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RESEARCH ARTICLE

Population attributable fraction of modifiable risk factors for dementia in Chile

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Abstract

Introduction: Projected dementia incidence in Latin America and the Caribbean for the next decades is overwhelming. Access to local data, stratified by sex, is imperative for planning precise dementia-prevention strategies.

Methods: We analyzed the individual and overall weighted population attributable fraction (PAF) of nine modifiable risk factors for dementia, in dementia-free subjects ≥45-years-old, using the 2016-2017 Chilean National Health Survey.

Results: The overall weighted PAF for modifiable risk factors was 45.8% (42.2% to 49.3%). Variables with the highest PAF were lower education, high blood pressure, hearing loss, and obesity. Women showed a greater overall weighted PAF: 50.7% (45.3% to -56.1%), compared to men: 40.2% (35.4% to 45.0%), driven by a higher PAF for physical inactivity and depression in women.

Discussion: The PAF for modifiable risk factors for dementia in Chile is higher than in previous world reports, due to a greater prevalence of cardiovascular risk factors. Women have a higher potential for dementia prevention.

HIGHLIGHTS:

- The proportion of dementia associated to modifiable risk factors in Chile is 45.8%.
- The main modifiable risk factors are high blood pressure, obesity, and hearing loss.
- Women had a greater prevalence of physical inactivity and depression than men.
- Chile had a greater prevalence of metabolic risk factors than other world regions.

KEYWORDS
cardiovascular, dementia, depression, hypertension, Latin America and the Caribbean, midlife, modifiable risk factors, obesity, physical inactivity, population attributable fraction, prevention

1 | INTRODUCTION

Latin America and the Caribbean (LAC) is one of the world's regions with the highest dementia prevalence in individuals ≥60 years of age.[1] Even more alarmingly, the number of people living with dementia is projected to increase 4-fold from 2015 to 2050,[2] due to the accelerated aging of the population.[1] Preventive strategies targeting modifiable risk factors for dementia might moderate this increment.[3–5] For instance, in some high-income countries (HICs) of North America and Europe, age-adjusted dementia incidence had been declining over the last decades.[6–8] This reduction could be attributed to overall higher educational levels and better control of cardiovascular morbidity.[6,7] Unfortunately, less than 5% of the research associated with dementia prevention has been carried out in LAC.[9,10] LAC is a very diverse region, both ethnically and culturally,[11] and according to the World Bank income classification,[11,12] it comprises low and middle-income countries (LMICs), upper middle-income countries, and HICs.

Previous reports on dementia prevention opportunities have focused on population attributable fractions (PAFs), which estimate the proportion of disease cases that would not occur in a population if an individual risk factor were eliminated.[10] In 2019, Mukadan et al. determined the PAF of nine potentially modifiable risk factors for dementia (lower education, hearing loss, hypertension, obesity, smoking, depression, physical inactivity, social isolation, and diabetes) in a representative population of LMICs[10]: China, India, and six LAC countries, with cross-sectional data from participants ≥65 years of age who were evaluated between 2004 and 2006.[13] This study reported that the overall weighted PAF in LAC was 55.8% (54.9 to 56.7), compared to 39.5% (95% confidence interval [CI] 37.5 to 41.6) in China and 41.2% (39.1 to 43.4) in India.[10] The overall weighted PAF in LAC was also higher than previous world estimations of 35% (34.1 to 35.9) using the same variables.[14] A lower estimation had been reported recently in Brazil of 32.3% (15.8 to 46.3); however, that report included only seven modifiable risk factors; hearing loss, one of the most important risk factors for dementia, was not included.[15]

Updating the analysis of the PAF for nine modifiable risk factors for dementia (lower education, hearing loss, high blood pressure, obesity, smoking, depression, physical inactivity, alcohol excess, and diabetes)[14] in an LAC country is highly relevant, given that previous study in this region was performed using data obtained more than 15 years ago.[10,13] It is important to note that the most relevant epidemiological changes regarding dementia incidence have occurred during the last 20 years.[7,16] Moreover, no previous study carried out in LAC has analyzed the PAF of modifiable risk factors for dementia during midlife and later-life stages[10,17]; this is especially important given that some risk factors related with dementia occur mainly in midlife.[6,14] In addition, there are no other reports of the PAF for multiple dementia risk factors stratified by sex, despite the relevance of sex regarding precise strategies for dementia prevention.[18]

Our aim is to estimate the individual and overall weighted PAFs of nine modifiable risk factors for dementia in Chile, and to compare them between sexes and between midlife and later-life stages.

