

The Impact of Anxiety, Depression, and Alcohol Use Disorder and Heavy Alcohol Consumption on Stroke Incidence: A Systematic Review

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Background. Stroke is a leading cause of death and disability worldwide, and common psychiatric conditions may be associated with its incidence. This review examined whether anxiety, depression, alcohol use disorder (AUD), and heavy alcohol consumption are associated with incident stroke in adults, and how consistent that evidence is. Because these conditions frequently co-occur and share plausible neurobiological and behavioral pathways, they were examined together within a transdiagnostic framework. It additionally incorporates psychological distress and chronic stress as a related, exploratory fourth construct.

Methods. A systematic search of PubMed, PsycINFO, and OpenAlex (adults, English, peer-reviewed), updated in September 2026 with expanded PubMed coverage and hand-searching/citation-chaining, identified observational cohort, case-control, and meta-analysis sources reporting incident stroke or, for exploratory H4, combined stroke/TIA outcomes; 34 sources were included. Primary studies were appraised with the Newcastle–Ottawa Scale, and meta-analyses were checked against selected AMSTAR-2 domains.

Results. Depression showed the most consistent association with incident stroke across sixteen sources (fourteen primary studies and two meta-analyses), with hazard and relative risks ranging from approximately 1.15 to 2.14 depending on symptom severity, persistence, and population (e.g., HR 1.41, 95% CI 1.32–1.50; RR 1.45, 95% CI 1.29–1.63). Heavy alcohol consumption showed a dose- and pattern-sensitive association across twelve studies, with heavy or binge-pattern intake linked to higher stroke risk (e.g., single-occasion drinking HR up to 3.41; a separate, earlier meta-analysis reported RR 1.64, 95% CI 1.39–1.93, for total stroke at >60 g/day), whereas light-to-moderate, regular intake was generally not associated with higher risk and was sometimes protective. Anxiety findings remained mixed across three studies: individual cohorts were positive (HR 1.14) or null (Rotterdam), but pooled evidence suggested a modest positive association (HR 1.24, 95% CI 1.09–1.41). (A separate cross-sectional cohort, NESDA, also reported no association but does not meet this review's incident-stroke eligibility criteria and is not counted here.) Psychological distress and chronic stress, examined across three studies with heterogeneous outcomes (two combine stroke with TIA), showed a suggestive but mixed pattern: MESA found associations with the combined stroke/TIA outcome (HR approximately 1.03–1.19), whereas the Caerphilly Study's overall stroke/TIA estimate did not reach significance, though it reported a clearer, significant association specifically for fatal ischemic stroke.

Conclusion. Depression and heavy or pattern-risky alcohol consumption were the most consistently associated with incident stroke, anxiety associations were mixed but modestly positive when pooled, and psychological distress/chronic stress showed a suggestive but outcome-mixed pattern that requires confirmation with a consistent, stroke-specific outcome. All evidence is observational and associative, not causal, and no clinical recommendations are drawn.

Keywords: anxiety; depression; alcohol use disorder; heavy alcohol consumption; stroke incidence; systematic review; transdiagnostic mechanisms; psychological distress; chronic stress

Introduction

Stroke is the second leading cause of death in the world, killing around 6.6 million people every year since 2019. Reported associations between mental illness and stroke have prompted interest in psychiatric conditions as potential cor-

relates of stroke risk. A substantial proportion of the global population experiences mental health challenges, which has motivated research into whether these conditions are associated with stroke incidence.

A stroke is scientifically defined as a loss of blood flow to the brain, causing damages in brain tissue due to lack of oxygen and nutrients entering the blood vessels¹. Strokes can

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occur due to blood clots and damaged blood vessels located in the brain. This pathophysiology can cause symptoms such as numbness, weakness of body, speech problems, writing problems, dizziness, and language confusion.

There are two main types of strokes, the most common out of the two is an Ischemic stroke which occurs when the blood flowing to the brain is blocked or reduced, preventing oxygen and nutrients from entering the brain tissue. The second type of stroke is a Hemorrhagic stroke, which occurs when a blood vessel located in the brain ruptures and bleeds out. These two types of strokes arise from common risk factors such as pregnancy, obesity, diabetes, smoking, and high blood pressure. However, these strokes vary in pathophysiology, explaining why some of the risk factors differ. Given that these are common and well-established risk factors for stroke, it is important to consider others that may contribute to the high prevalence of mortality of stroke.

Theoretical framework

This review is grounded in a transdiagnostic neurobiological framework, which proposes that anxiety, depression, and alcohol use disorder (AUD) share overlapping neurobiological and behavioral pathways that are each associated with elevated cerebrovascular risk^{2,3}. Rather than treating these conditions as independent risk factors, the transdiagnostic perspective recognizes common underlying processes, dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, chronic low-grade systemic inflammation, autonomic nervous system dysregulation, and maladaptive health behaviors, each of which has an established association with vascular pathology.

HPA-axis dysregulation. Anxiety and depression are associated with chronic activation of the HPA axis and sustained elevation of cortisol, which is in turn associated with endothelial dysfunction, increased platelet aggregability, and hypertension⁴. Excessive alcohol consumption is similarly associated with HPA dysregulation.

Systemic inflammation. Depression is reliably associated with elevated pro-inflammatory markers including C-reactive protein and interleukin-6^{5,6}, which are associated with accelerated atherosclerosis and thrombotic risk.

Autonomic dysregulation. Anxiety is associated with sympathetic hyperactivation and reduced heart-rate variability, which are associated with endothelial damage and arrhythmias such as atrial fibrillation, a recognized embolic source in ischemic stroke.

Behavioral pathways. Beyond direct neurobiology, all three conditions are associated with vascular risk-factor accumulation through shared behaviors — physical inactivity, poor diet, smoking, and reduced treatment adherence, while AUD is additionally associated with hypertension, atrial fibrillation, and hypercoagulability^{7,8}. The framework therefore posi-

tions these conditions as converging on cerebrovascular risk through partly shared mechanisms.

Consistent with this framework, mental illnesses including anxiety, alcohol use disorder, and depression are often linked with risk factors of stroke through various biological mechanisms. Anxiety activates the hypothalamic–pituitary–adrenal (HPA) axis causing chronic stress and constant release. This is associated with damage to blood vessels, which may relate to an increased risk of ischemic stroke. Anxiety is also linked to the autonomic nervous system (ANS) dysregulation, which disrupts the balance between the body's fight-or-flight response and the rest-and-digest state, and is associated with hypertension. Depression is linked to chronic low-grade inflammation, with higher levels of inflammatory markers like C-reactive protein and interleukin-6. This can lead to problems in the blood vessels (endothelial dysfunction) and is associated with an increased risk of blood clots (thrombosis). Depression is associated with unhealthy lifestyle behaviors, such as smoking, physical inactivity, poor diet, obesity, diabetes, and hypertension. Alcohol use disorder is directly linked to hypertension, atrial fibrillation, increased blood clotting, inflammation, liver disease, increased blood pressure, and unhealthy habits. These effects are associated with other cardiovascular diseases which co-occur with an increased occurrence of stroke.

According to the American Psychological Association (APA), anxiety is defined as an emotion defined by mental and physical symptoms of tension in which an individual expects negative events occurring soon, causing symptoms such as tense muscles, faster heart beats, and breathing more rapidly. In relation to another mental illness, Alcohol use disorder (AUD) is defined as a failed attempt to fulfill daily obligations and responsibilities due to alcohol-seeking behavior, with the requirement to achieve common alcohol effects such as tolerance. Depression can be defined as a negative affective state, ranging from unhappiness and discontent to an extreme feeling of sadness, pessimism, and despondency, that interferes with daily life. Various physical, cognitive, and social changes also tend to co-occur, including altered eating or sleeping habits, lack of energy or motivation, difficulty concentrating or making decisions, and withdrawal from social activities.

