Risk factors for the neurodegenerative dementias in the Western Pacific region

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Summary

The Western Pacific Region (WPR) is characterized by a group of socioeconomically, culturally, and geopolitically heterogenous countries and represents a microcosm of the global endemic of neurodegeneration. This review will chart the known risk factors for dementia across the WPR. We explore the intersection between the established risk factors for dementia including the *biomedical and lifestyle* (cardiovascular and metabolic disease, sleep, hearing loss, depression, alcohol, smoking, traumatic brain injury, genetics) and *social determinants* (social disadvantage, limited education, systemic racism) as well as incorporate neuroimaging data, where available, to predict disease progression in the WPR. In doing so, we highlight core risk factors for dementia in the WPR, as well as geographical epicentres at heightened risk for dementia, to orient future research towards addressing these disparities.

Keywords: Dementia; Ageing; Risk factor; Health equity; Western Pacific Region

Introduction

The onset of neurodegenerative dementias reflects the cumulative contribution of modifiable and non-modifiable risk factors across the life course.[1] An increased number of risk factors overall may contribute to an earlier age of onset and separately, may exacerbate disease progression and reduce survival. With a rapid increase in global dementia cases predicted over the coming decades, and in the absence of currently effective cures or treatments for dementia, it is imperative to understand the role of risk factor modification to prevent or delay disease onset and to slow progression.

The predicted increase in dementia cases will not affect all countries and regions equally.[2] The largest increases are predicted in low- to middle-income countries, reflecting an absolute increase in the population and rapid growth in older populations in these regions.[2] High-income countries, however, are not immune from an overall increase in dementia prevalence, despite declining incidence, and Indigenous populations within these countries face a disproportionate burden of dementia.[1,3]

The Western Pacific Region (WPR) is socioeconomically, culturally, and geopolitically diverse, and the prevalence of dementia risk factors varies widely across countries in the region. Over 245 million people aged 65 years and older live in the WPR, with this number set to double by 2050, transforming many WPR countries from ageing to aged societies.[4] Given that age is a major contributor to dementia risk, it may seem unsurprising that dementia prevalence across the WPR mirrors the evolving population distribution between low to high-income countries (see Fig. 1). Alzheimer disease (AD) is the most prevalent dementia subtype in the region, including East Asia, where the ageing population has contributed to a shift away from vascular dementia as the most common subtype.[5] Within country estimates of all neurodegenerative dementias in older populations range from 1.6% in Singapore to 4.5% in Vietnam to 25% in Japan.[6–8] There is also within-country variation. For example, the prevalence of dementia and cognitive impairment for women aged over 60 years in China is significantly higher than the population-wide estimate of 6.9%.[9] Dementia risk also increases with rurality in some countries.[9,10]

The prevalence data for dementia is sparse and heterogeneous in part due to changing diagnostic criteria and methodologies for measuring the disease.[11] Additional regional variation in biomedical and psychosocial risk factors, as well as poor access to healthcare due to economic hardship, geographical location and/or lower health literacy further contribute to differing estimates.[11,12]

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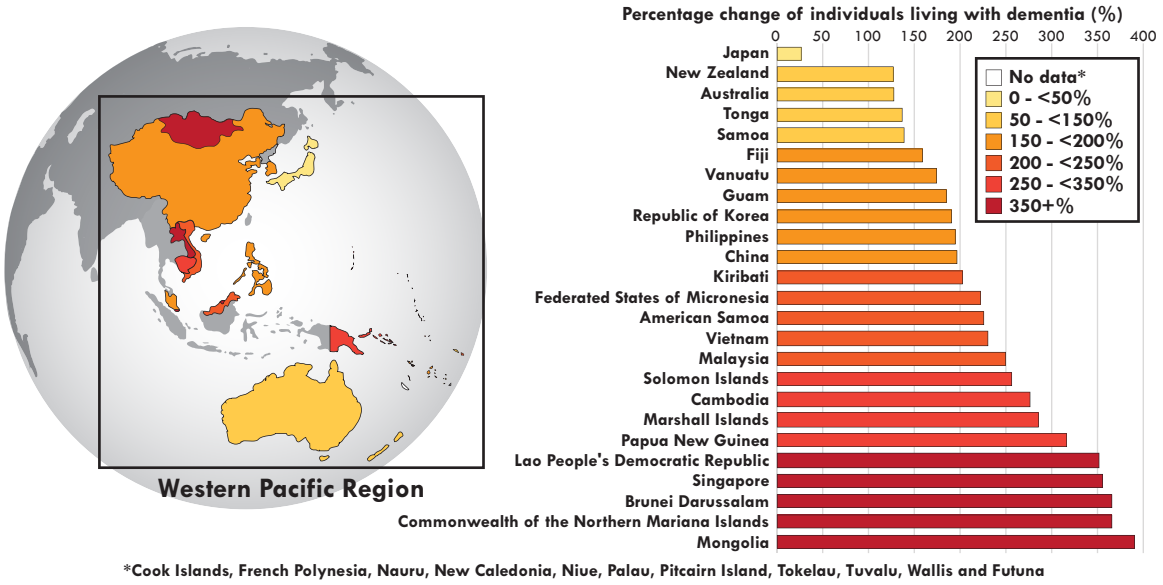

Fig. 1: **Predicted percentage change between 2019 and 2050 in all-age number of individuals with dementia by country in the WPR (Source: Nichols et al., 2022).**[2]

In many low-income countries, such as Vanuatu and Papua New Guinea, there is limited access to primary care facilities and poor coverage of health information systems.[13] Despite rapid economic growth and recent major primary care reform in China, insufficient training of primary care physicians in preventative health continues to pose a challenge to management of dementia risk factors, particularly cardiovascular disease.[14] The gap in primary care diagnostic pathways for dementia is an issue seen in many countries in the WPR and compounds a lack of access to routine dementia diagnosis and management, including dementia-specific medications. Without established pathways for dementia care, there is a greater dependence on informal and social care, deepening the indirect economic costs of dementia, particularly for women.[15,16]

Overall, the region is underprepared for the structural, financial, and human resources required for adequate dementia care.[17] Only four countries in the region – the Republic of Korea, Japan, Australia, and Aotearoa New Zealand – have national dementia plans in place.[18] Currently, most people living with dementia are cared for by family members without appropriate training or governmental support. Stigma relating to the disease also influences healthcare-seeking behaviors.[17] In this context, targeted and culturally appropriate approaches to limit disease onset and progression in the WPR are vital.