RESEARCH IN CONTEXT

1. Systematic review: We reviewed the literature (PubMed) for research studies investigating the "Population attributable fraction (PAF) of risk factors for dementia." We found nine studies, most of them carried out in Europe, the United States, and Asia, analyzing only seven risk factors, without including hearing loss. When comparing between world regions, Latin America and the Caribbean (LAC) had the highest overall PAF of nine risk factors for dementia, but it used data from 2006.
2. Interpretation: We updated the LAC data by using the 2017 Chilean National Health Survey. The weighted PAF of nine modifiable risk factors for dementia was 45.8 (42.2 to 49.3); women presented a higher PAF than men, with depression and physical inactivity being the main drivers of the difference.
3. Future directions: For more precise prevention strategies, future analysis should include local updated data about the relative risk of dementia risk factors, and must be stratified by sex.

2 | METHODS

2.1 | Study design

We analyzed the data from the third Chilean National Health Survey (Ch-NHS) carried out between October 2016 and March 2017, which collected health information from a representative sample of Chileans over 15 years of age. This survey was commanded by the Chilean Ministry of Health and carried out by the Pontificia Universidad Católica de Chile. The sample design was probabilistic, geographically stratified, and multi-staged. It included 6233 participants (household response rate 66%, rejection rate 9.8%) who were interviewed during a first visit using structured questionnaires. In a second visit, anthropometric and laboratory measurements were obtained by trained personnel. All participants provided written informed consent.[19]

2.1.1 | Subject selection

Our analysis included subjects ≥45 years of age, as this group presents the highest risk of developing dementia within the next 20 years. We excluded from the total sample those participants with suspected cognitive impairment by using the shortened Chilean version of the Mini-Mental State Examination (SCh-MMSE) (cutoff score <13/19).[20]

2.1.2 | Health problems associated with dementia

We selected the nine risk factors listed below, which have been associated with dementia in recent meta-analysis.[10,14] For a prevalence

TABLE 1 Definitions of the nine dementia risk factors used for the analysis

Lower education: When not receiving more than primary education in early life (<7 years of scholarship)
Hearing loss: Self-reported by the negative response to any of these questions: Do you think you hear normally by both ears? Are you able to follow a TV program at a volume acceptable to others? Are you able to follow a conversation of three or more people?[19]
High Blood Pressure: If systolic blood pressure (SBP) >140 mm Hg (the average of three measurements with the participant in a sitting position after 20 min rest), independently if subjects had the diagnosis of hypertension or where in treatment for it.
Obesity: Body mass index (BMI) ≥ 30 was calculated by dividing weight (kilograms) by height (meters squared)
Smoking: Self-reported by the affirmative response to: Do you currently smoke cigarettes?
Depression: Suspected major depression in the last 12 months according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), was assessed with the Composite International Diagnostic Interview Short Form for depression (CIDI-SF) by a trained interviewer.
Physical inactivity: Defined when scored as low physical activity according to the Global Physical Activity Questionnaire version 2 (GPAQ),[21] previously validated in Latin America and the Caribbean (LAC).
Diabetes: Self-report and/or medical treatment for diabetes, or fasting blood glucose ≥126 mg/dL (≥7.0 mmol/L).
Alcohol excess: (>21 units/week) was measured using two questions of the validated Chilean version[22] of the Audit questionnaire: When you drink alcohol, how many drinks (units) do you usually have on average per day? How often do you drink any alcoholic beverage? The results were shifted-up 20.3% to match results from the apparent per-capita alcohol consumption.

estimate, whenever possible, we used the same dichotomic definition of the studies where the relative risk for the association with dementia was obtained.[4,5,10,14]

2.2 | Data analyses

All analyses were performed using the statistical software R project (packages survey, psych), considering the weights of the sample design and the maximum complete cases available. No imputation procedure was used for missing data. The prevalence of the dementia risk factors was estimated using criteria described in Table 1. We used the relative risk (RR) attributed to each risk factor reported in previous cohort studies that compared the risk of developing dementia between people with and without the presence of the corresponding risk factor.[4,5,10,14] Further on, by using the prevalence and the RR of each risk factor, we estimated each individual PAF.[10,14]

Eq. 1. *Population Attributable Fraction (PAF)*

$$PAF = P(RR-1)/(1+P[RR-1]) \quad (1)$$

P = Prevalence, RR = relative risk of each risk factor.

To include uncertainty around the PAF's estimation, we used Monte Carlo simulations (n = 10,000) according to distributional assumptions (beta distributions for prevalence and normal distributions for the logarithm of relative risks). The mean and the 2.5% and 97.5% quantiles obtained from PAF distributions were reported.

Because the PAFs from different risk factors share similar causal mechanisms, each individual PAF was weighted using the *communalities*, which are the proportion of common variance between them, extracted from a principal component analysis based on a tetrachoric correlation matrix. To decide how many components would be used to obtain communalities, we used a parallel analysis method.[23]The retained components were then used to calculate the communalities.

