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Supplementary appendix

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Appendix: Gender inequalities as contributors to dementia in Latin America and Caribbean Countries: what factors are missing from research?

Table of contents

Sex differences in the determinants of dementia.....	1
Biological reactions to acute and chronic stress and possible influence on dementia.....	1
Available data differentiating sex/gender in LAC countries.....	2
Teenage pregnancy.....	2
Levels of education and occupational segregation.....	2
Access to the healthcare system.....	2
Food insecurity.....	2
Overweight/ obesity.....	2
Gender-based violence.....	2
Smoking.....	2
Alcohol consumption.....	3
Consortia initiatives in LAC.....	3
References.....	3

Sex differences in the determinants of dementia

The higher prevalence of dementia in women is strongly associated with biological factors. In this context, the term sex expresses the chromosomal, hormonal, and reproductive differences between men and women ^{1,2}.

Regarding chromosomal factors, some theories proposed that the differences in genomics, such as women having two X chromosomes and men having one X and one Y ^{1,2} chromosome, could not be responsible only for phenotypical characteristics but also for susceptibility to some sex-specific diseases ³. Associations were found between the X chromosome and cognitive changes in women, whereas in men, X chromosome gene expression was linked with neuropathological tau burden ⁴. However, this study did not include ethnic minorities, but only white North American participants, which does not allow for generalization of the findings.

Sex hormone levels can also contribute to explaining sex differences in dementia risk since there are significant hormonal changes across women's life course. For instance, estrogen can protect the brain by eliciting the production of antioxidants ⁵. Although a decline of estrogen levels during menopause was associated with dementia in women, evidence is mixed regarding hormone levels and dementia in men ⁶.

Regarding pregnancy, findings showed that pregnancy might be protective against vascular contributions to cognitive impairment and related dementia, however, pregnancy also increases the risk of stroke, particularly for those women who experience vascular disease during pregnancy, i.e. eclampsia, so pregnancy as a risk factor for dementia would depend on associated health events during pregnancy ⁷.

Moreover, cardiovascular diseases were consistently shown as risk factors for dementia ⁸, and have an earlier onset and a higher prevalence in men than women. Conversely, women seem to have a higher risk of stroke in later life ⁹. Although these results might be the norm in studies regarding sex ¹⁰, O'Neil and colleagues highlighted the fact that (social) gender is largely neglected, which leaves little room for intervention since the terms sex and gender are often used analogously and assumed to be constant and overlapping. Furthermore, changes in cardiovascular risk factors seem to be a sum of factors since early life, i.e., drinking and/or smoking ¹¹, consequently gender roles might influence and shape health behaviors during the life course.

Population-attributable fractions (PAFs) estimate the proportion of cases that would not exist in a population if an individual risk factor was eliminated. PAFs risk factors for specific LAC populations are beginning to be studied ^{12,13}. A study from Chile found significant sex differences with a higher PAF of risk factors in women in comparison with men (50.7% vs. 40.2%), mainly driven by higher physical inactivity and depression in women ¹⁴. These results support the importance of stratifying the risk factor analysis by sex and looking for hidden factors that explain these differences.

Biological reactions to acute and chronic stress and possible influence on dementia

Women and men appear to have different hormone releases and reuptake responses to stress. Sex-specific modulation of glucocorticoid stress response has been reported: Although men experience higher increases in hormone levels during acute stress ¹⁵, women experience more detrimental chronic stress and, consequently, might have more deleterious effects from it in later life ¹⁶. Moreover, the cyclical fluctuations of estrogen and progesterone increase stress responses in women, leading to greater susceptibility to mood disorders. These hormonal responses have an advantage for women only during youth, when women appear to be comparatively better protected from severe psychotic illnesses, however, women are more vulnerable than men to depression and anxiety ¹⁷. Congruently, a study observing cerebral activation during stressful activities showed a gender-specific neural activation to stress response; women presented limbic activations (an area involved mainly with emotional response) while men showed asymmetric prefrontal activity (an area involved with "fight or flight" response) ¹⁸.

Studies have shown the effects of life-event-related stress on later-life cognitive decline ^{19,20}. Specifically, higher childhood stress, everyday life and work stress, and traumatic events seem to be associated with higher odds of developing dementia ²⁰⁻²³. Furthermore, allostatic overload, i.e., chronic and excessive activation of immune, neuroendocrine, cardiovascular, and metabolic systems due to stressful life exposures ²⁴, has been suggested to play an important role in the pathophysiology of cognitive impairment and dementia ^{25,26}. Allostatic overload can increase the outbreak of varied diseases, such as cardiovascular, depression, and diabetes, by insulin resistance ²⁵. Furthermore, prolonged physiological dysregulations can lead to several dysfunctions due to oxidative reactions, to name a few, epigenetic dysregulation influencing gene expression and cellular aging ²⁷.