Objective of this paper

The diversity of dementia prevalence and risk factor burden across the WPR represents a case study for the global endemic of neurodegeneration. Given the predicted rapid increase in dementia cases internationally, this timely review will focus on charting the known risk factors for dementia across the WPR to provide a comprehensive roadmap for targeted risk reduction, broadening of clinical trial enrolments, and long-term planning for the economic burden of dementia. We will explore the intersection between the established risk factors for dementia including the *biomedical and lifestyle* (cardiovascular and metabolic disease, sleep, hearing loss, depression, alcohol and smoking, traumatic brain injury, genetics) and *social determinants* (social disadvantage, less education, systemic racism) as well as incorporate neuroimaging data, where available, to predict disease progression. The discussion will review the risks for AD, vascular dementia, and dementia with Lewy bodies (DLB) collectively, with additional commentary on the unique genetic and metabolic risk factors for the frontotemporal lobar degeneration (FTLD) syndromes.

Search strategy and selection criteria

References for this literature review were identified through searches of Ovid via Medline, EmBASE via Medline, and PubMed. The search terms included "risk factor" as well as a separate search including the reviewed risk factors individually (e.g., smoking, hypertension or "blood pressure") and "dementia" and/or "cognitive impairment" or "Alzheimer's disease" or "vascular dementia" or "frontotemporal lobar degeneration" or "frontotemporal dementia" or "primary progressive aphasia" or "progressive nonfluent aphasia" or "Lewy body disease" or "amyotrophic lateral sclerosis" or "motor neurone disease" and "Western Pacific" or "Asia Pacific" or "Oceania" or "Australasia" and each

country's name separately from 2000 until July 2023. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated based on originality, accessibility, and relevance to the broad scope of this review.

Risk factors for Alzheimer's disease and vascular dementia

In light of the shortage of country-specific data on the population attributable risk (PAR) for dementias in the WPR, this review will outline the regional variation in the known risk factors for dementia onset and progression (see Table 1). Given the substantial clinicopathological overlap between AD and vascular dementia and their synergistic risk factor profile,[19] we will discuss these subtypes collectively, drawing on insights from the recent Lancet Commission on Dementia Prevention, Intervention and Care.[1] Age and male sex remain the strongest risk factors for DLB,[20,21] with variation in the operational definition and overlapping clinicopathology contributing to the range in disease prevalence across the WPR.[22]

Low educational attainment

Quality childhood education is important for reducing dementia risk, especially for girls, given the higher incidence of all-cause dementia in women.[1] Lower levels of educational attainment are associated with a higher risk of dementia and cognitive impairment and represent the most significant modifiable risk factor in China.[7,23–25] Access to education depends on socioeconomic factors, rurality, disability, ethnicity, language, and gender, in turn influencing the PAR for dementia.[23,26,27] There is a pressing need to improve government policies to address these barriers, with 20% of children under the age of 10 in the WPR unable to read or understand simple text.[28] In the Federated States of Micronesia, Tuvalu, and the Republic of Marshall Islands, more than 10% of children do not attend primary school.[29] In East Asia, a major contributor to lack of childhood education is parental labour migration internally and internationally.[30]

Improved education, and by extension, health literacy, is linked with better community understanding of dementia and its associated risks.[31,32] Whilst improved childhood educational attainment is vital, cognitive engagement and employment throughout mid- and later-life may also reduce dementia risk.[1] Work is underway in East Asia and Australasia to explore the effectiveness of cognitive and physical therapies on dementia risk reduction in people with mild cognitive impairment and dementia.[33–35]

Cardiometabolic/cardiovascular risk

Cardiometabolic disturbance encapsulates the risks of obesity, central adiposity, elevated blood pressure, and glucose metabolism and represents a major modifiable risk factor for AD and vascular dementia in mid-life.[1] There is also growing evidence that some cardiometabolic risk factors may also influence DLB. The prevalence of cardiovascular risk factors for dementia in the WPR is generally under-recognized due to limited community awareness and inadequate health service delivery with affordability of drug treatments a major barrier to management.[5,25,36,37]

Obesity

Overweight and obesity are significant public health challenges in the WPR with one third of adults classified as overweight or obese in 2014; in Australasia and the Pacific Island countries this figure is over 60%.[38] The epidemic of obesity reflects a rapid dietary transition from traditional culinary cultures to increased availability and affordability of foods and beverages rich in sugars, fats, and salt, accompanied by reduced opportunity for physical activity.[38–41]

The obesity epidemic occurs alongside persisting malnutrition in children and adults in some low- to middle-income countries, including China, Fiji, Mongolia, and Tuvalu, reflecting the 'double burden' of disease and challenges for public health policy targeting this risk factor.[42,43] In Papua New Guinea, almost 50% of children under five fail to reach their growth potential, while the prevalence of overweight among this cohort is 14%, one of the highest in the region.[43]

The PAR of obesity toward dementia occurs independently of blood pressure, lipid, and glycaemic indices.[44] In Australia and Aotearoa New Zealand, the unadjusted PAR of obesity is 17.0% and 18.7% respectively.[27,45] The risk is higher in Indigenous populations in Aotearoa New Zealand and Australia compared to European and Asian populations within these nations.[46] These findings may reflect the disproportionate representation of Indigenous peoples in socioeconomically disadvantaged areas susceptible to obesogenic influences.[27] Visceral adiposity, independent of an overall raised body mass index, is also an independent predictor for cognitive decline across multiethnic Asian populations in Singapore.[44]

