# Population attributable fractions of a wide range of peripheral diseases for the burden of dementia


## Authors

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## Abstract

Growing evidence suggests that peripheral diseases serve as risk factors for dementia, but the population-level burden of dementia associated with various peripheral diseases remained unknown. By conducting systematic review and Bayesian meta-analyses to estimate the relative risks of 26 peripheral diseases across nine systems with dementia, including 202 articles searched from the PubMed until 06 September 2024, 16 peripheral diseases were identified as associated with increased risk of dementia. With the relative risks estimated from meta-analyses, prevalences extracted from the Global Burden of Disease Study, and communalities among these 16 peripheral diseases derived from the UK Biobank, we analyzed the population attributable fractions (PAF) of these 16 peripheral diseases for dementia, stratified by sex, age, socio-demographic index levels, world regions and countries, and trends from 1990 to 2021. Globally, these peripheral diseases collectively were related to a combined PAF of 33.18% (95% CI 16.80–48.43) of dementia burden, corresponding to 18.8 million prevalent cases. The leading ten PAF contributors were periodontal diseases (6.10% [0.95–10.28]), cirrhosis and other chronic liver diseases (5.51% [1.77–8.86]), age-related and other hearing loss (4.70% [3.51–6.06]), blindness and vision loss (4.30% [3.43–5.05]), and type 2 diabetes mellitus (3.80% [3.06–4.53]), chronic kidney disease (2.74% [1.53–4.02]), osteoarthritis (2.26% [0.41–4.12]), stroke (1.01% [0.86–1.17]), ischemic heart disease (0.97% [0.69–1.29]), and chronic obstructive pulmonary disease (0.92% [0.34–1.54]). This study revealed that a series of peripheral diseases were associated with increased risk of dementia and collectively were related to about one-third of global dementia burden, highlighting the need for targeted public health strategies.

## Main text

Dementia, a multifactorial cognitive disorder, is the leading cause of death and disability among older people globally,[1] and is recognized as a major global health challenge according to the World Health Organization.[2] It is estimated that over 55 million individuals worldwide are living with dementia, and this number is forecasted to triple by 2050, imposing an increasingly heavy burden on families and the wider society.[3] Despite the emergence of disease modifying treatments, there still is an urgent need for proactive management of risk factors to prevent dementia.[4] Systematically investigating the risk factors and their contributions to the burden of dementia is essential for developing global health strategies.[5]

Population attributable fraction (PAF) is an epidemiologic metric widely used to assess the fraction of disease cases attributed to a specific exposure, assuming the cases that would not have occurred if the exposure was eliminated.[6] Previous studies have used PAF to estimate the proportion of dementia cases related to various risk factors.[7] Recently, the Lancet Commission report was updated to summarize that about 45% of global dementia cases could be related to 14 modifiable risk factors, encompassing lifestyle factors, social factors, environmental exposures, and common age-related chronic diseases.[4] Nevertheless, beyond these well-established risk factors, emerging population-based studies revealed that many other modifiable conditions may be substantially associated with the onset of dementia.[8, 9, 10, 11, 12]

From biological mechanism studies and population-based epidemiological studies, a substantial body of evidence has shown that peripheral organs dysfunction or systemic diseases (hereinafter referred to as peripheral diseases) contribute to brain damage[13] and are associated with increased risk of dementia,[8, 9, 10, 11, 12] such as cardiovascular disease,[14, 15] impaired lung

function,[16, 17] liver cirrhosis,[18, 19] chronic kidney disease,[20] periodontal disease,[21, 22, 23, 24] and so on. The potential mechanisms may include metabolic disorders, systemic inflammation, immune dysregulation, diminished waste clearance capacity, and microbiome alterations.[13] These findings collectively suggest that the development of dementia involves systemic factors throughout the body. However, there still is a lack of comprehensive assessment of the collective and individual PAF of various peripheral diseases for dementia at the population level, and a systematic review and meta-analysis is required to estimate the relative risks (RRs) of peripheral diseases with dementia, which are necessary for PAF calculation. Considering the association of peripheral diseases on dementia, we propose that peripheral diseases might contribute substantially to the burden of dementia in the population and targeting those influential conditions might offer an opportunity to mitigate dementia burden.

Over the past decades, significant changes in lifestyle, ecological environment, and socioeconomic development have led to distinct shifts in the spectrum of diseases.[25] Moreover, the global burden of dementia, as well as its risk factors, exhibits age-related patterns, sex differences, and geographical heterogeneity.[3, 25] It may be anticipated that the PAF of peripheral diseases for dementia would increase in aging populations due to chronic disease accumulation. The PAF related to increasingly prevalent risk factors, such as diabetes,[26] would rise over time. Geographically, low-middle income regions may suffer higher PAF related to vision loss,[27] but lower PAF related to diabetes than developed regions,[26] owing to healthcare resource and lifestyle factors disparities. Hence, it is necessary to assess the age, sex, and region-specific PAF of various peripheral diseases to dementia as well as the temporal trends to inform the public health strategies and healthcare resource allocation tailored to local populations.

Hereupon, this study aimed to assess the global, regional, and national PAF of a wide range of peripheral diseases for dementia, across sex, age groups, socioeconomic development levels, and world regions and countries, as well as the temporal trends, to provide epidemiological evidence for devising precise public health strategies to mitigate the burden of dementia and improve global cognitive health.

## Results

### Global burden of dementia

Globally, in 2021, the estimated all age prevalence rate of dementia was 0.72% (95% uncertainty interval [UI] 0.63–0.82), with approximately 56.9 million cases (49.4–65.0). Female had a higher dementia prevalence than male (prevalence rate, 0.92% [0.80–1.05] vs 0.52% [0.45–0.60]; cases number, 36.1 million [31.5–41.1] vs 20.8 million [17.8–23.8]). From 1990 to 2021, the prevalence rate and cases of dementia rose by 76.3% (73.1–79.7) and 160.8% (156.1–165.9), respectively, with a greater percentage increase in male than female (prevalence rate, 83.9% [79.5–87.6] vs 71.9% [68.9–75.4] increase; cases number, 171.1% [164.7–176.6] vs 155.3% [150.8–160.4] increase) (Figure 1 A–B, Supplementary Table 1). Dementia prevalence rate increased with age, rising from 295.8 (209.1–399.1) per 100,000 people in 50–54 age group to 13,002.2 (10,368.1–16,184.7) per 100,000 people in 80–84 age group with an approximately doubling trend every five years from age 50 to 80, after which the increase rate slowed, while the prevalent cases number reached a peak within the 80–84 age group (Figure 1 C–D, Supplementary Table 1). There were geographical disparities in the prevalence of dementia worldwide. The prevalence rate of dementia increased with SDI levels (Figure 1 E–

F), reaching up to 2.22% (1.91–2.53) in High-income Asia Pacific and down to 0.12% (0.10–0.13) in Western Sub-Saharan Africa. The detailed spatial distribution of the prevalence of dementia across Global Burden of Disease Study (GBD) regions and countries is shown in Supplementary Figure 1, Supplementary Data 1. Globally, in 2021, dementia resulted in 36.3 million DALYs (17.2–76.9), yielding a DALY rate of 460.4 (218.4–974.1) per 100,000 (Supplementary Table 1). The patterns of DALYs due to dementia across age, SDI levels, and over time paralleled those of dementia prevalence (Supplementary Figures 2-3).

**Systematic review and Bayesian meta-analyses for the association of peripheral diseases with dementia**

Based on the "non-communicable diseases" category in GBD, we initially included 26 common peripheral diseases across nine systems that had been reported to be associated with higher dementia risk in the literature,[8, 9, 10, 11, 12] including audiovisual disorders (blindness and vision loss, age-related and other hearing loss), digestive diseases (cirrhosis and other chronic liver diseases, peptic ulcer disease, gastritis and duodenitis, pancreatitis, appendicitis, gallbladder and biliary diseases, and inguinal, femoral, and abdominal hernia), oral disorders (periodontal diseases, edentulism, and caries of permanent teeth), metabolic and endocrine system diseases (type 2 diabetes mellitus [T2DM]), chronic kidney disease (CKD), cardiovascular diseases (stroke, ischemic heart disease, atrial fibrillation and flutter, and lower extremity peripheral arterial disease), osteoarthritis, chronic obstructive pulmonary disease (COPD), and immune-mediated inflammatory diseases (multiple sclerosis, inflammatory bowel disease, psoriasis, atopic dermatitis, asthma, and rheumatoid arthritis).[28] The definition and ICD codes for each included peripheral disease are described in Supplementary Table 2.

