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Original Article

Global, regional, and national burden of dementia attributable to mood disorders: a comparative risk assessment study

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ABSTRACT

Background: Mood disorders, particularly depressive and bipolar disorders, have emerged as potentially modifiable risk factors for dementia. However, the burden of dementia attributable to mood disorders remains unquantified. We aimed to quantify that burden among adults aged 45 years and older using a comparative risk assessment approach.

Methods: A literature search was performed in PubMed, Embase, and MEDLINE to identify cohort studies that assessed the association between mood disorders and subsequent dementia from database inception to 9th April 2025. Random-effects models were used to derive pooled risk ratios (RRs). Assuming a 5-year lag between mood disorders and dementia onset, we calculated population attributable fractions (PAFs) and age-standardized disability-adjusted life year (DALY) rates (ASDRs) at global, regional, and national levels. Temporal trends in ASDR were analyzed using joinpoint regression to estimate average annual percentage change.

Results: 77 articles were included. The pooled RR for all-cause dementia was 1.90 (95% confidence interval [CI]: 1.70, 2.12) for depressive disorders, and 3.10 (95% CI: 2.21, 4.35) for bipolar disorder. For dementia subtypes, depressive disorders showed an association with Alzheimer's disease (RR: 2.57, 95% CI: 2.05, 3.23), and bipolar disorder was associated with vascular dementia (RR: 3.67, 95% CI: 2.42, 5.57). In 2016, the global PAFs of dementia attributable to depressive disorders were 4.79% (95% CI: 3.19%, 6.58%) in males and 5.56% (95% CI: 3.56%, 7.84%) in females. PAFs for bipolar disorder were 1.22% (95% CI: 0.65%, 2.01%) in males and 1.34% (95% CI: 0.71%, 2.18%) in females. In 2021, the global ASDR of dementia attributable to depressive disorders was 89.61 (95% CI: 34.80, 192.24) per 100,000 population, while the global ASDR for bipolar disorder was 15.91 (95% CI: 5.56, 37.87) per 100,000 population.

Conclusion: Since mood disorders are a substantial contributor to dementia burden, integrating mental health management into public health policies is essential.

1. Introduction

Dementia, a progressive neurocognitive disorder characterized by deterioration in memory, thinking, and behavior, represents a major and growing public health challenge in the context of global population aging [1]. The number of people living with dementia is projected to rise from 57.4 million in 2019 to 152.8 million by 2050 [2], with profound consequences for individuals, families, and healthcare systems worldwide [3]. As curative treatments remain elusive, there is an urgent global imperative to identify modifiable risk factors as a critical strategy to mitigate the future burden of dementia. The 2024 Lancet Commission on dementia prevention, intervention, and care estimates that approximately 45% of dementia cases globally could be prevented or delayed by addressing modifiable risk factors, such as depression, hearing loss, diabetes, less education, and air pollution [4].

Among these, mood disorders, specifically depressive disorders and

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bipolar disorder, have emerged as important and modifiable, yet underrecognized contributors. Epidemiological studies have consistently linked mid- or late-life and recurrent depression with increased risk of dementia [5,6]. Bipolar disorder, although less frequently studied in this context, is increasingly recognized as a potential modifiable risk factor, with evidence pointing to elevated dementia risk among individuals with a history of bipolar disorder [4]. Potential mechanisms that link depression to dementia involve hypothalamic-pituitary-adrenal (HPA) axis dysregulation leading to hippocampal atrophy or inflammatory changes, reduced neurotrophic support, and shared vascular pathways [7–9]. Similarly, bipolar disorder may contribute to dementia through neurobiological pathways shared with depression, alongside distinct mechanisms such as cumulative neurotoxicity from mood episodes, mitochondrial dysfunction, and accelerated cellular aging [10–13].

Despite growing evidence, the strength and consistency of the association between mood disorders and dementia remain variable across populations, and the population-level impact of mood disorders on the burden of dementia remains poorly quantified. While depression is already included in global dementia prevention frameworks and is estimated to account for around 3% of dementia cases, the estimate is primarily based on the mixed depressive disorders and subclinical symptoms [4]. This leaves a gap regarding the focus on depressive disorders, which are of greater clinical significance. Moreover, bipolar disorder has received limited attention in global dementia risk models. The population attributable fraction (PAF) provides an epidemiological estimate of the proportion of dementia that could theoretically be prevented if a given risk factor was eliminated [14]. Quantifying the attributable burden through metrics such as PAFs and disability-adjusted life years (DALYs) is essential for prioritizing public health interventions [15,16]. While global estimates help set overall health priorities, regional and national estimates are also necessary to account for geographical and socioeconomic variations, enabling prevention strategies tailored to different contexts [17].

To address these gaps, we conducted a systematic review and meta-analysis to quantify the relative risk of dementia associated with depressive and bipolar disorders. Using a comparative risk assessment (CRA) framework and data from the Global Burden of Disease (GBD) study, this study also aimed to quantify the global, regional, and national proportion and burden of dementia due to mood disorders among individuals aged 45 years and above from 1995 to 2021.

2. Methods

The analytic approach consisted of two stages (Fig. 1). First, we conducted a systematic review and meta-analysis to pool the risk ratios (RRs) for the association between mood disorders and subsequent dementia. In the second stage, based on the prevalence of mood disorders,