Research gap

Although prior reviews have examined anxiety, depression, or AUD individually in relation to stroke, few have jointly synthesized evidence across all three conditions within a single transdiagnostic framework or directly compared the strength and consistency of their associations with stroke incidence. The existing literature is further characterized by heterogeneity in how the psychiatric exposures are operationalized (clin-

ical diagnosis versus self-report screening) and how stroke is ascertained (neuroimaging-confirmed versus self-report or death-certificate based), which limits direct cross-study comparison. The present review addresses these gaps.

Scope of the review

To keep the research question precise, the scope of this review is defined as follows. The outcome of interest is incident stroke (new stroke events occurring during follow-up), not stroke prevalence. The population is adults (aged 18 years and older). For the psychiatric exposures, the review distinguishes clinically diagnosed conditions (established with structured instruments such as the CIDI or DSM/ICD criteria)⁹ from symptom-based measures (validated self-report scales such as the HADS or PHQ-9), and reports which was used in each study. For alcohol, the review explicitly distinguishes formally diagnosed alcohol use disorder (AUD) from quantity-based heavy alcohol consumption, because the included studies measure these differently and they are not equivalent. The exploratory H4 category also includes studies with a combined stroke/TIA outcome; these are identified separately and do not provide stroke-only estimates. Finally, all included evidence is observational (prospective cohorts, case-control studies, and meta-analyses of observational studies); no randomized or interventional evidence was sought or included, so all findings are interpreted as associations rather than causal effects.

This review has five aims: (1) to synthesize evidence on the association between anxiety and stroke incidence; (2) to synthesize evidence on the association between depression and stroke incidence; (3) to synthesize evidence on the association between alcohol exposure and stroke incidence, while distinguishing clinically diagnosed AUD from quantity-based heavy alcohol consumption; (4) to appraise the methodological quality of the included evidence; and (5) to synthesize evidence on the association between psychological distress/chronic stress and stroke incidence, as a construct related to, but conceptually distinct from, clinically defined anxiety and depression.

Three directional, confirmatory hypotheses were specified *a priori*:

H1. Anxiety will be positively associated with stroke incidence (higher rates of incident stroke among individuals with anxiety than without).

H2. Depression will be positively associated with stroke incidence, with pooled estimates expected to indicate an elevated relative risk compared with individuals without depression.

H3. Heavy alcohol consumption will be positively associated with stroke incidence, whereas light-to-moderate consumption will show a weaker or null association (a dose-response, J-shaped pattern). Because the included studies predominantly measure alcohol by quantity rather than by for-

mal diagnosis, the association specific to clinically diagnosed AUD is treated as a separate, exploratory question. The comparison across the three conditions in aim 4 is treated as exploratory.

H4 (exploratory). Psychological distress and chronic stress, as constructs related to but distinct from clinically defined anxiety and depression, were expected to show a positive but likely attenuated association with stroke incidence relative to clinically significant depression.

Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses¹⁰ guidelines. The study selection process is summarized in the PRISMA flow diagram (Figure 1).

Literature search strategy

To improve literature coverage and reduce the risk of missing relevant studies, three electronic databases were systematically searched: PubMed (MEDLINE), PsycINFO (via APA PsycNET), and OpenAlex. The following Boolean search string was applied in each database: (“stroke” OR “cerebrovascular accident” OR “cerebrovascular disease”) AND (“anxiety” OR “anxiety disorder”) AND (“depression” OR “depressive disorder” OR “major depressive disorder”) AND (“alcohol use disorder” OR “alcohol abuse” OR “heavy drinking”). The PubMed search was re-run in September 2026 with broadened terms (adding “psychological distress,” “chronic stress,” and additional alcohol drinking-pattern terms) and supplemented by expanded hand-searching and citation-chaining, to broaden the literature base underlying this review.

The 2021–2026 publication-date restriction applied to the electronic database search (the PubMed component was updated through September 2026); studies identified through hand-searching and reference-list screening were not excluded solely based on publication year. Filters applied were: adults, English language, and peer-reviewed document types (books and documents, clinical trials, meta-analyses, randomized controlled trials, reviews, and systematic reviews). The searches were run on March 14, 2026, with a supplementary expanded search run on September 18, 2026. The number of records retrieved was: PubMed *n* = 25, PsycINFO/APA PsycNET *n* = 14, and OpenAlex *n* = 34, plus 47 records identified through hand-searching (Google Scholar, citation-chaining, and reference lists of included reviews). This yielded 120 records in total before de-duplication (see the PRISMA flow diagram, Figure 1).

Inclusion and exclusion criteria

Studies were included if they met all the following criteria and excluded otherwise. Published in peer-reviewed journals: studies included have undergone the peer-review process, ensuring that experts in the field have examined and validated the research methods and findings. Relevance to the topic: studies had to report an association between at least one of the three conditions (anxiety, depression, or AUD) and stroke. English language publication: only studies published in English were considered, allowing better comparison across studies.

Data extraction

Data were extracted independently using a standardized extraction form. For each study the following were extracted: first author, year, country, study design, sample size, participant age range, exposure measure (clinical diagnosis vs. self-report scale), stroke outcome measure, effect size (hazard ratio, odds ratio, or relative risk) with 95% confidence interval, and covariates adjusted for. Study design and methodology, sample size and characteristics, and statistical analyses and significance levels were recorded for each selected study

Quality assessment

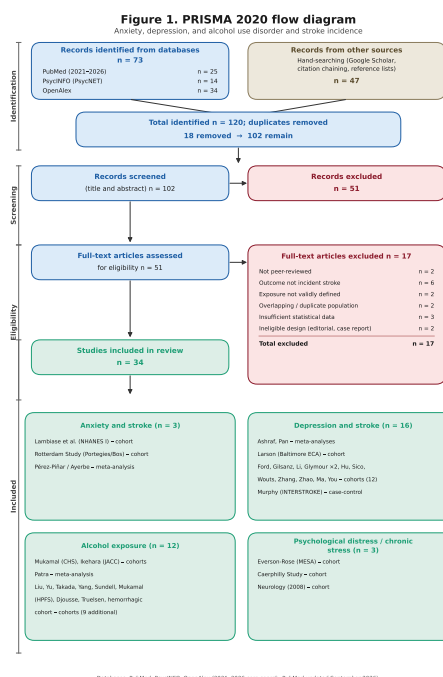
The methodological quality and risk of bias of each included cohort and case-control study were assessed using the Newcastle–Ottawa Scale (NOS), which rates studies across three domains: Selection (0–4 stars), Comparability (0–2 stars), and Outcome (0–3 stars), for a maximum of 9 stars. Studies scoring ≥ 7 was rated high quality, 5–6 moderate, and < 5 low. Included systematic reviews and meta-analyses were checked against selected AMSTAR-2 critical domains; overall 16-item confidence grades were not assigned. The completed quality ratings are reported in the Results (Table 5). For the one included case-control study, the case-control variant of the Newcastle–Ottawa Scale (Selection, Comparability, and Exposure domains) was used in place of the cohort variant.

Statistical approach

Because the included studies were clinically and methodologically heterogeneous in exposure definition and outcome ascertainment, findings are synthesized narratively and, where studies reported comparable effect sizes, these are tabulated with 95% confidence intervals. Effect estimates are reported as extracted from each source; associative (not causal) language is used throughout because all included designs are observational. Where a formal meta-analysis is not appropriate owing to heterogeneity, no pooled estimate is computed, and this is stated as a limitation.