147 Systematic review and Bayesian meta-analyses were performed to estimate the pooled
148 RRs of these 26 peripheral diseases with dementia for population-level PAF estimation. The
149 systematic literature search for studies assessing the association between peripheral diseases
150 and dementia was performed in PubMed up to 06 September 2024, and 202 articles meeting
151 the eligibility criteria (as described in Methods) were included (Figure 2), with 1 to 24 articles
152 for each disease (Supplementary Table 3 and Figures 4-29). Details of the characteristics and
153 quality assessment of the included studies were described in the Supplementary Data 2.
154 Bayesian meta-analysis approach was used for pooled RRs estimation for each peripheral
155 disease. Diseases with only one supporting article were excluded from analysis, including
156 peptic ulcer disease, gastritis and duodenitis, gallbladder and biliary diseases, and hernia. A
157 total of 16 peripheral diseases with significant pooled RR (lower limit of 95% confidence
158 interval [CI] >1) were identified as associated with increased risk of dementia (Figure 3), which
159 were further supported by Bayes factors ($BF_{10}$) > 1 (Supplementary Figure 30), and then
160 underwent following PAF analysis, including blindness and vision loss, age-related and other
161 hearing loss, cirrhosis and other chronic liver diseases, periodontal diseases, T2DM, CKD,
162 stroke, ischemic heart disease, atrial fibrillation and flutter, osteoarthritis, COPD, multiple
163 sclerosis, inflammatory bowel disease, atopic dermatitis, asthma, and rheumatoid arthritis. The
164 heterogeneity ($\tau$) of these associations ranged from ‘low’ to ‘moderate’ (Supplementary Table
165 4). Sensitivity analyses using different prior distributions in the Bayesian meta-analysis model
166 yielded consistent results (Supplementary Table 5).
167 The certainty of evidence for these associations was assessed with the Grading of
168 Recommendations, Assessment, Development and Evaluations (GRADE) framework. The

evidence was rated as moderate for 6 diseases (periodontal diseases, atrial fibrillation and flutter, stroke, osteoarthritis, COPD, and rheumatoid arthritis), low for 12 diseases (blindness and vision loss, age-related and other hearing loss, cirrhosis and other chronic liver diseases, edentulism, T2DM, CKD, ischemic heart disease, atopic dermatitis, multiple sclerosis, psoriasis, inflammatory bowel disease, and asthma), and very low for 4 diseases (pancreatitis, appendicitis, caries of permanent teeth, and lower extremity peripheral arterial disease) (Supplementary Table 4).

**PAF calculation for dementia related to peripheral diseases**

To allow the estimation of each peripheral disease's unique PAF and their collective PAF for dementia, the communality among the 16 peripheral diseases, which reflects the variance in observed variables explained by common factors, was calculated based on the UK Biobank study sample. Individual-level data from 502,441 participants who were followed up until 30 June 2021 was used to capture the cases of each included peripheral disease. The ICD codes (aligned with the definition of GBD) and the data fields used to identify peripheral diseases in the UK Biobank are described in Supplementary Table 2 and Table 6. Our communality analysis found five principal components, explaining 51% of the total variance among the included 16 peripheral diseases, indicating a substantial overlap in the prevalence of these peripheral diseases, which was then accounted for in our weighted PAF estimates. After adjusting the communality between these 16 peripheral diseases, the overall weighted PAF related to all these 16 peripheral diseases for dementia amounted to 33.18% (95% CI 16.80–48.43) globally in 2021 (Figure 3).

These peripheral diseases were categorized into 9 classes according to the major organ or

system involved. For the 9 classes of peripheral disease, the weighted PAFs ranged from 0.64% (95% CI 0.10–1.20) for immune-mediated inflammatory diseases to 9.00% (6.93–11.11) for audiovisual disorders. The top ten individual diseases were periodontal diseases (6.10% [0.95–10.28]), cirrhosis and other chronic liver diseases (5.51% [1.77–8.86]), age-related and other hearing loss (4.70% [3.51–6.06]), blindness and vision loss (4.30% [3.43–5.05]), T2DM (3.80% [3.06–4.53]), CKD (2.74% [1.53–4.02]), osteoarthritis (2.26% [0.41–4.12]), stroke (1.01% [0.86–1.17]), ischemic heart disease (0.97% [0.69–1.29]), and COPD (0.92% [0.34–1.54]) (Figure 3).

**Trends of overall PAF for dementia related to peripheral diseases**

Globally, from 1990 to 2021, the overall PAF for dementia related to peripheral diseases increased slightly from 30.00% (95% CI 14.26–45.02) to 33.18% (16.80–48.43), with a percentage change rate of 10.58%. Consistent with the largely increased prevalence rate and case numbers of dementia over the past decades, the global overall related prevalence rate for dementia increased from 0.12% (0.058–0.18) in 1990 to 0.24% (0.12–0.35) in 2021, with a percentage change of 94.9%, while the related case numbers increased from 6.5 million (3.1–9.8) in 1990 to 18.8 million (9.5–27.5) in 2021, with a percentage change of 188.42% (Figure 4 A–C, Supplementary Table 7).

With increasing age, both the overall PAF and the related prevalence rates of dementia increased. The overall PAF increased from 20.85% (95% CI 8.97–32.94) in 40–44 age group to 49.99% (29.41–66.54) in 95+ age group, with no obvious difference between female and male. The overall related prevalence rate increased from 0.003% (0.001–0.005) in 40–44 age group to 16.09% (9.46–21.42) in 95+ age group while the overall related cases number peaked

in the 80–84 age group. Female had higher overall related prevalence rate and more overall related cases than male (Figure 4 D–F, Supplementary Table 7).

Among five SDI levels regions, the overall PAF was relatively stable, ranging from 30.68% (95% CI 15.13–45.35) in low SDI regions to 34.12% (17.53–49.4) in middle SDI region. Consistent with the increased prevalence rate of dementia with advanced SDI levels, the overall related prevalence rate of dementia was largest in high SDI regions (0.496% [0.244, 0.737]) and lowest in low SDI regions (0.051% [0.025–0.075]). The overall related case number was substantially higher in regions of middle to high SDI levels than in regions with lower SDI levels, peaking in middle SDI regions (5.73 million [2.94–8.29]) and lowest in low SDI (0.56 million [0.28–0.84]). (Figure 4 G–I, Supplementary Table 7).

At the regional level, South Asia recorded the highest overall PAF at 35.39% (95% CI 18.22–50.76), while Eastern Sub-Saharan Africa had the lowest at 27.98% (13.24–42.24). Nationally, American Samoa in Oceania had the highest PAF at 38.52% (21.12–53.83), and Madagascar in Eastern Sub-Saharan Africa had the lowest at 24.57% (12.77–36.96) (Supplementary Figure 31, Supplementary Data 1). The overall related dementia prevalence rate was highest in the High-income Asia Pacific region (0.70% [0.35–1.03]), especially in Japan (0.84% [0.42–1.25]), and was lowest in Western Sub-Saharan Africa region (0.033% [0.016–0.050]), but at national levels, Somalia in Eastern Sub-Saharan Africa had the lowest overall related dementia prevalence rate (0.023% [0.011–0.035]). The overall related case numbers were highest in East Asia (6.1 million [3.2–8.8]), mainly contributed by China (5.9 million [3.1–8.6]) (Supplementary Figure 31, Supplementary Data 1).

**Trends of PAF for dementia related to 9 classes of peripheral diseases**

Globally, from 1990 to 2021, consistent with the change of prevalence rate of these peripheral diseases, the PAF related to T2DM exhibited a continuously upward trend from 2.05% (95% CI 1.64–2.49) in 1990 to 3.80% (3.06–4.53) in 2021 with a percentage change of 85.1%, followed by audiovisual disorders (percentage change 15.43%), osteoarthritis (percentage change 12.32%), cirrhosis and other chronic liver diseases (percentage change 10.52%), COPD (percentage change 6.01%), while the PAF related to immune-mediated inflammatory diseases showed a decreasing trend (percentage change −45.41%). Except for immune-mediated inflammatory diseases, the prevalence rate and case numbers of dementia related to the other 8 classes of peripheral diseases had consistently increased since 1990 (Figure 5 A–C, Supplementary Table 7, Figure 32-33).

In 2021, compared to male, female had higher PAF related to osteoarthritis (2.66% [95% CI 0.49–4.79] vs 1.84% [0.33–3.39], female to male ratio 1.45), immune-mediated inflammatory diseases (0.73% [0.12–1.36] vs 0.55% [0.09–1.03], ratio 1.33), and CKD (2.89% [1.61–4.22] vs 2.58% [1.43–3.80], ratio 1.12), but had lower PAF related to cardiovascular diseases (1.98% [1.54–2.47] vs 2.45% [1.89–3.08], ratio 0.81) and T2DM (3.64% [2.93–4.34] vs 3.97% [3.19–4.73], ratio 0.92) (Supplementary Table 7, Figure 32-33).

With increasing age, the PAF related to audiovisual disorders, cardiovascular disease, CKD, osteoarthritis, COPD, and immune-mediated inflammatory disease steadily incremented. In contrast, the PAF related to cirrhosis and other chronic liver diseases, periodontal diseases, and T2DM showed an initial increase followed by a subsequent decline, with peaks in about 75-79, 50-59, and 75-79 age groups respectively. These trends were generally similar between

female and male. The prevalence rate related to each class of peripheral diseases increased with age and the related cases numbers peaked in the 80–84 age group, in alignment with the epidemic pattern of dementia, with audiovisual disorders, cirrhosis and other chronic liver diseases, cardiovascular diseases, CKD, and T2DM emerging as the leading contributors in the 80–84 age group. (Figure 5 D–F, Supplementary Table 7, Figure 34-35).