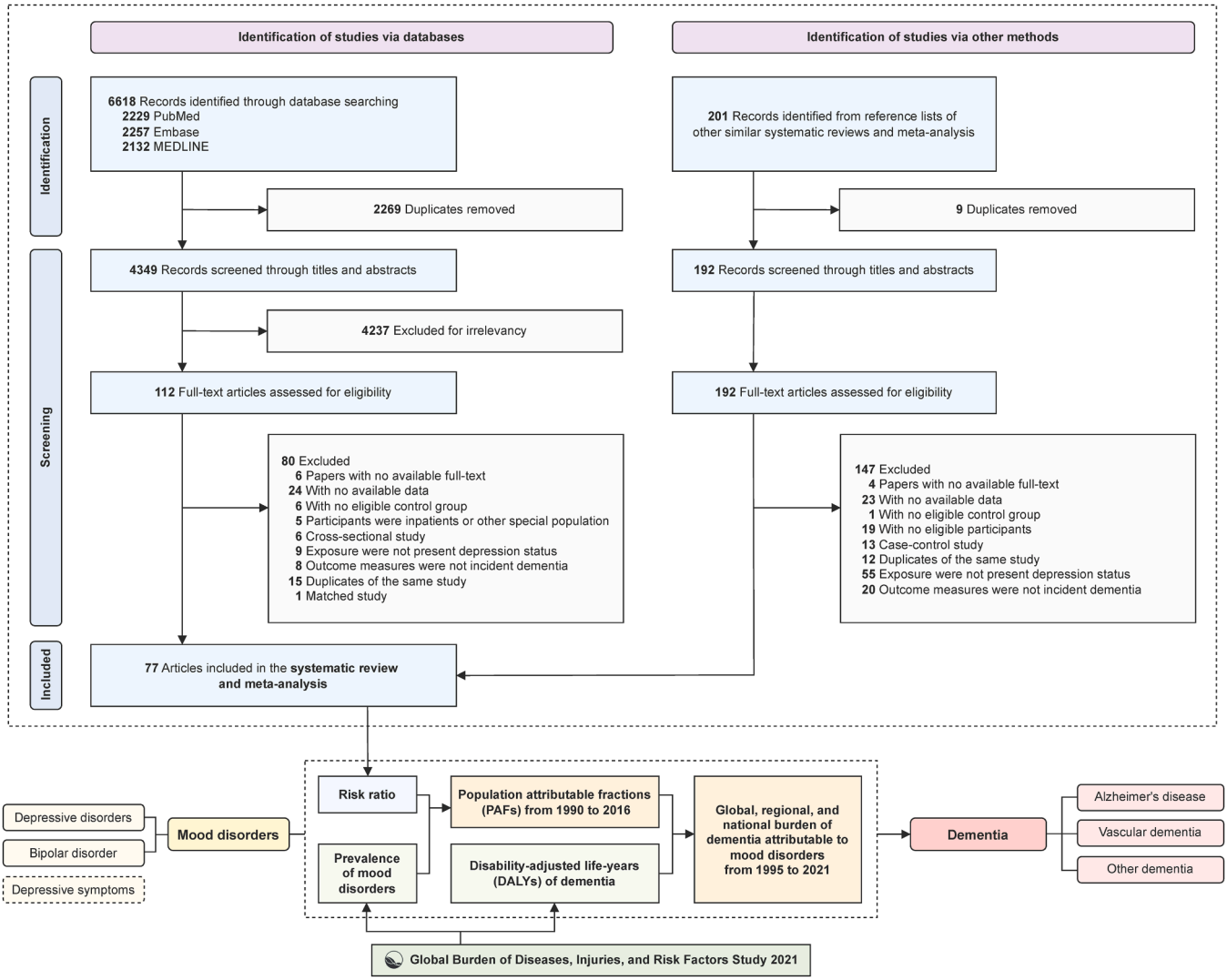

Fig. 1. Study framework for estimating the disease burden of dementia attributable to mood disorders.

PAFs were calculated to estimate the proportion of dementia cases due to mood disorders among individuals aged 45 years and above. The global, regional, and national attributable burden of dementia was then quantified by applying PAFs to DALYs of dementia. The first stage of this study was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines [18,19]. The review protocol was registered in the PROSPERO database (CRD420251009167).

2.1. Search strategy and selection criteria

A comprehensive literature search was performed in PubMed, Embase, and MEDLINE, to identify cohort studies exploring the association between mood disorders and subsequent dementia, without restrictions on language (all non-English language articles were reviewed after translation into English by Google Translate). First, we searched for previous systematic reviews and meta-analyses published from database inception to 15th July 2024 (detailed in **Table S1-S2**), and screened the reference lists of these articles to identify potentially relevant original studies. The most recent search date reported in all eligible reviews (31st July 2020) was identified as the starting date for our following updated searches, which were performed to identify newly published original studies up to 9th April 2025 (detailed in **Table S3**). We also screened the reference lists of all included articles to identify additional eligible studies.

After removing duplicate records across databases, two researchers (LZ and JW) independently screened titles and abstracts, followed by full-text review, to determine study eligibility. Articles were included if they were original cohort studies that reported effect estimates (RRs, hazard ratios [HRs], or odds ratios [ORs]) of incident dementia in individuals with mood disorders compared to those without. Additionally, articles reporting the association between depressive symptoms assessed by scales or self-reports and subsequent dementia were also retained. We excluded articles that were conducted in specialized populations (e.g., inpatients), along with reviews, editorials, abstracts, case reports, and letters. For multiple publications from the same cohort or database, the one with the most comprehensive results or the largest sample size was retained.

2.2. Data extraction and quality assessment

Data were extracted independently by two researchers (LZ and JW) using a standardized data extraction form. For each included article, the following information was collected: 1) study characteristics: title, author(s), publication year, investigation year, study location, study design, and follow-up period; 2) population characteristics: inclusion and exclusion criteria, sample size, female proportion, and baseline age (reported as mean, median, or range); 3) exposure: definition and diagnostic/assessment methods of depressive disorders and bipolar disorder (e.g., clinical diagnosis, self-reported prior diagnosis), and depressive symptoms (e.g., scales, self-reported depressive symptoms); 4) outcome: types of dementia (e.g., Alzheimer's disease [AD], vascular dementia [VaD]) and case definition; 5) effect estimates: RRs, HRs, and ORs with corresponding 95% confidence intervals (CIs). Quality assessment was performed using the Newcastle-Ottawa Scale (NOS) for cohort studies, to evaluate the selection, comparability, and outcome [20]. Studies were assigned scores ranging from zero to nine, with those scoring ≥ 7 categorized as good quality, those scoring 4 to 6 as fair quality and those scoring ≤ 3 as poor quality.

Any discrepancies during the process of screening, data extraction, and quality assessment were resolved by discussion to achieve consensus, or by suggestions from a senior researcher (PS).

2.3. Statistical analysis

2.3.1. Meta-analysis

Despite not incorporating time unit, RRs could be represented by HRs and numerically approximated by ORs in studies with low event rates (<10%) [21]. Therefore, we considered RRs as the primary measure of effect estimates, and both HRs and ORs were treated as equivalent to RRs [22,23]. For articles reporting multiple subgroup estimates from the same sample, a single pooled effect size was derived by a fixed-effect meta-analysis. The pooled RRs were generated by random-effects meta-analysis (DerSimonian and Laird method), with the *I*-squared (I^2) statistic $\geq$ 50% indicating substantial heterogeneity [24]. Publication bias was examined through funnel plots. For analyses encompassing ten or more studies, Egger's and Begg's tests were conducted. To adjust for publication bias, the Duval and Tweedie nonparametric trim-and-fill method was employed under a random-effects model [25]. Besides, a leave-one-out sensitivity analysis was performed to assess the influence of individual studies on the overall pooled estimate. Additionally, given the sufficient data on depressive disorders, a multilevel meta-regression model was applied to generate sex-specific RRs, to facilitate subsequent stratified burden analysis by sex.

