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Global, regional, and national burden of dementia attributable to depression among people living with diabetes: a comparative risk assessment study

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Abstract

Background This study aimed to assess the burden of dementia attributable to depression among individuals with diabetes, and to examine inequalities across countries and sexes.

Methods The population attributable fractions (PAFs) and generalized impact fractions (GIFs) for dementia attributable to depression among individuals with diabetes from 1990 to 2016 were calculated by combining the corresponding prevalence of depression and diabetes comorbidity with the relative risks obtained from a systematic review and meta-analysis of cohort studies. Assuming a 5-year lag between depression and dementia onset, these estimates were applied to dementia disability-adjusted life years (DALYs) from 1995 to 2021. Cross-country inequalities were assessed using the slope index of inequality (SII) and the concentration index, and sex differences were related to the Gender Inequality Index (GII).

Results The global PAFs for dementia attributable to depression among individuals with diabetes increased from 1.58% (95% confidence interval [CI] 1.10%, 2.17%) in 1990 to 2.63% (95%CI 1.81%, 3.61%) in 2016. Correspondingly, age-standardized DALYs rates (ASDRs) rose from 22.88 (95%CI 8.75, 50.05) DALYs per 100,000 population in 1995 to 38.08 (95%CI 14.70, 82.51) DALYs per 100,000 population in 2021. This upward trend was consistent across both sexes, with females higher than males. Regionally, the Eastern Mediterranean region reported the highest attributable burden (54.95 DALYs per 100,000 population, 95%CI 20.87, 120.12) in 2021, while the South-East Asia region had the lowest (26.14 DALYs per 100,000 population, 95%CI 9.57, 58.65). Within the socio-demographic index (SDI) regions, those with higher SDI generally had a higher burden. In 2021, the SII was 8.49 (95%CI 0.96, 16.02) and the concentration index was 0.1000 (95%CI 0.0657, 0.1342) globally. In countries with higher GII, the attributable burden among females was relatively greater compared to males.

Conclusion Our research highlights the need for both physical and mental interventions among individuals affected by depression and diabetes, to reduce dementia risk and its associated burden.

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Keywords Dementia, Depression, Diabetes, Meta-analysis, Attributable burden, Global burden of disease

Introduction

Dementia is a progressive and debilitating neurological disorder, characterized by a decline in cognitive function and loss of independence in daily life [1]. Driven by rapid population aging and demographic transitions, dementia has emerged as one of the most pressing global health challenges of the 21 st century, bringing an extensive burden on individuals, caregivers, and the society at large [2–5]. In 2019, an estimated 57.4 million people were living with dementia globally, a figure projected to nearly triple to 152.8 million by 2050 [4]. Also, dementia is a leading cause of death, disability, and dependency among older adults, with global economic costs exceeding one trillion US dollars in 2019 [6]. Despite its growing impact and decades of research, no disease-modifying treatments are currently available, which underscores the urgent need for preventive strategies that address modifiable risk factors.

The 2024 report of the Lancet Commission on Dementia Prevention, Intervention, and Care has highlighted 14 modifiable risk factors that collectively account for approximately 45% of dementia cases worldwide [7]. These factors include depression, diabetes, smoking, hypertension, obesity and other conditions that can be mitigated through public health interventions [7]. Among these, depression has emerged as a particularly significant risk factor, with robust evidence linking it to an increased risk of cognitive decline and dementia [8, 9]. Potential underlying mechanisms include chronic systemic inflammation, neuroendocrine dysregulation, structural changes in the hippocampus, and vascular dysfunction [10, 11]. Similarly, diabetes, another well-established risk factor for dementia, shares overlapping pathological pathways with depression [12, 13]. Notably, depression is nearly twice as prevalent among individuals with diabetes compared to the general population [14, 15], and this comorbidity has been shown to significantly increase the risk of dementia [16].

While prior studies have explored the independent roles of diabetes and depression to dementia with geographical limits, critical gaps exist in understanding how the coexistence of depression and diabetes contributes to dementia burden at global, regional, and national levels [7, 17]. This gap is particularly concerning given the parallel global increases in the prevalence of diabetes and depression, both of which are expected to drive future increases in dementia burden [18, 19]. Furthermore, the burden of depression, diabetes, and dementia is unevenly distributed across different demographic and geographic strata. For example, while the prevalence of diabetes is relatively comparable between sexes, women are disproportionately affected by both depression and dementia, suggesting potential sex-specific vulnerabilities [20, 21]. Socioeconomic and cultural factors, including access to healthcare, also influence these disparities. Gender inequality, as measured by indices such as the gender inequality index (GII), may further shape sex-specific differences in the burden of dementia attributable to depression among individuals with diabetes [22]. However, the extent to which these factors contribute to observed disparities in dementia burden remains poorly understood. Investigating these disparities is essential to inform evidence-based prevention strategies for dementia and to prioritize interventions that target high-risk populations in the context of aging populations and rising multimorbidity.

To fill these research gaps, this study utilized a comparative risk assessment (CRA) framework to quantify the global, regional, and national burden of dementia attributable to depression among individuals with diabetes from 1995 to 2021. Additionally, we sought to explore cross-country inequalities in the attributable burden and examined the association between relative sex differences in the attributable burden and national gender inequality levels.

Methods

Study overview

The overall CRA framework employed in this study is illustrated in Fig. 1. The analysis consisted of three stages. First, a systematic review and meta-analysis was conducted to estimate the pooled relative risk ratio (RRs) for the association between depression and subsequent risk of dementia among individuals with diabetes. Second, population attributable fractions (PAFs) were calculated to determine the proportion of dementia cases attributable to the co-occurrence of depression and diabetes, assuming a 5-year time lag, for the period 1990–2016. Third, PAFs were applied to the calculation of disability-adjusted life-years (DALYs) for dementia, which represents the attributable burden of dementia from 1995 to 2021. Additionally, we evaluated absolute and relative cross-country inequalities in the attributable burden of dementia, and the association between gender inequalities and relative sex difference in the attributable burden. To estimate the potential reductions in dementia burden under hypothetical scenarios, the generalized impact fractions (GIFs) were calculated, assuming a 30% reduction in diabetes prevalence as well as depression prevalence ratio among individuals with diabetes.

This study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews

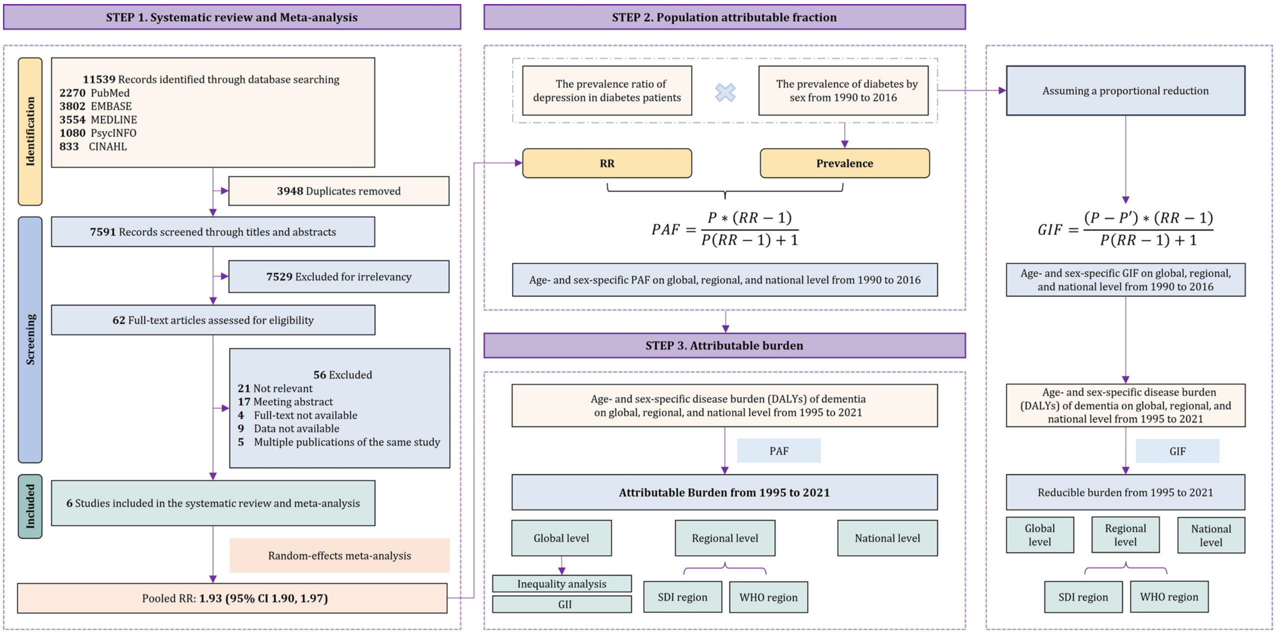


Fig. 1 Study framework. RR, risk ratio; CI, confidence interval; PAF, population attributable fraction; DALYs, disability-adjusted life years; WHO, World Health Organization; SDI, socio-demographic index; GII, gender inequality index

and Meta-Analyses (PRISMA) guidelines and the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statement [23, 24]. The systematic review protocol was prospectively registered on PROSPERO (ID: CRD42024606925).