The distribution of PAFs exhibited distinct patterns among different SDI regions. Generally, compared to lower SDI regions, high SDI regions had lower PAF related to audiovisual disorders, cirrhosis and other chronic liver diseases, and periodontal diseases, but manifested higher PAF related to T2DM, CKD, osteoarthritis, COPD, and immune-mediated inflammatory diseases. Variations across high-middle, middle, and low-middle SDI regions were relatively small. Specifically, high-middle SDI regions showed highest PAF of cardiovascular diseases, middle SDI regions showed highest PAF of audiovisual diseases and cirrhosis and other chronic liver diseases, low-middle SDI regions showed highest PAF of periodontal diseases. There also was distinct magnitude of sex disparities among different SDI regions, with the greatest discrepancy of PAF related to T2DM and cirrhosis and other chronic liver diseases (male higher to female) and immune-mediated inflammatory disease (female higher to male) observed in high SDI regions and COPD in low-middle SDI regions (female higher to male) (Figure 5 G–I, Supplementary Table 7, Figure 36-37). The detailed distribution across the world of the PAFs related to each class of peripheral diseases is shown in Supplementary Figure 38-46 and Supplementary Data 1.

**Specific trends of PAF for dementia related to 16 individual peripheral diseases**

From 1990 to 2021, the rankings of PAF for dementia related to 16 individual peripheral

diseases were relatively stable, while T2DM moved up from the sixth to the fifth, ischemic heart disease rose from the tenth to the ninth, and COPD climbed from the eleventh to the tenth. Specifically, the PAF of T2DM showed a substantial increase (percentage change 85.1%). Conversely, the PAF of asthma (percentage change −50.5%) sharply decreased. Although the PAF of most immune-mediated inflammatory diseases decreased, rheumatoid arthritis showed an upward trend (percentage change 15.5%). The PAF of cirrhosis and other chronic liver diseases increased by percentage change 10.5% (Figure 6).

The overall PAF increased from 15.8% (6.97–25.67) in people aged under 70 years to 45.18% (25.65–61.70) in people aged above 70 years. There also was a marked shift in PAF rankings for dementia between these two age groups. In people under 70 years, cirrhosis and other chronic liver diseases ranked highest, while in those aged above 70 years, age-related and other hearing loss emerged as the predominant contributor. Among the top five contributors, age-related and other hearing loss, cirrhosis and other chronic liver diseases, T2DM, and blindness and vision loss remained stably involved across both age groups. Periodontal diseases ranked the second in people under 70 and CKD ranked the fourth in people above 70. The PAFs for most diseases increased markedly with age, particularly for atrial fibrillation and atrial flutter (people aged above 70 to people aged under 70 ratio 18.96), COPD (ratio 10.56), and ischemic heart disease (ratio 9.76) (Supplementary Figure 47).

Compared to male, female had higher ranks of the PAF related to blindness and vision loss, stroke, and COPD, and lower ranks of age-related and other hearing loss and ischemic heart disease. Consistent with the sex disparities for the 9 classes of diseases mentioned above, all immune-mediated inflammatory diseases showed higher PAFs in female, especially rheumatoid

arthritis (female to male ratio 2.47). Conversely, all cardiovascular diseases showed higher PAFs in male, especially ischemic heart disease (ratio 0.72) (Supplementary Figure 48).

Among different SDI regions, a notable shift in the disease rankings was observed between high SDI regions and other regions. Compared to other SDI regions, high SDI region had higher ranks of the PAF related to T2DM, CKD, osteoarthritis, COPD, and asthma, but had lower ranks of cirrhosis and other chronic liver diseases, blindness and vision loss, and ischemic heart disease. The detailed ranks of the PAF related to 16 individual peripheral diseases in different SDI regions were shown in Supplementary Figure 49.

## Discussion

### Principal findings

In summary, our study investigated the burden of dementia related to a wide range of peripheral diseases, providing PAF estimates across sex, age, and socioeconomic development levels, as well as the temporal trends, on the global, regional, and national scales. We hereby proposed seven principal findings: 1) By conducting systematic review and Bayesian meta-analyses, 16 peripheral diseases were identified as associated with increased risk of dementia. 2) Globally, in 2021, these 16 peripheral diseases collectively were related to a combined PAF of 33.18% (95% CI 16.80–48.43) of the burden of dementia, corresponding to 18.8 (9.5–27.5) million dementia prevalent cases. 3) The leading ten peripheral diseases as ranked by PAF were periodontal diseases (6.10% [0.95–10.28]), cirrhosis and other chronic liver diseases (5.51% [1.77–8.86]), age-related and other hearing loss (4.70% [3.51–6.06]), blindness and vision loss (4.30% [3.43–5.05]), T2DM (3.80% [3.06–4.53]), CKD (2.74% [1.53–4.02]), osteoarthritis

(2.26% [0.41–4.12]), stroke (1.01% [0.86–1.17]), ischemic heart disease (0.97% [0.69–1.29]), and COPD (0.92% [0.34–1.54]). 4) The overall PAF increased slightly from 30.00% (14.26, 45.02) in 1990 to 33.18% (16.8, 48.43) in 2021. Notably, the PAF of T2DM had increased substantially by 85.1%. 5) With age increasing, the overall PAF escalated from 20.85% (8.97–32.94) in 40–44 age group to 49.99% (29.41–66.54) in 95+ age group, with great disparities in the PAF composition between older population aged over 70 years and population aged < 70 years. 6) Although the overall PAF estimates and trends were generally similar across sex, compared with male, female suffered higher PAF of osteoarthritis, immune-mediated inflammatory diseases, and CKD, but lower PAF of T2DM and cardiovascular diseases. 7) Generally, low SDI regions had higher PAF of audiovisual disorders, cirrhosis and other chronic liver diseases, and periodontal diseases, while high SDI regions manifested higher PAF of T2DM, CKD, osteoarthritis, COPD, and immune-mediated inflammatory diseases. Overall, these insights illustrate the multidimensional burden of dementia related to a wide range of peripheral diseases at the population level, highlighting the potential role of peripheral organ function in brain health and the possibility to target those influential peripheral diseases to mitigate the growing dementia burden.

In the situation of the rapidly increasing burden of dementia, brain health promotion has become a worldwide priority. While current disease modifying treatments still face significant challenges such as limited efficacy, frequent adverse events, low population generalizability, and substantial resource requirements,[29] it is essential to identify and manage risk factors for dementia prevention from a public health perspective. The Lancet Commission report 2024 recently summarized that 14 modifiable risk factors may account for about 45% of global

dementia cases, including lifestyle factors, social factors, environmental exposures, and several age-related chronic diseases.[4] However, merely identifying these risk factors is not sufficient. Over the years, a number of biological mechanism studies and population-based epidemiological studies have shown that peripheral organs dysfunction or systemic diseases contribute to brain damage[13] and are associated with increased risk of dementia,[8, 9, 10, 11, 12] suggesting that the development of dementia involves systemic factors throughout the body.[13] Accordingly, our study extends the estimates from the Lancet Commission report by quantifying the population-level association of a wide range of peripheral diseases with the burden of dementia by PAF calculation, providing a scope for assessing the burden of dementia related to peripheral diseases and highlighting the role of peripheral organ function in brain health. Our study, along with the Lancet Commission report, together provides information for developing public health strategy for dementia prevention. In addition, through meta-analyses, we updated the RRs of various peripheral diseases in 9 systems for dementia, supporting the concept that the development of dementia involves systemic factors throughout the body and various peripheral diseases serve as risk factors for dementia.[13] Through PAF analysis, we further depicted the population-level association of these conditions with the burden of dementia. Notably, we assessed the longitudinal trends of PAF from 1990 to 2021, as well as the discrepancies across sex, age, socioeconomic levels, world regions and countries, revealing the multidimensional inequities among populations. Our study offered epidemiological insights to inform the formulation of public health policies tailored to local contexts.

**Interpretation**

Peripheral organ dysfunction has been identified to disrupt brain homeostasis through pathways

365 including metabolic disorders, systemic inflammation, immune dysregulation, diminished
366 waste clearance capacity, and microbiome alterations.[13] Audiovisual deficiency could reduce
367 cognitive reserve by breaking brain structural and functional connectivity, as well as social
368 isolation due to impaired communication abilities.[30, 31, 32] Reduced hepatic capacity to clear
369 neurotoxic compounds, including amyloid-β, the hallmark of Alzheimer's disease, accelerates
370 the development of dementia.[19] Periodontal diseases contribute to neuroinflammation and
371 cognitive impairment via bacteremia.[21, 22, 23, 24] Beyond shared vascular risk factors, cardiac
372 pathology is linked to brain microstructural damage via cerebral hypoperfusion and ischemic
373 injury.[14, 15] CKD damages brain by vascular injury, cumulative uremic neurotoxins, and reduced
374 kidney neurotrophins.[20] Osteoarthritis is an age-related chronic inflammatory condition and
375 recent studies showed that the crosstalk of bone-brain mediated by bone-derived proteins,
376 extracellular vesicles, and bone marrow-derived cells, accelerates Aβ deposition and neuronal
377 degeneration.[33, 34] COPD could result in neuronal dysfunction through chronic hypoxemia.[16]
378 Furthermore, alterations in the gut or lung microbiome also play a role in dementia development
379 through microbial translocation, systemic immunity, abnormal metabolites.[18, 35] Collectively,
380 the intricate interplay between multiple peripheral organs and the brain highlights the vital need
381 to maintain whole-body health for brain health, especially in light of the aging populations and
382 rising dementia burden globally.