According to the established criteria (**Table S4**) [26], the credibility of the meta-analysis results were assessed and classified into five categories: class I (convincing), class II (highly suggestive), class III (suggestive), class IV (weak), and NS (nonsignificant).

2.3.2. Population attributable fraction and attributable burden

The estimation of PAFs and attributable burden was restricted to clinically defined mood disorders (depressive disorders and bipolar disorder), excluding depressive symptoms. Prevalence of mood disorders and DALYs of dementia for different sex and age groups (aged 45 years and above) at global, regional, and national level were derived from the GBD study 2021 (access at: https://gbd2021.healthdata.org/gbd-results/) [27]. The 204 countries or territories in the GBD study 2021 were grouped into five socio-demographic index (SDI) regions (high SDI, high-middle SDI, middle SDI, low-middle SDI, and low SDI) and six WHO regions (African region [AFR], region of Americas [AMR], European region [EUR], Eastern Mediterranean region [EMR], South-East Asia region [SEAR], and Western Pacific region [WPR]). The GBD study collects anonymized data compiled by the Institute for Health Metrics and Evaluation at the University of Washington. A waiver of informed consent was evaluated and approved by the University of Washington Institutional Review Board.

Based on the average median/mean follow-up period of the included articles, a 5-year lag between mood disorders and subsequent dementia was assumed. Therefore, the prevalence of mood disorders from 1990 to 2016 were derived to calculate PAFs, which were then applied to DALYs of dementia from 1995 to 2021. PAFs were estimated using Levin's formula [28]:

$$PAF = \frac{p \times (RR - 1)}{p \times (RR - 1) + 1}$$

Where p was the prevalence of mood disorders, and RR represented the pooled RR derived from meta-analysis. The attributable burden was calculated as follows:

$$Attributable\ burden = DALYs\ of\ \text{dementia} \times PAF$$

We described the distribution of sex- and age-specific dementia burden attributable to mood disorders across five SDI regions, six WHO regions, and 204 countries or territories. To enable comparisons across different years and regions, the direct standardization was applied based on the GBD world population age standard, to generate the age-standardized DALY rate (ASDR) and PAFs [29]. We employed a simulation-based approach, generating 1000 samples from log-normal

distributions for RRs and beta distributions for prevalence rates to calculate PAFs and their 95% CIs [30]. Similarly, 1000 samples were also drawn from the log-normal distribution of DALYs to propagate uncertainty into the estimates of attributable burden. To summarize the overall trends in ASDR changes from 1995 to 2021, the average annual percentage change (AAPC) was calculated using the underlying joinpoint model.

All statistical analyses were conducted in R (version 4.4.0) and Joinpoint Regression Program (version 4.9.0). A two-sided p value less than 0.05 and a 95% CI of RR that did not cross 1.00 was considered statistically significant.

3. Results

3.1. Systematic review and meta-analysis

A total of 6618 records were identified through database searching, and 201 additional records were identified from reference lists of previous systematic reviews and meta-analyses (Fig. 1 and **Figure S1**). After removing duplicate and irrelevant records, a total of 304 records (112 from databases and 192 from the aforementioned reference lists) were assessed through full-text review for eligibility. Finally, 77 articles were included (**Table S5**). The characteristics, quality scores, and full list of the included articles are shown in **Table S5-S8**. Approximately two-thirds of the included articles (n = 49, 63.64%) were published after 2015, most of which were conducted in high-income regions (n = 73, 94.80%). The quality scores ranged from 5 to 9, with 83.12% (n = 64) rated as good quality.

As is shown in Fig. 2 and **Figure S2**, the pooled RR for the association of depressive disorders with all-cause dementia was 1.90 (95% CI: 1.70, 2.12; I^2=97.90%; highly suggestive evidence). No evidence of publication bias was observed through funnel plot, Egger's test (t = 0.99, p = 0.33), and Begg's test (Z = 0.91, p = 0.36), while leave-one-out analysis indicated that no single study influenced the pooled RR (**Figure S3-S4**). For specific types of dementia, the pooled RRs were 2.57 (95% CI: 2.05, 3.23; I^2=97.80%; highly suggestive evidence) for AD, 1.78 (95% CI: 1.06, 2.99; I^2=96.70%; weak evidence) for VaD, and 5.91 (95% CI: 5.01, 6.98; I^2=29.80%; weak evidence) for other dementia (**Figure S5**). The results of funnel plots and leave-one-out analysis are presented in **Figure S6**. Based on the multilevel meta-regression model, the sex-specific RRs were 2.05 (95% CI: 1.73, 2.43) for males and 1.84 (95% CI: 1.56, 2.18) for females, which were subsequently applied to calculate PAFs.

For depressive symptoms, the pooled RR with all-cause dementia was 1.29 (95% CI: 1.20, 1.38; I^2=87.70%; highly suggestive evidence) (Fig. 2 and **Figure S7-S8**), which was presented using the trim-and-fill method to address publication bias (Egger's test: t = 3.03, p < 0.01; Begg's test: Z=−0.13, p = 0.90). Leave-one-out analysis supported the robustness of the pooled estimate (**Figure S9**). A significant association was also observed between depressive symptoms and AD (pooled RR: 1.37, 95% CI: 1.21, 1.54; I^2=87.30%; highly suggestive evidence), while the association with VaD was not statistically significant (p > 0.05) (detailed in **Figure S10-S11**).

The pooled RR for the association between bipolar disorder and all-cause dementia was 3.10 (95% CI: 2.21, 4.35; I^2=97.50%; highly suggestive evidence) (Fig. 2 and **Figure S12**). Visual inspection of the funnel plot suggested a slight asymmetry, while the trim-and-fill method did not impute any potentially missing studies, indicating no substantial evidence of publication bias (**Figure S13**). A leave-one-out analysis was performed using a fixed-effect model due to non-convergence of the random-effects model, indicating that the overall result was relatively robust (**Figure S14**). Bipolar disorder was associated with VaD (pooled RR: 3.67, 95% CI: 2.42, 5.57; I^2=55.00%; highly suggestive evidence) rather than AD (p > 0.05). Detailed results from these analyses, along with the corresponding funnel plots and leave-one-out analysis, are provided in **Figure S15-S16**.