Study selection (PRISMA)

Figure 1 presents the PRISMA 2020 flow diagram documenting the identification, screening, eligibility, and inclusion stages. Of 120 records identified (73 from databases — PubMed 25, PsycINFO 14, OpenAlex 34 — and 47 from hand-searching), 18 duplicates were removed, leaving 102 records that were screened by title and abstract (51 excluded); 51 full texts were assessed for eligibility (17 excluded), and 34 studies were included: 3 on anxiety, 16 on depression, 12 on alcohol exposure, and 3 on psychological distress/chronic stress (the exploratory H4 category includes two combined stroke/TIA outcome studies).



Description of included studies

Anxiety and stroke studies

Three sources examined the association between anxiety and incident stroke. Lambiasi et al.¹¹ analyzed 6,019 stroke-free participants from the First National Health and Nutrition Examination Survey (NHANES I), followed for a mean of 16.3 years, during which 419 incident strokes occurred. Anxiety symptoms were measured with the General Well-Being Schedule and modelled per one standard-deviation increase using Cox proportional-hazards regression. *Exposure measure: validated self-report symptom scale. Outcome: incident stroke from hospital/nursing-home discharge records and death certificates. Design: prospective cohort.*

Criterion	Inclusion	Exclusion
Study design	Prospective or retrospective cohort, case-control, systematic review, or meta-analysis of observational studies	Case reports, editorials, narrative reviews, conference abstracts, cross-sectional studies (cannot establish incident outcomes)
Population	Adults (≥ 18 years), stroke-free at baseline for incidence estimates	Pediatric samples; samples selected for pre-existing stroke where incidence cannot be derived
Exposure	Anxiety, depression, clinically diagnosed AUD, or quantified alcohol consumption/heavy drinking measured using a defined or validated instrument. Defined by clinical diagnosis (e.g. DSM-5, ICD-10, CIDI) or a validated self-report scale (e.g. HADS, PHQ-9)	Exposure not measured with a defined or validated instrument
Outcome	Incident stroke ascertained by imaging, medical records, registry, or death certificate; for exploratory H4 only, a combined incident stroke/TIA outcome is permitted and identified as such	Outcome not stroke (or stroke/TIA for exploratory H4), or stroke not distinguishable from other cardiovascular events
Language / peer review	English-language, peer-reviewed	Non-English; non-peer-reviewed (website, blog, organizational report)

The Rotterdam Study¹² was a population-based cohort using two baseline rounds. In 1993–1995, anxiety symptoms were measured with the Hospital Anxiety and Depression Scale–Anxiety (HADS-A) in 2,625 participants (mean age 68.4 years; 332 strokes over 32,720 person-years). In 2002–2004, anxiety disorders were assessed with the Munich Composite International Diagnostic Interview (CIDI) in 8,662 participants (mean age 66.1 years; 340 strokes over 48,703 person-years). *Exposure measure: HADS-A (symptoms) and CIDI (clinical disorder). Outcome: incident stroke via continuous medical-record monitoring. Design: prospective cohort.*

Contextual evidence (not part of the core incident-stroke synthesis): the NESDA-linked cohort¹³ (a study of cardiovascular disease in persons with depressive and anxiety disorders) compared 2,807 adults aged 18–65 (2004–2007) with current or past anxiety or depressive disorders, diagnosed using the CIDI and DSM criteria. *Exposure measure: clinical diagnostic interview. Outcome: cardiovascular events including stroke, assessed at a single baseline timepoint. Design: cross-sectional.* Because this design measures prevalent disease rather than incident stroke, it does not meet this review’s eligibility criteria (Table 1 legend) and is reported here for context only; it is excluded from Table 1, the anxiety-category count, Table 5, and Figure 1.

Finally, the Pérez-Piñar / Ayerbe et al.¹⁴ systematic review and meta-analysis pooled eight cohort studies to estimate the overall association between anxiety disorders and incident stroke.

Alcohol use disorder and heavy alcohol consumption studies

An important distinction applies to the alcohol evidence: the included studies measure alcohol exposure primarily by consumption quantity (light, moderate, or heavy drinking) rather than by a formal clinical diagnosis of AUD. The findings below therefore speak most directly to heavy alcohol consumption; where a study used a diagnostic definition this is

stated, and inferences specific to diagnosed AUD are made cautiously.

Mukamal et al.¹⁵ reported an association between alcohol consumption and stroke risk. This observational study began in the 1990s and consisted of 4,410 eligible men and women over the age of 65 selected at random from 4 US communities. Data were recorded annually until 1999 by recording the amount of alcohol intake that year. Neurologists unaware of previous records examined hospital notes, test results, and imaging studies, which verified the stroke occurrences. *Exposure measure: annual self-report questionnaire. Outcome: adjudicated, imaging-verified stroke. Design: prospective cohort (Cardiovascular Health Study).*

The second study analyzed is the Japan Collaborative Cohort Study (Ikehara et al.)¹⁶. This study observed 34,776 men and 48,906 women 40 to 79 years old between 1988–1990, with a 14.2-year follow-up period. The survey included questions about alcohol consumption, previous history of hypertension, diabetes and other chronic diseases, and habits related to smoking, diet, and exercise. *Exposure measure: self-report questionnaire. Outcome: stroke mortality (death certificate). Design: prospective cohort.*

A systematic review and meta-analysis of alcohol consumption and the risk of morbidity and mortality for different stroke types¹⁷ collected information from 26 different observational studies to analyze the association between stroke incidence and alcohol consumption. Data extraction included characteristics of the study population, year, country of origin, lead author, and study design.

Nine primary studies, incorporated into the core synthesis (Table 2), extended the alcohol evidence base across diverse populations and drinking-pattern definitions. In a prospective cohort of 22,091 adults in Chongqing, China, moderate and frequent (6–7 days/week) drinking was associated with lower total and ischemic stroke risk relative to abstention, while hemorrhagic stroke showed no significant association¹⁸,

a pattern consistent with a protective effect of steady, moderate intake. A rural Chinese cohort similarly reported that reducing or discontinuing alcohol consumption over time was associated with lower subsequent stroke risk.¹⁹ In contrast, several studies emphasized the hazards of irregular heavy or single-occasion drinking: a Japanese community cohort of over 20,000 adults found that risky single-occasion drinking substantially elevated stroke hazard even among otherwise low-to-moderate drinkers (HR 1.47 in men, 3.41 in women);²⁰ a Finnish cohort reported that a binge-drinking habit was independently associated with increased stroke risk;²¹ and the Health Professionals Follow-up Study found that drinking pattern and usual beverage, not only total weekly volume, modified ischemic stroke risk in men.²² A Korean national cohort of over 150,000 adults found a transient reduction in ischemic stroke risk among lighter, less-frequent drinkers that attenuated after seven years of follow-up.²³ Earlier foundational cohorts reached broadly similar conclusions: the Framingham Study reported a dose-dependent association between heavier alcohol intake and ischemic stroke risk,²⁴ the Copenhagen City Heart Study found that beverage type modified risk at comparable alcohol levels,²⁵ and a further cohort focused specifically on hemorrhagic stroke reported that heavier and irregular consumption was associated with increased hemorrhagic stroke risk.²⁶ Together with Mukamal et al.¹⁵, Ikehara et al.¹⁶, and Patra et al.¹⁷, these twelve studies reinforce a dose- and pattern-sensitive (J-shaped) relationship between alcohol and stroke.