383 Over the past decades, with the changes in lifestyle, ecological environment, and
384 socioeconomic development, the global disease landscape has undergone a substantial shift
385 from communicable diseases to non-communicable chronic diseases.[25] Owing to the growing
386 prevalence of most peripheral diseases, the overall PAF of peripheral diseases for dementia had

increased from 1990 to 2021. Remarkably, the global prevalence of T2DM surged by 96.9%, with a corresponding 85.1% increase in its PAF for dementia, underscoring the urgent need for effective measures to reverse this trend.

There were also great disparities in the PAF for dementia across age, sex, and SDI levels, due to variations in the prevalence of peripheral diseases. Aging is accompanied by the function decline of multiple physiological systems and frailty, which increases the vulnerability to multiple diseases and mortality.[36] Moreover, older people often suffer from multimorbidity, which is linked to more severe brain pathological changes and worse health outcomes, potentially contributing to a higher overall PAF in older people.[10, 37, 38]

Sex-specific prevalence disparities indicate distinct disease susceptibilities between female and male, arising from both biological factors and social determinants. Female is more susceptible to immune-mediated inflammatory diseases, a phenomenon influenced by sex hormones and a higher copy number of X-linked immune genes due to escape from X chromosome silencing.[39, 40] Subchondral bone loss and increased susceptibility due to postmenopausal estrogen decline result in higher risk of osteoarthritis in female.[41] Female is also more likely to develop CKD, not only because of complications during pregnancy, urinary tract infections, and systemic autoimmune diseases, but also due to the disparities in healthcare access, insufficient health awareness, and constraints on self-care by motherhood and domestic responsibilities, which delay the timely treatment for health conditions.[42, 43] Conversely, male exhibit higher prevalences of T2DM and cardiovascular diseases, potentially due to the lack of estrogen's protective effects and engagement in unhealthy behaviors such as smoking and drinking, especially in stressful occupations, which increase the susceptibility to vascular and

metabolic disorders in male.[44, 45, 46]

In developed regions, the prevalence of diabetes is higher, primarily due to risk factors including high BMI, preference for high-calorie foods, and sedentary lifestyles.[47] Environmental factors significantly impact immune tolerance. Rural environment has been reported as a protective factor against allergies and autoimmune diseases, whereas urban industrial agents increase these risks, contributing to higher prevalence in high SDI regions.[48, 49, 50] Osteoarthritis is more prevalent in high SDI regions potentially due to population aging, obesity, and physically demanding occupations that exacerbate joint deterioration.[51, 52] COPD is more prevalent in high SDI regions potentially because of widespread smoking and air pollution.[53] Moreover, electronic cigarettes are emerging as a significant risk factor beyond traditional tobacco.[54] CKD prevalence is also higher in high SDI regions, mainly owing to population aging and the widespread prevalence of diabetes and hypertension as key risk factors.[55] In low- and middle-income countries (LMICs), social inequality significantly exacerbates the burden of vision and hearing loss. Cataracts and uncorrected refractive errors are major causes of blindness worldwide. Limited accessibility and affordability to ophthalmic care, including surgery and glasses, contributes to the high prevalence of vision impairment in LMICs.[27, 32, 56] Simultaneously, occupational noise exposure, infections like otitis media, and limited healthcare access to hearing aids worsen the burden of auditory impairment in these regions.[57, 58] This inequality is also evident in dental issues such as periodontal disease due to insufficient dental care and inadequate hygiene practices in LMICs.[59, 60] Furthermore, LMICs bear higher burden of cirrhosis and other chronic liver conditions, particularly hepatitis B and C infections because of limited access to preventive vaccination and therapies.[61, 62]

Currently, global efforts in identifying and managing risk factors for dementia prevention are insufficient to counter the rising burden of dementia. Given the close interconnection between the brain and peripheral health, preserving peripheral organ health may be crucial for brain health. Since most peripheral diseases are preventable, addressing these diseases may present a feasible strategy that not only benefits the health of peripheral organs directly but also may be associated with improved brain health, which may contribute to improving overall human well-being. Our analysis suggests that peripheral diseases are substantially associated with the global burden of dementia, emphasizing the possibility for augmenting health investment in strategies that prioritize the management of these key conditions to mitigate the rising burden of dementia. For instance, periodontal disease prevention can consider implementing universal oral health education and dental health examinations and management for high-risk groups (e.g., adults >50 years, diabetics, and smokers), which aligns with existing initiatives like the Global Periodontal Health Project.[63] Liver cirrhosis prevention can call for expanding HBV vaccination programs as outlined in the World Health Organization's 2030 goal to eliminate viral hepatitis as a public health threat, and promoting public education on the harms caused by alcohol consumption.[64, 65] These interventions are feasible by building on established programs (e.g., Global Periodontal Health Project, World Health Organization 2030 hepatitis goals), cost-effective through low-cost vaccines preventing expensive-to-treat diseases and early education reducing long-term costs, and scalable via existing systems like schools/clinics for rapid high-risk-area rollout. Moreover, public health policies should also be more proactive to mitigate diseases with rapidly increasing trends, particularly diabetes, to address emerging health challenges effectively and forethoughtfully. Furthermore, in light of

the disparities between diverse populations across age, sex, and socioeconomic status, it is necessary to formulate more precise health policies and optimize healthcare resource allocation based on the specific impacts of peripheral diseases in specific regions and populations. Since PAF only indicates the theoretical maximum for reducing dementia burden, future studies should model realistic disease-controlling scenarios (e.g., 10-30% reductions via targeted interventions) to better inform achievable public health goals. In addition, as the interaction and combination of multiple diseases can significantly impact the risk of dementia,[10, 12] future research is needed to investigate the contribution of multimorbidity to the population burden of dementia. In summary, maintaining peripheral organs health may be an important component of global policies for brain health promotion and dementia prevention.

**Strengths and limitations**

Our research is distinguished by several advantages. Firstly, prevalence estimates were derived from the GBD 2021 dataset, which is recognized for its rigorous methodology and comprehensive global health data, enabling the multidimensional analyses across sex, age, SDI levels, world regions and countries, and the longitudinal trajectory. Secondly, our meta-analysis provides up-to-date RRs estimates of a wide range of peripheral diseases for dementia, supporting the substantial association of multiple organs dysfunction with the development of dementia. Thirdly, we obtained the communalities among these diseases from the UK Biobank study sample, which provides individual-level health data for over 500,000 community-dwelling participants. By incorporating communality weights in the PAFs calculation, we accounted for the interdependencies among risk factors, allowing calculating each peripheral disease's unique PAF and their combined PAF for dementia and avoiding overestimating the

combined PAF.

Our study also has limitations. Firstly, the selection of peripheral diseases always has a degree of subjectivity. While we primarily focused on common peripheral diseases in the "non-communicable diseases" category in GBD, the limited disease range covered by GBD also restricted the inclusion of other potential peripheral diseases in our analysis. Secondly, there is potential measurement bias of disease prevalence due to sparse and poor-quality data in specific regions.[25] The lack of dementia subtypes also limits our ability to assess PAF of specific subtypes, but assessment for all-cause dementia still is reasonable and helpful given the clinical overlap and most mutual risk factors of dementia. Thirdly, the UK Biobank participants were predominantly of European descent and there could be healthy volunteer bias, which may limit the generalizability to global population. However, the extensive sample size and abundant health data still enable the capacity to identify risk factors and their interconnection. Fourthly, in the meta-analysis part of this study, publication bias cannot be ignored, especially for risk factors based on limited evidence. Due to insufficient data sources, we did not consider the heterogeneity of RRs in sub-populations by sex, ethnicity, and world regions, the timing of risk factor exposure across life stages, and the changes in the strength of the association between risk factors and dementia over time. However, the primary objective of our meta-analysis was to derive pooled RRs for population-level PAF estimation. Fifthly, the calculation of PAF assumes a causal relationship.[6] However, the RRs derived from observational studies could be susceptible to confounding bias, potentially skewing our causal judgments and analysis results, and reverse causality was possible. Further studies are needed to confirm the causal effects between peripheral disease interventions and dementia prevention. Another common limitation

is the neglect of time delays between risk factor exposure and the onset of outcome in the PAF analysis.[66] Finally, our result could be underestimated when applying commonality weight to calculate combined PAF based on Levin's formula.[67] The PAF assumes the theoretical maximum reduction of dementia if the risk factor was completely eliminated, which may be practically infeasible.

## Conclusion

In summary, this study revealed that about one-third of global dementia burden is related to a series of peripheral diseases, underscoring the role of peripheral diseases in the development of dementia. Our findings indicated the potential to mitigate dementia incidence by proactive prevention of peripheral diseases and provided epidemiological insights to inform global and local health policies aimed at reducing the burden of dementia.

## Methods

### The Global Burden of Disease Study 2021

The Global Burden of Disease Study (GBD) 2021 assesses the health loss caused by 371 diseases and injuries across 204 countries and territories, along with the metrics for counts and rates of prevalence, incidence, mortality, and disability-adjusted life-years (DALYs), stratified by age groups, sex, and socio-demographic index (SDI) levels, over time spanning 1990 to 2021 (https://vizhub.healthdata.org/gbd-results). The methods for generating disease burden have been elaborated on the GBD website (https://ghdx.healthdata.org/gbd-2021).[25, 68] SDI is a composite indicator that reflects the socio-economic development level of a region, calculated by the geometric mean of the lag-distributed income per capita, average years of education, and the fertility rate among female under 25 years. A higher SDI indicates a more developed state. All countries and territories were categorized into low, low-middle, middle, high-middle, and high SDI quintiles.[68]

For the present study, we obtained the estimates of prevalence and DALYs for diseases of interest from the GBD 2021. The 95% uncertainty intervals (UIs) were calculated by taking 500 samples from the posterior distribution in the modeling process, with the 2.5th and 97.5th percentile values as the bounds.