Physical inactivity

Physical inactivity is closely linked to the rise of obesity as a major risk factor for the development of dementia. Lack of physical activity is prevalent across the WPR. Almost one third of older Malaysian adults lead inactive lives,[47] and in the Pacific Islands, between 41% and 62% of the population lead completely sedentary lives (see Table 1).[48] Physical inactivity is the largest contributor to potentially modifiable dementia risk overall, and across different ethnic groups in Australia.[46,49] Despite this, policy reform targeting reduced levels of physical inactivity has been slow and the cost of inaction on obesity and physical inactivity will contribute significantly to the rise in dementia cases in the WPR.[50]

Country	Risk factor								
	Limited education[a]	Obesity[b]	Physical inactivity[c]	Hypertension[d]	Diabetes[e]	Smoking[f]	Hearing loss[g]	Depression[h]	Alcohol use[i]
American Samoa	.	.	.	.	.	.	21.2 [20.5–21.9]	.	.
Australia	0.7	29.0 [25.3–32.9]	30.4 [23.7–37.9]	15.2 [11.5–19.4]	5.9 [4.0–8.2]	13.1	13.5 [12.8–14.3]	**5.9**	**10.5 [8.8–11.8]**
Brunei Darussalam	**21.1**	14.1 [10.5–18.3]	27.3 [18.5–38.3]	18.9 [13.5–25.2]	9.4 [5.9–13.7]	22.8	13.5 [12.8–14.1]	4	0.5 [0.8–1.6]
Cambodia	**22.2**	3.9 [2.5–5.6]	10.5 [6.9–15.7]	**26.1 [19.6–33.0]**	7.1 [4.6–10.4]	26.5	**22.0 [21.3–22.8]**	3.4	6.6 [5.1–8.1]
China	.	6.2 [4.7–7.9]	14.1 [10.1–19.4]	19.2 [14.9–24.0]	8.8 [6.0–12.4]	**41.1**	**22.6 [21.7–23.5]**	**4.2**	7.1 [5.7–8.3]
Cook Islands	.	**55.9 [50.2–61.5]**	18.5 [13.3–24.9]	22.3 [16.2–29.2]	**27.5 [19.8–35.6]**	22.7	21.0 [20.3–21.8]	.	.
Fiji	2.4	30.2 [24.5–36.0]	17.4 [12.5–23.6]	21.7 [15.6–28.7]	17.4 [11.5–24.3]	19.1	21.3 [20.6–22.1]	3.5	3.3 [2.9–4.8]
French Polynesia	.	.	.	17.6 [14.1–21.5]	.	.	.	.	.
Guam	.	.	.	21.5 [15.8–28.2]	.	.	21.0 [20.4–21.7]	.	.
Japan	0.13	4.3 [3.2–5.5]	35.5 [20.5–53.8]	**24.8 [18.8–31.1]**	6.7 [4.7–9.0]	26.3	13.6 [13.0–14.2]	**4.2**	8 [6.7–9.2]
Kiribati	.	46.0 [39.7–52.1]	**40.4 [31.2–50.2]**	.	22.3 [15.5–30.1]	**43.0**	21.7 [20.9–22.4]	3.1	0.5 [0.5–1.2]
Lao People's Democratic Republic	**31.2**	5.3 [3.5–7.6]	16.3 [12.3–20.3]	.	7.7 [5.0–10.8]	38.4	**22.0 [21.3–22.8]**	3.2	**10.7 [9–12.7]**
Macao SAR	.	.	.	.	.	.	.	.	.
Malaysia	6.9	15.6 [12.5–19.0]	38.8 [29.7–48.6]	22.9 [17.9–28.7]	11.1 [7.6–15.3]	32.1	21.5 [20.8–22.3]	3.8	0.9 [0.7–1.6]
Marshall Islands	.	**52.9 [46.7–59.1]**	**43.5 [33.8–53.7]**	21.3 [15.2–28.1]	21.1 [14.6–28.6]	32.3	21.5 [20.8–22.3]	.	.
Micronesia, Federated States of	.	45.8 [39.7–51.8]	36.6 [28.2–46.0]	**25.0 [18.9–32.0]**	22.0 [15.7–29.2]	.	21.5 [20.8–22.2]	3.1	2.5 [1.9–3.5]
Mongolia	4.3	20.6 [16.3–25.0]	18.6 [13.9–24.4]	**29.0 [22.5–35.9]**	11.7 [8.0–16.3]	**40.3**	18.0 [17.3–18.8]	**4.2**	8.2 [6.8–9.5]
Nauru	.	**61.0 [55.3–66.6]**	**42.1 [31.7–53.3]**	20.5 [14.6–27.7]	**29.2 [20.7–38.5]**	29.5	21.3 [20.6–22.1]	.	3.7 [2.8–4.7]
New Caledonia	.	.	.	.	.	.	.	.	.
New Zealand	0.9	30.8 [27.3–34.3]	**42.4 [35.3–49.8]**	16.2 [12.3–20.8]	6.9 [4.6–9.7]	12.8	13.6 [12.9–14.4]	**5.4**	**10.6 [8.6–11.5]**
Niue	.	50.0 [43.7–55.8]	6.9 [4.8–9.9]	24.2 [18.3–30.8]	**27.1 [19.8–34.8]**	.	21.2 [20.5–21.9]	.	**10.7 [9–12.3]**
Northern Mariana Islands, Commonwealth of the	.	.	.	.	.	.	21.1 [20.4–21.9]	.	.
Palau	.	**55.3 [49.3–61.2]**	**40.9 [31.1–51.3]**	22.9 [16.8–30.0]	23.2 [16.6–30.8]	20.5	21.2 [20.5–22.0]	.	.
Papua New Guinea	**37.9**	21.3 [15.6–27.5]	14.8 [9.7–21.9]	25.6 [18.4–33.5]	14.8 [9.2–21.8]	**40.4**	21.8 [21.1–22.6]	3	1.4 [0.9–2]
Philippines	2.7	6.4 [4.6–8.7]	39.7 [31.3–48.6]	22.6 [17.4–28.1]	7.2 [4.9–10.0]	31.8	**22.2 [21.4–22.9]**	3.3	6.9 [5.4–8.3]
Pitcairn Island	.	.	.	.	.	.	.	.	.
Republic of Korea	3.4	4.7 [3.6–5.9]	35.4 [20.9–52.9]	11.0 [8.2–14.3]	8.0 [5.5–11.0]	29.8	13.4 [12.7–14.0]	4.1	**9.7 [8–11.5]**
Samoa	.	47.3 [41.5–53.4]	12.6 [8.7–17.7]	24.0 [17.9–30.8]	**24.6 [17.1–32.6]**	25	21.5 [20.8–22.2]	3.2	2.7 [2.3–3.9]
Singapore	**15.3**	6.1 [4.2–8.3]	36.5 [21.7–54.3]	14.6 [10.8–19.0]	7.9 [5.5–10.8]	20.5	13.5 [12.8–14.1]	**4.6**	2 [1.8–2.8]
Solomon Islands	.	22.5 [17.5–27.9]	18.2 [13.0–24.8]	22.0 [15.7–29.0]	13.9 [8.8–20.5]	**40.0**	**21.8 [19.0–20.7]**	2.9	1.8 [1.3–2.5]
Tokelau	.	.	.	.	.	.	21.3 [20.6–22.1]	.	.
Tonga	0.7	48.2 [41.8–54.0]	17.4 [12.4–23.6]	23.7 [17.5–30.6]	**24.2 [17.2–32.0]**	37.4	21.3 [20.6–22.1]	3.2	0.8 [0.7–2]
Tuvalu	.	**51.6 [45.0–57.9]**	27.3 [20.5–35.4]	23.7 [17.6–31.2]	23.8 [17.1–31.2]	30.2	21.4 [20.8–22.2]	.	1.5 [1–2.1]
Vanuatu	.	25.2 [19.6–31.0]	8.0 [5.4–11.6]	**24.2 [17.3–31.5]**	15.9 [10.4–22.9]	20.5	21.6 [20.9–22.4]	3.1	2.3 [2.1–3.5]
Viet Nam	15.2	2.1 [1.4–3.1]	25.4 [18.9–33.1]	23.4 [18.0–29.4]	5.3 [3.4–7.6]	35.2	21.4 [20.7–22.2]	4.0	8.7 [6.7–10.7]
Wallis and Futuna	.	.	.	.	.	.	.	.	.