Eq. 2 *Contribution of each risk factor to the overall PAF.*

$$Weight = 1 - communality \quad (2)$$

Then weights were applied to produce the weighted PAFs. The weighted PAFs allow the estimation of a global PAF combining all nine risk factors as shown in Equation 3.

$$Overall\ PAF = 1 - [(1 - weight1 * PAF1)$$
$$(1 - weight2 * PAF2) \ldots (1 - weight9 * PAF9)] \quad (3)$$

Finally, individual weighted PAFs were re-calculated to add the overall PAF.

$$Weighted\ PAF = \frac{(individual\ weighted\ PAF)}{(\sum individual\ weighted\ PAF)} x\ (overall\ PAF) \quad (4)$$

We stratified the analyses by sex and two age groups: 45- 64-years-old or "midlife," and older than 65 years or "later-life." A secondary analysis was carried out in the later-life group excluding obesity and high blood pressure.[6] The overall PAF for the total Chilean population ≥45-years-old was obtained as averages of each overall PAF stratified by age and sex (reported in Table 4) weighted by the population distributions informed by the Chilean National Statistics Institute for 2017[24] reported in Table 2. The same procedure was done to obtain the overall PAF in ≥45-years-old stratified by sex (weighted by population proportion of each age group).

3 | RESULTS

Of the 3579 participants who were ≥45-years-old, 247 had suspected cognitive impairment and were further excluded from the analysis. The description of the sample stratified by sex and

TABLE 2 Demographic characteristics of the selected sample from the 2017 Ch-NHS and of the 2017 Chilean population

Variables			Number*	Survey proportion*	Chilean Population proportion 2017**
Sex	Women	45-64	1301	13%	12%
		≥65	869	6%	6%
	Men	45-64	736	12%	12%
		≥65	473	4%	5%
Age Groups	Midlife (45-64)	2037	25%	24%	
	Later life (≥65)	1342	10%	11%	
Total	≥45	3379	35%	35%	

*Without cognitive impaired subjects.
**According to Chilean census 2017[24].

TABLE 3 Prevalence of dementia risk factors, communalities, individual, and total weighted PAF in midlife and later life

		Midlife (45-64 years old)			Later life (≥65-years-old).				
Risk Factor	RR (95% CI)	Prevalence %	Com-munality	PAF %	Weighted PAF %	Prevalence %	Com-munality	PAF %	Weighted PAF %
Low Education	1.6 (1.3-2.0)	16.4 (13.6-19.3)	0.69	9.1 (4.5-14.4)	**3.3 (1.6-5.3)**	50.0 (43.9-56.2)	0.308	23.0 (12.5-33.4)	**11.6 (6.8-16.7)**
High blood pressure	1.6 (1.2-2.2)	23.5 (19.7-27.3)	0.83	12.5 (4.2-22.0)	**4.6 (1.3-7.9)**	55.0 (47.6-62.4)	0.4	24.5 (9.0-39.2)	**10.5 (4.5-16.3)**
Obesity	1.6 (1.3-1.9)	42.9 (37.7-48.0)	0.26	20.4 (12.1-29)	**9.5 (5.8-13.7)**	37.6 (31.8-43.5)	0.37	18.4 (10.7-26.5)	**8.5 (4.9-12.4)**
Hearing Loss	1.9 (1.4-2.7)	23.4 (19.6-27.2)	0.63	17.5 (7.9-27.9)	**4.9 (2.2-7.9)**	43.3 (37.0-49.5)	0.56	27.8 (13.5-41.8)	**9 (4.6-13.6)**
Smoking	1.6 (1.2-2.2)	30.5 (26.3-34.7)	0.42	15.5 (5.4-26.6)	**6.7 (2.4-10.8)**	12.8 (9.2-16.5)	0.42	7.3 (2.2-13.5)	**3.1 (0.7-5.7)**
Depression	1.9 (1.6-2.3)	19.8 (15.7-23.9)	0.65	15.1 (9.9-20.9)	**1.1 (0.7-1.6)**	9.8 (7.4-12.3)	0.39	8.2 (5.1-11.9)	**3.7 (2.1-5.5)**
Physical inactivity	1.4 (1.2-1.7)	33.6 (29.3-37.8)	0.59	11.9 (5.6-18.4)	**3.3 (1.6-5.3)**	46.7 (41.2-52.1)	0.28	15.6 (7.2-23.7)	**8.2 (4-12.6)**
Diabetes	1.5 (1.3-1.8)	20.1 (16.5-23.8)	0.63	9.2 (5.0-13.6)	**4.9 (2.6-7.5)**	32.5 (27.6-37.4)	0.87	14.0 (8.0-20.3)	**1.3 (0.7-2.1)**
Alcohol excess	1.2 (1.1-1.3)	5.4 (3.1-7.7)	0.3	1.1 (0.5-1.9)	**0.6 (0.2-1)**	1.4 (0.3-2.5)	0.41	0.3 (0.1-0.6)	**0.1 (0-0.3)**
Overall PAF					**38.8 (32.2-45.4)**				**56 (48.1-64)**

RR , relative risk; PAF, population attributable fraction. Data are means (2.5%-97.5% uncertainty intervals).

age groups is detailed in Table 2. Missing data details are in Table A1.