### Dementia definition

Dementia definition in this study referred to the term ‘Alzheimer's disease and other dementias’ in GBD 2021. It is a progressive, degenerative, and chronic neurological disorder typified by memory impairment and other neurological dysfunctions, defined based on the Diagnostic and

Statistical Manual of Mental Disorders (DSM) III, IV, or V, or the International Classification of Diseases (ICD) 9th or 10th criteria.[69] The ICD codes for dementia are described in the Supplementary Table 2. The GBD gives no incidence of dementia before age 40, given its extreme rarity under this age.

**Peripheral diseases inclusion**

Based on the "non-communicable diseases" category in GBD, we initially selected 26 common peripheral diseases across 9 systems that had been reported to be associated with higher dementia risk in the literature,[8, 9, 10, 11, 12] including audiovisual disorders (blindness and vision loss, age-related and other hearing loss), digestive diseases (cirrhosis and other chronic liver diseases, peptic ulcer disease, gastritis and duodenitis, pancreatitis, appendicitis, gallbladder and biliary diseases, and inguinal, femoral, and abdominal hernia), oral disorders (periodontal diseases, edentulism, and caries of permanent teeth), metabolic and endocrine system diseases (type 2 diabetes mellitus [T2DM]), chronic kidney disease (CKD), cardiovascular diseases (stroke, ischemic heart disease, atrial fibrillation and flutter, and lower extremity peripheral arterial disease), osteoarthritis, chronic obstructive pulmonary disease (COPD), and immune-mediated inflammatory diseases (multiple sclerosis, inflammatory bowel disease, psoriasis, atopic dermatitis, asthma, and rheumatoid arthritis).[28] The definition and ICD codes for each included peripheral disease are described in Supplementary Table 2.

**Bayesian meta-analysis for relative risks estimation**

We conducted a systematic review of articles assessing the risk of dementia associated with each included peripheral disease in the PubMed, up to September 06, 2024. The detailed search

strategy and flowcharts were described in Supplementary Table 3 and Figure 4-29, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[70] guidelines (Supplementary Table 8). The certainty of evidence for all associations was evaluated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework[71] (Supplementary Table 4). This systematic review was conducted in accordance with the protocol pre-registered on PROSPERO (CRD42024578910) under the title 'A systematic review of the risks of a series of peripheral diseases for dementia'. All revisions of the protocol were provided in Supplementary Table 9.

Briefly, we included original articles or systematic reviews that meet the following criteria: 1) examined the association between peripheral disease of interest and dementia (all-cause dementia, Alzheimer's disease, vascular dementia, or unspecified dementia); 2) utilized study designs of cross-sectional, case-control, or cohort, and reported relative risks (RRs), hazard ratios (HRs), or odds ratios (ORs) for dementia. The exclusion criteria were: 1) unclear definitions of dementia or peripheral diseases; 2) study samples not representative of the general population; 3) the confidence intervals (CI) for the effect measures were not obtainable.

The search strategy was built with three combining concepts in the [Title/Abstract] field in PubMed: (1) exposure, (2) outcome, and (3) effect value. The detailed search items for each peripheral disease were as follows: (1) Exposure (each specific peripheral disease): Blindness and vision loss: vision loss OR vision impair* OR visual loss OR visual impair* OR blindness OR eye disease* OR glaucoma OR cataract OR retinopathy OR macular degener*; Age-related and other hearing loss: hear* loss OR hear* impairment; Inguinal, femoral, and abdominal hernia: hernia; Gallbladder and biliary diseases: Gallbladder OR biliary; Cirrhosis and other

chronic liver diseases: Cirrhosis OR liver* OR hepatic*; Gastritis and duodenitis: gastritis OR duodenitis OR enteritis; Peptic ulcer disease: (peptic OR digestive OR gastri* OR duoden*) AND ulcer; Pancreatitis: Pancreatitis; Appendicitis: Appendicitis; Periodontal diseases: periodontal OR periodontitis OR gingivitis OR gingival OR oral OR teeth OR tooth; Edentulism: tooth loss OR teeth loss OR edentulism; Caries of permanent teeth: decay* OR Caries; Type 2 diabetes mellitus: T2DM OR diabetes; Chronic kidney disease: kidney OR nephro* OR "CKD" OR nephritic OR renal; Ischemic heart disease: ischemic heart OR ischaemic heart OR coronary heart OR coronary artery OR myocardial infarct* OR angina; Atrial fibrillation and flutter: atrial fibrillation OR atrial flutter; Stroke: stroke OR post-stroke; Lower extremity peripheral arterial disease: Peripheral arterial disease; Osteoarthritis: Osteoarthritis; Chronic obstructive pulmonary disease: COPD OR "Chronic obstructive pulmonary disease"; Rheumatoid arthritis: Rheumatoid arthritis; Atopic dermatitis: dermatitis OR eczema; Inflammatory bowel disease: "inflammatory bowel" OR "Crohn's" OR "ulcerative colitis"; Asthma: asthma; Multiple sclerosis: Multiple sclerosis; Psoriasis: Psoriasis. (2) Outcome: dementia OR Alzheimer's disease OR cognition OR cognitive. (3) Effect value: hazard ratio* OR "HR" OR "HRs" OR odd ratio* OR odds ratio* OR "OR" OR "ORs" OR Risk ratio* OR relative risk* OR "RR" OR "RRs". (Supplementary Table 3 and Figures 4-29)

Two authors (YY and ZD) independently screened articles and extracted study characteristics. Any discrepancies were resolved through discussion. In cases where multiple studies reported the same exposure and outcome from the same data source, only one study was selected, prioritizing the one with the larger sample size or better data applicability. The quality of articles was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS) for

cohort and case-control studies, and the Joanna Briggs Institute (JBI) scale for cross-sectional studies.[72, 73]

Our systematic review identified a total of 202 articles, with 1 to 24 articles for each disease, including audiovisual disorders (blindness and vision loss,[74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97] age-related and other hearing loss[84, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114]), digestive diseases (cirrhosis and other chronic liver diseases,[115, 116, 117, 118, 119, 120, 121, 122, 123, 124] peptic ulcer disease,[125] gastritis and duodenitis,[125] pancreatitis,[125, 126] appendicitis,[125, 127, 128] gallbladder and biliary diseases,[125] and inguinal, femoral, and abdominal hernia[129]), oral disorders (periodontal diseases,[23, 130, 131, 132, 133, 134, 135, 136] edentulism,[137, 138, 139, 140] and caries of permanent teeth[131, 132, 136]), metabolic and endocrine system diseases (T2DM),[141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161] CKD,[162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175] cardiovascular diseases (stroke,[176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198] ischemic heart disease,[182, 191, 192, 196, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214] atrial fibrillation and flutter,[113, 191, 192, 196, 206, 207, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227] and lower extremity peripheral arterial disease[196, 201, 228, 229]), osteoarthritis,[230, 231, 232, 233, 234, 235, 236] COPD,[8, 17, 237, 238, 239] and immune-mediated inflammatory diseases (multiple sclerosis,[8, 240, 241, 242, 243, 244] inflammatory bowel disease,[240, 243, 245, 246, 247, 248, 249, 250, 251] psoriasis,[240, 243, 252, 253, 254, 255, 256, 257, 258, 259] atopic dermatitis,[8, 260, 261, 262, 263] asthma,[8, 260, 263, 264, 265, 266, 267] and rheumatoid arthritis[234, 240, 243, 259, 268, 269, 270, 271, 272]). Details of the characteristics and quality assessment of the included studies were described in the Supplementary Data 2.

Bayesian meta-regression model was used for RRs estimation. Firstly, we obtained the RRs adjusted for age, sex, ethnicity, comorbidity, and other covariates, from each included

618 article. HRs were directly treated as RRs.[273] ORs were converted to RRs using a formula (RR=
619 $OR/[(1–P_0)+(P_0 *OR)]$, in which $P_0$ is the incidence of the outcome of interest in the non-
620 exposed group) provided by previous studies.[274, 275] Then, the pooled RRs and 95% CI of each
621 peripheral disease were synthesized using Bayesian meta-analysis with the R packages
622 metafor[276] and bayesmeta.[277, 278, 279] Diseases with only one supporting article were excluded
623 from analysis, including peptic ulcer disease, gastritis and duodenitis, gallbladder and biliary
624 diseases, and hernia. The Bayesian meta-analysis approach was used in this study for its ability
625 to provide robust pooled estimates and to quantify uncertainty, particularly advantageous when
626 dealing with a limited number of studies, as well as its capacity to directly quantify the
627 probability of different effect sizes through posterior distributions.[280, 281] In Bayesian statistics,
628 a weakly informative prior distribution was specified for the parameter to estimate. Within the
629 hierarchical model $\theta \sim N[\mu, \tau^2]$, the effect parameter $\mu$ was given by a normal distribution with
630 a mean of 0 (centered around a RR of 1.0),[281] and the heterogeneity parameter $\tau$ was set as a
631 half-Cauchy distribution (0, 0.3) to ensure that a $\tau$ value less than 0.3 had a 50% probability.[282,
632 283] Bayes factors (BF) represented a likelihood ratio that evaluated the comparative predictive
633 strength of two hypotheses, the null hypothesis ($H_0$) and the alternative hypothesis ($H_1$).[284, 285]

634 The results of Bayesian meta-analysis, along with the heterogeneity estimate $\tau$ and the
635 posterior and prior distributions, are shown in Supplementary Figure 50-71. The magnitude of
636 heterogeneity, quantified by the $\tau$ statistic on the log relative risk scale, was categorized as 'low'
637 for $\tau \leq 0.1$, 'reasonable' for $\tau$ between 0.1 and 0.5, 'fairly high' for $\tau$ between 0.5 and 1.0, and
638 'fairly extreme' for $\tau$ greater than 1.0.[286] Funnel plots were used to evaluate potential publication
639 bias or small-study effects through the assessment of asymmetry (Supplementary Figure 4-29).

