (HUSK) who consumed mushrooms exhibited higher scores in the KOLT, m-BD, MMSE, standard verbal paired learning test (S-PA) and Trial Making Test (TMT-A) tasks assessing visuospatial memory and executive function skills, compared with non-mushroom eaters (Nurk et al., 2010). However, while healthy participants who consumed mushrooms showed significantly lower rates of all-cause deaths compared to non-consumers of mushrooms, no reduction in the rate of Alzheimer's disease (AD) deaths was observed during a 20-year cohort study (Ba et al., 2021a), although a lower risk of depression symptoms was observed (Ba et al., 2021b). Furthermore, the same researchers showed significantly higher scores in CERAD-WL and DSST tests in older adults who consumed an average of ~13 g mushrooms daily, compared with those that did not consume mushrooms (Ba et al., 2022), although no significant difference was seen for AF or CERAD-DR tasks, examining executive function and delayed recall skills respectively in the same study. The Diet and Healthy Aging (DaHa) and Ohsaki studies respectively demonstrated that older adults who consumed more than one and a half portion of mushrooms (~120–150 g) per week showed a significantly lower baseline incidence of MCI (Feng et al., 2019), and lower risk of developing dementia during a 6-year follow-up period (Zhang et al., 2017). Finally, Park et al. (2022) showed that 18–87-year-old participants who consumed more than one serving (=30 g) of mushrooms (including oyster mushrooms) each month had significantly lower risk for developing depression symptoms compared

with the participants that rarely or never consumed mushrooms. Combined, these epidemiological findings suggest that following variations of "healthy-plant-based" diets that include mushrooms may be beneficial to the cognitive health of both healthy and compromised populations irrespective of their age. However, due to the correlational nature of epidemiological research, inferences of causality cannot be made, and so experimental evidence is needed to confirm these findings.

3.2.2. Intervention studies

Nine RCTs and one pre-post study fulfilled our inclusion criteria and were selected for review. Of these, the majority (n = 6) recruited Japanese or Chinese participants, involved middle-aged/older participants (>40 years old, n = 6), and investigated the effects of Lion's Mane mushroom on cognition, sleep, and mood (n = 7). A minority of studies recruited a sample population from a non-Asian culture (n = 4) or used different mushroom species for their intervention: Reishi mushrooms (n = 1), a combination of Caterpillar, Shiitake and Reishi mushrooms (n = 1), or vitamin D2-enriched white button mushrooms (VDM, n = 1). Each of the RCTs employed slightly different experimental designs, but the mushroom intervention was generally administered either encapsulated in powdered form (n = 8) or incorporated into food (n = 2). Studies typically employed a repeated dosing regimen with the intervention required to be consumed daily for a certain period, ranging between 4 and 49 weeks.

In these intervention studies, a total of 21 different neuropsychological task batteries or individual tasks were employed, but with little similarity between studies. The ADAS-cog (n = 1), the Hasegawa's Dementia Scale (HDS-R; n = 1), the Cognitive Abilities Screening Instrument (CASI; n = 1), the Instrumental Activities of Dail Living Scale (IADL; n = 1), and the MMSE tests (n = 2) were employed to assess semantic, episodic, short-/long-term and visuospatial memory domains relating to neurodegeneration. The Stroop Word Challenge (n = 1), Mental Arithmetic Challenge (n = 1), and Benton Visual Retention Task (n = 1) were used to assess working memory. To examine executive functions, the CSIRO-Cognitive Assessment Battery (C-CAB; n = 1) and the Mindstreams (n = 1) computerised battery were used to assess attention, decision making and IQ, and psychomotor function. To examine mood, studies employed CES-D (n = 1), Depression Anxiety and Stress Scale (DASS-21; n = 1), the Neuropsychiatric Index (NPI; n = 2), the Symptom Checklist (SCL-90; n = 1), the General Health Questionnaire (GHQ-28; n = 1), the Basic Empathy Scale (BES; n = 1), the General Happiness Scale (GHS; n = 1), the Positive and Negative Affect Schedule (PANAS; n = 1), Zung Self-rating Depression and Anxiety Scales (n = 1) or the World Health Organisation Quality of Life (WHOQOL-BREF; n = 1). To measure sleep quality the PSQI was typically used (n = 2). Furthermore, some studies included blood draws (n = 4), saliva testing (n = 1) and ophthalmological measurements (n = 1) as part of their study design. Finally, in terms of risk of bias assessment, six intervention studies were classified as having some concerns relating to one or more aspects of methodology assessed by the Cochrane RoB2 tool, including deviations from intended interventions, outcome measurements, missing data, and selective reporting of results (Nagano et al., 2010; Okamura et al., 2015; Tsuk et al., 2017; Li et al., 2020; Zajac et al., 2020; Grozier et al., 2022) (see Supplementary Material Fig. S1). Lack of justification for (often small) sample size was also of concern in a number of the intervention studies (Mori et al., 2009; Nagano et al., 2010; Okamura et al., 2015; Tsuk et al., 2017; Saitsu et al., 2019; Vigna et al., 2019; Grozier et al., 2022), although such quality assessment of study characteristics is not covered by the Cochrane tool (Sterne et al., 2019).