3.1 | Dementia risk factors characteristics

Risk factor prevalence, relative risk, individual unweighted and weighted PAFs, and communalities are shown stratified by age in Table 3, and by sex and age in Table 4.

After adjusting each individual PAF for communalities, the individual weighted PAF was significantly reduced (Tables 3 and 4).

3.1.1 | Comparison between age groups

The prevalence of the majority of the risk factors was greater in the later-life group (lower education, high blood pressure, physical inactivity, and diabetes). Meanwhile, smoking and depression were more prevalent in the midlife group; prevalence of obesity and alcohol excess presented no significant differences (Table 3, Figure 1). The communalities between risk factors were greater in the midlife group than in the later-life group, with six of nine risk factors presenting communalities > 0.5, versus two of nine in the later-life group. The overall PAF was higher in the later-life than in the midlife group: 56.0% (48.1 to 64.0) versus 38.8% (32.2 to 45.4), respectively (Table 3). The sensitivity analysis, excluding high blood pressure and obesity, from the overall PAF for subjects ≥65-years-old resulted in a significant drop in the total PAF to 32.8% (26.1 to 39.4) (Table A2).

3.1.2 | Comparison between sexes

Women showed a higher prevalence of depression and physical inactivity than men at both age groups, whereas alcohol excess was more prevalent in midlife men than in women (Table 4, Figure 1). Women tend to show a higher overall PAF than men at both age groups (Table 4 and Figure 2).

TABLE 4 Prevalence of dementia risk factors, communalities, individual, and total weighted PAF in midlife and later life separated by sex

MIDLIFE	Women Midlife					Men Midlife			
	RR (95% CI)	Prevalence %	Comm-unality	PAF %	Weighted PAF %	Prevalence %	Comm-unality	PAF %	Weighted PAF %
Low Education	1.6 (1.3-2.0)	19.7 (15.5-23.9)	0.69	10.6 (5.2-16.8)	**2.7 (1.2-4.3)**	13.0 (9.2-16.8)	0.47	7.3 (3.3-12.1)	**3.3 (1.4-5.38)**
High blood pressure	1.6 (1.2-2.2)	20.7 (15.5-25.9)	0.83	11.2 (3.5-20.0)	**1.5 (0.4-2.7)**	26.6 (21.1-32.0)	0.70	13.8 (4.6-24.2)	**3.52 (1.08-5.98)**
Obesity	1.6 (1.3-1.9)	48.7 (41.4-56.0)	0.26	22.6 (13.3-31.9)	**13.5 (8.5-18.6)**	36.4 (29.1-43.7)	0.49	17.9 (10.2-26.1)	**7.73 (4.49-11.2)**
Hearing Loss	1.9 (1.4-2.7)	24.1 (18.9-29.2)	0.63	17.9 (8-29.2)	**5.3 (2.3-8.6)**	22.7 (17.1-28.2)	0.82	17.0 (7.6-27.7)	**2.53 (1-4.2)**
Smoking	1.6 (1.2-2.2)	29.8 (24.5-35.1)	0.42	15.1 (4.9-26.0)	**7 (2.5-11.6)**	31.2 (24.7-37.7)	0.64	15.8 (5.1-27.2)	**4.75 (1.58-7.91)**
Depression	1.9 (1.6-2.3)	27.5 (20.8-34.1)	0.65	19.8 (13.2-27.3)	**5.7 (3.5-8.2)**	11.7 (7.0-16.5)	0.46	9.6 (5.2-14.7)	**4.4 (2.29-6.72)**
Physical inactivity	1.4 (1.2-1.7)	39.7 (33.6-45.9)	0.59	13.7 (6.3-21.2)	**4.5 (2.1-7.2)**	27.1 (21.1-33)	0.70	9.8 (4.4-15.8)	**2.44 (0.96-4.02)**
Diabetes	1.5 (1.3-1.8)	22.0 (17.2-26.9)	0.63	9.9 (5.5-15.0)	**2.9 (1.5-4.5)**	18.0 (12.5-23.5)	0.31	8.2 (4.4-12.9)	**4.73 (2.32-7.33)**
Alcohol excess	1.2 (1.1-1.3)	1.1 (0-2.5)	0.30	0.2 (0-0.6)	**0.2 (0-0.3)**	10.4 (5.7-15.1)	0.42	2.0 (0.9-3.6)	**1.02 (0.33-1.79)**
Overall PAF					**43.2 (36.2-50.4)**				**34.42 (28.6-40.19)**
LATER LIFE	**Women Later life**					**Men Later life**			
Low Education	1.6 (1.3-2.0)	52.4 (45.7-59)	0.30	23.8 (12.8-34.3)	**11.2 (6.4-16.2)**	46.9 (35.6-58.2)	0.32	21.9 (11.5-32.6)	**10.9 (6-16)**
High blood pressure	1.6 (1.2-2.2)	50.7 (43.3-58.2)	0.30	23.3 (8.9-37.5)	**10.8 (4.6-16.9)**	60.6 (46.7-74.4)	0.47	26.4 (9.9-41.8)	**10.4 (4.5-16)**
Obesity	1.6 (1.3-1.9)	43.6 (36.2-50.9)	0.29	20.7 (12-29.4)	**9.9 (5.9-14.3)**	30.0 (20.5-39.5)	0.47	15.2 (7.9-23.4)	**6 (3-9.5)**
Hearing Loss	1.9 (1.4-2.7)	41.4 (34.2-48.5)	0.37	27 (12.9-40.7)	**11.4 (5.9-17)**	45.8 (34.8-56.8)	0.44	29.1 (14.0-44.0)	**12 (6.4-17.8)**
Smoking	1.6 (1.2-2.2)	9.8 (6.3-13.3)	0.43	5.7 (1.7-10.9)	**2.2 (0.5-4)**	16.9 (9.8-23.9)	0.39	9.2 (2.6-17.9)	**4.2 (0.8-7.6)**
Depression	1.9 (1.6-2.3)	14.3 (10.2-18.3)	0.48	11.4 (7.0-16.6)	**4 (2.3-5.9)**	4.0 (2.2-5.8)	0.42	3.5 (1.9-5.8)	**1.5 (0.7-2.5)**
Physical inactivity	1.4 (1.2-1.7)	51.5 (44.6-58.5)	0.16	17 (8.2-25.9)	**9.5 (4.8-14.4)**	40.1 (31.3-49.0)	0.64	13.7 (6.4-21.6)	**3.7 (1.7-6)**
Diabetes	1.5 (1.3-1.8)	34.9 (28.3-41.6)	0.39	14.9 (8.4-21.9)	**6.1 (3.3-9.1)**	29.3 (22.2-36.5)	0.43	12.8 (7.1-19.3)	**5.4 (2.8-8.4)**
Alcohol excess	1.2 (1.1-1.3)	0.4 (0-1.1)	0.29	0.1 (0-0.3)	**0.1 (0-0.1)**	2.7 (0.5-4.9)	0.42	0.5 (0.2-1.2)	**0.2 (0-0.5)**
Overall PAF					**65.1 (57.3-73)**				**54.3 (45.8-62.6)**