Peripheral diseases with positive pooled RRs (lower 95% CI >1) were considered valid risk factors for dementia. Eventually, 16 peripheral diseases across 9 systems with increased risk of dementia were incorporated in the calculation of PAF for dementia (Supplementary Figure 30). We also conducted sensitivity analyses by modifying the prior distributions to $\tau \sim$ half-Cauchy (0, 0.5) or $\mu \sim$ Normal (0, 4) respectively.

**Calculation of population attributable fractions**

The individual PAF of each risk factor was calculated using Levin's formula: $PAF = P_e(RR_e - 1)/(P_e[RR_e - 1] + 1)$,[287] where $P_e$ is the prevalence of the peripheral disease, and $RR_e$ is the pooled RR for dementia associated with the disease from our meta-analysis.[4] Considering that dementia mostly occurs in people aged over 40 years, we used the prevalence in people aged over 40 years of these peripheral diseases estimated from the GBD 2021 (Supplementary Table 10-25). To calculate PAFs for age-sex-region-specific population subgroups, we used the subgroup-specific prevalence of peripheral diseases. Consistent with a previous study, the 95% CI of PAF was estimated based on the 95% CI of the estimated RR.[288]

To allow the estimation of each peripheral disease's unique PAF and their collective PAF for dementia and avoid over-estimation, the communality among the 16 peripheral diseases, which reflects the variance in observed variables explained by common factors, was calculated based on the UK Biobank study sample with R package psych, following the calculation methods in previous studies.[4, 289] Briefly, the steps included calculating tetrachoric correlations to generate correlation coefficients and correlation matrix of the 16 peripheral diseases that reflects the correlation between unobserved variables from observed variables, conducting principal component analysis on the correlation matrix to produce eigenvectors that represents

662 unobserved factors underlying all the variables that explain the variance observed, retaining
663 components with eigenvalues ≥1 that hold the most information about the data distribution, and
664 finally calculating communality as the sum of the squares of all factor loadings to determine
665 the variance in observed variables explained by common factors. The UK Biobank recruited
666 over 500,000 community-dwelling participants aged 37-73 years at 22 assessment centers
667 across England, Wales, and Scotland from 2006 to 2010, with ethical approval from the North
668 West Multi-Centre Research Ethics Committee (REC reference 11/NW/0382) and written
669 informed consent from participants.[290, 291] The UK Biobank resources can be accessed through
670 applications on their website (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-
671 access). At the baseline visit, participants provided detailed health information via touchscreen
672 and verbal interview questions and underwent physical assessment and gave a venous blood
673 sample. Health information was also obtained by the linkage to electronic health records. In the
674 current analysis, data from 502,441 participants who were followed up until 30 June 2021 was
675 used to capture the cases of each included peripheral disease. Of the 502,441 participants from
676 the UK Biobank to derive the communalities among peripheral diseases, the mean (standard
677 deviation) age was 56.5 (8.1) years, 54.4% were female, and 94.1% were of White ethnicity.
678 The ICD codes (aligned with the definition of GBD) and the data fields used to identify these
679 diseases in the UK Biobank are described in Supplementary Table 2 and Table 6. Our
680 communality analysis found five principal components, explaining 51% of the total variance
681 among the included 16 peripheral diseases, indicating a substantial overlap in the prevalence of
682 these peripheral diseases, which was then accounted for in our weighted PAF estimates.
683 Next, we calculated the overall PAF attributed to all peripheral diseases using the formula:

overall PAF=1− [(1− w*$PAF_1$)(1− w*$PAF_2$)(1− w*$PAF_3$)…], where each peripheral disease's PAF was weighted as: weight (w) = 1− communality. Then, we estimated the individual weighted PAF for each peripheral disease as: individual weighted PAF= ([individual PAF/∑ individual PAF] *overall PAF).[292] Finally, we calculated the related prevalence and cases of dementia for each risk factor by multiplying the weighted PAF by the prevalence and cases of dementia. We also analyzed the age, sex, and region-specific PAFs, and the related prevalence and number of cases of dementia, and the temporal trends from 1990 to 2021.

Statistical analyses in the study were performed with R software (version 4.4.1).

## Data availability statement

The Global Burden of Disease Study (GBD) 2021 is publicly available on the Global Health Data Exchange website (https://vizhub.healthdata.org/gbd-results/). The UK Biobank resources can be accessed through applications on their website (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access). All included literature in the meta-analysis is available in PubMed website (https://pubmed.ncbi.nlm.nih.gov/). The data extracted from studies included in the meta-analysis and the GBD dataset used in the study can be found on the Figshare website (https://doi.org/10.6084/m9.figshare.30634574). The UK Biobank data were used under license and are thus not publicly available.

## Code availability statement

The analytical methods in the study do not involve developing new computer code or algorithm that have not been previously reported. The analytical methods in the study had been described in detail in the manuscript, with citations to the sources containing the relevant methodology and code. Accordingly, the original code required to reanalyze the data in this paper is available from the corresponding author upon request.


## Acknowledgments

The data acquired from the UK Biobank in this study were under application number 70109. The UK Biobank received ethical approval from the North west Multi-Centre Research Ethics Committee (REC reference 11/NW/0382) and participants provided written informed consent. The Global Burden of Disease (GBD) is funded by the Bill & Melinda Gates Foundation.

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## Author contributions

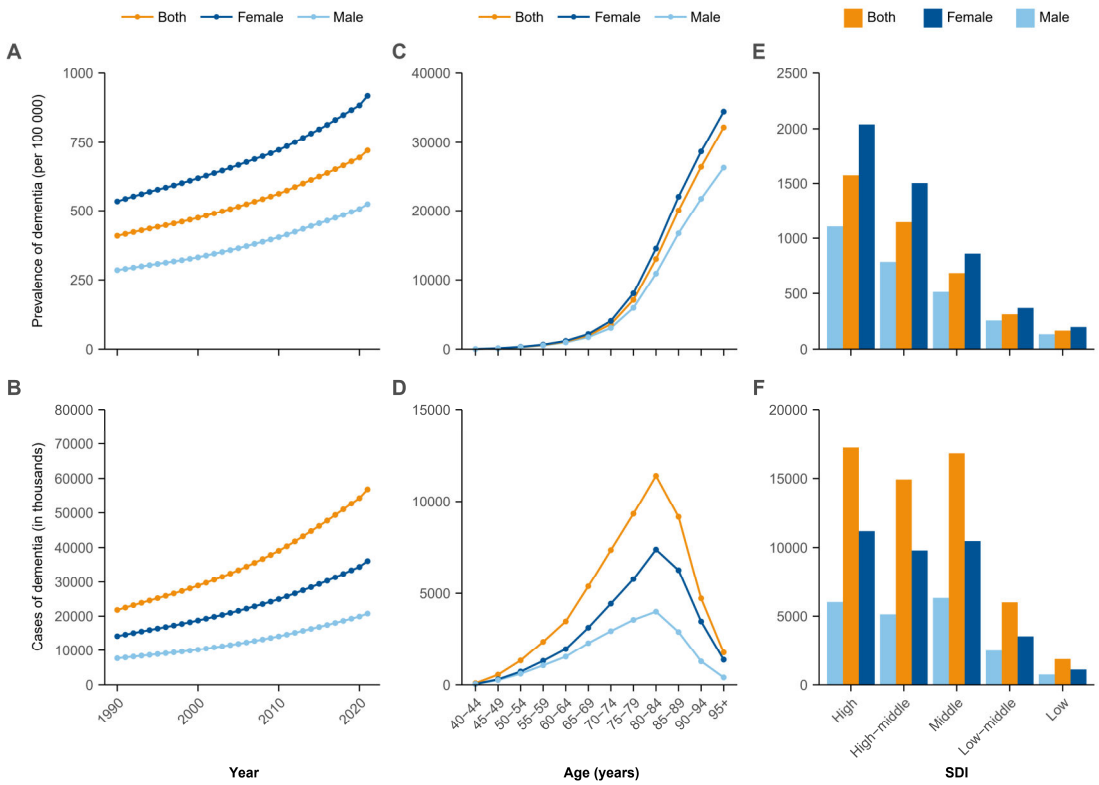
ZD, YY, QL, and SX are co-first authors. ZD, YY, QL, and YT designed the study. ZD, YY, QL, SX, YZ, and YT accessed the data, performed the statistical analysis, and verified the underlying data reported in the manuscript. ZD, YY, QL, and YT drafted the initial manuscript. All authors critically revised the manuscript for important intellectual content. YT supervised the study. All authors have full access to all of the data in the study and take responsibility to submit for publication. All authors have read and approved the final manuscript. YT has the final responsibility for the decision to submit for publication.