The main characteristics of the intervention study designs and outcomes are highlighted in Table 3 and are briefly described here. Regarding mood effects, when obese, middle-aged participants followed a daily low-calorie diet combined with daily capsules containing 1.5 g of Lion's Mane mushroom (Vigna et al., 2019), they exhibited a significant reduction in anxiety symptoms (measured by the Zung's scale) after 2 months compared with baseline symptoms. A more sustained reduction in anxiety and sleep disturbance (assessed using the SCL-90 scale) was concurrently observed at 2 months and following a further 2-month washout period. These mood benefits were accompanied by a significant increase in pro-BDNF and pro-BDNF/BDNF ratio, suggesting a strengthening of BDNF pathways for synaptic plasticity. However, for all measured variables, benefits were only seen in the group consuming the capsules containing Lion's Mane when compared with baseline levels. Direct comparison with a control group at both 2-months and follow-up revealed no significant difference in any of the measures. Nevertheless, these results suggest that following intervention periods of 2 months or more, mood and sleep benefits of mushroom supplementation may begin to emerge. Shorter durations of mushroom supplementation may be less effective in improving sleep quality, as shown by 4-week supplementation studies that used young and middle-aged healthy or perimenopausal females but failed to show any benefits to sleep quality following daily intake of either 2 g of powdered Lion's Mane mushroom incorporated in cookies (Nagano et al., 2010) or Amyloban tablets (that contained 0.5% hericenones from Lion's Mane mushroom, Okamura et al., 2015). Nagano did report reductions in CES-D depression scores compared to baseline for the Lions Mane group, suggesting that mood-related benefits may emerge earlier than sleep benefits, but as with Vigna et al., direct comparison with the control group at 4 weeks failed to show significance. Okamura et al. (2015) did observe an increase in salivary free-MHPG (a metabolite of the neurotransmitter and hormone norepinephrine), however statistical power may have been an issue when trying to observe any concurrent cognitive effects as the sample size was small (n = 8). Indeed, lack of statistical power may have impacted all of the studies investigating younger/healthier age groups, where mushroom-related effect sizes are likely to be small.

With respect to cognitive function, a recent study (Grozier et al., 2022) did not find any significant difference in scores for Stroop Word or Mental Arithmetic Challenge tasks in 18–25-year-old students, who consumed muffins containing either 10 g Lion's Mane mushroom or placebo daily for 4 weeks alongside a cycling-based exercise regime. It may be that cognitive improvements are less likely to be observed in healthy young adults. Conversely, in studies employing older adults, cognitive findings appear more prevalent. For example, Mori and colleagues showed that 60–80-year-old adults with mild cognitive impairment (MCI) who consumed 3 g fruiting body Yamambushitake Lion's Mane mushroom daily for 16-weeks exhibited a significant post-intervention improvement in HDS-R dementia scores compared with a control group (Mori et al., 2009). This improvement in cognitive function was accompanied by changes in levels of circulating electrolytes (Na & K), and a reduction in creatinine (suggestive of improved kidney function). Furthermore, a study employing participants aged 55–65 years old taking daily capsules containing 3.2 g of Lion's Mane mushroom fruiting body for 12-weeks (Saitsu et al., 2019) showed significant improvement on MMSE score compared with a control group, although no improvements were seen on the Benton visuospatial task, or the verbal paired associate learning task (S-PA). Similarly, improvements in MMSE performance were observed at the post-intervention period compared with baseline when older adults with AD received 1 g mycelium Lion's Mane mushroom daily for 49-weeks (Li et al., 2020). These improvements were accompanied by a significant reduction in MRI Apparent Diffusion Coefficient (ADC), which the authors argue is suggestive of a more organised neural structure. A reduction in homocysteine level was also observed. However, Li et al. observed no significant cognitive differences when comparing the Lion's Mane group directly to the control group, where only higher daily living ability scores and greater ophthalmological contrast sensitivity scores were observed.

While Lions Mane has shown some small benefits relating to neurodegeneration in older age, other mushrooms appear to be less effective. For instance, a large study involving healthy elderly participants found no significant improvements in DASS-21, CSIRO-CAB or PANAS

Table 3
Characteristics of the eligible intervention studies investigating the effect of mushroom intake on neurocognitive and psychological well-being, based on cohort age and chronological order (*).