Depression studies

A study by Ashraf et al.²⁷ followed PRISMA and MOOSE guidelines, including 10,091 articles screened and 44 studies within the meta-analysis, identified by a three-person research team. *Evidence type: meta-analysis of observational studies.*

A study by Larson et al.²⁸ was conducted as a thirteen-year follow-up to research conducted during 1993–1996. 1,920 participants were split into three groups: dysthymia only, major depression, and both. The authors evaluated the difference in stroke incidence between the three groups. *Exposure measure: diagnostic interview. Design: prospective cohort (Baltimore Epidemiologic Catchment Area).*

A further meta-analysis²⁹ examined the association between depression and incident stroke across studies documented through a systematic search of PubMed and Medline and hand-searching of bibliographies. *Evidence type: meta-analysis of prospective studies (n > 700,000 participants).*

Thirteen further primary studies, incorporated into the core synthesis (Table 3), reinforced the depression–stroke association across diverse populations, age groups, and exposure-measurement approaches. Large biracial and multi-cohort studies converge on a consistent, moderate-to-strong positive association: in the REGARDS cohort of 9,529 Black and

14,516 White US adults, depressive symptoms were associated with 25–54% higher stroke risk depending on symptom severity and adjustment, with no significant difference by race.³⁰ Using Health and Retirement Study (HRS) data, one cohort found stroke hazard was more than doubled among adults with persistently high depressive symptoms (HR 2.14) and remained elevated even among those whose symptoms later remitted (HR 1.66),³¹ and another similarly found that persistent-high and worsening depressive-symptom trajectories over six years were associated with 41–61% higher stroke risk.³² A further study examined eight-year trajectories of total, cognitive-affective, and somatic depressive symptoms in relation to incident stroke over a decade of follow-up in the HRS and English Longitudinal Study of Ageing (ELSA) cohorts, extending trajectory-based evidence to specific depressive-symptom dimensions.³³ Analyzing depression trajectories across CHARLS, ELSA, and HRS, a further study found that a consistently high depressive-symptom trajectory more than doubled stroke odds in China (OR 2.56) and nearly tripled for England (OR 2.96), with a smaller but still significant elevation in the US (OR 1.56).³⁴ Using cumulative depressive-symptom burden in CHARLS and HRS, another study found 30–53% higher stroke hazard in a clear dose-response pattern.³⁵ In China, multiple chronic diseases combined with depressive symptoms were associated with a threefold increase in stroke risk.³⁶ Findings extend to underrepresented clinical populations: in a cohort of over 13,800 US adults living with HIV, greater depressive-symptom severity was associated with a 16% increase in stroke risk, particularly among younger adults,³⁷ complementing a Veterans Aging Cohort Study analysis reporting depression as a risk factor for incident ischemic stroke specifically among HIV-positive veterans.³⁸ Earlier foundational HRS-based work found that depressive symptoms predicted incident stroke independently of memory impairment³⁹ and were associated with elevated stroke risk consistently across Hispanic, African-American, and White older Americans,⁴⁰ while a study of an elderly Dutch population found that depressive symptoms combined with pre-existing cardiac disease were associated with a markedly elevated risk of incident stroke.⁴¹ The INTERSTROKE case-control study, a companion analysis to the INTERSTROKE risk-factor study already discussed⁷, similarly found depressive symptoms associated with acute stroke risk across a large, geographically diverse international sample, extending the generalizability of the depression–stroke association beyond the North American, European, and East Asian cohorts that otherwise dominate this review.⁴² Together with Ashraf et al.²⁷, Larson et al.²⁸, and Pan et al.²⁹, these sixteen sources—fourteen primary studies and two meta-analyses—provide the largest body of evidence in this review.

Psychological distress and chronic stress studies

Three primary studies examine broader psychological distress and chronic stress constructs related to, but distinct from, clinically defined anxiety and depression, and constitute a new, exploratory category within this review (aim 5; hypothesis H4). In the Multi-Ethnic Study of Atherosclerosis (MESA), a cohort followed for a mean of 8.5 years found that higher depressive symptoms (HR 1.03 per CES-D point), chronic stress (HR 1.19), and hostility (HR 1.10) were each associated in separate adjusted models with the combined stroke/TIA outcome, with those in the highest tertiles of these measures facing 1.5- to more than 2-fold higher risk; anger was not significantly associated.⁴³ In the Caerphilly Study, a Welsh cohort of older men, an earlier analysis examined whether psychological distress, measured with the General Health Questionnaire, predicted ischemic stroke/TIA.⁴⁴ A further prospective cohort study examined both continuous psychological distress and clinically diagnosed major depressive disorder as predictors of incident stroke.⁴⁵ Together, these three studies (Table 4) suggest that associations with cerebrovascular outcomes may extend from subclinical distress and chronic stress to clinically diagnosed depression, although the outcomes differ across studies, consistent with the transdiagnostic framework guiding this review (see theoretical framework).

Results

Anxiety and stroke

Lambiase et al.¹¹ found that reporting more anxiety symptoms at baseline was associated with an increased risk of incident stroke after adjustment for standard biological and behavioral cardiovascular risk factors (HR = 1.14; 95% CI, 1.03–1.25, per 1-SD increase in anxiety). The association persisted after controlling for depression, race, sex, and socioeconomic factors. Strengths include the nationally representative sample and long follow-up; limitations include reliance on a self-report symptom scale rather than a clinical diagnosis, and the observational design, which precludes causal inference.

The Rotterdam Study reported more mixed findings. HADS-A score was not associated with stroke over the complete follow-up (adjusted HR 1.02; 95% CI 0.74–1.43 for HADS-A ≥ 8 versus < 8), but an elevated risk was observed over a shorter 3-year follow-up (adjusted HR 2.68; 95% CI 1.33–5.41). In the CIDI sample, any anxiety disorder was not associated with a higher stroke risk (adjusted HR 0.95; 95% CI 0.64–1.43). The authors concluded that anxiety symptoms were related to stroke only in the short term. This suggests that any association between anxiety and stroke may be time-dependent rather than sustained.

Contextual note (not part of the core synthesis). The NESDA study¹³ found that both depression and anxiety

were associated with cardiovascular diseases such as coronary artery disease, but found no significant association with stroke specifically. Because this cohort is cross-sectional (baseline prevalence of cardiovascular disease, not incident stroke during follow-up), it cannot speak to the incident-stroke question this review addresses and is not treated as one of the three core anxiety studies—it is reported here only for context.

Pooling across cohort studies, the Pérez-Piñar / Ayerbe meta-analysis found a significantly increased risk of stroke among patients with anxiety disorders, with an overall hazard ratio of 1.24 (95% CI 1.09–1.41; $P = 0.001$) and no significant between-study heterogeneity. As a synthesis of multiple prospective cohorts, this provides the strongest single estimate of the anxiety–stroke association among the sources reviewed, though it too rests on observational data.

Alcohol use disorder, heavy alcohol consumption, and stroke

Results from the Mukamal et al. study showed that during a mean of 9.2 years a total of 434 incident ischemic stroke cases occurred, following a U-shaped pattern: relative to long-term abstainers, the multivariate relative risks were 0.85 (95% CI 0.63–1.13), 0.75 (0.53–1.06), 0.82 (0.51–1.30), and 1.03 (0.68–1.57) for consumers of < 1 , 1–6, 7–13, and ≥ 14 drinks per week. Notably, this quadratic (U-shaped) trend was not statistically significant ($P = 0.06$), so the apparent lower risk among light drinkers should be interpreted cautiously. Limitations include self-reported alcohol intake and restriction to 4 US communities. The large sample size and long follow-up strengthen this evidence on the association between alcohol consumption and stroke.

The Japan Collaborative Cohort Study showed that 1,628 people died from stroke (864 men and 764 women), with sex-specific mortality rates (men 2.0, women 1.2 per 1,000). Male ex-drinkers showed the highest risk of stroke-related death. Limitations include reliance on a questionnaire, incomplete follow-up (25 of 45 communities), exclusion of binge drinking, and restriction to Japanese participants. The large sample and consistent follow-up support the reported association between alcohol consumption and stroke.