Systematic review

Search strategy and selection criteria

A comprehensive literature search was performed in PubMed, Embase, MEDLINE, PsycINFO, and CINAHL to identify eligible studies. The search strategy combined medical subject headings (MeSH) and free-text terms related to dementia, depression, and diabetes. The search was restricted to articles published from database inception to 12th July 2024, without language or geographic restrictions. The full search strategies for all electronic databases are provided in Table S1. Two researchers (CZ and CX) independently assessed the eligibility of all records in two review stages: the title and abstract screening stage and the full-text screening stage. Studies were included if they were observational in design (cross-sectional, cohort, or case-control), reported risk estimates (RR, odds ratio [OR], or hazard ratio [HR]) with 95% confidence intervals (CIs) for dementia associated with depression in individuals with diabetes. Studies conducted in specialized populations, such as inpatients or individuals with specific comorbidities, were excluded. Abstracts, case reports, reviews, viewpoints, and letters were also excluded. In cases of multiple publications from the same investigation, the one with the largest sample size or most comprehensive analysis was kept. Reference lists of the included articles were further scrutinized to complement the database searches.

Data extraction and quality assessment

Data were independently extracted from the included articles by the same two researchers (CZ and CX) using a pre-defined template. Extracted variables included: (1) bibliographic information: title, author(s), publication year, study period, study location, and study setting (urban, rural, or mixed); (2) characteristics of participants: sample size, inclusion and exclusion criteria, ethnicity, sex, and age; (3) risk estimates: definition and diagnostic methods of depression, diabetes, and dementia, RR/OR/HR, and 95%CI. If the estimate within an article was stratified by age, sex, etc., the corresponding stratified risk estimates were further extracted.

Since all included studies employed a cohort design, the quality assessment followed the Newcastle-Ottawa Scale (NOS) [25]. The NOS quality assessment scale is composed of three modules (selection, comparability, outcome) and evaluates the quality of cohort studies based on eight items. According to the semi-quantitative star system, each item in the comparability module could receive a maximum of two stars, while the remaining items could receive a maximum of one star. The maximum score was nine, with one star corresponding to one point. Articles were scored on a range of zero to nine points, and those with a score of seven or above were considered to be of high quality [26].

Disagreements during the phases of article selection, data extraction, and quality assessment were resolved by consensus through discussion or by consultations with a senior researcher (PS).

Diabetes prevalence and dementia disability-adjusted life years

The Global Burden of Disease 2021 study (GBD 2021) provides a comprehensive epidemiological estimation for 371 diseases and injuries by age and sex, across 204 countries and territories, with annual data available at global, regional, and national scales from 1990 to 2021 [27, 28]. In this study, the global, regional, and national age- and sex-specific prevalence of diabetes and DALYs rates of dementia, with their corresponding 95% uncertainty intervals (UIs) for adults aged 40 and over were extracted from the Global Health Data Exchange (GHDx) (Access: https://vizhub.healthdata.org/gbd-results/). A detailed description of data modeling is shown in Appendix 1. The 204 countries and territories in the GBD 2021 were categorized into six World Health Organization (WHO) regions (Africa region [AFR], Americas region [AMR], Europe region [EUR], Eastern Mediterranean region [EMR], South-East Asia region [SEAR], and Western Pacific region [WPR]) and five socio-demographic index (SDI) regions (high SDI, high-middle SDI, middle SDI, low-middle SDI, low SDI) according to their geographic locations or socioeconomic developmental levels.

We described the distribution of age-standardized DALYs rates (ASDR) per 100,000 population across sexes, WHO and SDI regions, and 204 countries/territories. To allow for comparisons across different years and locations, we applied a direct standardization based on the population weights from the GBD 2021 to calculate the age-standardized rates for all measures aged 40 and above [28, 29].

$$\boldsymbol{Age - standardized\, rate} = \frac{\sum \boldsymbol{N_i p_i}}{\boldsymbol{N}}$$

where $\boldsymbol{N_i}$ is the population size of the $\boldsymbol{i}$ age group in the GBD standard population, $\boldsymbol{p_i}$ is the rate of the disease in the $\boldsymbol{i}$ age group. $\boldsymbol{N}$ is the total population size of the GBD standard population.

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 [30].

Statistical analysis

Meta-analysis

RR represents a HR without considering time units, and it closely aligns with the OR in studies with low event rates. Thus, we considered RR, OR, and HR to be equivalent in our pooled estimates [31, 32]. Pooled RRs were estimated using a random-effects meta-analysis (DerSimonian and Laird). The heterogeneity of the included studies was assessed using the Q statistic (P < 0.05 indicating significant heterogeneity) and the I^2 index (values > 50% indicating substantial heterogeneity) [33, 34]. Publication bias was detected by funnel plots. To examine whether single studies had a disproportionately excessive influence, a leave-one-out sensitivity analysis was further conducted to evaluate the robustness of the pooled estimates.

Population attributable fractions and generalized impact fractions

PAFs were calculated to estimate the proportion of dementia cases attributable to the co-occurrence of depression and diabetes, using Levin's formula (formula 1):

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

where $\boldsymbol{p}$ represents the prevalence of comorbid depression and diabetes, and $\boldsymbol{RR}$ represents the pooled RR derived from the meta-analysis. The prevalence of comorbid depression and diabetes was calculated by multiplying the prevalence of diabetes in the general population (from the GBD 2021 database) and the prevalence ratio of depression in individuals with diabetes (from a large-scale meta-analysis, 0.18 [95%CI 0.12, 0.26] for males and 0.26 [95%CI 0.15, 0.37] for females) [22].

GIFs were calculated to simulate hypothetical reductions in dementia burden under graded reductions in the prevalence of depression and/or diabetes. The formula for GIF is:

$$\boldsymbol{GIF} = \frac{(\boldsymbol{p} - \boldsymbol{p\prime}) \times (\boldsymbol{RR} - 1)}{\boldsymbol{p} \times (\boldsymbol{RR} - 1) + 1} \tag{2}$$

where $\boldsymbol{p\prime}$ represents the counterfactual prevalence of comorbid depression and diabetes. When the prevalence is entirely mitigated, signified by $\boldsymbol{p\prime} = 0$, the GIF equals to PAF. A counterfactual scenario of a 30% reduction in the prevalence ratio of depression in individuals with diabetes or a 30% reduction in diabetes prevalence, aligned with the Sustainable Development Goals (SDGs) target for reducing non-communicable diseases, was simulated to estimate the corresponding reduction in dementia burden.

Attributable and reducible burden estimation

PAFs and GIFs from 1990 to 2016 were applied to estimate the attributable and reducible burden of dementia by sex, age, region, and year. A 5-year lag between depression and subsequent dementia among people living with diabetes was assumed for all calculations, therefore the time frame for attributable and reducible burden of dementia analysis was from 1995 to 2021. This 5-year lag was chosen to approximate the average follow-up years in the included cohort studies and is consistent with previous CRA studies in chronic disease [35]. Sensitivity analyses were also conducted, applying 10-year and 15-year lags (linking PAFs for 1990 to 2011 to DALYs in 2000 to 2021, and PAFs for 1990 to 2006 to DALYs in 2005 to 2021, respectively) to assess the robustness of our main findings.