3.2. Population attributable fraction and burden of dementia attributable to depressive disorders

The global PAFs of dementia attributable to depressive disorders by sex between 1990 and 2016 are shown in Fig. 3-A and **Table S9**. Between 1990 and 2016, the global PAFs increased from 4.73% (95% CI: 3.15%, 6.51%) to 4.79% (95% CI: 3.19%, 6.58%) among males, with corresponding increases from 5.50% (95% CI: 3.51%, 7.78%) to 5.56% (95% CI: 3.56%, 7.84%) observed among females. The variations across WHO regions and SDI regions are presented in Fig. 3-A and **Figure S17**. In 2016, AFR exhibited the highest PAFs (males: 6.84%, 95% CI: 4.53%, 9.42%; females: 7.37%, 95% CI: 4.69%, 10.36%), while the lowest PAFs were observed in AMR (males: 3.87%, 95% CI: 2.57%, 5.37%; females: 4.91%, 95% CI: 3.15%, 6.88%). Among SDI regions, low SDI region had the highest PAFs (males: 6.56%, 95% CI: 4.35%, 9.06%; females: 7.06%, 95% CI: 4.50%, 9.98%), whereas high SDI region had the lowest (males: 3.74%, 95% CI: 2.48%, 5.18%; females: 4.43%, 95% CI: 2.83%, 6.21%). Substantial variation at national level was also observed and presented in **Figure S18** and **Table S10-S11**.

In 1995, the global ASDR of dementia attributable to depressive disorders among individuals aged ≥ 45 years was 87.58 (95% CI: 33.48, 189.93) per 100,000 population, which increased to 89.61 (95% CI: 34.80, 192.24) in 2021 (Table 1), and was consistently higher among females than males throughout the study period (**Figure S19**). The age-specific attributable burden showed an increasing trend with advancing

Exposure	Outcome	Number of studies	RR (95% CI)	I-square (%)	P-value	Credibility
Mood disorders						
Depressive disorders	All-cause Dementia	28	1.90 (1.70-2.12)	97.90	< 0.0001	II
Depressive disorders	AD	14	2.57 (2.05-3.23)	97.80	< 0.0001	II
Depressive disorders	VaD	5	1.78 (1.06-2.99)*	96.70	0.029	IV
Depressive disorders	Other dementia	2	5.91 (5.01-6.98)	29.80	< 0.0001	IV
Bipolar disorder	All-cause Dementia	6	3.10 (2.21-4.35)	97.50	< 0.0001	II
Bipolar disorder	AD	2	4.50 (0.87-23.14)	96.90	0.0719	NS
Bipolar disorder	VaD	2	3.67 (2.42-5.57)	55.00	< 0.0001	II
Bipolar disorder	Other dementia	1	10.56 (8.21-12.33)	-	-	-
Depressive symptoms						
Depressive symptoms	All-cause Dementia	35	1.29 (1.20-1.38)*	87.70	< 0.0001	II
Depressive symptoms	AD	18	1.37 (1.21-1.54)	87.30	< 0.0001	II
Depressive symptoms	VaD	5	1.18 (0.89-1.56)*	92.00	0.2472	NS

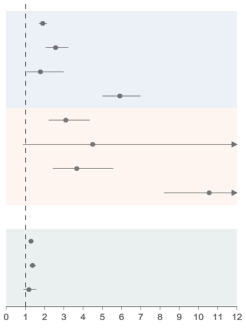

Fig. 2. Forest plot for associations of mood disorders and depressive symptoms with dementia.
Notes: RR, risk ratio; CI, confidence interval; AD, Alzheimer's disease; VaD, vascular dementia. *RRs were adjusted using the trim-and-fill method for publication bias. Credibility: Convincing (class I), Highly suggestive (class II), Suggestive (class III), Weak (class IV), and Non-significant (NS).