Patra et al.¹⁷ modeled stroke risk separately by stroke subtype, sex, and morbidity versus mortality across the 26 pooled observational studies, rather than reporting a single pooled relative risk for total stroke; subtype- and sex-specific estimates are reported in the original publication. For context, an earlier meta-analysis of the alcohol–stroke literature⁴⁶ found that heavy consumption (more than 60 g of ethanol per day) was associated with a relative risk of total stroke of 1.64 (95% CI 1.39–1.93), with a stronger association for hemorrhagic than ischemic stroke, whereas light-to-moderate consumption was associated with a lower or null risk of ischemic stroke. Limita-

Table 1 *Studies examining the association between anxiety and stroke incidence.*

Study	Sample size	Design	Key finding	Effect size (95% CI)
Lambiasse et al. (2014) ¹¹ , NHANES I	6,019 (419 strokes)	Prospective cohort	More anxiety symptoms associated with higher stroke risk	HR 1.14 (1.03–1.25) per 1-SD
Rotterdam Study – HADS-A (Portegies/Bos et al., 2016) ¹²	2,625 (332 strokes)	Prospective cohort	No association over full follow-up; raised risk at 3 years	HR 1.02 (0.74–1.43) full; 2.68 (1.33–5.41) at 3 y
Rotterdam Study – CIDI (Portegies/Bos et al., 2016) ¹²	8,662 (340 strokes)	Prospective cohort	Any anxiety disorder not associated with stroke	HR 0.95 (0.64–1.43)
Pérez-Piñar / Ayerbe et al. (2017) ¹⁴	8 cohort studies	Meta-analysis	Anxiety disorders associated with higher stroke risk	HR 1.24 (1.09–1.41)

Note. HR = hazard ratio; CI = confidence interval; SD = standard deviation; CIDI = Composite International Diagnostic Interview; HADS-A = Hospital Anxiety and Depression Scale–Anxiety. The NESDA cohort is cross-sectional and measured prevalent cardiovascular disease rather than incident stroke; it therefore does not meet this review’s eligibility criteria and is discussed only as contextual evidence in the text (Description of Included Studies; Discussion), not counted in this table, the anxiety-category total, or Table 5.

tions include reliance on the honesty of participants in observational studies, and use of autopsy reports, death certificates, or death registry data rather than CT confirmation for some included studies.

Across the twelve alcohol studies incorporated into Table 2, a dose- and pattern-sensitive relationship is evident. In Chongqing, China, moderate and frequent drinking were associated with lower stroke risk relative to abstention (total stroke HR 0.48, 95% CI 0.25–0.92, for 13–36 g/day; HR 0.60, 95% CI 0.37–0.96, for drinking 6–7 days/week), with no significant association for hemorrhagic stroke.¹⁸ In Japan, risky single-occasion (binge) drinking substantially elevated stroke hazard even among otherwise low-to-moderate drinkers (HR 1.47, 95% CI 1.01–2.13 in men; HR 3.41, 95% CI 1.50–7.79 in women).²⁰ In Korea, a large national cohort found a transient reduction in ischemic stroke risk among lighter, less-frequent drinkers (HR 0.71–0.80) that was limited to the first seven years of follow-up.²³ These findings, together with the Finnish binge-drinking cohort,²¹ the Health Professionals Follow-up Study,²² the Framingham Study,²⁴ the Copenhagen City Heart Study,²⁵ and the hemorrhagic-stroke-focused cohort,²⁶ converge on the conclusion that drinking pattern (frequency, regularity, and single-occasion intensity) and beverage type, not only total weekly volume, shape stroke risk, reinforcing hypothesis H3’s expectation of a dose-response, J-shaped pattern.

Depression and stroke

Major depression has an estimated 12-month prevalence of roughly 5.8–9.5% among women worldwide. This highlights the need to bring attention to sequelae of this disease.

The Ashraf study demonstrated an association between stroke and depression, with a hazard ratio of 1.41 — that is, people with depression were associated with a 41% higher likelihood of stroke than people without depression (HR 1.41; 95% CI 1.32–1.50). Antidepressant use was also associated with elevated stroke risk (HR 1.28; 95% CI 1.05–1.55), which complicates interpretation, and one included study showed no

association, widening the range of results. Overall, the meta-analysis reports a positive association between depression and stroke.

The Larson et al. study demonstrated that participants with a history of depressive disorder had approximately three times the risk of stroke as those without the disorder (RR 3.08, 95% CI 1.26–7.52), indicating an association between depression and stroke incidence independent of risk factors such as hypertension and diabetes.

Limitations include self-reported outcomes and possible confounding by factors such as tobacco use. These limitations mean the study demonstrates an association rather than a causal link.

The meta-analysis of over 700,000 participants reported that depression was associated with a 45% higher risk of first-ever stroke. Limitations include absence of adjustment for vascular risk factors, use of a nonspecific depression screening scale, and uncontrolled external factors such as tobacco use.

Across the sixteen depression sources (fourteen primary studies and two meta-analyses) incorporated into Table 3, the association with incident stroke is highly consistent. Across large US cohorts, depressive symptoms were associated with 25–61% higher stroke risk depending on symptom severity, persistence, and adjustment (REGARDS: HR 1.25–1.54;³⁰ HRS trajectory studies: HR 1.15–1.61;^{31,32} CHARLS/HRS cumulative burden: HR 1.30–1.53³⁵). Trajectory-based analyses spanning China, England, and the United States found that a consistently high depressive-symptom trajectory increased stroke odds by 56–196% (OR 1.56–2.96).³⁴ In a cohort of adults with multiple chronic diseases, the combination of chronic disease and depressive symptoms was associated with an approximately threefold increase in stroke risk.³⁶ Depression was also associated with elevated stroke risk in clinical subpopulations, including US adults living with HIV (16% higher risk per five-point higher PHQ-9 score)³⁷ and HIV-positive veterans.³⁸ The INTERSTROKE case-control study similarly found depressive symptoms associated with acute stroke risk across a large, geographically diverse international sample.⁴² Overall, depression studies reported a positive asso-

Table 2 *Studies examining the association between alcohol consumption and stroke.*

Study	Sample size	Study period	Key findings	Effect size (95% CI)
Mukamal et al. (2005) ¹⁵ (CHS)	4,410 (>65 y); 434 IS cases	Prospective cohort	U-shaped but non-significant; light drinkers nominally lowest risk	RR 0.75 (0.53–1.06) at 1–6/wk; 1.03 (0.68–1.57) at ≥14/wk (P trend 0.06)
Japan Collaborative Cohort (Ikehara et al., 2008) ¹⁶	83,682	Prospective cohort	Heavy drinking assoc. with higher stroke mortality; ex-drinkers highest	Heavy (≥46 g/d) men RR 1.67 (95% CI 1.17–2.38) vs light drinkers
Meta-analysis (Patra et al., 2010) ¹⁷ ; 26 obs. studies)	26 studies	Meta-analysis	Modeled total-, ischemic-, and hemorrhagic-stroke risk separately by subtype, sex, and morbidity vs. mortality; did not report one single pooled total-stroke estimate	Subtype/sex-specific estimates; no single pooled RR reported
Liu et al. (2023) ¹⁸ , Chongqing, China	22,091 (310 strokes)	Prospective cohort	Moderate/frequent drinking associated with lower total and ischemic stroke risk; no association for hemorrhagic stroke	HR 0.48 (0.25–0.92) at 13–36 g/d; 0.60 (0.37–0.96) at 6–7 d/wk
Yu et al. (2021) ¹⁹ , rural China	Not reported in abstract	Prospective cohort	Reducing/discontinuing alcohol consumption associated with lower subsequent stroke risk	Direction only; not quantified in narrative synthesis
Takada et al. (2025) ²⁰ , CIRCS Japan	20,487 (8,026 men; 12,461 women)	Prospective cohort	Risky single-occasion drinking (RSOD) elevated stroke hazard among low-to-moderate drinkers	HR 1.47 (1.01–2.13) men; 3.41 (1.50–7.79) women
Yang et al. (2020) ²³ , Korea NHIS-NSC	152,469	Prospective cohort	Transient reduction in ischemic stroke risk among lighter, less-frequent drinkers; attenuated after 7 years	HR 0.71 (0.59–0.85) group I; 0.80 (0.68–0.93) group III
Sundell et al. (2008) ²¹ , Finland	Not reported in abstract	Prospective cohort	Binge-drinking habit independently associated with increased stroke risk	Direction only; not quantified in narrative synthesis
Mukamal et al. (2005) ²² , HPFS	Not reported in abstract	Prospective cohort	Drinking pattern and usual beverage — not only total volume — modified ischemic stroke risk in men	Direction only; not quantified in narrative synthesis
Djousse et al. (2002) ²⁴ , Framingham Study	Not reported in abstract	Prospective cohort	Dose-dependent association between heavier alcohol intake and ischemic stroke risk	Direction only; not quantified in narrative synthesis
Truelsen et al. (1998) ²⁵ , Copenhagen City Heart Study	Not reported in abstract	Prospective cohort	Beverage type (wine vs. beer/spirits) modified stroke risk at comparable alcohol levels	Direction only; not quantified in narrative synthesis
Klatsky et al. (2002) ²⁶ , Alcohol drinking and hemorrhagic stroke, Neuroepidemiology	Not reported in abstract	Prospective cohort	Heavier and irregular consumption associated with increased hemorrhagic stroke risk	Direction only; not quantified in narrative synthesis