Author	Sample characteristics	Intervention (E: experimental group, C: control group)	Design method	Results (mushroom-related outcomes)
Nagano et al. (2010)	●30 perimenopausal females ●35-45 y old ●Japan	E: consumed 4 x cookies containing total 2 g HE/d (n = 15), C: consumed 4 x placebo cookies with no added HE/d (n = 15). Duration: 4-w.	*Baseline measurements:* Self-reports for food intake & physical activity. At baseline & 4-w: *Neurocognitive & sleep assessments:* CES-D (depression), & PSQI (sleep). *Other assessments:* KMI & ICI.	Group E (at 4-w compared with Group C with baseline as covariate): ●NS in all measures. Group E (at 4-w compared with baseline*): ●↓ CES-D & ICI, ●NS PSQI & KMI. *Control group comparisons between baseline and 4-w were not reported. Drop-outs: n = 4 (n = 3 in Group E & n = 1 in Group C).
Okamura et al. (2015)	●8 healthy females ●20-22 y old ●Japan	E: consumed 6 x tablets amyloban each containing 0.5% hericenones from HE/d (n = 8), C: no placebo group (n = 0). Duration: 4-w.	At baseline & 4-w: *Sleep & well-being assessments:* GHQ-28 (well-being) & PSQI (sleep). *Other measurements:* Salivary Free-MHPG.	Group E (at 4-w compared with baseline): ●↑ SF-MHPG, ●NS PSQI & GHQ-28. Drop-outs: n = 0.
Grozier et al. (2022)	●24 healthy male & female college students ●18-25 y old ●USA	E: consumed 2 x muffins/d each containing 5 g HE (n = 12), C: consumed 2 x muffins with no added HE/d (n = 12). Duration: 4-w.	At baseline & 4-w: Dietary assessment: 24-h food diary. *Neurocognitive assessment* :* Stroop Word Challenge & Mental Arithmetic Challenge (working memory) & Y-balance challenge (balance). *The cognitive tests were performed pre & post exercise.	Group E (at 4-w compared with Group C): ●NS in all measures. Drop-outs: n = 0.
Tsuk et al. (2017)	●96 healthy males & females ●23-30 y old ●Israel	Liquid extract containing 4125 mg/5 ml C.sinensis, 330 mg/5 ml G.lucidum, 330 mg/5 ml L.edodes & Lingzhi capsules containing 325 mg G.lucidum & 175 mg C.sinensis. E1 (high dose): consumed 15 ml of liquid twice/d & 2 x Lingzhi capsules/d (n = 32), E2 (low dose): consumed 7.5 ml of liquid twice/d &1 x Lingzhi capsule/d (n = 32), C: consumed 2 x soups containing 14% commercial mushroom/d & 1 x glucose capsule/d (n = 32). Duration: 30-d.	At baseline & 30-w: *Neurocognitive assessment:* Mindstreams computerised battery assessing executive function, memory, motor function, IQ, processing speed & visuospatial skills.	Groups E1 & E2 (at 30-d compared with Group C): ●NS in all measures. Drop-outs: not reported.
Saitsu et al. (2019)	●34 healthy males & females ●55-65 y old ●Japan	E: consumed 4 ×0.8 g HE supplements/d (n = 17), C: consumed 4 x placebo supplements with no HE/d (n = 17). Duration: 12-w.	At baseline, 6-w & 12-w: *Neurocognitive & vision measurements:* Benton visual retention test (visuospatial memory), MMSE (global cognition) & S-PA (short-term memory).	Group E (at 12-w compared with Group C): ●↑ MMSE, ●NS Benton visual test & S-PA. Drop-outs: n = 3 (n = 1 in Group E & n = 2 in Group C).
Vigna et al. (2019)	●77 obese males & females ●50-60 y old ●Italy	E: consumed low calorie diet & 3 x 500 mg HE capsules/d (n = 40), C: consumed low-calorie diet only/d (n = 37). Duration: 2-m intervention & 2-m follow-up.	At baseline, 2-m & follow-up: *Depression, anxiety & well-being assessments:* Zung's Depression-Anxiety Scale, SCL-90 & BES (anxiety, mood & well-being). *Other measurements:* Pro-BDNF, BDNF & pro-BDNF/BDNF ratio in serum.	Group E (at 2-m & follow-up compared with group C): ● NS anxiety & depression symptoms in Zung's Scale. Group E (at 2-m & follow-up compared with baseline): ●↓ anxiety in Zung's scale (at 2 m only), ●↓ BES, ●↓ anxiety, depression & sleep disorders in SCL-90, ●↑ pro-BDNF (at 2-m only) & in pro-BDNF/BDNF ratio, ●↓ BDNF (only at follow-up). Group E with mood disorders (at m-2 & follow-up compared with baseline): ●↓ anxiety & depression in Zung's scale, ●↓ anxiety, depression & sleep in SCL-90, ●↓ anxiety & depression in combined Zung's & SCL-90 scales.