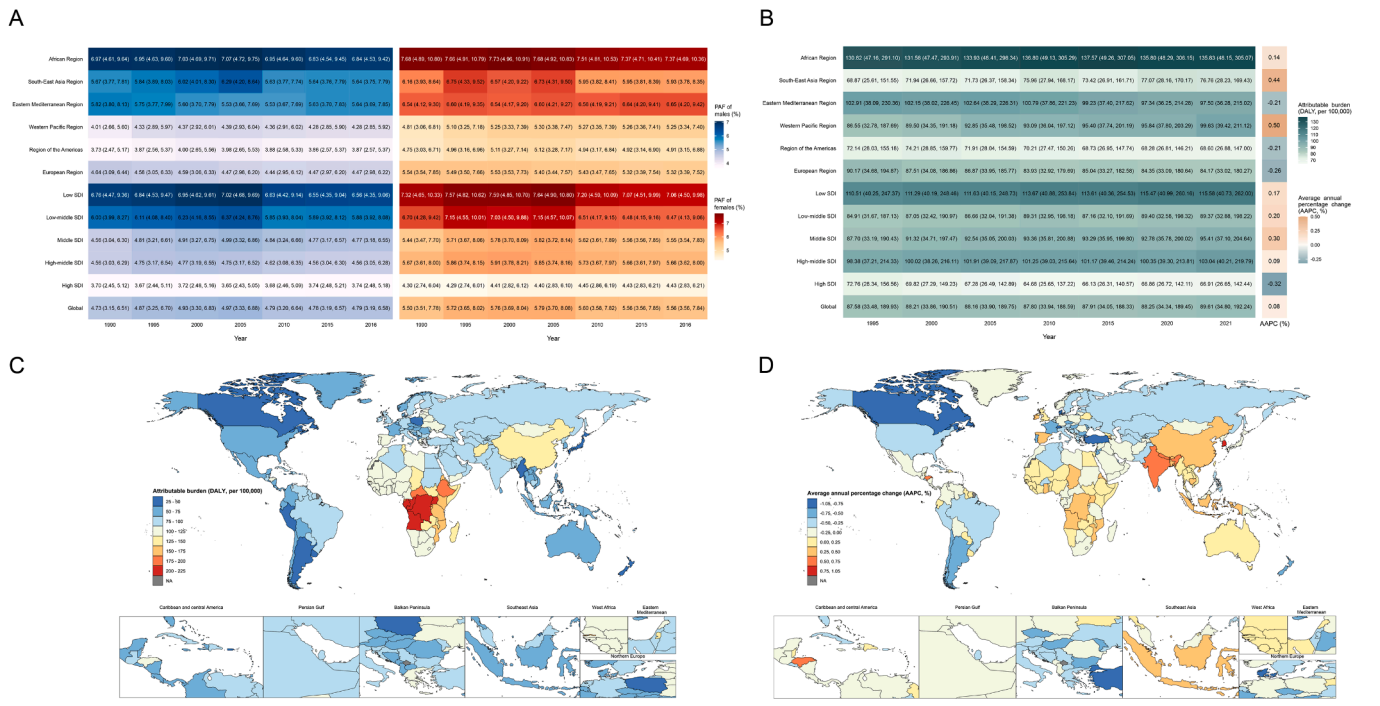

Fig. 3. Global, regional, and national population attributable fraction and age-standardized DALY rate of dementia attributable to depressive disorders.
Notes: SDI, socio-demographic index; PAF, population attributable fraction; DALY, disability-adjusted life-year; ASDR, age-standardized DALY rate; AAPC, average annual percentage change. Panel A: Global and regional PAF of dementia attributable to depressive disorders by sex between 1990 and 2016. Panel B: Global and regional ASDR and AAPC of dementia attributable to depressive disorders between 1995 and 2021. Panel C: National ASDR of dementia attributable to depressive disorders in 2021. Panel D: National AAPC of ASDR for dementia attributable to depressive disorders between 1995 and 2021. Source: Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.

age (**Table S12**). From 1995 to 2021, the ASDR showed a slight increase, with an AAPC of 0.08% (95% CI: 0.04%, 0.11%) in the total population (Fig. 3-B). At the regional level, the highest ASDR in 2021 was observed in AFR (135.83, 95% CI: 48.15, 305.07) and lowest in AMR (68.60, 95% CI: 26.88, 147.00), while WPR showed the largest increase in ASDR (AAPC: 0.50%, 95% CI: 0.40%, 0.60%) and EUR the greatest decrease (AAPC: −0.26%, 95% CI: −0.29%, −0.24%). Across SDI regions, the ASDR in 2021 was highest in low SDI region (115.58, 95% CI: 40.73, 262.00) and lowest in high SDI region (66.91, 95% CI: 26.65, 142.44), while the largest increase in ASDR was observed in middle SDI region (AAPC: 0.30%, 95% CI: 0.23%, 0.36%) and the greatest decrease in high SDI region (AAPC: −0.32%, 95% CI: −0.38%, −0.26%). At the national level, the top five highest ASDRs in 2021 were observed in Uganda, Gabon, Republic of the Congo, Democratic Republic of the Congo, and Angola, all of which were located in AFR and low or middle SDI regions (Fig. 3-C and **Figure S20**). As is shown in Fig. 3-D, the largest increase in ASDR from 1995 to 2021 was found in South Korea (AAPC: 1.05%, 95% CI: 0.84%, 1.26%), while Canada exhibited the greatest decline (AAPC: −1.05%, 95% CI: −1.26%, −0.84%). The age-specific attributable burden in 2021 at regional and national levels are presented in **Table S13-S16**.

3.3. Population attributable fraction and burden of dementia attributable to bipolar disorder

The global PAFs for dementia attributable to bipolar disorder between 1990 and 2016 are provided in Fig. 4-A and **Table S17**. The PAFs showed a decline between 1990 and 2016, from 1.26% (95% CI: 0.67%, 2.07%) to 1.22% (95% CI: 0.65%, 2.01%) for males, and from 1.41% (95% CI: 0.75%, 2.31%) to 1.34% (95% CI: 0.71%, 2.18%) for females, respectively. At the regional level, variations across WHO and SDI regions are presented in Fig. 4-A and **Figure S21**. In 2016, the highest PAFs were found in AMR for males (1.83%, 95% CI: 0.98%, 2.88%) and in EUR for females (2.05%, 95% CI: 1.09%, 3.36%), whereas WPR exhibited the lowest PAFs for both sexes (males: 0.67%, 95% CI: 0.36%, 1.11%; females: 0.74%, 95% CI: 0.40%, 1.23%). Across SDI regions, high SDI region showed the highest PAFs for both sexes (males: 1.52%, 95% CI: 0.80%, 2.43%; females: 1.82%, 95% CI: 0.96%, 2.87%), while the lowest PAFs were observed in high-middle SDI region for males (1.02%, 95% CI: 0.54%, 1.70%) and middle SDI region for females (1.14%, 95% CI: 0.61%, 1.88%), respectively. Variations were also observed across countries and territories, as shown in **Figure S22** and **Table S18-S19**.

The global ASDR of dementia attributable to bipolar disorder among individuals aged ≥ 45 years decreased from 16.62 (95% CI: 5.78, 39.59) in 1995 to 15.91 (95% CI: 5.56, 37.87) per 100,000 population in 2021, with higher rates observed in females than males (Table 1 and **Figure S23**). The age-specific attributable burden also showed an increasing trend with advancing age (**Table S20**). The ASDR declined slightly from 1995 to 2021, with an AAPC of −0.18% (95% CI: −0.21%, −0.16%) in the total population (Fig. 4-B). Across WHO regions, the highest ASDR in 2021 was found in EUR (21.58, 95% CI: 7.58, 50.36) and lowest in SEAR (9.58, 95% CI: 3.22, 23.37), whereas SEAR exhibited the largest increase in ASDR (AAPC: 0.28%, 95% CI: 0.21%, 0.34%) and WPR the greatest decrease (AAPC: −0.08%, 95% CI: −0.11%, −0.05%). For SDI regions, the ASDR in 2021 was the highest in high SDI region (20.27, 95% CI: 7.28, 47.08) and lowest in low-middle SDI region (12.02, 95% CI: 4.04, 29.22), while the largest increase in ASDR was found in low-middle SDI region (AAPC: 0.23%, 95% CI: 0.19%, 0.26%) and the greatest decrease in high-middle SDI region (AAPC: −0.21%, 95% CI: −0.25%, −0.17%). At the national level, the top five highest ASDRs in 2021 were observed in Italy, Israel, Brazil, New Zealand, and Belgium, most of which were from EUR and high SDI regions (Fig. 4-C and **Figure S24**). As presented in Fig. 4-D, the largest increase in ASDR from 1995 to 2021 was found in India (AAPC: 0.43%, 95% CI: 0.30%, 0.57%), while Cyprus showed the greatest decline (AAPC: −0.45%, 95%

Table 1
The global age-standardized DALY rate per 100,000 population of dementia attributable to mood disorders from 1995 to 2021 (aged ≥ 45 years, assuming a 5-year lag period).