Cross-country inequality analysis in attributable burden

The absolute and relative cross-country inequalities in the burden of dementia attributable to depression among individuals with diabetes were quantified by the slope index of inequality (SII) and concentration index, respectively. The SII quantified absolute inequality by regressing the national ASDR on an SDI-associated relative position scale, defined as the midpoint of the population range ranked by cumulative SDI [36]. A weighted linear regression model was used to account for heteroscedasticity. The concentration index was calculated by numerical integration under the Lorenz curve. This curve plots the cumulative proportion of ASDR against the cumulative relative distribution of the population ranked by SDI [36]. The SII and concentration index would equal zero when the health indicator is evenly distributed. A negative SII/concentration index represents a greater concentration of disease burden among lower SDI countries, while a positive value denotes a concentration in higher SDI countries. A greater absolute value of the SII/concentration index indicates a greater inequality.

The association between sex difference of attributable burden and gender inequality

To demonstrate the association between gender-related societal inequity and sex disparities in the burden of dementia attributable to depression among individuals with diabetes, we constructed locally estimated scatterplot smoothing (LOESS) regression to explore the association between the relative sex difference of ASDR in each nation and their corresponding GII in 1995 and 2021. The GII is a composite metric of gender inequality incorporating three dimensions: reproductive health, empowerment and the labour market [22]. A higher GII value indicates more disparities between females and males and the more loss to human development. A higher relative sex difference indicates that the attributable burden for females is relatively higher compared to males.

$$\boldsymbol{Relative\ sex\ difference = \frac{ASDR_{female}}{ASDR_{male}}}$$

Estimation of uncertainty

Employing a simulation-based approach and assuming independence between components, we generated 1,000 samples from log-normal distributions for RRs and beta distributions for prevalence rates to calculate the PAFs and GIFs and their corresponding 95%CIs [37]. Similarly, we generated 1,000 samples from the log-normal distribution of DALYs rates and ASDR to propagate the uncertainty of attributable and reducible burden.

All analyses and visualizations were conducted in R version 4.3.2 (https://www.r-project.org). All statistical tests were two-sided, and *P*-values < 0.05 were considered statistically significant.

Results

Systematic review and meta-analysis

The process of systematic review is illustrated in Fig. 1. A total of 11,539 records were initially identified in the literature search. After removing 3,948 duplicates, 7,591 titles and abstracts were screened, of which 7,529 were excluded. Of the remaining 62 articles retrieved for full-text review, six articles were included in the systematic review and meta-analysis. The full list and detailed characteristics of the included studies are provided in Tables S2-S3. All included studies were published between 2010 and 2021, with five scoring as high quality (Table S4).

The meta-analysis yielded a pooled RR of 1.93 (95%CI 1.90, 1.97) for the association between depression and subsequent dementia among individuals with diabetes (Figure S1). No evidence of publication bias was detected (Figure S2). Sensitivity analysis confirmed the robustness of the pooled estimate, with RRs ranging from 1.93 to 2.08 (Figure S3).

Population attributable fraction

Globally, the PAFs for dementia attributable to depression among individuals with diabetes increased from 1.58% (95%CI 1.10%, 2.17%) in 1990 to 2.63% (95%CI 1.81%, 3.61%) in 2016 (Table 1; Fig. 2). In 2016, PAFs varied by age, peaking at 75–79 years before declining slightly. For this age group, the PAF was 4.32% (95%CI 3.02%, 5.84%) overall, with females exhibiting higher PAFs than their male counterparts (4.49% [95%CI 2.55%, 6.96%] vs. 3.79% [95%CI 2.32%, 5.58%]) (Fig. 2 and Table S5).

Temporal trends indicated consistent increases in PAFs across all regions. Regional variations in PAFs across WHO regions and SDI regions are presented in Fig. 2, Figure S4 and Tables S6-S11. In 2016, the EMR had the highest PAF at 3.93% (95%CI 2.73%, 5.34%), while the AFR had the lowest PAF at 2.06% (95%CI 1.41%, 2.84%). Among SDI regions, the High SDI region had the highest PAF in 2016 at 2.93% (95%CI 2.04%, 3.98%), whereas the

Table 1 The global population attributable fraction from 1990 to 2016 and attributable burden from 1995 to 2021 of dementia attributable to depression among people living with diabetes

Year	**PAF (%, 95%CI)**				**ASDR (DALYs, per 100,000 population, 95%CI)**		
	Both	**Male**	**Female**	**Year**	**Both**	**Male**	**Female**
1990	1.58 (1.10, 2.17)	1.38 (0.84, 2.05)	1.68 (0.95, 2.63)	1995	22.88 (8.75, 50.05)	16.20 (5.46, 36.97)	26.96 (9.50, 61.88)
1991	1.61 (1.10, 2.23)	1.41 (0.86, 2.10)	1.72 (0.97, 2.69)	1996	23.32 (8.85, 50.92)	16.60 (5.59, 37.89)	27.62 (9.74, 63.35)
1992	1.65 (1.13, 2.29)	1.45 (0.88, 2.15)	1.77 (1.00, 2.77)	1997	23.85 (9.07, 52.04)	16.99 (5.73, 38.73)	28.37 (9.48, 63.56)
1993	1.69 (1.15, 2.34)	1.48 (0.90, 2.20)	1.81 (1.03, 2.83)	1998	24.38 (9.27, 53.18)	17.38 (5.86, 39.64)	29.03 (9.70, 65.02)
1994	1.72 (1.18, 2.38)	1.51 (0.92, 2.25)	1.85 (1.05, 2.89)	1999	24.86 (9.46, 54.20)	17.72 (5.98, 40.40)	29.64 (9.91, 66.37)
1995	1.75 (1.20, 2.42)	1.54 (0.94, 2.29)	1.88 (1.07, 2.94)	2000	25.26 (9.61, 55.08)	18.03 (6.09, 41.11)	30.13 (10.08, 67.44)
1996	1.79 (1.22, 2.47)	1.57 (0.96, 2.33)	1.92 (1.09, 3.00)	2001	25.69 (9.80, 55.91)	18.39 (6.22, 41.89)	30.68 (10.29, 68.57)
1997	1.83 (1.25, 2.53)	1.61 (0.98, 2.39)	1.96 (1.11, 3.07)	2002	26.35 (10.03, 57.49)	18.89 (6.37, 43.02)	31.50 (10.53, 71.14)
1998	1.88 (1.29, 2.60)	1.66 (1.01, 2.46)	2.01 (1.14, 3.15)	2003	27.06 (10.32, 58.94)	19.42 (6.55, 44.18)	32.31 (10.82, 72.86)
1999	1.93 (1.32, 2.66)	1.70 (1.04, 2.51)	2.06 (1.17, 3.22)	2004	27.69 (10.58, 60.28)	19.87 (6.73, 45.11)	33.03 (11.07, 74.45)
2000	1.97 (1.35, 2.71)	1.73 (1.06, 2.56)	2.10 (1.19, 3.28)	2005	28.26 (10.79, 61.61)	20.29 (6.85, 46.17)	33.66 (11.29, 75.85)
2001	2.00 (1.37, 2.75)	1.76 (1.07, 2.61)	2.13 (1.21, 3.33)	2006	28.64 (10.98, 62.25)	20.55 (6.95, 46.66)	34.10 (11.45, 76.79)
2002	2.04 (1.42, 2.79)	1.79 (1.09, 2.65)	2.17 (1.23, 3.38)	2007	29.19 (11.27, 63.47)	20.94 (7.06, 47.63)	34.60 (11.65, 77.80)
2003	2.08 (1.44, 2.83)	1.80 (1.09, 2.68)	2.20 (1.25, 3.44)	2008	29.66 (11.47, 64.44)	21.10 (7.11, 48.09)	35.13 (11.84, 78.95)
2004	2.11 (1.47, 2.88)	1.83 (1.11, 2.73)	2.22 (1.25, 3.47)	2009	30.10 (11.64, 65.40)	21.46 (7.23, 48.94)	35.24 (11.85, 78.70)
2005	2.15 (1.48, 2.95)	1.86 (1.13, 2.77)	2.25 (1.27, 3.52)	2010	30.58 (11.77, 66.38)	21.81 (7.33, 49.80)	35.74 (12.02, 80.37)
2006	2.18 (1.50, 2.99)	1.89 (1.15, 2.81)	2.28 (1.29, 3.57)	2011	31.03 (11.94, 67.36)	22.14 (7.46, 50.46)	36.24 (12.21, 81.40)
2007	2.22 (1.53, 3.04)	1.92 (1.17, 2.86)	2.32 (1.31, 3.62)	2012	31.53 (12.16, 68.33)	22.55 (7.62, 51.36)	36.79 (12.41, 82.61)
2008	2.26 (1.55, 3.10)	1.96 (1.19, 2.92)	2.34 (1.32, 3.66)	2013	32.12 (12.40, 69.53)	23.06 (7.80, 52.47)	37.06 (12.54, 82.62)
2009	2.30 (1.58, 3.16)	2.00 (1.21, 2.97)	2.37 (1.34, 3.72)	2014	32.79 (12.62, 71.16)	23.57 (8.00, 53.54)	37.78 (12.72, 84.37)
2010	2.34 (1.61, 3.21)	2.04 (1.24, 3.03)	2.42 (1.36, 3.78)	2015	33.43 (12.91, 72.35)	24.11 (8.15, 54.88)	38.43 (13.03, 85.57)
2011	2.39 (1.64, 3.27)	2.09 (1.27, 3.10)	2.46 (1.39, 3.85)	2016	34.09 (13.20, 73.63)	24.66 (8.39, 55.81)	39.23 (13.30, 87.92)
2012	2.44 (1.68, 3.35)	2.13 (1.30, 3.17)	2.51 (1.42, 3.93)	2017	34.89 (13.47, 75.55)	25.27 (8.56, 57.35)	40.12 (13.58, 89.98)
2013	2.50 (1.72, 3.42)	2.18 (1.33, 3.24)	2.57 (1.45, 4.02)	2018	35.68 (13.78, 77.29)	25.86 (8.76, 58.65)	41.01 (13.92, 91.82)
2014	2.55 (1.75, 3.49)	2.23 (1.36, 3.31)	2.62 (1.48, 4.10)	2019	36.39 (14.04, 78.88)	26.41 (8.96, 59.83)	41.84 (14.08, 94.08)
2015	2.59 (1.78, 3.55)	2.27 (1.38, 3.36)	2.66 (1.51, 4.17)	2020	36.94 (14.28, 79.92)	26.84 (9.11, 60.83)	42.44 (14.40, 95.05)
2016	2.63 (1.81, 3.61)	2.30 (1.40, 3.42)	2.71 (1.53, 4.24)	2021	38.08 (14.70, 82.51)	27.67 (9.34, 62.88)	43.75 (14.88, 97.87)