RR = relative risk. PAF = population attributable fraction. Data are means (2.5%-97.5% uncertainty intervals).

3.2 | The total overall PAF in subjects ≥45-years-old

The total overall PAF in subjects ≥45-years-old was 45.8% (42.2 to 49.3). Although it resulted in a higher overall PAF in women (50.7%, 45.3 to 56.1) than in men (40.2%, 35.4 to 45.0).

4 | DISCUSSION

This is the first study of the population attributable fraction of risk factors for dementia in Chile, and the first one that compares multiple dementia risk factors by sex. We found that 45.8% of dementia cases could be attributed to nine modifiable dementia risk factors. Women presented a higher overall PAF of dementia risk factors than men; likewise, the PAF was higher in later-life than in midlife.

The greater overall PAF in later-life than in midlife is related to the higher prevalence of the majority of the risk factors in the later-life group. The risk factors with the highest individual weighted PAF for dementia in the later-life group were lower education, high blood pressure, and hearing loss, whereas in the midlife group, the variables with the highest individual weighted PAF were obesity, smoking, and hearing loss. To compare our results with other studies of PAFs for dementia risk factors, differences in methodology must be taken into account (considering the evaluation of communalities between risk factors, risk factor definition, and type and number of risk factors included), as well as the source of the risk factors used in the analysis. Because PAFs from different risk factors share similar causal mechanisms, we adjusted each individual PAF by communalities; therefore, we discuss only studies that weighted their PAFs between risk factors. The overall weighted PAF in the later-life group of our study was similar to the results of the previous largest LAC study that analyzed a pooled PAF of six other LAC countries: 55.8% (54.9 to 56.7), using similar nine risk factors (we used alcohol excess instead of social isolation), for a population ≥65-years-old.[10] Accordingly, they found the same risk factors with the highest individual PAF,[10] conferring important reliability to our results.