## Competing interests

The authors declare no competing interests.

## Figure

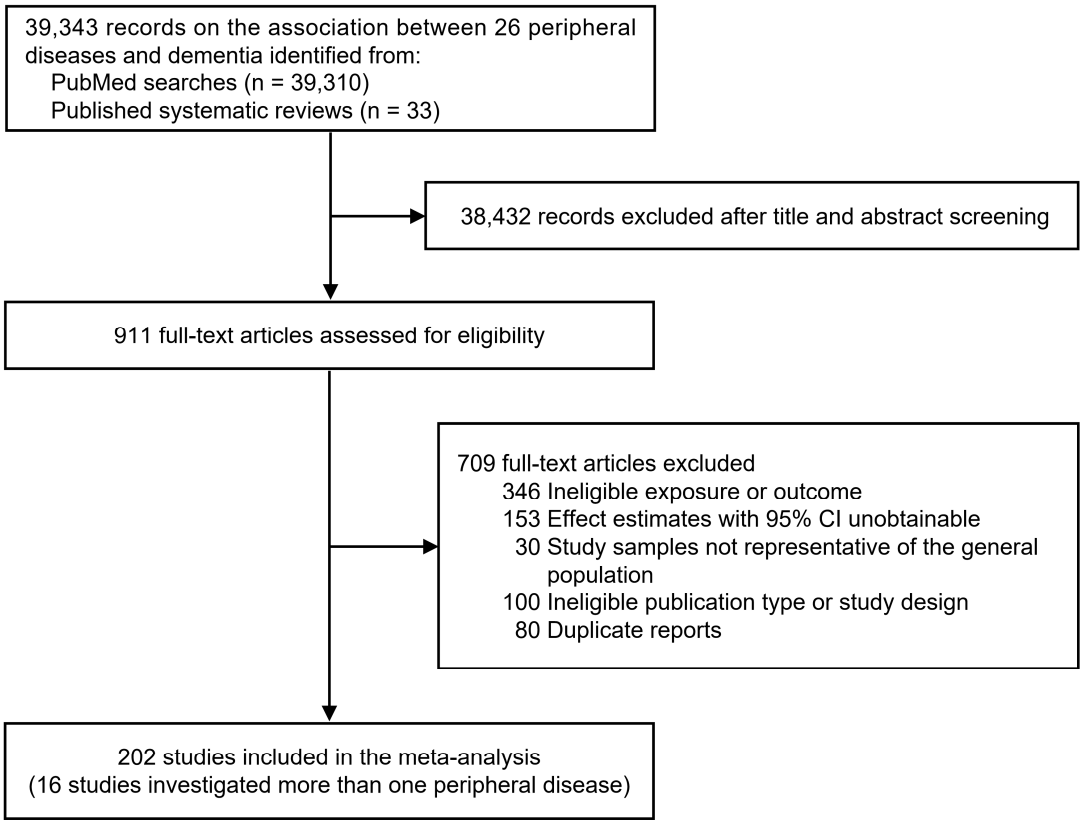
**Figure 1. Global prevalence and cases of dementia stratified by sex.**




The temporal trends from 1990-2021 (A–B) and variations across age groups (C–D) and different SDI regions (E–F) for the prevalence and cases of dementia.

Abbreviation: SDI=socio-demographic index.

745 **Figure 2. Flowchart of study selection for the meta-analysis.**

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747 n indicates the number of studies. Abbreviation: CI=confidence interval.

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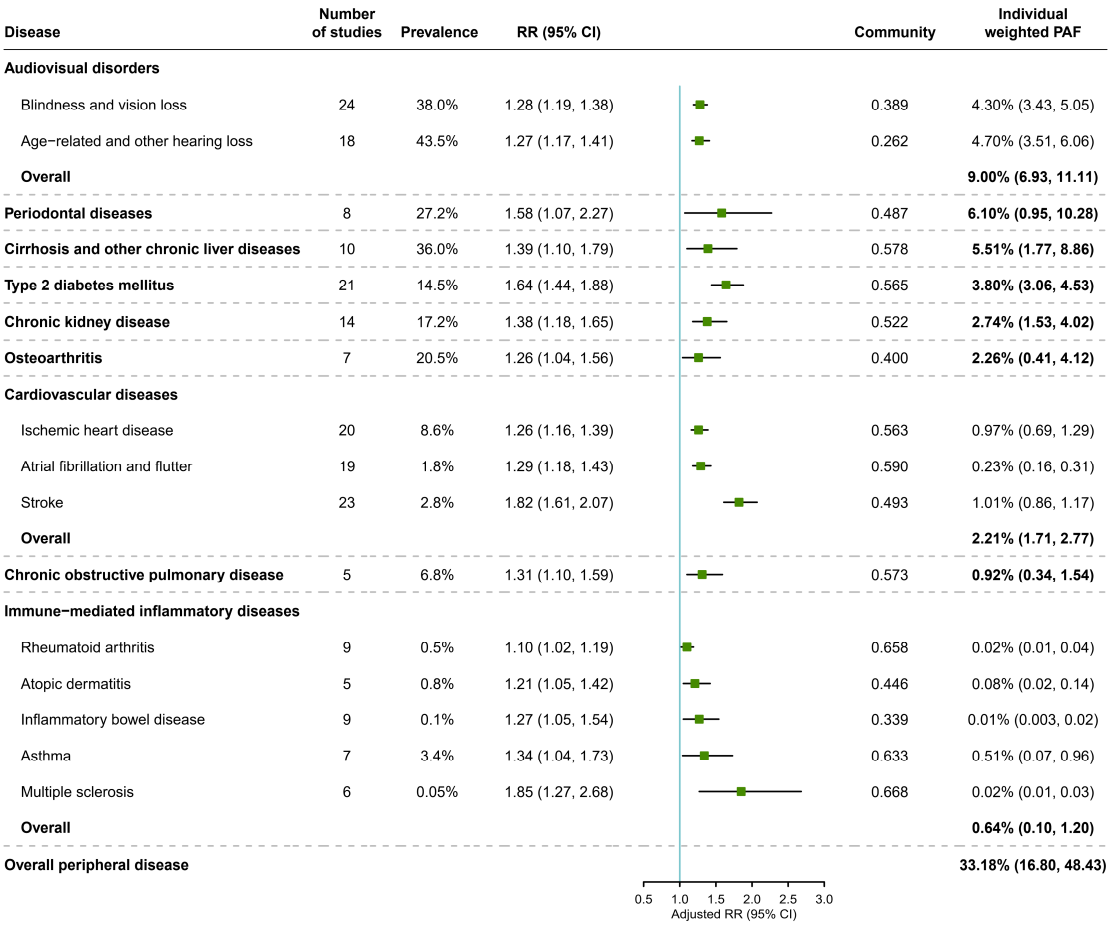
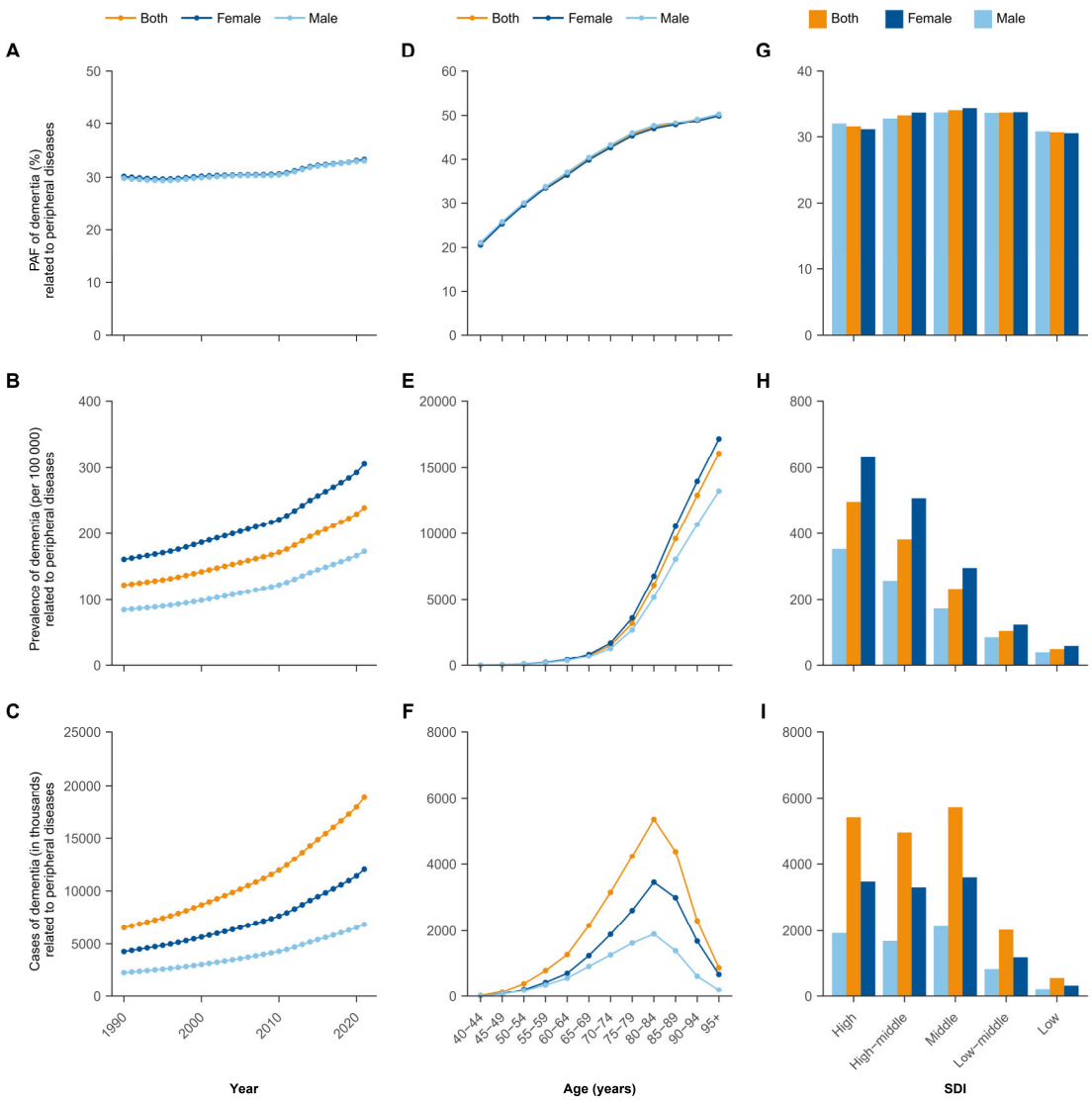
**Figure 3. RR, prevalence, and PAF of 16 peripheral diseases across 9 systems.**