Year	Depressive disorders (95% CI)			Bipolar disorder (95% CI)		
	Overall	Male	Female	Overall	Male	Female
1995	87.58 (33.48, 189.93)	70.73 (26.55, 153.86)	104.43 (40.41, 225.99)	16.62 (5.78, 39.59)	13.32 (4.55, 32.25)	19.92 (7.02, 46.93)
1996	87.92 (33.62, 190.48)	70.85 (26.60, 154.01)	104.98 (40.64, 226.95)	16.60 (5.77, 39.54)	13.30 (4.53, 32.23)	19.90 (7.01, 46.84)
1997	88.05 (33.77, 190.33)	70.85 (26.64, 153.78)	105.25 (40.89, 226.87)	16.56 (5.77, 39.38)	13.27 (4.52, 32.11)	19.84 (7.01, 46.66)
1998	88.22 (33.91, 191.07)	70.90 (26.61, 154.29)	105.53 (41.20, 227.85)	16.53 (5.74, 39.38)	13.24 (4.50, 32.09)	19.81 (6.98, 46.66)
1999	88.30 (33.90, 190.96)	70.86 (26.56, 153.75)	105.74 (41.23, 228.17)	16.50 (5.74, 39.22)	13.20 (4.49, 31.83)	19.79 (6.98, 46.60)
2000	88.21 (33.86, 190.51)	70.81 (26.59, 153.30)	105.60 (41.13, 227.72)	16.46 (5.72, 39.14)	13.18 (4.48, 31.81)	19.74 (6.97, 46.47)
2001	88.07 (33.91, 190.02)	70.76 (26.62, 152.97)	105.38 (41.19, 227.06)	16.42 (5.72, 39.03)	13.15 (4.49, 31.82)	19.68 (6.96, 46.24)
2002	88.19 (33.81, 190.16)	70.86 (26.66, 153.20)	105.51 (40.96, 227.13)	16.40 (5.70, 39.07)	13.15 (4.48, 31.81)	19.66 (6.92, 46.33)
2003	88.22 (33.96, 189.79)	71.01 (26.71, 153.48)	105.44 (41.20, 226.10)	16.36 (5.70, 38.93)	13.14 (4.48, 31.81)	19.59 (6.92, 46.04)
2004	88.16 (33.96, 189.54)	71.00 (26.76, 153.44)	105.31 (41.15, 225.64)	16.31 (5.68, 38.79)	13.11 (4.47, 31.69)	19.52 (6.88, 45.90)
2005	88.16 (33.90, 189.75)	71.08 (26.66, 154.00)	105.24 (41.14, 225.50)	16.30 (5.66, 38.83)	13.12 (4.47, 31.82)	19.48 (6.84, 45.84)
2006	87.87 (33.97, 188.96)	70.86 (26.83, 152.82)	104.87 (41.10, 225.09)	16.23 (5.65, 38.54)	13.06 (4.48, 31.48)	19.40 (6.83, 45.59)
2007	87.77 (33.95, 188.83)	70.97 (26.74, 153.39)	104.57 (41.16, 224.27)	16.20 (5.65, 38.43)	13.07 (4.46, 31.60)	19.32 (6.84, 45.26)
2008	87.75 (33.99, 188.61)	71.01 (26.83, 153.28)	104.48 (41.14, 223.93)	16.15 (5.64, 38.27)	13.05 (4.46, 31.50)	19.25 (6.82, 45.03)
2009	87.76 (33.95, 188.74)	71.10 (26.84, 153.50)	104.43 (41.06, 223.98)	16.11 (5.64, 38.17)	13.05 (4.47, 31.51)	19.17 (6.81, 44.82)
2010	87.80 (33.94, 188.59)	71.20 (26.82, 153.77)	104.39 (41.07, 223.42)	16.08 (5.66, 38.05)	13.06 (4.46, 31.58)	19.09 (6.85, 44.52)
2011	87.80 (33.98, 188.01)	71.12 (26.95, 153.18)	104.48 (41.01, 222.84)	16.04 (5.66, 37.88)	13.04 (4.47, 31.45)	19.04 (6.85, 44.31)
2012	87.68 (33.99, 187.77)	70.96 (26.95, 152.98)	104.40 (41.03, 222.56)	16.00 (5.64, 37.79)	13.02 (4.47, 31.38)	18.97 (6.82, 44.21)
2013	87.62 (34.04, 187.18)	70.94 (26.91, 152.72)	104.29 (41.17, 221.64)	15.97 (5.63, 37.68)	13.03 (4.48, 31.35)	18.91 (6.79, 44.02)
2014	87.76 (34.00, 187.74)	71.00 (27.01, 152.62)	104.52 (41.00, 222.86)	15.96 (5.62, 37.73)	13.03 (4.49, 31.30)	18.89 (6.76, 44.15)
2015	87.91 (34.05, 188.33)	71.27 (26.97, 153.71)	104.55 (41.12, 222.96)	15.95 (5.64, 37.69)	13.06 (4.47, 31.52)	18.84 (6.80, 43.86)
2016	87.96 (34.34, 188.25)	71.15 (27.20, 152.87)	104.78 (41.47, 223.63)	15.91 (5.62, 37.56)	13.00 (4.49, 31.22)	18.81 (6.74, 43.90)
2017	88.11 (34.33, 189.01)	71.34 (27.12, 154.11)	104.87 (41.55, 223.90)	15.88 (5.58, 37.74)	13.01 (4.45, 31.33)	18.76 (6.72, 44.15)
2018	88.13 (34.29, 188.87)	71.41 (27.15, 153.89)	104.85 (41.42, 223.85)	15.83 (5.58, 37.47)	12.98 (4.44, 31.25)	18.67 (6.73, 43.69)
2019	88.20 (34.23, 189.80)	71.47 (27.26, 154.29)	104.93 (41.20, 225.32)	15.79 (5.53, 37.54)	12.96 (4.44, 31.17)	18.62 (6.63, 43.91)
2020	88.25 (34.34, 189.45)	71.58 (27.28, 154.16)	104.92 (41.39, 224.74)	15.74 (5.51, 37.40)	12.94 (4.44, 31.12)	18.53 (6.58, 43.68)
2021	89.61 (34.80, 192.24)	72.73 (27.51, 157.19)	106.50 (42.10, 227.30)	15.91 (5.56, 37.87)	13.10 (4.47, 31.60)	18.72 (6.65, 44.14)

Notes: DALY, disability-adjusted life-year; CI, confidence interval.

CI: −0.48%, −0.41%). The age-specific attributable burden in 2021 at regional and national levels are presented in **Table S21-S24**.