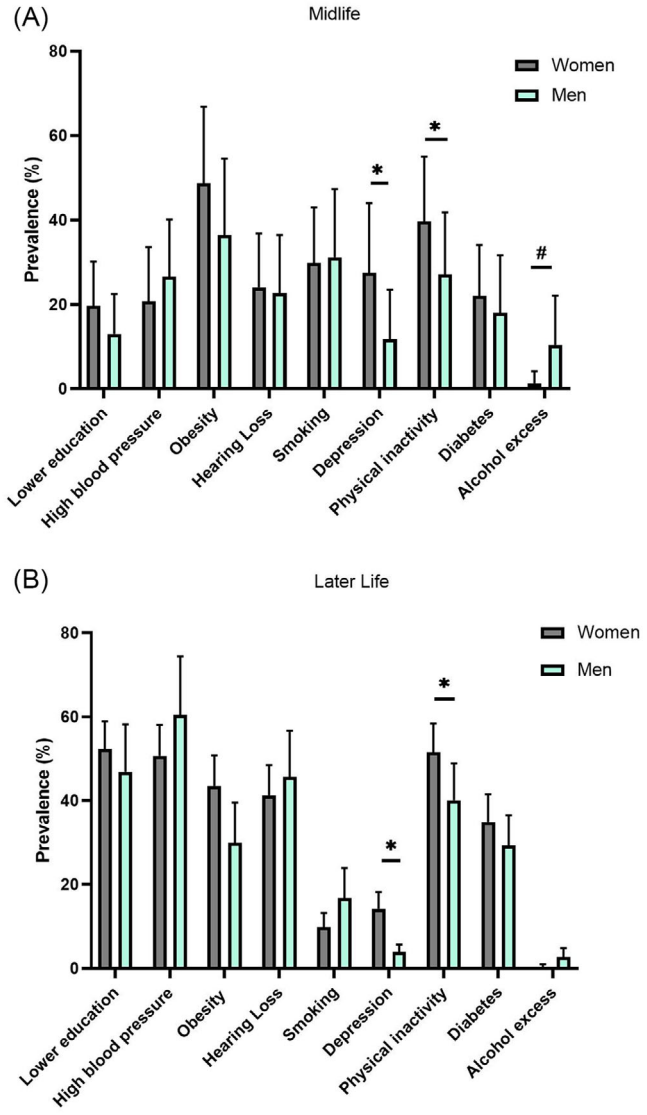

FIGURE 1 Sex comparison of dementia risk factors prevalence. (A) Midlife, (B) Later life. *Women had larger prevalence than men; #men had larger prevalence than women

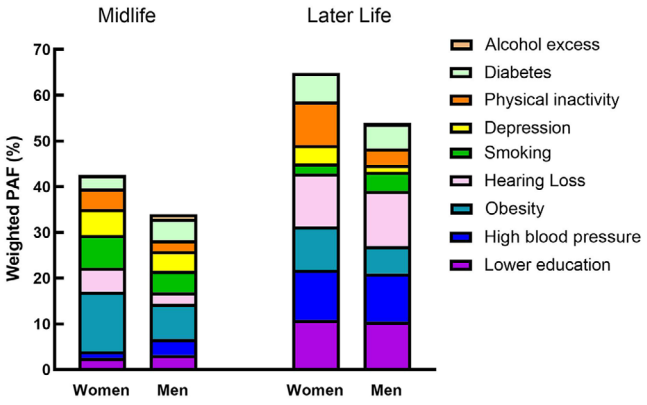

FIGURE 2 Individual and overall weighted population attributable fraction (PAF) for dementia risk factors stratified by sex and age groups

When comparing with the global PAF of the 2017 world report, 35.0% (34.1-35.9),[14] which analyzed similar nine risk factors in the population ≥45-years-old, our overall weighted PAF of 45.8% (42.2 to 49.3) was greater. These differences are driven by the higher prevalence of metabolic risk factors in Chile (high blood pressure, obesity, and diabetes), which doubles or triples the world estimations.[4,5,14,25] Consequently, after excluding high blood pressure and obesity from the overall PAF in subjects ≥65-years-old, this value would drop significantly (Table S2) resulting in an overall PAF in subjects ≥45-years-old similar to the world proportion. A recent meta-analysis incorporated three additional risk factors compared to the previous world report, encompassing a total of 11 risk factors for dementia (including alcohol excess, traumatic brain injury, and air pollution), increasing the overall PAF of the 2020 world report to 40%.[25] Other studies analyzed only seven risk factors (lower education, hypertension, obesity, smoking, depression, physical inactivity, and diabetes), excluding hearing loss and social isolation.[4,5,15,26–28] These studies showed an important variability in the overall PAF for dementia risk factors, from 24% in Mozambique[15] to 48% in Australia,[26] with the great majority presenting an overall PAF near 30%.[15,27,28] This would leave our overall weighted PAF in subjects ≥45-years-old in the highest range.[26] This variability is determined largely by the different prevalence of some risk factors.[26]