CI, confidence interval; PAF, population attributable fraction; ASDR, age-standardized disability-adjusted life year rate; DALYs, disability-adjusted life years

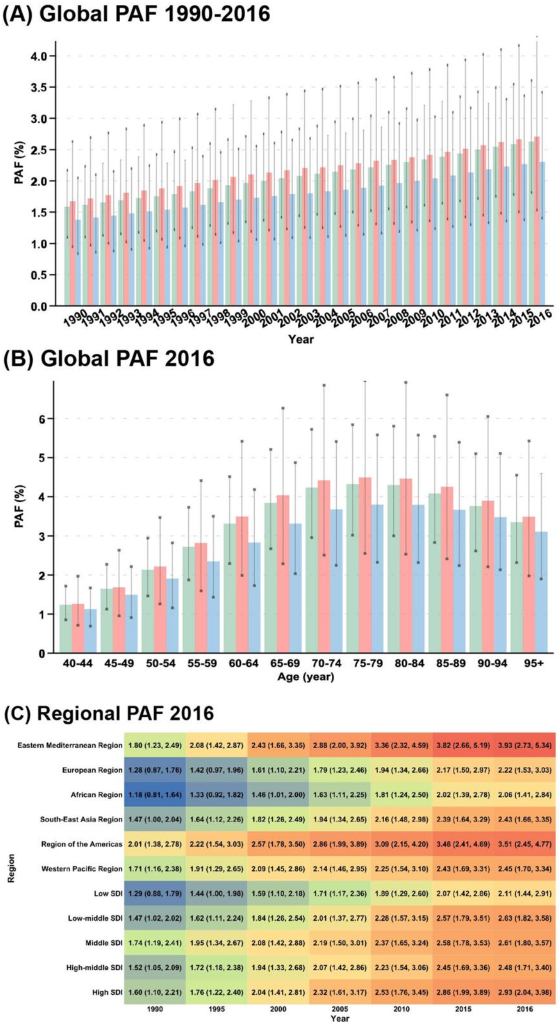
Low SDI region had the lowest at 2.11% (95%CI 1.44%, 2.91%).

At the national level, substantial variability in PAFs was observed (Figure S5, and Table S12-S18). Small island nations in the WPR reported the highest PAF in 2016, including the Marshall Islands, American Samoa, Cook Islands, Niue, and Tokelau.

Attributable burden of dementia attributable to depression among diabetes individuals

Correspondingly, the global ASDRs of dementia attributable to depression in individuals with diabetes increased from 22.88 (95%CI 8.75, 50.05) DALYs per 100,000 population in 1995 to 38.08 (95%CI 14.70, 82.51) DALYs per 100,000 population in 2021 (Table 1). This upward trend was consistent across both sexes, with a higher attributable burden consistently observed in females compared to males. Figure S6 illustrates the relative sex difference in the attributable burden and its association with the GII in 1995 and 2021. In countries with higher GII (greater gender inequality), the attributable burden among females was relatively greater compared to males. The attributable burden for dementia increased with advanced age, with the highest attributable burden observed among individuals aged 95 years and above. In this age group, the attributable burden in 2021 was 1422.18 (95%CI 507.99, 3227.52) DALYs per 100,000 population in the total population, with males at 1036.55 (95%CI 330.47, 2437.97) DALYs per 100,000 population and females at 1599.58 (95%CI 500.21, 3742.48) DALYs per 100,000 population (Fig. 3 and Table S19). Sensitivity analyses assuming 10-year and 15-year lags resulted in slightly smaller attributable burden compared with the main analysis assuming a 5-year lag period (Table S20-S23).

A disproportionately higher attributable burden was also observed in countries with higher SDI, as indicated by positive values of SII and concentration index. From 1995 to 2021, the SII increased slightly from 8.38 (95%CI 3.82, 12.95) in 1995 to 8.49 (95%CI 0.96, 16.02) in 2021, while the concentration index rose from 0.0913 (95%CI 0.0585, 0.1242) in 1995 to 0.1000 (95%CI 0.0657, 0.1342) in 2021 (Fig. 3 and Figure S7).



	1990	1995	2000	2005	2010	2015	2016
Eastern Mediterranean Region	1.80 (1.23, 2.49)	2.08 (1.42, 2.87)	2.43 (1.66, 3.35)	2.88 (2.00, 3.92)	3.36 (2.32, 4.59)	3.82 (2.66, 5.19)	3.93 (2.73, 5.34)
European Region	1.28 (0.87, 1.76)	1.42 (0.97, 1.96)	1.61 (1.10, 2.21)	1.79 (1.23, 2.46)	1.94 (1.34, 2.66)	2.17 (1.50, 2.97)	2.22 (1.53, 3.03)
African Region	1.18 (0.81, 1.64)	1.33 (0.92, 1.82)	1.46 (1.01, 2.00)	1.63 (1.11, 2.25)	1.81 (1.24, 2.50)	2.02 (1.39, 2.78)	2.06 (1.41, 2.84)
South-East Asia Region	1.47 (1.00, 2.04)	1.64 (1.12, 2.26)	1.82 (1.26, 2.49)	1.94 (1.34, 2.65)	2.16 (1.48, 2.98)	2.39 (1.64, 3.29)	2.43 (1.66, 3.35)
Region of the Americas	2.01 (1.38, 2.78)	2.22 (1.54, 3.03)	2.57 (1.78, 3.50)	2.86 (1.99, 3.89)	3.09 (2.15, 4.20)	3.46 (2.41, 4.69)	3.51 (2.45, 4.77)
Western Pacific Region	1.71 (1.16, 2.38)	1.91 (1.29, 2.65)	2.09 (1.45, 2.86)	2.14 (1.46, 2.95)	2.25 (1.54, 3.10)	2.43 (1.69, 3.31)	2.45 (1.70, 3.34)
Low SDI	1.29 (0.88, 1.79)	1.44 (1.00, 1.98)	1.59 (1.10, 2.18)	1.71 (1.17, 2.36)	1.89 (1.29, 2.60)	2.07 (1.42, 2.86)	2.11 (1.44, 2.91)
Low-middle SDI	1.47 (1.02, 2.02)	1.62 (1.11, 2.24)	1.84 (1.26, 2.54)	2.01 (1.37, 2.77)	2.28 (1.57, 3.15)	2.57 (1.79, 3.51)	2.63 (1.82, 3.58)
Middle SDI	1.74 (1.19, 2.41)	1.95 (1.34, 2.67)	2.08 (1.42, 2.88)	2.19 (1.50, 3.01)	2.37 (1.65, 3.24)	2.58 (1.78, 3.53)	2.61 (1.80, 3.57)
High-middle SDI	1.52 (1.05, 2.09)	1.72 (1.18, 2.38)	1.94 (1.33, 2.68)	2.07 (1.42, 2.86)	2.23 (1.54, 3.06)	2.45 (1.69, 3.36)	2.48 (1.71, 3.40)
High SDI	1.60 (1.10, 2.21)	1.76 (1.22, 2.40)	2.04 (1.41, 2.81)	2.32 (1.61, 3.17)	2.53 (1.76, 3.45)	2.86 (1.99, 3.89)	2.93 (2.04, 3.98)