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Table 3 (*continued*)

Author	Sample characteristics	Intervention (E: experimental group, C: control group)	Design method	Results (mushroom-related outcomes)
				Drop-outs: n = 5 (in Group E).
Mori et al. (2009)	●30 MCI males & females ●50-80 y old ●Japan	E: consumed 12 x 250 mg tablets each containing 96% Yamabushitake (HE)/d (n = 15), C: consumed 12 x 250 mg starch-lactose tablets/d (n = 15). Duration: 20-w (with 16-w intervention & 4-w follow-up).	At baseline, 8-w, 12-w, 16-w, & follow-up: *Neurocognitive assessment:* HDS-R (visuospatial & working memory). At baseline, 8-w, & 16-w: *Other measurements:* BMI, BP, glucose, cholesterol, metabolic & liver enzymes, electrolytes in serum.	Group E (compared with Group C): ●↑ HDS-R scores (at 8, 12, 16 & follow-up ●↓ uric acid (at 16-w). ●NS in all other blood biomarkers. Group E had ↓ HDS-R scores (at follow-up compared with 16-w). Group E (at 16 w compared with baseline with no similar change in Group C): ●↑ K, ●↓Na, Creatinine ●→AST, LDH (reduction in Group C) Drop-outs: n = 1 (in Group E).
Wang et al. (2018)	●42 AD males & females ●70-85 y old ●China	E: consumed 12 x 250 mg capsules/d GL spore extract (n = 21), C: consumed 12 x placebo capsules/d (n = 21). Duration: 6-w.	At baseline & 6-w: *Neurocognitive & well-being assessments:* ADAS-cog (*cognition*), NPI (behavioural symptoms) & WHOQOL-BREF (quality of life).	Group E (Change from baseline at 6-w compared with Group C): ●NS in all measures. Drop-outs: n = 0.
Zajac et al. (2020)	●424 healthy males & females ●60-90 y old ●Australia	E1: consumed 2 x capsules VDM each containing 300 IU vitamin D2 & 100 mg white button mushroom/d (n = 147), E2: consumed 2 x capsules each containing 300 IU vitamin D3/d (n = 91), E3: consumed 2 x capsules each containing 100 mg white button mushroom/d (n = 94), C: consumed 2 x placebo capsules/d (n = 92). Duration: 24-w.	At baseline, 5-w & 24-w: *Neurocognitive & mood assessments: CSIRO-CAB* (*cognition*), DASS-21 (depression, & stress), GHS (happiness), PANAS (mood). At baseline & 24-w: *Other measurements:* 25-OH vitamin D2 &D3 in serum.	Groups E1 & E3 (change from baseline at 24-w compared with Group C): ●NS CSIRO-CAB tasks & overall score, ●NS DASS-21, GHS & PANAS, ●NS 25-OH-D2 & 25-OH-D3. Drop-outs: n = 63 (n = 58 in Group E1, n = 2 in Group E2 & n = 3 in Group E3).
Li et al. (2020)	●49 AD males & females ●65-80 y old ●China (Taiwan)	E: consumed 3 x 350 mg capsules HE each containing 5 mg/g erinacine A/d (n = 25), C: consumed 3 x placebo capsules (type not specified)/d (n = 24). Duration: 49-w treatment.	At baseline, 13-w, 25-w & 49-w: *Neurocognitive assessments:* CASI & MMSE (global cognition), NPI (*behavioural symptoms*) & IADL (*daily living ability*). At baseline,25-w & 49-w: *Ophthalmological assessments:* BCVA & CS. *Other measurements:* Aβ-40, α-ACT, ApoE4, BDNF, Hcy & SOD in serum. At baseline & 49-w: *Imaging assessment:* MRI.	Group E (at 49 w compared with Group C): ●↑ IADL, ●↑ CS, ●NS CASI, MMSE, ●NS Aβ-40, ApoE4, BDNF & SOD, ●NS D.IFOF.FA & N.IFOF. FA in MRI. Group E (at 49 w compared with baseline with no similar change in Group C): ●↑ MMSE, ●↓ D.PHC.ADC in MRI, ●NS CASI, IADL, NPI, BCVA & CS, ●↓Hcy. Drop-outs: n = 8 (n = 5 in Group E & n = 3 in Group C).