95% confidence intervals presented in square brackets where available from raw data. Countries with the five highest prevalence for each risk factor are presented in bold. Prevalence is age-standardized unless otherwise indicated. Data for obesity, physical inactivity, hypertension, diabetes, and alcohol use obtained from the World Health Organization, Western Pacific Health Data Platform (https://data.wpro.who.int). Data for smoking obtained from Web Annex VI: Global Tobacco Control Policy Data (https://www.who.int/publications/i/item/WHO-HEP-HPR-TFI-2021.10). Data for depression obtained from Mental Health Atlas WHO Global Health Estimates (https://www.who.int/data/gho/indicator-metadata-registry/imr-details/5281). Data on limited education obtained from Robert J. Barro and Jong-Wha Lee: http://www.barrolee.com/; Education Statistics (https://data.worldbank.org/). Data on hearing loss obtained from Supplement to: GBD 2019 Hearing Loss Collaborators. Hearing loss prevalence and years lived with disability, 1990–2019: findings from the Global Burden of Disease Study 2019. *Lancet* 2021; 397: 996–1009. [a]Limited education = people aged 15 years+ with no formal education 2010. [b]Obesity = BMI ≥30 among adults 2016. [c]Physical inactivity = insufficient physical activity among adults aged 18 years+ 2016. [d]Hypertension = Raised blood pressure (systolic blood pressure ≥140 or diastolic blood pressure ≥90 mmHg) among adults aged 18 years+ 2015. [e]Diabetes = fasting blood glucose ≥7 mmol/L among adults aged 18 years+ 2014. [f]Smoking = current smoking among adults aged 15 years+ 2019. [g]Hearing loss = includes all severities of hearing loss 2019. [h]Depression = estimated population-based prevalence of persons with depression in the previous year 2015. [i]Total annual alcohol per capita among people aged 15 years+ in liters 2018.

Table 1: **Prevalence (%) of known risk factors for neurodegenerative dementias across the Western Pacific region.**

Hypertension

Hypertension is prevalent throughout the WPR and is an independent contributor to cardiovascular disease, as well as AD, vascular dementia and DLB.[48,51–53] Traditional South-East Asian culinary culture emphasizes the use of salted and fermented foods.[54] However, widespread urbanization and economic development has seen the introduction of higher salt consumption more broadly and is a major risk factor for the development of mid-life hypertension.[52] In a recent population-based study of older adults in the Philippines, the prevalence of hypertension was double

that of the global age-standardized prevalence.[55] Steep increases in the prevalence of hypertension are being seen in Kiribati, Tonga, and Tuvalu as well as within rural areas of China.[14,56] Importantly, Australian data shows that adequate treatment of hypertension reduces both cerebrovascular disease as well as AD neuropathology.[57]

Obesity is also a major driver of hypertension and is proposed to account for a third of the increase in midlife hypertension in Samoa.[58] Across Aotearoa New Zealand, the relative contribution of hypertension to dementia risk is 3.8 times higher than global estimates, and again reflects the relatively higher contribution from Māori and Pacific Islander groups, which are disproportionately affected by obesity.[27] Overall, both detection and control remain suboptimal across the region, particularly within health resource poor areas.[14] The development of community awareness programs and improved treatment strategies have contributed to lower prevalence in some countries including Korea, Taiwan, and Japan.[56]