Fig. 2 The population attributable fraction of dementia attributable to depression among people living with diabetes. Notes: (**A**) Global PAF from 1990 to 2016; (**B**) Global PAF by age groups in 2016; (**C**) Regional PAF in 2016. PAF, population attributable fraction

Regional variations in attributable burden of dementia across WHO regions and SDI regions are presented in Fig. 3, Figure S8 and Tables S24-S29. In all regions, attributable burden of dementia due to depression among individuals with diabetes increased over time. Across WHO regions, the EMR had the highest ASDR in 2021 at 54.95 (95%CI 20.87, 120.12) DALYs per 100,000 population, while the SEAR had the lowest at 26.14 (95%CI 9.57, 58.65) DALYs per 100,000 population. Across SDI regions, the attributable burden of dementia showed a distinct gradient, with higher SDI regions generally having higher attributable burden. In 2021, the High SDI region had the highest ASDR at 43.06 (95%CI 17.22, 91.02) DALYs per 100,000 population and the Low SDI region had the lowest attributable burden of 26.38 (95%CI 9.36, 60.17) DALYs per 100,000 population.

National estimates of attributable burden for 204 countries/territories are shown in Figure S9, and Table S30-S36. The Marshall Islands recorded the highest attributable burden in 2021, followed by Afghanistan, American Samoa, Bahrain, and Qatar.

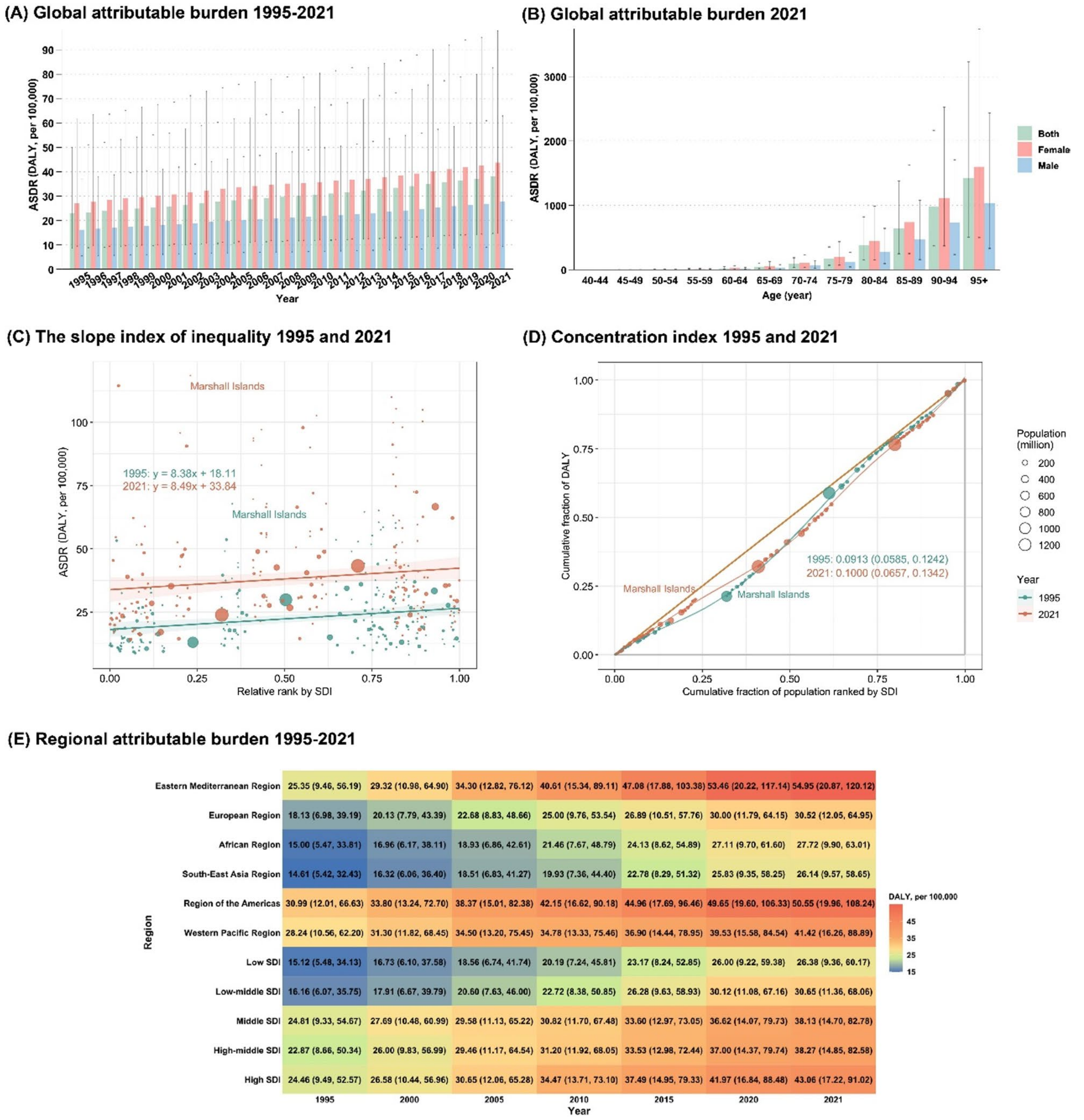
Generalized impact fraction and reducible burden of dementia attributable to depression among diabetes

The GIF and the corresponding reducible burden of dementia are displayed in Fig. 4 and Figure S10-S15. A 30% reduction in the prevalence of diabetes and a 30% reduction in the prevalence ratio of depression among diabetes individuals in 2016 would result in a global GIF of 0.24% (95%CI 0.16%, 0.33%). This reduction would correspond to a potential decrease in the dementia burden in 2021 by 3.41 (95%CI 1.31, 7.41) DALYs per 100,000 population.

Discussion

This study provides the first comprehensive global, regional, and national assessment of the burden of dementia attributable to depression among individuals with diabetes. By combining systematic review, meta-analysis, and burden estimation using the CRA framework, we highlight the significant and growing contribution of comorbid depression and diabetes to the global dementia burden over the past three decades (1995–2021). Our meta-analysis identified a significant association between depression and subsequent dementia in individuals with diabetes, with a pooled RR of 1.93 (95%CI 1.90, 1.97). Globally, the ASDR of dementia attributable to depression among individuals with diabetes increased from 22.88 to 38.08 per 100,000 population from 1995 to 2021. This trend was observed in both sexes, with the attributable burden escalating with advanced age. Notably, we found substantial geographical and socioeconomic variations in the attributable burden, with the highest attributable burden in the EMR, WPR, and High SDI regions. Our analysis also revealed gender-based disparities, with females consistently experiencing a higher attributable burden, especially in countries with greater gender inequality.