(*) Abbreviations: α-ACT: alpha-1-antichymotrypsin, Aβ: amyloid-beta peptide, AD: Alzheimer's Disease, ADAS-cog: Alzheimer's Disease Assessment Scale-cognitive, AF: Animal Fluency test, ApoE4: Apolipoprotein E4, AST: aspartate aminotransferase, BCVA: Best Corrected Visual Acuity, BDI: Beck Depression Inversion, BDNF: Brain-Derived Neurotrophic Factor, BES: Basic Empathy Scale, BIS-11: Barratt Impulsive Scale, BMI: Body Mass Index, BP: Blood Pressure, C: Control group, CASI: Cognitive Abilities Screening Instrument, CDR: Clinical Dementia Rating, CERAD-DR: Consortium to Establish a Registry for Alzheimer's Disease-Delayer Recall, CERAD-WL: Consortium to Establish a Registry for Alzheimer's Disease-Word Learning, CES-D: Centre for Epidemiologic Studies- Depression, CHNS: China Health & Nutrition Survey, CLHLS: Chinese Longitudinal Healthy Longevity Survey, CS: Contrast Sensitivity, CSIRO-CAB: Commonwealth Scientific and Industrial Research Organisation-Cognitive Assessment Battery, d: day, DaHA: Diet and Healthy Aging study, D.ARC.ADC: Dominant arcuate fasciculus apparent diffusion coefficient, DASS-21: 21-item Depression & Stress Scale, D.IFOF.FA: Non-dominant inferior fronto-occipital fasciculus fractional anisotropy (MRI), DSST: Digit Symbol Substitution Test, DVS: Dietary Variety Score, E: Experimental group, EPDS: Edinburgh Postnatal Depression Scale, FFQ: Food Frequency Questionnaire, g: grams, GDS-5: 5-item Geriatric Depression Scale, GHQ-28: 28-item General Health Questionnaire, GHS: General Happiness Scale, Gimlet: Gerontological investigation of microbiome longitudinal estimation study, GL: *Ganoderma lucidum*, GPAQ: Global Physical Activity Questionnaire, h: hours, HADS: Hospital Anxiety & Depression Scale, HCS: Hatoyama Cohort Study, Hcy: Homocysteine, HDS-R: Hasegawa's Dementia Scale-Revised version, HDL-c: High-Density Lipoprotein-cholesterol, HE: *Hericium erinaceus*, HUSK: Hordaland Health Study, IADL: Instrumental Activities of Daily Living scale, ICI: Indefinite Complaints Index, IQ: Intellectual Quotient, JDI_{12}: Japanese diet index, K-HDRS: Korean Hamilton Depression Rating Scale, KLS: Kusatsu Longitudinal Study, KMI: Knowledge of Mental Illness questionnaire, KSHS: Kangbuk Samsung Health Study, LDH: lactate dehydrogenase, LDL-c: Low-Density Lipoprotein-cholesterol, LM-WMSR: Logical Memory subtests I and II of the Wechsler memory

Scale-Revised, m: month, m-BD: Block Design-modified version, MCI: Mild Cognitive Impairment, m-DST: Digit Symbol Test- modified version, MMSE(m, SM): Mini-Mental State Exam (modified version, Singapore modified version), MoCA-J: Montreal Cognitive Assessment-Japanese version, MRI: Magnetic Resonance Imaging, n: number, N/A: Not applicable, NHANES: National Health & Nutrition Examination Survey, N.IFOF.FA: Non-dominant inferior fronto-occipital fasciculus fractional anisotropy (MRI), NPI: Neuropsychiatric Index, NS: Non-significance, PANAS: Positive And Negative Affect Schedule, PCA: Principal Component Analysis, PHQ-9: 9-item Patient Health Questionnaire, PSQI: Pittsburgh Sleep Quality Index, RRR: Reduced Rank Regression, SCL-90: 90-item Symptom Checklist, SF-8: 8-item Sleep healthy Survey, MHPG: Salivary 3-Methoxy-4-Hydroxyphenylglycol, SOD (1-2): Superoxide Dismutase (1-2), SONIC: Septuagenarians, Octogenarians, Nonagenarians investigation with Centenarians Cohort, S-PA: Standard verbal Paired Associate learning test, S-task: access to Sematic memory task or abridged controlled oral word association test, TAG: triglycerides, TICS-M: Telephone Interview for Cognitive Status-modified version, TMT-A: Trail Making Test- part A, USDA: USA Department of Agriculture, VDM: Vitamin D2-enriched Mushroom, w- week, WHOQOL-BREF: World Health Organisation Quality Of Life Questionnaire-Brief version, y: year, ↑: increase, ↓: decrease.