Diabetes

The 2020 review by Livingston et al. established type 2 diabetes mellitus as a risk factor for incident dementia, irrespective of the type of medical management.[1] The data is less clear for DLB, with conflicting evidence on the relationship both outside and within the WPR.[20,59]

The WPR has one of the highest rates of diabetes in the world, particularly in Kiribati, the Marshall Islands, and Nauru (see Table 1).[60] The risk of dementia attributable to diabetes occurred independently of smoking, hypertension, and obesity in a Mongolian outpatient-based study.[61] However, the risk is amplified by comorbid cardiovascular disease and smoking, as demonstrated in Korean and Taiwanese population cohorts.[62,63] Multidomain interventions, such as the J-MIND-Diabetes trial in Japan, are needed to better target modifiable risk factors for dementia in people with diabetes.[64]

Smoking

Globally, tobacco smoking is a recognized risk factor for incident dementia. However, the data is less conclusive in the WPR, where tobacco smoking prevalence varies widely, from 14 to 16% in Australia and Aotearoa New Zealand up to 52% in Kiribati (see Table 1).[65] A Singaporean population-based study showed that current smokers had a 20% increased risk of cognitive impairment compared to non-smokers,[66] whereas a large Mendelian randomization analysis in Chinese and Japanese populations and a Taiwanese study found no association between smoking and AD.[67,68] Whilst smoking is protective against Parkinson disease, predominantly an α-synucleinopathy, it is not a consistent risk or protective factor for DLB, possibly due to overlap between α-synuclein and AD pathology in the disease process.[20,69]

Despite the variability in incident dementia risk, there are continued efforts to reduce tobacco smoking in the WPR. More than 80% of member countries have established bans on promotion of tobacco products, with Australia implementing an annual tax on all cigarette sales.[70] However, the rising use of nicotine delivery devices, particularly in younger populations, and their relationship to incident dementia require further assessment.

Air pollution

Confounding smoking-related data is the high prevalence of air pollution across the region. Ambient (outdoor) exposure largely due to industrial and transport sources and smoke from household (indoor) solid fuels used for cooking contribute to the cumulative exposure.[71,72] A study in Hong Kong also showed that indoor incense burning, which is a religious ritual commonly practiced among older adults within Chinese and other Asian societies, was associated with poorer cognitive performance and reduced brain connectivity.[73] Country-wide improvements in policies to reduce outdoor and indoor air pollution are required.

Hearing loss

The 2020 Lancet Commission on Dementia Prevention and Care identified hearing loss as the most significant modifiable risk factor for dementia globally, a risk which is largely mitigated by hearing aid use.[1,74] 546 million people in the WPR live with hearing loss, 7% (38 million) are children.[75] The association between hearing impairment and incident dementia, as well as the beneficial impact of hearing aid use, is supported by studies across Japan, China, Korea, Singapore, Vietnam, Australia, and Aotearoa New Zealand.[27,45,76–80] Within Australia, up to 40% of Aboriginal and Torres Strait Islander children experience otitis media, making this population one of the most at risk for hearing loss globally.[81] The association between hearing loss and MCI and dementia has been consistently demonstrated in this population.[82–84]

Much of the work to prevent hearing loss focuses on perinatal and childhood risk minimization, including immunization, adequate maternal and childcare practices, management of common ear conditions and rational use of medications to limit ototoxic effects.[85] However, access to hearing services varies widely across the WPR with a mixed method study in Cambodia identifying lack of quality ear specific services as a major barrier to preventing advanced ear disease.[86] Hearing services are also under-resourced in the Pacific Islands and several countries, including Fiji, Kiribati, and Samoa, have established audiology partnerships with Australia and Aotearoa New Zealand to improve access.[87] With recent work by Wasano and colleagues[88] demonstrating reduction in hearing thresholds from 20 to 30 years, screening for hearing impairment prior to onset of midlife should be considered.

Depression

Depression is estimated to affect more than 66 million people in the WPR.[89] Limited access to mental health services, financial constraints, and social exclusion of persons with mental health illness impair accurate detection and treatment.[89,90] In China, depression prevalence is estimated at 1.5%, relatively uncommon compared to Australian and Aotearoa New Zealand estimates (13.3% and 19.1% respectively), reflecting contextual and cultural factors[25,27,45] including the preferential expression of somatization, reduced health seeking behaviors and health system barriers.[91] Depression literacy is low across Cambodia, Fiji, and the Philippines and is postulated to contribute to unhealthy coping mechanisms, including alcohol misuse.[90]

The contribution of depression to incident dementia is confounded by reverse causation, where depressive symptoms may result from early dementia neuropathology.[1] In Australia, Aotearoa New Zealand and China, the adjusted PAR for depression ranges from 0.5% (China) to 4.2% (Australia and Aotearoa New Zealand) with all studies using lifetime prevalence estimates.[25,27,45] In the Philippines, depression in the 2 years prior to dementia diagnosis was associated with vascular dementia but not AD.[55] The PAR also varies within regions and countries, with Pacific Island peoples in Aotearoa New Zealand and First Nations peoples in the Torres Strait having a reduced risk (2.0%) compared to national estimates.[26,27] However, other studies identify depression and psychological distress as a major health concern for older Aboriginal people in Australia with systemic racism and childhood adversity a chief contributor.[92] Equipping populations with grassroots approaches to education and detection, especially within the family and community setting, may improve early recognition within the region.[90]

Alcohol use

The WPR has one of the highest rates of alcohol consumption among adults with total pure alcohol per-capita consumption of 7.3 L annually, almost 10% more than global estimates.[93] Low and middle-income countries have seen a dramatic increase over the last two decades, with heavier alcohol use displayed by men.[7,55]

Studies evaluating alcohol use and its relationship to incident dementia are confounded by comorbidities, including smoking and depression. Heavy alcohol use is a known risk factor for neurodegeneration but there remains doubt about the contribution of mild to moderate consumption on cognitive impairment.[1] Quantifying alcohol consumption accurately can be hampered by under reporting.[27] Overall, the population attributable dementia risk for alcohol in the WPR appears to be non-significant or low,[27,66] although dedicated assessment in countries with the highest alcohol consumption (Cook Islands, Niue, Lao People's Democratic Republic) is required.