Note. RR = relative risk; IS = ischemic stroke; g/d = grams of ethanol per day. The Mukamal CHS estimates are for ischemic stroke, and the quadratic trend was not statistically significant ($P = 0.06$). The heavy-drinking total-stroke pooled RR of 1.64 (1.39–1.93) comes from an earlier meta-analysis (Reynolds et al.⁴⁶), not from Patra et al.¹⁷, whose analysis reports subtype- and sex-specific estimates rather than this single pooled figure. Effect sizes not reported in the source abstract are marked “not quantified in narrative synthesis” rather than estimated.

ciation between depressive symptoms or disorder and incident stroke, strengthening confidence in H2.

Psychological distress, chronic stress, and stroke

In MESA, higher depressive symptoms, chronic stress, and hostility were each associated with the combined stroke/TIA outcome in separate adjusted models (HR 1.03 per CES-D point, 95% CI 1.01–1.04; HR 1.19 for chronic stress, 95% CI 1.05–1.34; HR 1.10 for hostility, 95% CI 1.01–1.19), with the highest-exposure groups facing 1.5- to more than 2-fold elevated risk.⁴³ The Caerphilly Study examined psychological distress (GHQ) as a predictor of combined ischemic stroke/TIA; the overall association did not reach statistical significance (HR 1.45, 95% CI 0.98–2.14), although the authors reported a clearer, statistically significant association specifically for fatal ischemic stroke.⁴⁴ A further prospective cohort examined psychological distress and major depressive disorder as predictors of stroke.⁴⁵ Taken together (Table 4), these findings are suggestive of an association between psychological distress/chronic stress and cerebrovascular risk, but the

picture is mixed by outcome: two of the three studies combine stroke with TIA rather than reporting stroke alone, and the Caerphilly Study’s own combined stroke/TIA estimate was not statistically significant. Because H4 was not pre-registered a priori and its constituent studies use heterogeneous outcomes and distress measures, these results should be interpreted as hypothesis-generating rather than confirmatory.

Quality assessment results

Newcastle–Ottawa Scale ratings for the 30 included cohort and case-control primary studies are presented in Table 5. Twenty of the 30 studies were rated high quality (≥7 of 9 stars) and 10 were rated moderate quality (5–6 stars); none were rated low quality. Most of the cohorts used large, population-representative samples with adjusted, validated stroke ascertainment; studies rated moderate quality were generally limited by self-reported stroke outcomes or by incomplete published detail on comparability adjustment.

AMSTAR-2 appraisal of included meta-analyses. The four included meta-analyses were checked against selected

Table 3 *Studies examining the association between depression and stroke incidence.*

Study	Sample size	Study period	Key findings	Effect size (95% CI)
Ashraf et al. (2024) ²⁷	44 studies	Meta-analysis	Depression moderately raises stroke risk; antidepressant use also elevated	HR 1.41 (1.32–1.50); antidepressants HR 1.28 (1.05–1.55)
Larson et al. (2001) ²⁸ , Baltimore ECA	1,703–1,920	Prospective cohort	Depressive-disorder history associated with higher stroke risk	RR 3.08 (1.26–7.52)
Pan et al. (2011) ²⁹ , meta-analysis	>700,000	Meta-analysis	~40% higher first-ever stroke risk	RR 1.45 (1.29–1.63)
Ford et al. (2021) ³⁰ , REGARDS	24,045 (1,262 strokes)	Prospective cohort	Depressive symptoms associated with higher stroke risk; no race difference	HR 1.25–1.54 (severity/adjustment-dependent)
Hu et al. (2022) ³⁶ , CHARLS	8,389	Prospective cohort	≥ 2 chronic diseases + depressive symptoms associated with markedly higher stroke risk	~3.0-fold risk (CI not extracted)
Sico et al. (2021) ³⁸ , VACS	HIV-positive veterans	Prospective cohort	Depression associated with incident ischemic stroke among HIV-positive veterans	Direction only; not quantified in narrative synthesis
Li et al. (2022) ³² , HRS	11,002	Prospective cohort	Persistent-high/worsening depressive-symptom trajectories associated with higher stroke risk	HR 1.41 (1.17–1.71) worsening; 1.61 (1.21–2.16) persistent-high
Gilsanz et al. (2015) ³¹ , HRS	16,178	Prospective cohort	Stable-high/remitted depressive symptoms associated with higher stroke risk	HR 2.14 (1.69–2.71) stable-high; 1.66 (1.22–2.26) remitted
Glymour et al. (2010) ³⁹ , HRS	Not reported in abstract	Prospective cohort	Depressive symptoms predicted incident stroke independently of memory impairment	Direction only; not quantified in narrative synthesis
Glymour et al. (2012) ⁴⁰ , HRS	Not reported in abstract	Prospective cohort	Elevated depressive symptoms associated with stroke across Hispanic, African American, White groups	Direction only; not quantified in narrative synthesis
Wouts et al. (2008) ⁴¹ , Netherlands	Not reported in abstract	Prospective cohort	Depressive symptoms + pre-existing cardiac disease associated with markedly elevated stroke risk	Direction only; not quantified in narrative synthesis
Zhang et al. (2026) ³³ , HRS/ELSA	Not reported in abstract	Prospective cohort	Depressive-symptom trajectories (incl. somatic subtype) associated with incident stroke	Direction only; not quantified in narrative synthesis
Zhao et al. (2026) ³⁴ , CHARLS/ELSA/HRS	17,258 (646 strokes)	Prospective cohort (3 cohorts)	Consistently high depressive trajectory associated with higher stroke odds in all 3 cohorts	OR 2.56 (1.62–4.04) CHARLS; 2.96 (1.28–6.84) ELSA; 1.56 (1.03–2.36) HRS
Ma et al. (2025) ³⁷ , US PWH cohort	13,817 (173 strokes)	Prospective cohort	Greater depressive-symptom severity associated with higher stroke risk, especially in younger adults	16% higher risk per five-point higher PHQ-9 score
You et al. (2026) ³⁵ , CHARLS/HRS	16,145 (CHARLS 8,861; HRS 7,284)	Prospective cohort (2 cohorts)	Cumulative depressive-symptom burden associated with higher stroke hazard, dose-response pattern	HR 1.53 (1.17–1.99) CHARLS; 1.30 (1.06–1.58) HRS
Murphy et al. (2023) ⁴² , INTERSTROKE	32-country case-control	Case-control	Depressive symptoms associated with acute stroke risk internationally	Direction only; OR not extracted from abstract

Note. HR = hazard ratio; RR = relative risk; OR = odds ratio. Murphy et al. is a case-control study; all other listed primary studies are prospective cohorts. Effect sizes not reported in the source abstract are marked “not quantified in narrative synthesis” rather than estimated.