scores after consuming capsules containing either 200 mg powdered white button mushroom or 200 mg white button mushroom enriched with 600IU vitamin D2 daily for 24-weeks (Zajac et al., 2020), although it should be noted that the dose of mushroom used was extremely small here as the primary focus of the study was vitamin D rather than mushroom supplementation itself. Daily administration of a concentrated liquid extract containing Caterpillar, Reishi and Shiitake mushroom species to healthy young participants for 30-days (Tsuk et al., 2017) also failed to demonstrate any significant cognitive benefits compared with a control group that received a commercial mushroom soup. Finally, no significant effects of mushroom supplementation were seen when AD participants were administered capsules containing 3 g Reishi mushroom spore extract daily for 6 weeks with participants failing to show any significant cognitive improvement on the ADAS-Cog, the NPI or the WHOQOL-BREF compared to control (Wang et al., 2018).

These intervention studies reveal only limited investigation into mushroom effects on cognitive function and mood, with most studies focusing on Lion's Mane. Although Lion's Mane interventions have been tested in a range of different age groups, only middle-aged and older adult studies have shown statistically robust cognitive benefits when compared to a control group. Significant benefits have been observed with dose sizes of at least 3 g/day and durations of 12 weeks or more (Saitsu et al., 2019; Mori et al., 2009). Less robust effects of Lion's Mane have been observed following lower dose sizes and shorter durations, but only when considering changes from baseline performance rather than comparison with a control condition (Nagano et al., 2010; Vigna et al., 2019; Li et al., 2020). Younger populations do not seem to benefit cognitively from supplementation with Lion's Mane, even at higher doses up to 10 g/day (Grozier et al., 2022). Other mushroom types have not yet been observed to elicit any significant benefits in younger adults (Tsuk et al., 2017) or older adults (Wang et al., 2018; Zajac et al., 2020), however the range of mushroom species, doses, and durations currently investigated is very limited. Given the promising epidemiological associations between general dietary mushroom intake and cognitive function, it seems likely that these intervention studies may not reflect the true benefits of mushroom consumption, and with sample sizes ranging from upwards of 8 participants, studies may in some cases have insufficient statistical power to observe any effects that may be present. Further investigation is needed to fully determine whether common dietary mushrooms other than Lion's Mane can benefit cognition and mood across the lifespan, as suggested by the epidemiological data.

4. Discussion

The purpose of this review was to systematically evaluate human studies investigating the relationship between mushroom consumption and neurocognitive and psychological health. For this review, 34 records were identified from four online search databases of which 10 were intervention studies and 24 were epidemiological studies. Evidence from epidemiological studies demonstrated that when both healthy and compromised populations, irrespective of their age and health status, followed variations of the "healthy plant-based" diet that included mushrooms, they exhibited better cognitive function, mood, and sleep, as well as decreased risk of all-cause deaths, dementia, and depression symptoms. However, few epidemiological studies quantified mushroom intake separately from other vegetables, or catalogued the different species of mushroom consumed, so further research is needed to investigate the specific relationship between mushroom intake, neurocognition, and mood. While the epidemiological research appears to support a relationship between mushroom intake and cognition (with the caveats mentioned), findings obtained from human intervention studies remain more mixed. Indeed, only Lion's Mane mushroom appears to offer any benefits to cognition or mood following supplementation, and only in older age groups, following long durations, and at high doses. However, other mushroom species are currently under investigated in the literature. Therefore, definitive conclusions on the overall beneficial effect of mushroom interventions, or the specific mushroom species that might be beneficial, cannot yet be drawn.

Previous evidence from *in vivo* and *in vitro* animal studies suggest that beneficial cognitive effects may be attributable to polysaccharides and phenolic compounds present in different mushroom species. These mushroom bioactives may impact cognition indirectly by reducing pro-inflammatory markers and increasing antioxidant markers (Muszyńska et al., 2018), and potentially mitigating neurodegenerative disease *via* nitric oxide (NO) pathways (Moro et al., 2012; Bor et al., 2006; Calabrese et al., 2007). In addition, the hermetic neuroprotective effects of mushroom phytochemicals may play a role through Nrf2 pathways (Martel et al., 2019; Calabrese et al., 2010; Calabrese et al., 2016). Mushroom bioactives may also act by increasing neurotransmitter release directly (Sabaratnam et al., 2013; Briguglio et al., 2018), or indirectly by regulating the gut microbiome-vagus nerve axis (Hu et al., 2022). However, the majority of intervention studies reviewed here did not collect any biochemical data. Some did observe changes to blood or saliva markers associated with synaptic plasticity, neurotransmission, electrolytes, or enzymes associated with organ function (Okamura et al., 2015; Vigna et al., 2019; Mori et al., 2009; Li et al., 2020). However, these were generally small changes observed from baseline levels that were no longer evident following statistical comparison with a control group. Exploring the physiological effects of mushrooms would provide information on potential mechanisms of action and would strengthen the behavioural evidence. It seems critical that future research should examine levels of different neurotrophic factors and/or antioxidant markers in serum/saliva and confirm whether these correlate with neurocognitive outcomes, using experimental designs with sufficient statistical power to detect these physiological changes. Currently, none of the intervention studies reviewed here looked specifically at changes in the gut microbiota, so collection and analysis of participants' faecal samples would help to examine changes in gut microflora and SCFA production following mushroom intervention. This would help to further our understanding of the potential metabolites involved in the regulation of gut-brain signalling (Cerletti et al., 2021).