Sleep

Disturbances of sleep, including nocturnal awakenings, poor sleep quality and efficiency and aberrant sleep duration are common in older people, are pronounced in those at risk for dementia,[94] increase dementia risk[95] and are significant contributors to disability.[96,97] Sleep disturbance affects more than 90% of patients with DLB and is a major source of patient and caregiver distress.[98,99] Sleep disorders such as obstructive sleep apnoea are also associated with an increased risk of dementia[94,100,101] and gold standard treatment options are available.[102] Since sleep may play a pivotal role in clearance of neurotoxins including amyloid-β and tau, early detection and treatment of sleep disturbance is likely to be beneficial for optimizing brain health.[103]

In the WPR, the impact of sleep on incident dementia is of growing interest. Korea and Japan consistently rank as having the lowest sleep duration of OECD countries.[104] In a scoping review of Pacific Ocean peoples, disrupted sleep patterns were the most common sleep-related issue.[105] Shorter sleep duration and disrupted sleep architecture are more commonly reported by Aboriginal and Torres Strait Islander peoples and Māori than non-Indigenous Australians and New Zealanders.[49,106] The reasons underpinning poor sleep health are multifactorial and range from rapid socioeconomic development with increased vocational and caring demands,[107] to increased rates of obstructive sleep apnoea and poor sleep health practices.[106] With greater understanding of the interrelationship between sleep and cognition, there is growing interest in promoting healthy sleep and healthy brain ageing across the region, with interventions ranging from light therapy to melatonin and behavioral interventions.[108,109]

Traumatic brain injury

Severe traumatic brain injury (TBI) is associated with the development of hyperphosphorylated tau and an elevated risk of dementia and AD,[1] although not DLB.[110] There is also growing recognition of chronic traumatic encephalopathy (CTE) as a unique entity within the neurodegenerative dementias, based largely on research arising from sport-related concussion.[111,112]

The aetiology and severity of TBI varies according to age and sex, with road traffic accidents and sporting injuries more common in men from the teenage years to midlife and falls seen equally among men and women in later life, globally and across the WPR.[2,113–115] Inter-tribal war and violence further contribute to high rates of TBI in Papua New Guinea.[116] It is likely that other causes of TBI, such as intimate partner violence, are under-recognized.[115]

The prevalence of TBI in the WPR is high and increasing.[117] Despite this, there is limited data on its relationship to incident dementia. Ma'u and colleagues demonstrated an adjusted PAR of between 3.5 and 3.9% across major ethnic groups in Aotearoa New Zealand.[27]

Rates of TBI in Aboriginal communities in Australia are particularly high and contribute to dementia risk.[82,118] An Australian-based study demonstrated a low prevalence of neuropathologically-confirmed CTE in the general population, in people with and without neurodegenerative diseases.[119] Further work is required to explore the relationship between TBI and later life dementias in the WPR.

Social isolation

Higher levels of social engagement are an established protective factor against incident dementia.[1] Markers of social engagement include contacting friends, engaging in social or work activities, or participating in community groups.[120] A detailed assessment of social contact is difficult to obtain at an administrative level, where cohabitating with others is often used as a (more insensitive) proxy for social contact.[26]

Social isolation has been shown to increase the risk of incident dementia in Chinese, Japanese, Taiwanese, New Zealand and Australian population cohorts, a finding exacerbated by the restrictive public health measures taken during the COVID-19 pandemic.[27,121–123] People living with dementia and their caregivers are also more likely to report being socially isolated further compounding the problem and leading to more rapid decline.[124]

The range of the PAR of social isolation amongst different ethnic groups within WPR countries may reflect the varying importance of family and community.[26,27] Work in Australia and Aotearoa New Zealand consistently demonstrates lower reports of social isolation in Māori and Pacific peoples and Aboriginal and Torres Strait Islander peoples compared to non-Indigenous New Zealanders and Australians.[26,27] Connection with community and family structures within these populations are often prioritized and can be protective against some early life stressors.[82,125,126] Further research is required to evaluate the protective role of family bonds, community participation, connection to land, and spirituality in relation to healthy brain ageing.

Genetics and ethnicity

Genetic and lifestyle risk factors contribute to the development of Alzheimer's and vascular dementia with the majority of the global population at low to intermediate genetic risk.[127] The apolipoprotein E (*APOE*) ε4 allele is considered the strongest genetic risk factor for the development of AD in the general population, but prevalence of the allele and its clinical effect varies according to ethnicity.[128] *APOE* ε4 has also been shown to increase in the risk of DLB in Japanese and Korean cohorts and may influence the deposition of concomitant AD pathology.[129,130]

Across the WPR, *APOE* ε4 allele frequency ranges from 9% in Japan to 25% in Chinese populations.[131,132] The *APOE* ε4 allele frequency in Laotian ethnic minorities is higher compared to the general population (31.3% vs 12.0%).[131] Within Australia, the *APOE* ε4 allele frequency in Aboriginal Australians is 24%, higher than the global estimate of 14% for the Caucasian population.[83]