Table 4 *Studies examining the association between psychological distress/chronic stress and stroke incidence.*

Study	Sample size	Study period	Key findings	Effect size (95% CI)
Everson-Rose et al. (2014) ⁴³ , MESA	~6,749	Prospective cohort	Depressive symptoms, chronic stress, and hostility each associated with the combined stroke/TIA outcome in separate adjusted models	HR 1.03/pt (CES-D); 1.19 (chronic stress); 1.10 (hostility)
May et al. (2002) ⁴⁴ , Caerphilly Study	Not reported in abstract	Prospective cohort	Psychological distress (GHQ) examined as predictor of ischemic stroke/TIA	Overall ischemic stroke estimate 1.45 (0.98–2.14), not statistically significant; clearer association for fatal ischemic stroke
Surtees et al. (2008) ⁴⁵ , Psychological distress and MDD, Neurology	Not reported in abstract	Prospective cohort	Psychological distress and major depressive disorder examined as predictors of stroke	Direction only; not quantified in narrative synthesis

Note. HR = hazard ratio; MESA = Multi-Ethnic Study of Atherosclerosis; GHQ = General Health Questionnaire. The MESA and Caerphilly outcomes combine stroke with TIA rather than reporting stroke alone; the Caerphilly Study’s overall stroke/TIA estimate (95% CI 0.98–2.14) did not reach statistical significance, though a stronger, significant association was reported specifically for fatal ischemic stroke.

AMSTAR-2 critical domains. Because the remaining items were not documented in a full appraisal, no overall confidence ratings are summarized in Table 6.

All four meta-analyses assessed publication bias (C15), including Pan et al.²⁹ Pan et al. reported funnel plots and a Begg test. Table 6 records selected domain observations only;

Table 5 Newcastle–Ottawa Scale quality ratings of included studies.

Study	Selection /4	Comparability /2	Outcome /3	Total /9	Rating
Lambiase et al. (2014) ¹¹ , NHANES I	4	2	3	9	High
Rotterdam Study (Portegies/Bos et al., 2016) ¹²	4	2	3	9	High
Mukamal et al. (2005) ¹⁵ (CHS)	4	2	3	9	High
Japan Collaborative Cohort (Ikehara et al., 2008) ¹⁶	4	2	2	8	High
Larson et al. (2001) ²⁸	3	2	2	7	High
Ford et al. (2021) ³⁰ , REGARDS	4	2	2	8	High
Hu et al. (2022) ³⁶ , CHARLS	3	1	2	6	Moderate
Sico et al. (2021) ³⁸ , VACS	3	2	2	7	High
Li et al. (2022) ³² , HRS	3	2	2	7	High
Gilsanz et al. (2015) ³¹ , HRS	3	2	2	7	High
Glymour et al. (2010) ³⁹ , HRS	3	1	2	6	Moderate
Glymour et al. (2012) ⁴⁰ , HRS	3	1	2	6	Moderate
Wouts et al. (2008) ⁴¹ , Netherlands	3	1	2	6	Moderate
Zhang et al. (2026) ³³ , HRS/ELSA	3	2	2	7	High
Zhao et al. (2026) ³⁴ , CHARLS/ELSA/HRS	4	2	1	7	High
Ma et al. (2025) ³⁷ , US PWH cohort	4	2	2	8	High
You et al. (2026) ³⁵ , CHARLS/HRS	3	2	2	7	High
Liu et al. (2023) ¹⁸ , Chongqing	4	1	1	6	Moderate
Yu et al. (2021) ¹⁹ , rural China	3	1	2	6	Moderate
Takada et al. (2025) ²⁰ , CIRCJS Japan	4	2	2	8	High
Yang et al. (2020) ²³ , Korea NHIS-NSC	4	2	2	8	High
Sundell et al. (2008) ²¹ , Finland	3	1	2	6	Moderate
Mukamal et al. (2005) ²² , HPFS	4	2	2	8	High
Djousse et al. (2002) ²⁴ , Framingham	4	2	2	8	High
Truelsen et al. (1998) ²⁵ , Copenhagen City Heart Study	3	2	2	7	High
Klatsky et al. (2002) ²⁶ , Alcohol/hemorrhagic stroke, Neuroepidemiology	3	1	2	6	Moderate
Everson-Rose et al. (2014) ⁴³ , MESA	4	2	2	8	High
May et al. (2002) ⁴⁴ , Caerphilly Study	3	1	2	6	Moderate
Surtees et al. (2008) ⁴⁵ , Psychological distress/MDD, Neurology	3	1	2	6	Moderate
Murphy et al. (2023) ⁴² , INTERSTROKE (case-control variant)	3	2	2	7	High

Ratings: high ≥ 7 , moderate 5–6, low <5 . The case-control variant (Selection, Comparability, Exposure) was used for Murphy et al. (INTERSTROKE), so its third-column value reflects the Exposure domain rather than the cohort Outcome domain. Meta-analyses (Pérez-Piñar/Ayerbe, Ashraf, Pan, Patra) are appraised separately with AMSTAR-2 in Table 6.

Table 6 Selected AMSTAR-2 critical domains for the four included meta-analyses.

Meta-analysis	Protocol a priori (C2)	Adequate search (C4)	Exclusions justified (C7)	RoB assessed (C9)	Meta-method appropriate (C11)	RoB in interpretation (C13)	Publication bias (C15)	Overall
Pérez-Piñar/Ayerbe (2017) ¹⁴	Yes	Yes	Partial	Yes	Yes	Yes	Yes	Not assigned
Ashraf et al. (2024) ²⁷	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not assigned
Pan et al. (2011) ²⁹	No	Yes	No	Yes	Yes	Yes	Yes	Not assigned
Patra et al. (2010) ¹⁷	Partial	Yes	Partial	Yes	Yes	Yes	Yes	Not assigned

Note. C-numbers refer to AMSTAR-2 critical domains (C2 protocol registered before the review; C4 comprehensiveness of the literature search; C7 list and justification of excluded studies; C9 risk-of-bias assessment of included studies; C11 appropriateness of meta-analytic methods; C13 accounting for risk of bias when interpreting results). Publication bias (C15) is also a critical AMSTAR-2 domain. All four reviews assessed publication bias: Pérez-Piñar/Ayerbe used a funnel plot; Ashraf et al. used Egger’s test and a trim-and-fill analysis; Pan et al. used funnel plots and a Begg test; and Patra et al. used Begg and Egger tests. Thus C15 is recorded as Yes for all four. “Partial” entries for C2 and C7 concern critical domains and cannot be reclassified as non-critical weaknesses. The seven displayed domains alone do not support a reproducible overall AMSTAR-2 grade, which requires appraisal of all 16 items.

overall confidence grades have been withheld pending a documented 16-item appraisal, including an explicit rule for interpreting partial responses in critical domains.

Discussion

Across the included studies, anxiety, depression, and heavy alcohol consumption showed varying associations with stroke incidence, although the strength and consistency of these associations differed by exposure, study design, and measurement method. Interpreted through the transdiagnostic framework outlined in the Introduction, this pattern is consistent with the possibility that partly shared mechanisms: HPA-axis dysregulation, inflammation, autonomic dysregulation, and health behaviors — underlie the associations, although the observational designs cannot confirm these pathways.