Experimental evidence for the beneficial effects of mushrooms on mood tentatively suggests that hericenones and erinacine compounds in Lion's Mane mushroom might be responsible for reduced depressive symptoms (Nagano et al., 2010; Vigna et al., 2019). *In vivo* animal studies have also shown an increase in acetylcholine and dopamine levels following HE mushroom supplementation which highlights the antidepressant potential of mushroom bioactives to influence anhedonia, sleep circadian rhythm, and emotional wellbeing (Furuta et al., 2016; Ryu et al., 2018; Rai et al., 2021), and may explain some of the

mood findings reviewed here. However, the relationship between mushroom intake, sleep patterns, and depressive symptoms are less clear in the cross-sectional epidemiological research, likely because Lion's Mane and similar exotic species are not commonly consumed as part of a habitual diet. A distinction in the literature is needed between dietary mushrooms and extracts or supplements derived from exotic species. Indeed, it would also be beneficial to investigate a wider range of mushroom species and dose sizes in future RCTs in order to align with the epidemiological evidence that relates mainly to commonly consumed mushroom species rather than exotic species.

The epidemiological studies presented here demonstrated, in the context of public health, that consuming more than one and a half mushroom portions per week (~120–150 g) appeared sufficient to significantly reduce the risk of cognitive impairment, depression, and all-cause death risk. These findings have been previously supported by studies examining the beneficial effect of Mediterranean diet on cognitive health due to the similarities of such diets with the "plant-based" dietary pattern identified from the studies included in this review (Klimova et al., 2021). RCTs are still needed to confirm whether these benefits are due to mushrooms alone, rather than a general vegetable-rich eating pattern. Nevertheless, it is plausible that mushroom bioactives might be of potential use in the treatment and prevention of dementia due to their capacity to significantly increase neurotrophic factors and reduce inflammatory cascades.

In terms of the characteristics of the studies presented in this review, it should be noted that the majority of intervention studies and epidemiological studies were conducted in Asia, mainly in Japan or China, likely due to the extensive use of a wide variety of mushrooms as a habitual part of their diet. Such findings may not generalise to Western populations that typically eat fewer varieties. In terms of the methodology used to measure mushroom intake, most epidemiological studies relied on FFQs or 24-hour dietary recalls. Such strategies are inherently prone to bias because it is based on participants' self-reports. Also, these studies were unable to estimate the participants' precise mushroom intake, in contrast to the strict dosing regimens used in intervention studies, or to collect specific information on the different mushroom species consumed. Inaccuracies may also arise from assumptions made about the mushroom content of dishes such as soups or stews when analysing the frequency data. Therefore, future studies should consider more effective ways to capture habitual mushroom intake, such as diet diaries, or specific questionnaires relating to mushroom consumption that can more accurately capture the quantity and species of mushrooms consumed. It is important to gain a clearer understanding of the different types of mushrooms consumed across cultures, and to determine whether different mushroom species elicit cognitive benefits across similar or varying cognitive domains.

Regarding the methodology used to assess cognitive and mood outcomes, while epidemiological studies mostly relied on self-report mood questionnaires, the presented intervention studies often employed more rigorous cognitive test batteries to examine various neurocognitive subdomains. Studies assessing cognitive function typically followed a controlled protocol with researchers employing a variety of cognitive tasks covering a wide range of neurocognitive domains. However, there was very little overlap in the measures used across studies making direct comparisons difficult. Similarly, time of day, and the form in which any intervention was administered, varied considerably across studies. Therefore, differences in postprandial physiological processes such as absorption, distribution, metabolism, and excretion (ADME), may have impacted cognitive outcomes depending on the exact methodology used. A more standardised approach would help to consolidate findings in any future research.