In summary, in Chile the overall PAF is similar to previous LAC reports, and to other HICs that presented a high prevalence of metabolic risk factors, such as Australia and Portugal.[4,10,14,15,26] These results suggest that the advanced epidemiological transition in Chile has been associated with a rapidly increased incidence of metabolic risk factors, especially obesity and diabetes.[29] Indeed, obesity accounted for the highest PAF for dementia during midlife for both sexes. In Chile, both obesity and underweight had been associated with cognitive impairment in subjects older than 60.[30] The proportion of subjects with obesity has increased significantly during the last decade in Chile and worldwide,[19] with a higher proportion in women than in men.[19,31] Worryingly, Chile, Mexico, and Costa Rica are the countries with the highest prevalence of child obesity (2- to 19-years-old) worldwide[31]. In fact, in LAC, high body mass index is the main risk factor for age-adjusted disability-adjusted life-years (DALYs) of all causes.[12] Closely associated with overweight and obesity[12], diabetes has been increasing during the last decades in Chile[19] and worldwide,[12] being especially significant in the midlife group. In relation to high blood pressure in Chile, 55% of persons ≥65-years-old have a systolic blood pressure (SBP) >140 mm Hg, which is similar to the prevalence of high blood pressure in other LAC countries[12] and the United States,[5] but is much higher than that reported in other parts of the world.[12] Although most epidemiological studies[4–6,10,14] suggest that midlife, but not late-life, high blood pressure is associated with an increased risk of dementia,[4,6] longitudinal cohorts demonstrate that the persistence of high SBP into later-life also increases the risk of dementia.[32] Furthermore, there is increasing evidence for the benefits of reducing SBP in older people,[33] as high blood pressure. is the leading cause for attributable DALYs in persons >50-years-old worldwide.[12] In accordance with the greater prevalence of metabolic risk factors for dementia in Chile, high cardiovascular risk factors are the main risk factors for mild cognitive

impairment in "Latinos" living in the United States.[34] Similarly, an anatomopathological study in Brazil[35] showed a greater prevalence of vascular dementia than in other parts of the world.

Comparable to other reports,[10,14,25] hearing loss was one of the most significant risk factors for dementia in our study, both in midlife and later-life.[14] The association between hearing loss and dementia has been established for subjects ≥45-years-old with a hearing threshold >25 dB.[36] One of the limitations of our study is that we do not have an objective measurement of hearing loss, and self-report probably underestimates the real prevalence of hearing impairment compared with audiometry in subjects >50-years-old who tend to underreport hearing loss.[37] Despite this limitation, self-perceived hearing loss is also associated with an accelerated cognitive decline.[38] Because it is closely related with the aging process, the number of subjects with disabling hearing loss is expected to increase, and 80% of the population with this condition live in LMICs.[39] Another prevalent risk factor was current smoking, mostly present in the midlife group in our study. In fact, smoking is one of the modifiable risk factors with the highest PAF for dementia[4] worldwide. Fortunately, its prevalence is descending globally.[12]

Lower education was mostly significant in the older group, where more than 50% of the population have fewer than 7 years of formal education. This risk factor has been described as presenting the highest PAF for dementia worldwide, given its great estimated prevalence.[4,8,10,25] It is associated with a lower cognitive reserve, a greater proportion of risk factors, and an increased risk of brain injury.[40] Fortunately, Chile has established 12 years of compulsory and free schooling, similarly to many other LAC countries,[11] and consequently this risk factor is declining in LAC.

Our most novel result was the sex differences in dementia risk factors. We found that women had a higher overall PAF for dementia risk factors than men. This was driven by the greater prevalence of physical inactivity and depression, and a tendency for obesity in women compared to men (Table 4, Figures 1 and 2). The prevalence of depression was almost 3-fold higher in women than in men, at each age group, reflecting a higher burden of depression in Chile, similar to worldwide reports.[41] Multiple meta-analyses have corroborated that a history of depression throughout the life course confers an increased risk for later developing Alzheimer's disease and other dementias.[4,5,14] Our study's reported prevalence of depression in the last 12 months was similar to previous Chilean reports of lifetime prevalence of affective disorders, showing 16.7% to 18.4% in midlife and 10% in subjects ≥65-years-old, conferring consistency to our data.[42]

Our study revealed physical inactivity as one of the main drivers of a higher PAF in women than in men, being more prevalent in women than in men worldwide, especially in low socioeconomic backgrounds.[43] This finding matches other studies, which estimate that physical inactivity is one the most important risk factors for dementia in women in LMIC.[44] In Chile, physical inactivity had been associated previously with cognitive impairment in persons >60-years-old,[45] most probably given its relation to the majority of metabolic risk factors and cardiovascular disease, as it is one of the main modifiable factors for noncommunicable diseases.[43]

Our findings most likely reflect global differences in sociocultural status between sexes, as women have less access to a complete education,[11,] coupled with more familiar responsibilities such as child and parent care,[46] which is associated with a lower income and a higher burden of mental morbidity.[41] These findings are of special relevance for health policies in dementia prevention, because women present a higher prevalence of Alzheimer's disease and other dementias than men.[18] In addition, women live longer, thus contributing a greater proportion to dementia burden.[18]

4.1 | Study strengths and limitations

We employed data from the 2017 Ch-NHS, a nationally representative sample of the Chilean population. Furthermore, the Ch-NHS allows us to assess several risk factors in an objective and reliable manner (SBP, anthropometrics, fasting glucose) instead of using self-reported data.[17] Unlike other studies,[4,5,14,15,26] all of our analyses (prevalence, communalities, and overall PAF) come from the same information source, assuring a high internal consistency. In addition, the overall PAF was adjusted considering the communalities between risk factors. Unfortunately, the Ch-NHS did not have reliable data for some risk factors that have been related with dementia; however, said variables present a lower effect size: social isolation (individual weighted PAF <1% in a previous LAC study[17]), traumatic brain injury (PAF = 3%), and air pollution (PAF = 2%).[17]