4. Discussion

This study provides a quantification of the global, regional, and national burden of dementia attributable to mood disorders among individuals aged 45 and above from 1995 to 2021. The global PAFs of dementia that could be attributable to depressive disorders in 2016 were 4.79% among males and 5.56% among females, respectively. In 2021, the global burden of dementia attributable to depressive disorders was 89.61 DALYs per 100,000 population, showing a slight increase from 1995. This estimate was higher than other established risk factors such as high fasting plasma glucose (66.42 DALYs per 100,000 population) and high body mass index (32.86 DALYs per 100,000 population) [31]. Although associated with a higher individual-level risk, the global attributable burden of bipolar disorder decreased in 2021 relative to 1995. Specifically, the PAFs in 2016 were 1.22% for males and 1.34% for females, while the corresponding burden in 2021 was 15.91 DALYs per 100,000 population. While this population-level burden was relatively modest compared to depressive disorders, it remains significant given the severity of the condition and its potential link to VaD. The attributable burden from depressive disorders was disproportionately higher in AFR and low SDI regions, whereas that from bipolar disorder was concentrated in EUR and high SDI regions.

We provide up-to-date estimates supporting the role of mood disorders in contributing to dementia. In line with previous studies [32], depressive disorders were associated with a nearly two-fold increase in the risk of all-cause dementia, with a particularly strong link to AD. This association is thought to be driven by shared neurobiological pathways such as HPA axis dysregulation, persistent neuroinflammation, oxidative stress, and reduced neurotrophic support, which accelerate brain aging and hippocampal atrophy [8,33–36]. Moreover, depressive symptoms presented a weaker but still significant risk, suggesting a potential dose-response relationship where the clinical severity of depression correlates with the magnitude of subsequent dementia [37]. However, alternative explanations should also be considered. For example, depressive symptoms occurring in late life may represent prodrome of dementia rather than an independent risk factor [38]. Certain psychotropic medications, such as benzodiazepines, may be associated with cognitive decline [39]. In comparison, the association linked to bipolar disorder was relatively higher than that observed for depressive disorders, and also showed a specific predilection for VaD rather than AD. However, the more limited evidence base underscores the need for cautious interpretation. This link may be explained by the cumulative neurotoxic insult from recurrent manic episodes and a greater level of comorbidities [40,41]. Meanwhile, similar confounding

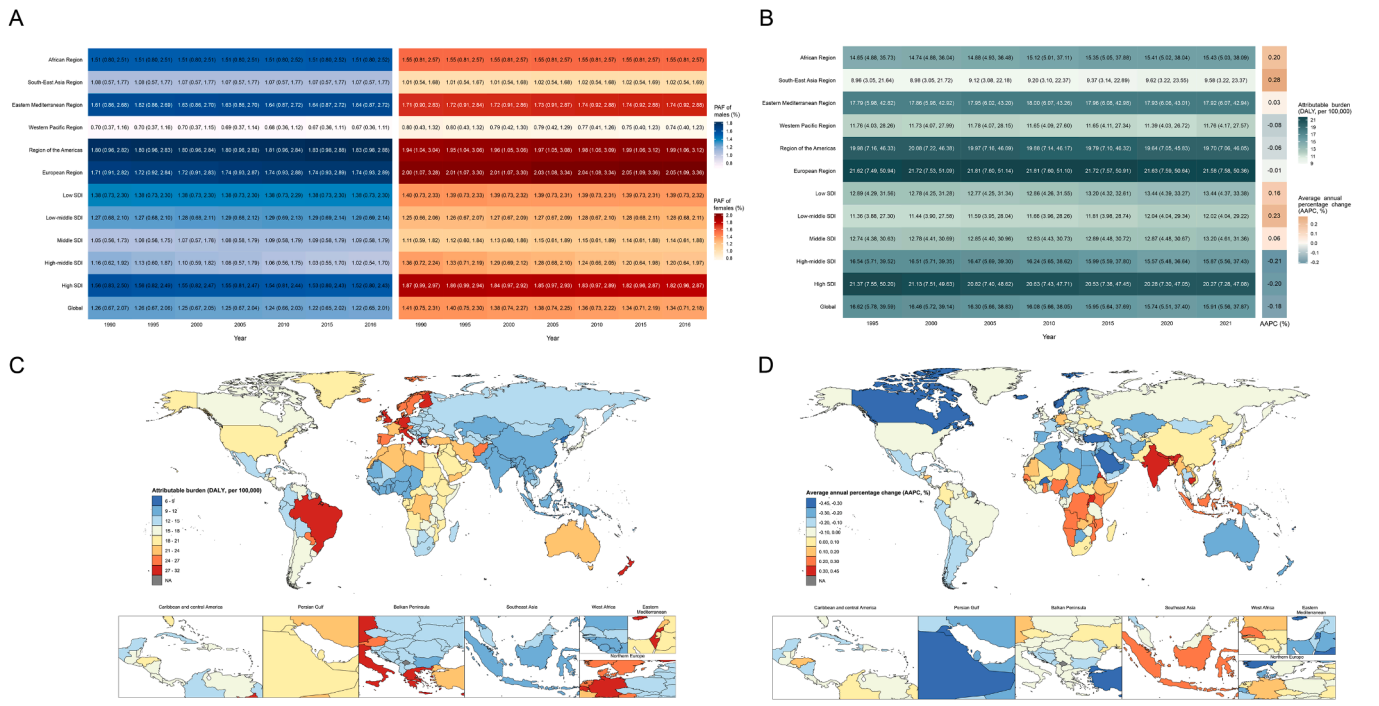

Fig. 4. Global, regional, and national population attributable fraction and age-standardized DALY rate of dementia attributable to bipolar disorder.
Notes: SDI, socio-demographic index; PAF, population attributable fraction; DALY, disability-adjusted life-year; ASDR, age-standardized DALY rate; AAPC, average annual percentage change. Panel A: Global and regional PAF of dementia attributable to bipolar disorder by sex between 1990 and 2016. Panel B: Global and regional ASDR and AAPC of dementia attributable to bipolar disorder between 1995 and 2021. Panel C: National ASDR of dementia attributable to bipolar disorder in 2021. Panel D: National AAPC of ASDR for dementia attributable to bipolar disorder between 1995 and 2021. Source: Institute for Health Metrics and Evaluation. Used with permission. All rights reserved.

factors, particularly vascular comorbidities and drug therapies (e.g., benzodiazepines and mood stabilizers like valproic acid), may also contribute to the observed association in bipolar disorder [39,42,43]. Beyond these biological pathways, psychosocial factors may also play a role. Specifically, mood disorders could lead to social withdrawal, unhealthy lifestyles, substance abuse, and disruption of educational or occupational attainment, all of which potentially reduce cognitive reserve [44–46]. There is also evidence suggesting that improvement in mood disorders, achieved through interventions such as psychological therapy, is associated with a lower risk of subsequent dementia [47]. Collectively, these findings support the role of mood disorders as a critical risk factor, implying that effective management could offer a vital window for dementia prevention.