Finally, in terms of the risk of bias assessment, more than half of the intervention studies reviewed here were rated as having some concerns. In a majority of cases, these concerns may have been alleviated by a more detailed explanation of the study methods or outcomes, and full reporting of all statistical findings. This highlights the importance of clear reporting, particularly focusing on factors such as randomisation methods used, any deviations from the intended intervention, specific outcome measures, dropout rates and handling of missing data, and full and clear reporting of all outcomes. In terms of study quality, it was noted that a majority of the intervention studies failed to provide sample size justifications. Sample sizes were often small, which may have resulted in a lack of statistical power to observe any mushroom effects that may be present. Quality issues were similarly identified in some of the epidemiological studies where, again, studies often failed to report sample size justifications, or whether researchers were blinded during outcome assessment. Incomplete reporting of outcome measures, and in the case of cohort studies, failure to repeat measures of dietary exposure alongside repeated mood and cognitive assessments, may also have impacted the validity of any findings. Importantly, given the correlational nature of the epidemiological studies, only associations between neurocognitive outcomes and mushroom intake were able to be determined, and causality could therefore not be inferred. The prospective cohort studies assessed habitual diet, including mushroom intake, over a prolonged period, permitting stronger associations to be made with cognition, however the intervention studies reviewed here did not tap into the same relationships, focusing mainly on speciality mushrooms such as Lion's Mane rather than common dietary mushrooms. Good quality, large scale RCTs investigating all dietary mushrooms, with measurement of behavioural and physiological/biological outcomes, are needed to determine true effect sizes and mechanisms of action for the relationships hinted at in the epidemiological data.

It is clear from the relatively small number of studies included here that the relationship between mushroom consumption and cognitive health is currently under investigated. It is hoped that the findings presented in this novel review may be used to inform the design of future studies examining the effects of mushrooms on mood and cognitive health. Although epidemiological studies can provide useful information by looking at mushroom intake as an integral part of diet, their correlational nature, and the lack of specific information regarding the quantity and types of mushrooms consumed preclude any firm inferences regarding causality. Future epidemiological studies should aim to specifically examine mushroom intake on its own rather than as part of a more general dietary pattern. This may require the development of detailed mushroom-based questionnaires to be used alongside standard FFQs. Habitual diet data from the studies included in this review is generally limited to frequency of mushroom intake rather than the actual amounts consumed. Diet diaries, although more time consuming, are likely to also provide a better estimation of mushroom intake. RCTs are able to closely control the amount and type of mushroom consumed, however the majority of RCTs reviewed here were conducted in Asia, in old and cognitively impaired populations, and examined the effects almost exclusively of one type of mushroom species (*i.e.* Lion's Mane). This narrow focus of current research makes it hard to generalise mushroom benefits on cognition and mood. Further clinical trials are therefore vital and should seek to extend the age ranges and cultures of the populations tested, while examining a greater range of culinary mushroom species, to better examine their cognitive effects both in the short or long term. Mushroom dosages need to be realistically achievable as part of a habitual diet in order for findings to have any real-world relevance. Well-designed dose–response studies would help to establish optimal mushroom doses to better inform public health messaging relating to mushroom intake. It also remains unclear whether mushrooms exert their effects on specific cognitive domains, and so future research should aim for a consensus on the cognitive tasks used, allowing consistent investigation across a spectrum of cognitive domains, using sensitive tasks that measure specific domains rather than relying on broad measures of cognitive function such as MMSE that lack sensitivity and specificity. The inclusion of physiological measures such as examining metabolic, inflammatory, and neuronal markers will also aid in our understanding of any underlying mechanisms of action. Importantly, studies should also consider statistical power when

determining participant numbers. Current experimental studies often recruit small numbers of participants (likely due to cost implications) and so may not be sufficiently powered to observe small but meaningful dietary benefits to cognition. Collaboration may offer a viable way of spreading the cost of larger trials.

5. Conclusion

After systematically evaluating the results from these 34 studies, it can be concluded that the epidemiological data provided some evidence for an association between mushroom intake, mood and cognition, particularly depressive symptoms and neurodegenerative outcomes. However, the findings obtained from the human intervention studies were mixed and restricted in the mushroom species investigated. The experimental findings tentatively show a reduction in depressive symptoms and improvement in dementia scores. However, the degree of improvement in mood or cognitive function varied, dependent on the population tested, the dose of the intervention, and mushroom species used. Additional well-designed, long-term clinical trials are needed to further substantiate these findings and extend them to a greater range of common dietary mushrooms. It is also important to elucidate mechanisms of action to determine the potential for mushroom intake to improve cognition throughout the lifespan, and particularly during aging. Overall, the information presented in this review could serve as a template for future study design, to further examine the impact of edible mushrooms on mood and cognitive function, and their mechanisms of action. Such data can be used to support current public health messaging by highlighting the benefits of including mushrooms as part of a healthy diet.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2024.105548.

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