A limitation that is common to all studies regarding PAFs for modifiable risk factors for dementia, is related to the relative risk data, as it has been obtained from other populations,[4,5,14] with data obtained more than 15 years ago for many variables,[4,5] and it is presented as dichotomic variables instead of as a continuous relation between the risk factor magnitude and dementia risk. Another limitation is related with the use of the SCh-MMSE for excluding subjects with cognitive impairment, as there is evidence of it being unsensitive for detecting subjects with mild cognitive impairment and dementia.[47]

5 | CONCLUSIONS

A very large proportion of the dementia burden in Chile could be attributed to modifiable risk factors. This overall PAF is similar to other LAC countries, but it is higher than in other world regions, a difference that was associated with the higher prevalence of metabolic risk factors in our population.[12] Women showed a higher overall weighted PAF than men, driven by a higher prevalence of physical inactivity and depression, demonstrating the importance of future analyses stratified by sex for precise preventive strategies.

Evaluating the best action plans for reducing the prevalence of noncommunicable diseases in LAC, especially obesity, diabetes, and hypertension, is urgent.[2,29] Possibly the most cost-effective approach would be population based, including the promotion of a healthy lifestyle from early life,[48] with special emphasis on physical activity in women,[44] and involving multiple levels of society (education, transportation,

urbanization, and health services), including strategies to prevent hearing loss, such as the reduction to noise exposition.[14,39] In older adults who already present cardiovascular risk factors, multi-domain interventions promoting a healthy lifestyle and a strict control of SBP levels has demonstrated effectiveness in reducing chronic diseases and cognitive decline.[6,25] Thus evaluating the feasibility of multi-intervention trials for dementia prevention in LAC will be an opportunity for policymakers in this region.[49]

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CONFLICTS OF INTEREST

None of the authors have any conflict of interest to declare. The funding sources do not have any competing interest in the elaboration of this manuscript.

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APPENDIX

TABLE A1 Missing data

	Age group	Diabetes	Alcohol Excess	Obesity	High Blood Pressure	Physical Inactivity	Low Education
Women	45-64	165 (13%)	138 (11%)	115 (9%)	112 (9%)	42 (3%)	17 (1%)
	≥65	116 (13%)	114 (13%)	96 (11%)	91 (10%)	27 (3%)	8 (1%)
	Total	281 (13%)	168 (12%)	211 (10%)	203 (9%)	69 (3%)	25 (1%)
Men	45-64	120 (16%)	113 (15%)	92 (12%)	90 (12%)	34 (5%)	7 (1%)
	≥65	57 (12%)	55 (12%)	46 (10%)	42 (9%)	15 (3%)	4 (1%)
	Total	177 (15%)	168 (14%)	138 (11%)	132 (11%)	49 (4%)	11 (1%)
Total	45-64	285 (14%)	251 (12%)	207 (10%)	202 (10%)	76 (4%)	24 (1%)
	≥65	173 (13%)	169 (13%)	142 (11%)	133 (10%)	42 (3%)	12 (1%)
	Total	458 (14%)	420 (12%)	349 (10%)	335 (10%)	118 (3%)	36 (3%)

The number (percentage) of subjects with missing data at each variable is shown.

TABLE A2 Individual and overall weighted PAF for dementia risk factors in later life group after excluding high blood pressure and obesity

	Total ≥65-years-old	Women ≥65-years-old	Men ≥65-years-old
Risk Factor	**Weighted PAF %**	**Weighted PAF %**	**Weighted PAF %**
Low Education	7.6 (4.3-11.2)	11.1 (6.4-16.1)	7.6 (4.1-11.7)
Hearing Loss	10.2 (5.7-14.9)	12.2 (6.7-17.8)	13.5 (7.8-19.1)
Smoking	3.4 (0.8-6.3)	2.3 (0.4-4.4)	2.7 (0.6-5.2)
Depression	2.9 (1.6-4.5)	4.1 (2.3-6.2)	1.9 (0.8-3.3)
Physical Inactivity	6.3 (3.2-9.8)	9 (4.7-13.6)	4.2 (1.9-7.1)
Diabetes	2.2 (1.1-3.4)	6.5 (3.6-9.8)	2.8 (1.4-4.6)
Alcohol Excess	0.2 (0.1-0.3)	0.1 (0-0.2)	0.2 (0-0.4)
Overall PAF	**32.8 (26.1-39.4)**	**45.2 (37.2-53.3)**	**32.9 (26.3-39.6)**

PAF, population attributable fraction. Data are means (2.5%-97.5% uncertainty intervals).