Our findings align with previous studies that suggest depression is a significant risk factor for developing dementia among individuals with diabetes. A systematic review and meta-analysis has shown that depression in individuals with diabetes increased dementia risk by 82%, which is consistent with studies in the United States and Denmark [38–41]. Additionally, Johnson et al. demonstrated that the comorbidity of depression and diabetes has a pronounced impact on dementia via inflammatory and metabolic pathways compared with those without this comorbidity [42]. These findings support that depression and diabetes probably share common biological

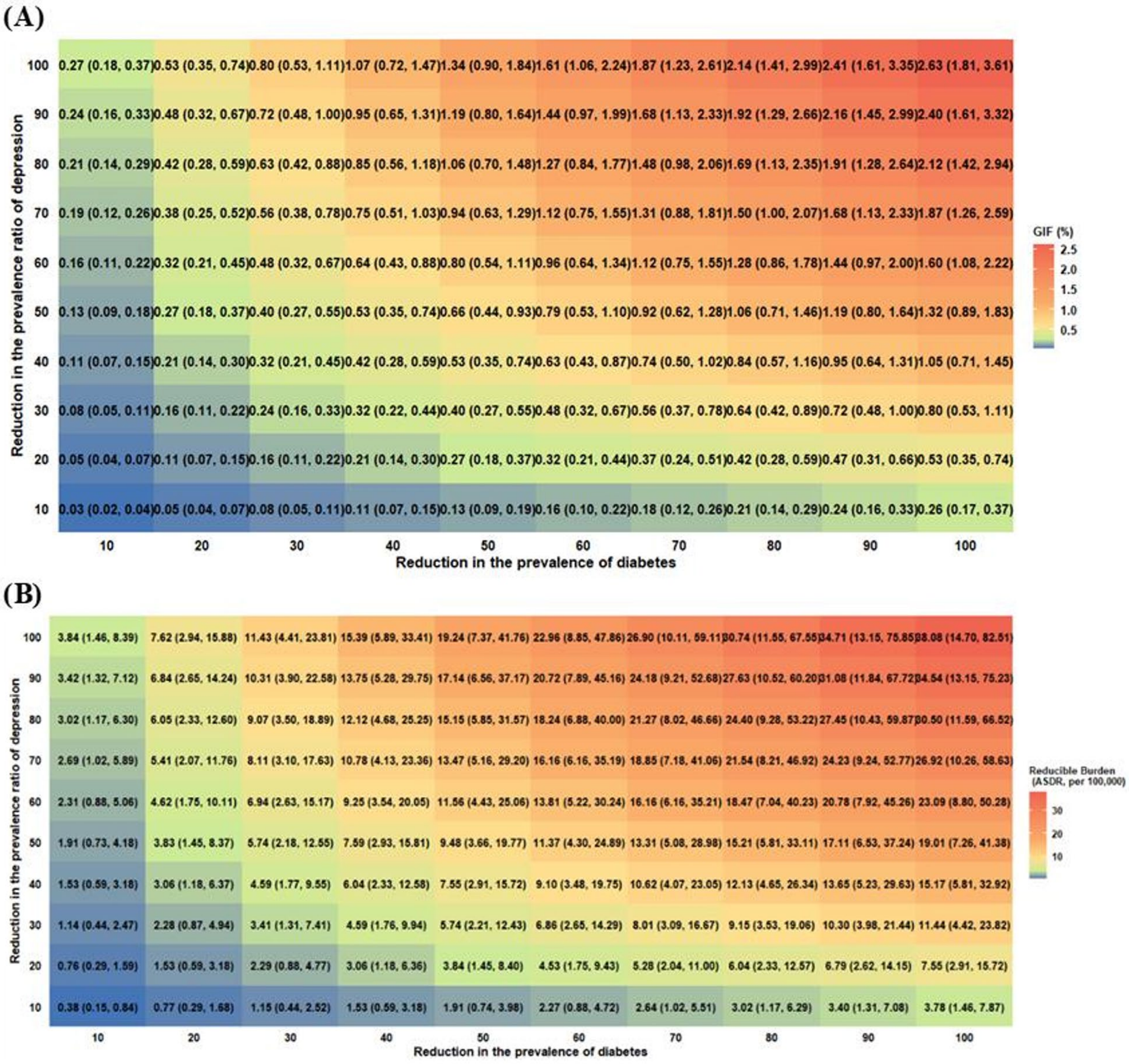


Region	1995	2000	2005	2010	2015	2020	2021
Eastern Mediterranean Region	25.35 (9.46, 56.19)	29.32 (10.98, 64.90)	34.30 (12.82, 76.12)	40.61 (15.34, 89.11)	47.08 (17.88, 103.38)	53.46 (20.22, 117.14)	54.95 (20.87, 120.12)
European Region	18.13 (6.98, 39.19)	20.13 (7.79, 43.39)	22.68 (8.83, 48.66)	25.00 (9.76, 53.54)	26.89 (10.51, 57.76)	30.00 (11.79, 64.15)	30.52 (12.05, 64.95)
African Region	15.00 (5.47, 33.81)	16.96 (6.17, 38.11)	18.93 (6.86, 42.61)	21.46 (7.67, 48.79)	24.13 (8.62, 54.89)	27.11 (9.70, 61.60)	27.72 (9.90, 63.01)
South-East Asia Region	14.61 (5.42, 32.43)	16.32 (6.06, 36.40)	18.51 (6.83, 41.27)	19.93 (7.36, 44.40)	22.78 (8.29, 51.32)	25.83 (9.35, 58.25)	26.14 (9.57, 58.65)
Region of the Americas	30.99 (12.01, 66.63)	33.80 (13.24, 72.70)	38.37 (15.01, 82.38)	42.15 (16.62, 90.18)	44.96 (17.69, 96.46)	49.65 (19.60, 106.33)	50.55 (19.96, 108.24)
Western Pacific Region	28.24 (10.56, 62.20)	31.30 (11.82, 68.45)	34.50 (13.20, 75.45)	34.78 (13.33, 75.46)	36.90 (14.44, 78.95)	39.53 (15.58, 84.54)	41.42 (16.26, 88.89)
Low SDI	15.12 (5.48, 34.13)	16.73 (6.10, 37.58)	18.56 (6.74, 41.74)	20.19 (7.24, 45.81)	23.17 (8.24, 52.85)	26.00 (9.22, 59.38)	26.38 (9.36, 60.17)
Low-middle SDI	16.16 (6.07, 35.75)	17.91 (6.67, 39.79)	20.60 (7.63, 46.00)	22.72 (8.38, 50.85)	26.28 (9.63, 58.93)	30.12 (11.08, 67.16)	30.65 (11.36, 68.06)
Middle SDI	24.81 (9.33, 54.67)	27.69 (10.48, 60.99)	29.58 (11.13, 65.22)	30.82 (11.70, 67.48)	33.60 (12.97, 73.05)	36.62 (14.07, 79.73)	38.13 (14.70, 82.78)
High-middle SDI	22.87 (8.66, 50.34)	26.00 (9.83, 56.99)	29.46 (11.17, 64.54)	31.20 (11.92, 68.05)	33.53 (12.98, 72.44)	37.00 (14.37, 79.74)	38.27 (14.85, 82.58)
High SDI	24.46 (9.49, 52.57)	26.58 (10.44, 56.96)	30.65 (12.06, 65.28)	34.47 (13.71, 73.10)	37.49 (14.95, 79.33)	41.97 (16.84, 88.48)	43.06 (17.22, 91.02)

Fig. 3 The attributable burden of dementia due to depression among people living with diabetes. Notes: (**A**) Global attributable burden from 1995 to 2021; (**B**) Global attributable burden by age groups in 2021; (**C**) the slope of inequality in 1995 and 2021; (**D**) concentration index in 1995 and 2021; (**E**) Regional attributable burden in 2021. PAF, population attributable fraction; ASDR, age-standardized disability-adjusted life year rate; DALY, disability-adjusted life year; SDI, socio-demographic index

mechanisms, particularly in the context of insulin resistance, which has been implicated in Alzheimer disease (AD) [43]. Depression and diabetes are both associated with decreased insulin sensitivity, a key contributor to cognitive decline [44, 45]. Moreover, individuals with both diabetes and depression are more likely to present additional cardiovascular risk factors such as obesity and a sedentary lifestyle, which may together exacerbate macrovascular complications and cerebrovascular events, further increasing dementia risk, including AD and vascular dementia [40, 46, 47].