In a large US population-based study, Belloy et al. demonstrate that the *APOE4* allele confers a higher risk for East Asians compared to other ethnicities, with no protective effect seen for *APOE2*.[133] The phenotypic influence of this allele across a diversity of backgrounds is less established and there is a need for greater genomic data diversity to better understand molecular risk.[134] Minority populations in particular face disproportionate socioeconomic, cultural, and environmental inequities including, but not limited to, loss of cultural connectivity and childhood stress related to colonization (see Fig. 2).[26,82,83,135–137] Therefore, the impact of genetic risk must be understood in the context of these additional modifiable risk factors. Within the Australian migrant community, there are also marked disparities in the risk factors for dementia compared to people born in Australia, reflecting the pervasive effects of trauma, displacement, and loss on the process of brain ageing.[138] The influence of past (and continuing) societal attitudes and treatment on the biological present cannot be ignored and further analysis of the epigenetic changes that result is required.[139]

Non-Alzheimer's disease risk factors

Frontotemporal lobar degeneration syndromes

Frontotemporal dementia is understudied across the WPR, contributing to under-recognition and diagnosis in the community as well as healthcare settings. This review will focus primarily on genetic factors and metabolic disturbance although the authors acknowledge the need to explore other risk factors, including education, hearing loss and social isolation, and highlight the work of the Frontotemporal Dementia Prevention Initiative to expand the understanding of the disease, particularly in Australia and Aotearoa New Zealand.[140]

Genetic risk factors

Frontotemporal dementia contributes to younger onset dementia in the WPR with stronger genetic influences compared to AD and vascular dementia.[141,142] Chromosome 9 open reading frame 72 (*C9orf72*), microtubule-associated protein tau (*MAPT*), and progranulin (*GRN*) are the commonest monogenic mutations in the FTLD syndromes, with *MAPT* the most frequent pathogenic variant in a recent review of FTD in a Chinese population.[143] Research in Japanese and Chinese cohorts suggest similar clinical and neuropathological phenotypes compared to Caucasian populations.[144] However,

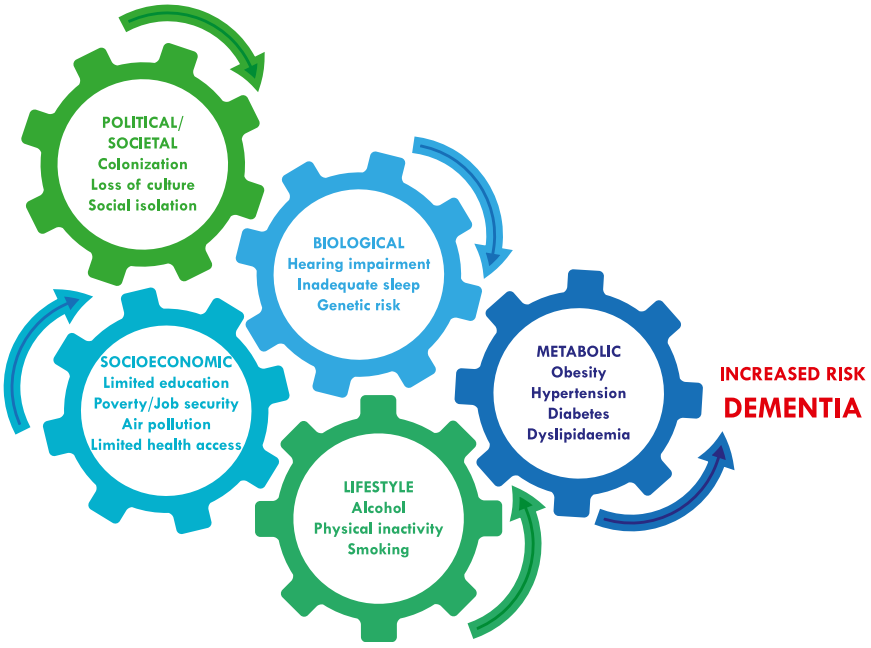

Fig. 2: **The interplay of multiple population- and individual-level risk factors for neurodegenerative dementias across the life course.**

cultural factors may contribute to reduced detection of FTD with significant under-reporting by families.[145]

Globally, 40% of FTD cases are associated with an autosomal dominant pattern of inheritance, with bvFTD and the non-fluent subtype of primary progressive aphasia (PPA) the most common phenotypes of genetic FTD.[146] With the significant genetic overlap between FTD and amyotrophic lateral sclerosis (ALS), much of the epidemiology of genetic risk for FTD in the region comes from the growing body of evidence related to ALS. There is a lower prevalence of *C9orf72* in Chinese and Korean populations compared to European populations.[147,148]

Abnormal accumulation of tau and/or TDP-43 accounts for the majority of pathologically confirmed FTD syndromes, as well as ALS.[149] Within the Western Pacific nation of Guam and the Kii peninsula in Japan, the role of TDP-43 in both FTD and ALS has been of much interest. The Guam parkinsonism–dementia complex (G-PDC) and Guam-ALS (G-ALS) are neurodegenerative disorders of TDP-43 accumulation with a clinical phenotype characterized by progressive cognitive impairment and extrapyramidal signs or motor neuron dysfunction.[147,150,151] Genetic risk is likely to partly account for the high prevalence of G-ALS disease on the Kii peninsula, with 20% of patients in this region harbouring the *C9orf72* expansion, although declining disease prevalence over the past half-century suggests that environmental factors may also influence disease manifestation.[151,152]

Metabolic disturbance

Changes in eating behavior represent one of the core behavioral criteria for diagnosis of FTD,[153] with alterations in lipid metabolism, insulin levels and central adiposity well-established as part of the FTD disease spectrum.[154–157] The subsequent increase in BMI, however, is less than would be expected given the observed hyperphagia.[158–160] Accordingly, there is debate as to whether eating changes in FTD may be a neuroprotective response.[161]

Lipid levels may also affect onset in ALS and FTD. Studies in Australasian and Asian populations suggest that there is an increased incidence of hyperlipidemia in those with ALS and that this may positively influence survival.[155,162] With rising obesity and metabolic dysfunction seen in some Western Pacific countries, further analysis of the intersection between diet, lipid levels and genetic predisposition in the onset and progression of FTD is of vital importance.[155]

Risk factors for disease progression

Much of the large-scale disease prevention strategies are informed by population-level risk. Clinical and pathological heterogeneity at the individual case level, however, contribute to non-linear disease progression across the dementias. As the era of therapeutic trials and precision medicine approaches, there is growing interest in more accurate prediction of disease onset and progression using objective, multidomain metrics of clinical, imaging and biomarkers of disease to predict disease outcomes in individual patients.