Anxiety in context. The evidence on anxiety was mixed. Lambiase et al. (NHANES I) and the Pérez-Piñar/Ayerbe meta-analysis reported positive associations with stroke, whereas the Rotterdam Study found no association over full follow-up (only a short-term elevation). (A separate cross-sectional cohort, NESDA, also reported no association between anxiety and cardiovascular disease including stroke, but because it measures prevalent disease at a single timepoint rather than incident stroke, it does not meet this review's eligibility criteria and is treated as contextual evidence only, not part of the core anxiety synthesis.) This inconsistency among the three core anxiety studies appears partly methodological: the positive findings came from long-follow-up cohorts and a pooled meta-analysis, while the Rotterdam null finding came from analyses using a clinical interview rather than a symptom scale. The Rotterdam results suggest any anxiety–stroke association may be concentrated in the short term. Overall, anxiety shows a weaker and less consistent association with stroke than depression.

Depression in context. All three depression sources reported positive associations: Ashraf et al. (HR 1.41), Larson et al. (RR 3.08), and Pan et al. (RR 1.45). These converge despite different designs, strengthening confidence in the association. Potential mechanisms include inflammation and HPA-axis activity, though antidepressant use was itself associated with elevated risk, raising the possibility of confounding by indication. This conclusion is further reinforced by thirteen additional primary studies spanning the United States, China, and international multi-country samples, all of which reported positive associations between depressive symptoms or depressive disorder and incident stroke, including large biracial cohorts,³⁰ depressive-symptom trajectory studies,^{31–35} a study of comorbid chronic disease burden,³⁶ and studies in clinical subpopulations such as adults living with HIV.^{37,38} The INTERSTROKE case-control study similarly found depressive symptoms associated with acute stroke risk across a large, ge-

ographically diverse international sample.⁴² Across the sixteen depression sources now in the core synthesis (fourteen primary studies and two meta-analyses), findings were consistently positive in direction, the most consistent pattern of association in this review. The consistency of this association across highly heterogeneous populations, exposure measures, and follow-up designs strengthens confidence that it is not attributable to a single population or measurement approach.

Alcohol in context. The Mukamal and Ikehara cohorts and the 26-study meta-analysis were consistent with a dose-response (J-shaped) association, in which heavy drinking was associated with increased risk while light-to-moderate consumption was associated with lower or null risk. Mechanisms plausibly include alcohol-associated hypertension, atrial fibrillation, and coagulation changes. A caveat is that these studies characterize alcohol by consumption quantity rather than by a formal AUD diagnosis; the association therefore applies most directly to heavy alcohol consumption, and the extent to which it generalizes to clinically diagnosed AUD remains uncertain. Nine additional primary studies extend this dose-response pattern across China, Japan, Korea, Finland, Denmark, and the United States,^{18, 19, 20, 23, 21, 22, 24, 25, 26} with several studies further indicating that drinking pattern, frequency, regularity, and single-occasion (binge) intensity, and beverage type shape risk independently of total weekly volume.^{20–22,25} Across all twelve alcohol studies, this pattern-sensitivity nuances H3: rather than a simple linear or even a strictly monotonic J-shaped curve defined by average consumption alone, stroke risk associated with alcohol appears to depend jointly on quantity, frequency, and drinking pattern.

Psychological distress in context. Beyond formally diagnosed anxiety and depression, three studies in this exploratory category (Table 4) offer a suggestive but mixed picture: MESA found chronic stress, hostility, and subclinical psychological distress associated with a combined stroke/TIA outcome, while the Caerphilly Study's overall stroke/TIA association did not reach significance, though it reported a clearer, significant association specifically for fatal ischemic stroke.^{43,44,45} Because two of the three studies combine stroke with TIA rather than reporting stroke alone, and because the size and significance of the association vary by outcome, this evidence is weaker and less consistent than the effect sizes observed for clinically significant depression. These findings are consistent with the transdiagnostic framework's premise that overlapping stress-related neurobiological pathways, rather than any single diagnostic category, may underlie shared vascular risk, but given the outcome heterogeneity and non-significant overall estimate, they should be treated as hypothesis-generating rather than confirmatory.

Cross-cutting themes. Anxiety, depression, and AUD frequently co-occur, so estimates for any single condition may partly reflect shared variance with the others. Few included

studies adjusted for the other two exposures, so the independent contribution of each condition remains uncertain, a key target for future research. Psychological distress and chronic stress showed a suggestive but outcome-mixed association with stroke/TIA risk alongside anxiety, depression, and alcohol exposure.

Limitations

Several limitations qualify these conclusions. First, exposures were measured heterogeneously (clinical diagnosis vs. self-report scales), which limits comparability. Second, stroke outcomes were ascertained variably (imaging-confirmed vs. registry or death certificate). Third, all included primary studies were observational, so causality cannot be inferred and associative language is used throughout. Fourth, publication bias is possible, as null findings are less likely to be published. Fifth, comorbidity among the three conditions makes it difficult to isolate independent effects. Sixth, several major cohorts (NHANES, Rotterdam) are drawn from predominantly older, Western populations, limiting generalizability. Seventh, Web of Science was not searched because institutional access was unavailable; although OpenAlex was used as an additional multidisciplinary database and reference lists were hand-searched, relevant studies indexed exclusively in other databases may have been missed. These constraints mean the review characterizes associations, not causal effects. Fifth, several effect sizes could not be independently verified and are reported as directional findings only (marked “not quantified in narrative synthesis” in Tables 2–4) rather than estimated. Sixth, the psychological distress/chronic stress category (H4) is exploratory; its three constituent studies used heterogeneous distress measures (CES-D, General Health Questionnaire, clinical MDD diagnosis) and heterogeneous outcomes (two combine stroke with TIA rather than reporting stroke alone), and one study’s overall stroke/TIA estimate was not statistically significant, which limits the strength of conclusions that can be drawn about this construct specifically.

Conclusion

This review examined whether anxiety, depression, and alcohol exposure are associated with incident stroke, and the three a priori hypotheses can now be evaluated against the reviewed evidence. H1 (anxiety) was partially supported: the evidence was mixed, with positive associations in some cohorts (Lambiasi) and in the pooled meta-analysis (HR 1.24), but a null finding in the Rotterdam Study. H2 (depression) was supported: all sixteen depression sources (fourteen primary studies and two meta-analyses) reported positive associations with incident stroke, the most consistent finding of this review. H3 (alcohol) is supported as well: across twelve

alcohol studies, drinking pattern, frequency, regularity, and single-occasion intensity, and beverage type appear to shape stroke risk independently of total weekly volume, rather than a simple dose-response relationship defined by quantity alone. H4 (psychological distress and chronic stress), an exploratory hypothesis, was suggestive but mixed by outcome across its three constituent studies (Table 4): MESA’s associations were with a combined stroke/TIA outcome rather than stroke alone, and the Caerphilly Study’s overall stroke/TIA estimate did not reach significance (HR 1.45, 95% CI 0.98–2.14) though it reported a clearer, significant association specifically for fatal ischemic stroke. Because H4 is hypothesis-generating rather than confirmatory, and because its constituent studies used heterogeneous distress measures and heterogeneous stroke-related outcomes, this finding should be interpreted as preliminary and in need of purpose-designed prospective confirmation using a consistent, stroke-specific outcome.

The principal methodological implication is that future prospective studies should jointly measure all three psychiatric exposures within the same cohort, adjust for their comorbidity so that the independent contribution of each can be estimated, and use standardized, validated methods to define both the exposures (clinical diagnosis versus symptom scale) and the stroke outcome (imaging-confirmed incident stroke). Because the underlying studies are observational, such research is needed before any causal relationship can be established. Future prospective studies should adopt standardized, validated measures of psychological distress and chronic stress, given that the three studies identified in this category to date used heterogeneous instruments (CES-D, General Health Questionnaire, clinical MDD diagnosis) that are not fully interchangeable. A pre-registered, purpose-designed test of H4 within a cohort that also measures anxiety, depression, and alcohol use would allow the independent contribution of chronic psychological distress to be distinguished from that of its more established, more extensively studied counterparts.

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