At the global level, both the PAFs and ASDRs of dementia attributable to depression among individuals with diabetes nearly doubled over the past three



(A)

Reduction in the prevalence ratio of depression	10	20	30	40	50	60	70	80	90	100
100	0.27 (0.18, 0.37)	0.53 (0.35, 0.74)	0.80 (0.53, 1.11)	1.07 (0.72, 1.47)	1.34 (0.90, 1.84)	1.61 (1.06, 2.24)	1.87 (1.23, 2.61)	2.14 (1.41, 2.99)	2.41 (1.61, 3.35)	2.63 (1.81, 3.61)
90	0.24 (0.16, 0.33)	0.48 (0.32, 0.67)	0.72 (0.48, 1.00)	0.95 (0.65, 1.31)	1.19 (0.80, 1.64)	1.44 (0.97, 1.99)	1.68 (1.13, 2.33)	1.92 (1.29, 2.66)	2.16 (1.45, 2.99)	2.40 (1.61, 3.32)
80	0.21 (0.14, 0.29)	0.42 (0.28, 0.59)	0.63 (0.42, 0.88)	0.85 (0.56, 1.18)	1.06 (0.70, 1.48)	1.27 (0.84, 1.77)	1.48 (0.98, 2.06)	1.69 (1.13, 2.35)	1.91 (1.28, 2.64)	2.12 (1.42, 2.94)
70	0.19 (0.12, 0.26)	0.38 (0.25, 0.52)	0.56 (0.38, 0.78)	0.75 (0.51, 1.03)	0.94 (0.63, 1.29)	1.12 (0.75, 1.55)	1.31 (0.88, 1.81)	1.50 (1.00, 2.07)	1.68 (1.13, 2.33)	1.87 (1.26, 2.59)
60	0.16 (0.11, 0.22)	0.32 (0.21, 0.45)	0.48 (0.32, 0.67)	0.64 (0.43, 0.88)	0.80 (0.54, 1.11)	0.96 (0.64, 1.34)	1.12 (0.75, 1.55)	1.28 (0.86, 1.78)	1.44 (0.97, 2.00)	1.60 (1.08, 2.22)
50	0.13 (0.09, 0.18)	0.27 (0.18, 0.37)	0.40 (0.27, 0.55)	0.53 (0.35, 0.74)	0.66 (0.44, 0.93)	0.79 (0.53, 1.10)	0.92 (0.62, 1.28)	1.06 (0.71, 1.46)	1.19 (0.80, 1.64)	1.32 (0.89, 1.83)
40	0.11 (0.07, 0.15)	0.21 (0.14, 0.30)	0.32 (0.21, 0.45)	0.42 (0.28, 0.59)	0.53 (0.35, 0.74)	0.63 (0.43, 0.87)	0.74 (0.50, 1.02)	0.84 (0.57, 1.16)	0.95 (0.64, 1.31)	1.05 (0.71, 1.45)
30	0.08 (0.05, 0.11)	0.16 (0.11, 0.22)	0.24 (0.16, 0.33)	0.32 (0.22, 0.44)	0.40 (0.27, 0.55)	0.48 (0.32, 0.67)	0.56 (0.37, 0.78)	0.64 (0.42, 0.89)	0.72 (0.48, 1.00)	0.80 (0.53, 1.11)
20	0.05 (0.04, 0.07)	0.11 (0.07, 0.15)	0.16 (0.11, 0.22)	0.21 (0.14, 0.30)	0.27 (0.18, 0.37)	0.32 (0.21, 0.44)	0.37 (0.24, 0.51)	0.42 (0.28, 0.59)	0.47 (0.31, 0.66)	0.53 (0.35, 0.74)
10	0.03 (0.02, 0.04)	0.05 (0.04, 0.07)	0.08 (0.05, 0.11)	0.11 (0.07, 0.15)	0.13 (0.09, 0.19)	0.16 (0.10, 0.22)	0.18 (0.12, 0.26)	0.21 (0.14, 0.29)	0.24 (0.16, 0.33)	0.26 (0.17, 0.37)

(B)

Reduction in the prevalence ratio of depression	10	20	30	40	50	60	70	80	90	100
100	3.84 (1.46, 8.39)	7.62 (2.94, 15.88)	11.43 (4.41, 23.81)	15.39 (5.89, 33.41)	19.24 (7.37, 41.76)	22.96 (8.85, 47.86)	26.90 (10.11, 59.11)	30.74 (11.55, 67.55)	34.71 (13.15, 75.85)	38.08 (14.70, 82.51)
90	3.42 (1.32, 7.12)	6.84 (2.65, 14.24)	10.31 (3.90, 22.58)	13.75 (5.28, 29.75)	17.14 (6.56, 37.17)	20.72 (7.89, 45.16)	24.18 (9.21, 52.68)	27.63 (10.52, 60.20)	31.08 (11.84, 67.72)	34.54 (13.15, 75.23)
80	3.02 (1.17, 6.30)	6.05 (2.33, 12.60)	9.07 (3.50, 18.89)	12.12 (4.68, 25.25)	15.15 (5.85, 31.57)	18.24 (6.88, 40.00)	21.27 (8.02, 46.66)	24.40 (9.28, 53.22)	27.45 (10.43, 59.87)	30.50 (11.59, 66.52)
70	2.69 (1.02, 5.89)	5.41 (2.07, 11.76)	8.11 (3.10, 17.63)	10.78 (4.13, 23.36)	13.47 (5.16, 29.20)	16.16 (6.16, 35.19)	18.85 (7.18, 41.06)	21.54 (8.21, 46.92)	24.23 (9.24, 52.77)	26.92 (10.26, 58.63)
60	2.31 (0.88, 5.06)	4.62 (1.75, 10.11)	6.94 (2.63, 15.17)	9.25 (3.54, 20.05)	11.56 (4.43, 25.06)	13.81 (5.22, 30.24)	16.16 (6.16, 35.21)	18.47 (7.04, 40.23)	20.78 (7.92, 45.26)	23.09 (8.80, 50.28)
50	1.91 (0.73, 4.18)	3.83 (1.45, 8.37)	5.74 (2.18, 12.55)	7.59 (2.93, 15.81)	9.48 (3.66, 19.77)	11.37 (4.30, 24.89)	13.31 (5.08, 28.98)	15.21 (5.81, 33.11)	17.11 (6.53, 37.24)	19.01 (7.26, 41.38)
40	1.53 (0.59, 3.18)	3.06 (1.18, 6.37)	4.59 (1.77, 9.55)	6.04 (2.33, 12.58)	7.55 (2.91, 15.72)	9.10 (3.48, 19.75)	10.62 (4.07, 23.05)	12.13 (4.65, 26.34)	13.65 (5.23, 29.63)	15.17 (5.81, 32.92)
30	1.14 (0.44, 2.47)	2.28 (0.87, 4.94)	3.41 (1.31, 7.41)	4.59 (1.76, 9.94)	5.74 (2.21, 12.43)	6.86 (2.65, 14.29)	8.01 (3.09, 16.67)	9.15 (3.53, 19.06)	10.30 (3.98, 21.44)	11.44 (4.42, 23.82)
20	0.76 (0.29, 1.59)	1.53 (0.59, 3.18)	2.29 (0.88, 4.77)	3.06 (1.18, 6.36)	3.84 (1.45, 8.40)	4.53 (1.75, 9.43)	5.28 (2.04, 11.00)	6.04 (2.33, 12.57)	6.79 (2.62, 14.15)	7.55 (2.91, 15.72)
10	0.38 (0.15, 0.84)	0.77 (0.29, 1.68)	1.15 (0.44, 2.52)	1.53 (0.59, 3.18)	1.91 (0.74, 3.98)	2.27 (0.88, 4.72)	2.64 (1.02, 5.51)	3.02 (1.17, 6.29)	3.40 (1.31, 7.08)	3.78 (1.46, 7.87)

Fig. 4 The global generalized impact fraction in 2016 and reducible burden in 2021 of dementia attributable to depression among people living with diabetes. Notes: (**A**) generalized impact fraction; (**B**) reducible burden. GIF, generalized impact fraction; ASDR, age-standardized disability-adjusted life year rate

decades. The increase in ASDRs indicates that, even after accounting for population aging and demographic change, the relative dementia burden associated with comorbid depression and diabetes has also increased over time. While the proportion of depression-attributable dementia among individuals with diabetes peaked at 75–79 years and declined slightly thereafter, the attributable burden increased consistently with advanced age. This decline in PAFs may be due to competing risks and mortality from other age-related conditions, such as cardiovascular diseases or cancers, which dilute the relative contribution of depression to dementia risk in older individuals [48, 49]. Similar to our findings, Katon et al. reported that more dementia cases could be accounted for by the interaction between depression and diabetes among individuals under age 65 relative to their older counterparts [39]. Given this age-specific pattern, early interventions targeting depression and diabetes in middle-aged populations could substantially mitigate the risk and progression of dementia. This highlights the importance of identifying and managing these modifiable risk factors during the critical window of midlife to prevent or delay cognitive decline in later life.