The green solid cubes represent the relative risks for dementia associated with each peripheral disease, with horizontal bars indicating the 95% confidence intervals.

Abbreviation: RR=relative risk, PAF=population attributable fraction.

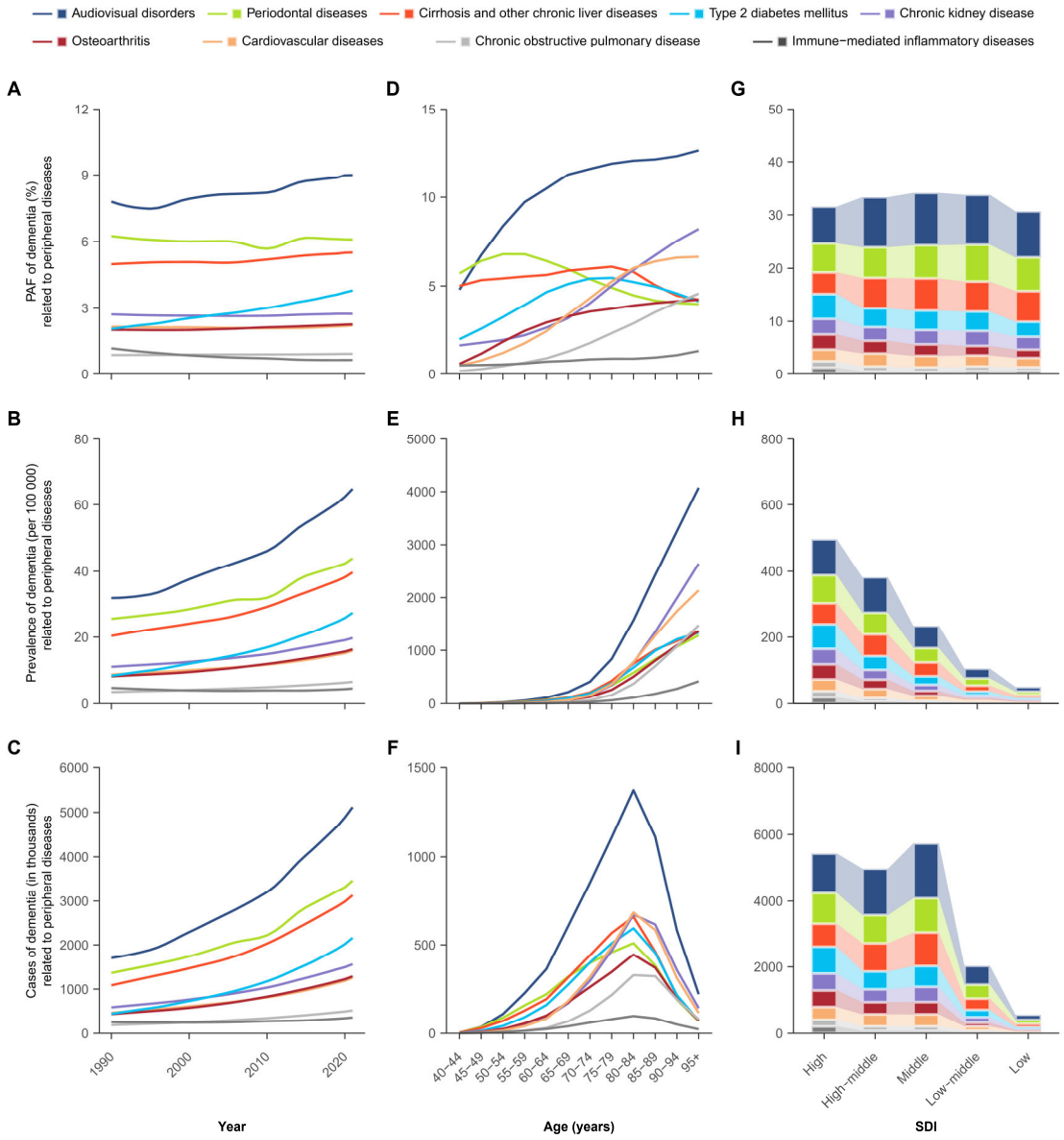
**Figure 4. PAF, prevalence, and cases of dementia related to overall peripheral diseases stratified by sex.**




The temporal trends from 1990-2021 (A–C) and variations across age groups (D–F) and different SDI regions (G–I) for the PAF, prevalence, and cases of dementia related to overall peripheral diseases.

Abbreviation: PAF=population attributable fraction, SDI=socio-demographic index.

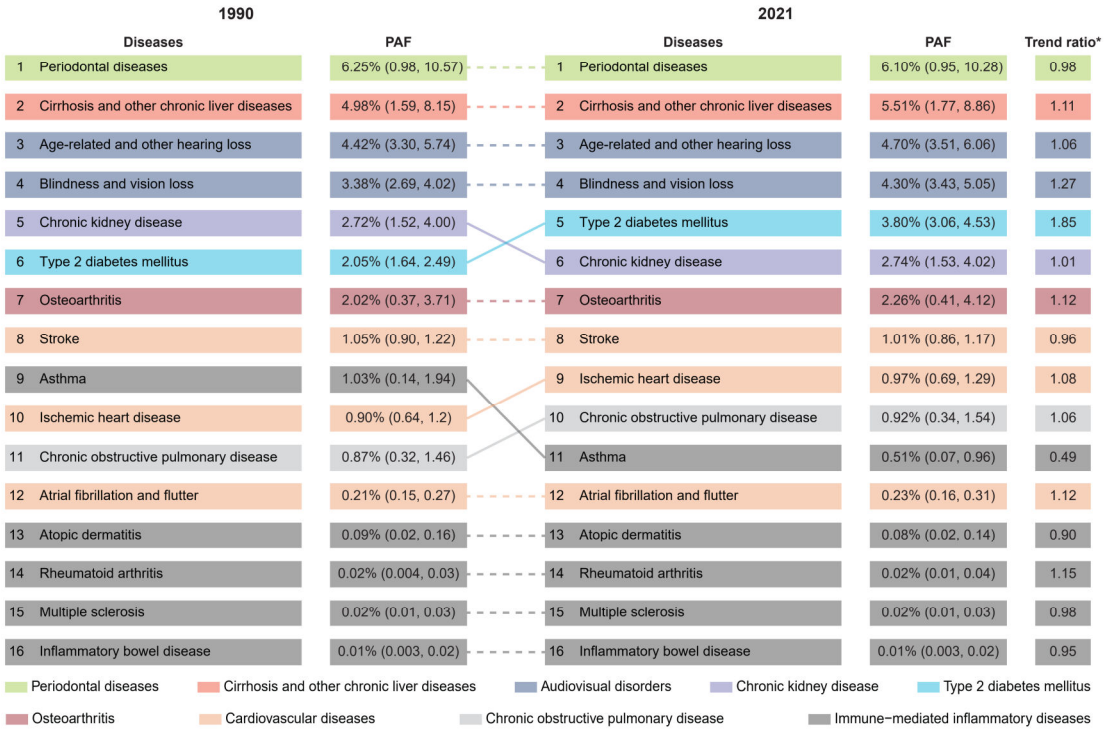
**Figure 5. PAF, prevalence, and cases of dementia related to 9 classes of peripheral diseases.**




The temporal trends from 1990-2021 (A–C) and variations across age groups (D–F) and different SDI regions (G–I) for the PAF, prevalence, and cases of dementia related to 9 classes of peripheral diseases.

Abbreviation: PAF=population attributable fraction, SDI=socio-demographic index.

**Figure 6. Temporal trends of PAF ranking of dementia related to 16 peripheral diseases, 1990-2021.**




*The PAF ratio of 2021 to 1990.

Abbreviation: PAF=population attributable fraction.

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