Translating the individual RR estimates identified in our meta-analysis into population-level impact, the PAFs of dementia were also driven by the prevalence of the underlying mood disorders. Despite representing a lower RR compared to bipolar disorder, depressive disorders accounted for a significantly larger proportion of the dementia burden. While the Lancet Commission reported the PAF of depression (3%) on the evidence base that mixed depressive disorders and subclinical symptoms, our estimate offers a nuanced perspective by focusing on the more severe impact of clinically defined depressive disorders [4]. A systematic review and meta-analysis also reported PAFs of dementia attributable to depression ranging from 7.3% to 8.3% [15]. Moreover, the PAFs of depressive disorders observed in this study are comparable to, or even higher than other conditions that contribute to dementia, such as periodontal diseases (6.10%), age-related and other hearing loss (4.70%), and type 2 diabetes (3.80%) [17]. In contrast, while bipolar disorder represents a high-risk phenotype, its lower prevalence limits its total contribution to the dementia burden, and comparative evidence for bipolar disorder remains scarce. The substantial magnitude of the attributable fractions suggests that mood disorders, particularly depressive disorders, represent a critical target for dementia prevention.

Globally, the burden of dementia attributable to depressive disorders was not only significant but also exhibited an upward trend since 1995, signifying a shifting landscape of dementia risk factors. Since the management of other risk factors like cardiovascular diseases has received certain improvements globally, less effectively managed contributors such as depressive disorders represent a critical, yet often overlooked, target for further risk reduction [48–50]. Conversely, the lower attributable burden from bipolar disorder trended slightly downward, which might be plausibly linked to advances in the long-term clinical management of the condition, particularly the more widespread use of mood stabilizers (e.g., lithium) [10]. For both mood disorders, the attributable burden was consistently higher among females. This disparity likely extends beyond the higher prevalence of these conditions in females and may indicate a sex-specific vulnerability [51]. Moreover, the attributable burden for both conditions increased steeply with elevated age, reflecting the intersection of cumulative biological damage from mood disorders with the age-related degeneration in brain reserve [52].

A critical finding of this study is the concentration of dementia burden attributable to depressive disorders in low SDI region, particularly in AFR. In these settings, depressive disorders often remain untreated due to limited access to mental healthcare, prolonging exposure to chronic psychological distress and neurobiological alterations [53,54]. Additionally, the coexistence of infectious and nutritional comorbidities in low-resource contexts, as well as lower educational attainment, could further exacerbate neurodegenerative processes [55,56]. In contrast, the attributable burden due to bipolar disorder was the highest in EUR and high SDI regions, where diagnostic recognition and treatment access are more advanced. Improved survival and chronic pharmacological management in these populations allow the long-term cognitive consequences of the disease to manifest as dementia later in life [57]. However, the lower burden observed in low SDI region may also partly reflect underdiagnosis, misclassification, and data limitation rather than genuine epidemiological differences [58]. Given the limited

awareness of bipolar disorder and the shortage of trained mental health professionals in these settings, its contribution to dementia burden may be underestimated within the current evidence base. Taken together, our findings call for a dual approach consisting of an urgent scale-up of mental health services in low SDI region, and a proactive focus on long-term surveillance and intervention for cognitive impairment among individuals with bipolar disorder in high SDI region.

The diverse patterns observed across geographical and socioeconomic scales suggest that dementia prevention strategies should be adapted to different contexts. Global health initiatives need to set mood disorders as primary targets for risk reduction. In low-resource settings, expanding mental health services within primary care is essential to mitigate the impact of untreated conditions. In developed regions, healthcare systems should implement cognitive monitoring for older individuals with mood disorders, especially bipolar disorder. National health strategies may also benefit from using localized burden estimates to prioritize the most affected and vulnerable populations. Future research should focus on using biomarkers and neuroimaging to clarify causal pathways, and distinguish mood disorders from prodromal dementia. There is also a need for intervention trials to evaluate whether effective psychiatric management could significantly lower the long-term risk of dementia.

By integrating a systematic review and meta-analysis within the CRA framework, this study provides the quantification of the global, regional, and national burden of dementia attributable to mood disorders. The clear differentiation between the two mood disorders could help to elucidate their distinct patterns of attributable burden, and highlight the potential influence of health system and socioeconomic factors. Nevertheless, several limitations should be acknowledged. First, despite the use of rigorous inclusion criteria, substantial heterogeneity was observed, which may be introduced by variations across the included studies (e.g., diagnostic criteria, covariate adjustment). Second, the precision of risk estimated across demographic groups may be limited due to a lack of hierarchical data for calculating sex- or age-specific RRs of dementia and its subtypes. Third, the CRA assumed a causal relationship between mood disorders and dementia. While cohort studies provide some support for this link, a definitive causality cannot be fully established due to potential residual confounding and bidirectional associations [9]. Future high-quality research is needed to validate this causal relationship and evaluate the effectiveness of targeted interventions. Finally, the GBD estimates of mood disorders prevalence and dementia DALYs rely on modeled data, particularly for countries with limited epidemiological surveillance, which could lead to underestimation or overestimation of attributable burden.

5. Conclusion

This study demonstrates that mood disorders, which are significantly associated with dementia, are a substantial contributor to the burden of dementia at global, regional, and national level. Future research is needed to further refine risk estimates, elucidate the mechanisms linking mood disorders to dementia, and develop cost-effective interventions for high-risk populations. Integrating mental health management into public health policies might have the potential to reduce the dementia burden and improve health outcomes.

Data availability

The data utilized in this article are publicly available on the Global Burden of Disease webpage (https://gbd2021.healthdata.org/gbd-results/).

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Ethics approval and consent to participate

Ethics approval was not required for this systematic review and meta-analysis. Additionally, as the GBD study did not involve any personal or sensitive information, no ethical approval was necessary for the execution of this study.

Declaration of generative Al and AI-assisted technologies in the writing process

We have not used any AI at all.

CRediT authorship contribution statement

Jing Wu: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation. **Jiali Zhou:** Writing – review & editing. **Shiyi Shan:** Writing – review & editing. **Ke Tang:** Writing – review & editing. **Longzhu Zhu:** Writing – review & editing, Data curation. **Jiayao Ying:** Writing – review & editing. **Xinyu Liu:** Writing – review & editing. **Peige Song:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100559.

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