Females consistently experienced a higher attributable burden compared to males, a disparity likely influenced by both biological factors and societal factors.

For biological factors, hormonal influences on dementia risk may predispose women to a higher burden of cognitive decline, particularly post-menopause [50]. Besides, although diabetes prevalence is comparable between sexes, depression is more common among females than among males, suggesting that females have a greater likelihood of comorbid depression and diabetes [20, 21]. In addition, societal factors, such as gender inequities in healthcare access and treatment, could exacerbate this difference in burden [50]. Moreover, females generally have higher ASDRs of dementia and longer life expectancy than males, resulting in a greater attributable burden among females. Multiple interrelated mechanisms, including the effects of sex steroid hormones on brain aging, and sex-related differences in brain structure and function, contribute to the higher dementia-related DALY burden observed in females [51]. Our analysis of the GII also revealed that countries with higher gender disparities tend to have a greater relative burden of dementia among females at the ecological level, underscoring the complex interplay between gender, health, and social inequities. To address gender inequities in both high- and low-income settings, equitable healthcare policies and targeted interventions will be critical to reducing the dementia burden, particularly among females.

Across WHO regions, both the highest PAF and attributable burden were observed in the EMR region, likely driven by the relatively high prevalence of depression and the population aging trend and limited healthcare resources in many countries of EMR region [52, 53]. As for the national level, however, the great majority of the top five countries with the highest PAF and attributable burden are located in the WPR region. This is probably because in recent decades, the prevalence of diabetes among both sexes has shown an ongoing growing trend in almost all countries in the WPR region, which may be ascribed to multiple factors such as physical inactivity, poor dietary habits, and increasing prevalence of obesity [54, 55]. Due to rapid urbanization and social pressures, the WPR region also faces growing mental health challenges while access to appropriate mental health care may be limited [55, 56]. Moreover, as the process of population aging accelerates, there is an urgent demand for targeted health and social care that meets the needs of individuals with comorbid diabetes and depression in this region, as well as preventing them from developing dementia [57].

Higher SDI regions were associated with greater dementia burdens attributable to depression among individuals with diabetes. Significant cross-country inequalities in the attributable burden of dementia were also revealed, with higher SDI countries reporting higher attributable burdens in both 1995 and 2021. This gradient likely reflected differences in the prevalence of depression and diabetes, healthcare access, and diagnostic capacities across countries. Significant increases in the disease burden of depression among high SDI regions from 1990 to 2021 were observed, which could be attributable to the higher competitiveness and social stress in regions with higher level of economic development [58, 59]. Besides, mental health issues might be less stigmatized in regions with higher SDI, where the individuals could be more prone to seek diagnosis and treatment [60]. On the other hand, higher SDI regions were found to have higher life expectancy in most cases, because of their better healthcare condition, social welfare, and standard of living, leading to higher risks and disease burden of dementia among individuals as they live longer [61]. Conversely, underdiagnosis and underreporting of depression, diabetes and dementia in low-SDI settings may result in an underestimation of the true burden in these regions.

An important finding of our study is the potential for substantial reductions in the burden of dementia through preventative strategies targeting depression and diabetes. For instance, a hypothetical 30% reduction in both the prevalence of diabetes and the prevalence ratio of depression among individuals with diabetes, in line with SDGs, could reduce global dementia ASDRs by 3.41 per 100,000 population, corresponding to a global GIF of 0.24% in 2021. Evidence from previous studies suggests that integrated management of depression and diabetes, combined with lifestyle modifications such as improved diet and physical activity, could reduce the incidence of dementia by as much as 21% [17]. Collaborative care models in primary care, which deliver stepped antidepressant management and brief psychotherapy, have achieved substantially higher depression response and remission rates among older adults and patients with comorbid depression and chronic illness compared with usual care [62, 63]. Moreover, small clinical studies have demonstrated that controlling both glycemia and depression can reverse cognitive decline, highlighting the potential for early intervention to mitigate dementia risk [64]. Public health initiatives should prioritize early screening and integrated care for individuals with comorbid depression and diabetes. Effective management of these conditions, alongside broader efforts to address systemic inequities in healthcare access and gender disparities, may provide significant opportunities to reduce the global dementia burden.

To our knowledge, this is the first study to comprehensively evaluate the global burden of dementia attributable to depression among individuals with diabetes from 1995 to 2021. By utilizing a range of data sources, including the GBD study, we were able to generate comprehensive burden estimates, examine temporal trends and regional disparities, and estimated the potential impact of preventative strategies aligned with the SDGs. However, some limitations of the study also warrant consideration. First, cohort studies that assessed the association between depression and subsequent dementia among diabetes individuals were limited. Due to the limited and heterogeneous reporting of stratified estimates, we were unable to derive robust sex-, age-, or region-specific pooled RRs. As a result, the global, regional, and national estimations of PAFs were based on a single pooled RR that was generalized to all ages, sexes, and countries. Also, because we lacked age-, country- and time-specific prevalence ratio of depression among people with diabetes, we assumed that the proportion of individuals with diabetes who have depression is similar across age groups, regions, and years. This assumption may not fully capture geographic and temporal variation in the comorbidity of depression and diabetes. As more geographically diverse cohort data become available, future research could derive stratified RRs and prevalence ratios to further refine these estimates. Second, underreporting and underdiagnosis of depression and dementia, particularly in low- and middle-income countries, may have led to an underestimation of the attributable burden. Third, while our study highlights the burden attributable to depression among individuals with diabetes, it does not imply causal relationships, which cannot be definitively established through observational data alone. As such, our findings should be interpreted with caution. Fourth, although we included cohort studies and imposed a 5-year lag between depression and dementia, late-life depression may still partly reflect prodromal dementia. Fifth, the analysis linking the GII to sex differences in attributable dementia burden is based on country-level ecological associations without adjustment for potential confounding factors. Therefore, the observed correlation between higher GII and relatively greater female burden should not be interpreted as evidence of a causal effect of gender inequality. Finally, our 30% reduction scenario was optimistic, illustrating the potential upper bound of impact under ambitious intervention scale-up. Future studies should examine more conservative, policy-informed scenarios.

Our study provides valuable insights into the burden of dementia attributable to depression among individuals with diabetes, and carries important policy implications. By offering comprehensive global, regional, and national assessment of the attributable burden and incorporating metrics of inequality (i.e., GII, SII, and concentration index), our research underscores the need for targeted public health interventions. Understanding its geographical and socioeconomic variability can help optimize resource allocation and tailor region-specific strategies for the prevention and management of dementia. Furthermore, as mental health rises on the global health agenda, understanding the impact of comorbid depression is crucial for shaping effective public health responses and policy decisions. These findings can assist policymakers and healthcare providers in designing interventions to reduce the global, regional and national burden of dementia attributable to depression among individuals with diabetes.

Conclusion

This study provided a comprehensive assessment of the global dementia burden attributable to depression among individuals living with diabetes, highlighting significant regional disparities and upward trends over the past three decades. Achieving reductions in the prevalence of depression and diabetes could meaningfully decrease the global dementia burden. Public health strategies should prioritize early screening, integrated care models, and effective management of depression and diabetes, to mitigate the risk of dementia and promote healthy aging worldwide.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-026-02167-3.

Supplementary Material 1

Supplementary Material 2

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Author contributions

PS designed the study. SS collected and analyzed the data. SS and JW prepared the first draft. SS and JW revised the manuscript with comments from JZ, CZ, CX, JZ, JY, YZ, SH, PS and IR. All authors interpreted results, commented on drafts of the paper and approved the final version. The corresponding author attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data availability

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

Declarations

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.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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