Alzheimer and vascular dementias

Whilst medial temporal lobe grey matter is commonly viewed as the primary site of AD pathological changes,

evidence from structural and functional connectivity imaging studies shows significant micro- and macrostructural white matter loss is associated with cognitive change.[163,164] These changes can occur independently of PET-proven amyloid accumulation and suggest the need to consider the contribution of cardiovascular risk factors to the progression of AD as well as its onset.[164] For example, in stroke survivors, white matter neurodegeneration, a crude marker of elevated cardiovascular risk, is amplified compared to the stroke-free population and linked to early cognitive impairment.[165,166]

Translation of imaging findings to a predictive tool for individual patients requires longitudinal assessment of ethnically diverse cohorts with stratification by concomitant vascular disease. For example, the burden of cerebral small vessel disease is higher in Asian populations, with white matter intensities significantly more prevalent in Han Chinese compared to Caucasian Australians.[167,168] Within Asian populations, a higher burden of cortical and subcortical atrophy is seen in the Malay and Indian populations in Singapore compared to the Chinese population.[169] Future computational and statistical modelling that incorporates demographic, clinical, imaging and biomarker data are likely to be most effective at predicting individual disease progression.[170]

Frontotemporal lobar degenerative syndromes

Large-scale, longitudinal follow up studies of patients with FTD are lacking, particularly in the WPR. Nonetheless, observational cohort studies support several clinical factors that influence disease progression. Patients with FTD-ALS overlap progress more rapidly than patients with pure ALS or pure FTD,[171] and those with FTD-ALS and initial motor onset progress more rapidly than those with cognitive onset, suggesting that motor function affects survival.[172] The metabolic changes seen in FTD-ALS patients are of particular interest with lower total cholesterol levels a predictor of shorter survival in some cohorts.[173,174]

Monogenic mutations in *MAPT* and *GRN* and autosomal dominant mutations are predictors of poorer survival in FTD.[175–177] Work by the Diagnosing Inherited Non-Alzheimer Dementia and New Zealand Genetic Frontotemporal Dementia studies is of particular interest in the Australasian region which will help to examine the interplay between genetic risk and environmental influences on disease progression.[178]

A multifaceted manifesto for change

Models of dementia care differ vastly across the WPR, reflecting differences in disease perception and detection. Dementia literacy is low across the region, particularly in low- and middle-income countries.[32] Existing work shows a prominent misconception among the public that dementia is a normal part of ageing and is not preventable.[179] However, such surveys rarely canvas public impressions of dementia risk and prevention in Asian or low- and middle-income countries, where stigma relating to dementia and factors such as filial piety and elder care are often culturally embedded.[17,180]

Even with adequate detection of disease, much of the WPR is under-resourced to manage the predicted dementia epidemic. With the breadth of established risk factors for dementia spanning biomedical, social, and cultural factors, a multidisciplinary approach is critical. The Worldwide FINGERS network highlights the potential for multidisciplinary prevention pathways, now involving several Western Pacific countries (China, Australia, Japan, Korea, Singapore) in tailored versions of the multi-domain intervention trial comprising diet, physical and social activity, cognitive training, and vascular and metabolic monitoring.[181] Outside population-based research trials, a collaborative health and social care approach in community and specialist care is likely to address multiple risk factors concurrently and facilitate local adaptation of global risk reduction guidelines.[182] In particular, more focus is required on delaying dementia diagnosis in women in the WPR by increasing educational opportunities and including studies that evaluaate the effects of pregnancy and menopause on dementia risk.[9]

Involvement of the WPR in large scale population based longitudinal studies is imperative to provide accurate results from diverse ethnic and cultural regions. Additionally, involvement of Western Pacific countries will also afford access to pharmaceutical trials and new treatment approaches. The recent accelerated approval of disease modifying therapies in the United States of America provides a window into the sheer scale of resources required for the early detection and treatment of AD.[183] Patients will need access to biomarker and imaging assessments and consideration must be given to the use and reimbursement of genotype testing.[184] Current gene therapies for the FTLD syndromes also involve significant costs.

The authors strongly advocate for the rapid development of a whole-of-society, adaptive and targeted approach for dementia risk reduction and care in the WPR. Further research is required to understand the major determinants of dementia within the sociocultural, economic, and geopolitical diversity in the region. The experiences of countries with older populations and established dementia cases can be used to inform models of dementia care in neighbouring countries as they face rapid growth in both dementia cases and risk factors for the disease. Widespread financial and educational changes need to be made to support dementia diagnosis, including education and support for family caregivers, training for health and social care professionals, and appropriate community-based,

integrated care for older adults that also fosters technological and social innovation to promote healthy ageing.

Contributors

Dr Antonia Clarke literature search, co-design of figures, writing, editing, and finalizing the manuscript. Professor Amy Brodtmann writing and editing the manuscript. Professor Muireann Irish writing and editing the manuscript. Dr Loren Mowszowski writing and editing the manuscript. Dr Kylie Radford writing and editing the manuscript. Professor Sharon L. Naismith writing and editing the manuscript. Professor Vincent C.T. Mok writing and editing the manuscript. Professor Matthew C. Kiernan writing and editing the manuscript. Professor Glenda M. Halliday writing and editing the manuscript. Associate Professor Rebekah M. Ahmed conceptualizing the review, writing, editing, verifying and finalising the manuscript.

Data sharing statement

This review is a summary of peer-reviewed, published reports and articles which readers may access as required.

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