Available data differentiating sex/gender in LAC countries

Teenage pregnancy

Adolescent mothers are heterogeneous group with large differences among LAC countries, eg., the percentage of indigenous adolescent mothers by 15-19 years old (2010–2011) in Brazil was 26.4%, Costa-Rica 24.7%, Ecuador 18.3%, Mexico 14%, Panama 30.7%, and Uruguay 11.6%, while nonindigenous in Brazil was 11.8%, Costa-Rica 10.8%, Ecuador 16.8%, Mexico 12.2%, Panama 12.7%, and Uruguay 9.4%²⁸.

Levels of education and occupational segregation

Levels of education in LAC increased significantly from 2000 to 2018, a period in which completion rates increased from 79% to 95% in the early years of elementary education, from 59% to 81% in the final years of elementary education, and from 42% to 63% in high school education. Regarding levels of education, women have a higher probability than men in almost all countries of LAC of finishing high school, except for Haiti and Guatemala²⁹.

The formal labor force participation of women was around 50% compared to 80% of men. In 2014, Honduras, Guatemala, Guyana, Mexico, Belize, Nicaragua, Panama, Costa Rica, El Salvador, Suriname, and Argentina had less than 50% of their labor force as women.³⁰ Moreover, in most of the LAC countries informal work is significantly more prevalent among women³¹

Access to the healthcare system

It is worth mentioning that one important index of access to the healthcare system among women is prenatal care, but disparities can be observed in LAC, with only Cuba, Antigua and Barbuda, The Bahamas, Chile, and Uruguay having the lowest levels of deaths per birth (≤ 10 per 1,000) healthcare in eight LAC countries³².

Food insecurity

Data showed an increase in the disparity between men and women regarding moderate and severe food insecurity, 41.8% of LAC women suffered from moderate to severe food security compared to 32.2% of men.³³ Looking at the LAC countries the report verified that the differences are more likely to be observed in Mesoamerica than in South America³⁴.

Overweight/ obesity

Overweight affects more than half of the adult population, in 2016 eight countries (Argentina, Bahamas, Dominican Republic, Mexico, Costa Rica, Venezuela, Chile, Uruguay, ARG) were leading the ranking with a prevalence of more than 60%. While obesity affects more than 25% of adults in eight countries (Bahamas, Dominica, Dominican Republic, Mexico, Argentina, Chile, Uruguay, Suriname). In addition, women are more likely to be obese than men, with the difference being more than 10% in 19 LAC countries³⁴.

Gender-based violence

The percentage of married or in-union women who have experienced physical or sexual violence by an intimate partner range from 17% - 20% in the Dominican Republic to slightly more than half in Bolivia, around 53% - 64%³⁵.

Smoking

A global study has shown a significant decrease in smoking over time in LAC; in addition, even in men, the prevalence of smokers in most LAC countries was below the prevalence in European and Asian countries, except for Chile, Argentina, and Uruguay³⁶. For women, prevalence is even lower in most LAC, but in some countries higher, such as Chile, Uruguay, and Argentina³⁷, which probably reflects greater gender equality since the increase in female smokers is related to lower disapproval of smoking among women³⁸.

Alcohol consumption

similar patterns are observed in the population of LAC countries, positively the consumption of pure alcohol annually per capita is 6.5 liters, which is below Europe (10.1 liters) and North America (9.9 liters) ³⁹. The numbers vary among countries, i.e., about 54% of Brazilian men compared to 27.30% of women, while in Argentina and Chile, these numbers are higher for both, 80% of men and 56% women, and 80% men and 56% women, respectively ⁴⁰.

Consortia initiatives in LAC

Attempts to target risk factors are starting to emerge in LAC through some consortia initiatives to allow a regional and harmonized approach to dementia diagnosis and to permit comparisons among countries. The Latin American and Caribbean Consortium on dementia (LAC-CD) on the Multi-partner consortium to expand dementia research in Latin America (RED-LAT) and LATAM-FINGERS.

The Multi-Partner Consortium to Expand Dementia Research in Latin America (ReDLat): has aim to detect characteristics of genetic, and social-economic factors that influence and lead to Alzheimer's and frontotemporal dementia in LAC (Argentina, Brazil, Chile, Colombia, Mexico, Peru) relative to the US⁴¹.

The Latin American Initiative for Lifestyle Intervention to Prevent Cognitive Decline (LatAm-FINGERS) is the first initiative to bring together 12 LAC countries in a non-pharmacological intervention to reduce cognitive decline. The intervention targets risk factors using a multi-domain approach that includes physical exercise, diet, cognitive training, socialization, and cardiovascular health monitoring. This trial was harmonized with previous and ongoing high-income country initiatives (the original Finger trial and de U.S.POINTER) but has been adapted to be respectful of local idiosyncrasies and feasible in the Latin American population. LatAm-Fingers is being launched in 14 LAC countries to explore modifiable risk factors and also investigate the effects of non-pharmacological interventions involving lifestyle modifications ^{42,43}. Furthermore, LatAm-FINGERS is building a larger dataset in LAC with clinical outcomes on people at risk for dementia, including a biobank with DNA, and MRI data.

Moreover, research groups among the LAC countries have also agreed on the development of genetic and biomarker studies for dementia, clinical trials, and translational research ^{42,44}.

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