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Editorial: *Hypertension, Cognitive Decline, and Mild Cognitive Impairment among diverse Hispanics/Latinos: Study of Latinos-Investigation of Neurocognitive Aging Results (SOL-INCA)*

Title:

Hypertension and mild cognitive impairment: Understanding the complexities of the relationship in understudied populations

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Abstract

The association between hypertension and mild cognitive impairment (MCI) is complex. Both are increasing in prevalence worldwide and will have disproportionate effects on lower income countries across Latin America. Despite this, there is insufficient evidence investigating this relationship in this region or those of Hispanic or Latino ancestry in higher income countries. In this context, the Study of Latinos-Investigation of Neurocognitive Aging represents a unique dataset. Although more research is required, Márquez and colleagues show that hypertension in this population in the United States is associated with decline in cognitive measures and greater odds of MCI over seven years follow-up.

Main Manuscript

It is important to understand the relationship between future risk of cognitive decline and modifiable risk factors, given the growing evidence that up to 40% of cases of dementia may be preventable [1]. High blood pressure (BP) is one of the most established predictors of incident cognitive impairment [2]. Hypertension, especially when diagnosed in mid-life, increases the risk for mild cognitive impairment (MCI) and dementia across multiple longitudinal studies, systematic reviews and meta-analyses [3,4,5]. Hypertension is associated with Alzheimer's disease (AD), vascular dementia (VaD) and mixed AD-VaD subtypes, which represent approximately 85% of all cases [6]. Multiple direct and indirect interacting pathophysiological mechanisms are recognised to contribute to the development of cognitive decline by hypertension [7]. Appropriate pharmacological treatment to reduce BP may lower this risk [2].

At population-level, the global population attributable fraction (PAF) of hypertension for dementia is estimated at 15.8% across 186 countries [8]. Data show variation by age and geographic location. Those diagnosed at younger ages, and individuals in Latin America and the Caribbean, have the highest PAF [8]. In 2019, this region had the overall second highest prevalence of hypertension, estimated at 37.6%, with approximately 4,476,200 cases of dementia of which 18% were attributable to high BP. In contrast, during the same period, North America had a lower prevalence (34.1%) and only 15% were attributable to hypertension [8]. This represents a marked change for a condition that was previously associated with higher rather than low and middle income counties countries, a trend that is expected to continue [9]. Notably, the prevalence of hypertension in younger (30-44 years) and middle-aged (45-54 years) adults in Latin America and the Caribbean is higher than other regions. These age groups have the highest hazard ratio (HR) of hypertension for dementia [8].

Such evidence provides an impetus for early detection and treatment, targeted to higher risk populations, to reduce cognitive decline and hence the global burden of dementia [10]. From a public health perspective, it is important to understand the natural history and the relationship between these two common conditions and in particular how these behave and vary in different populations. While these data support the need to examine populations in Latin America and the Caribbean, is likely that there are commonalities among individuals of Latino and Hispanic decent living in other regions including in the United States (US); these may also have a higher PAF, hidden within the data. These likely share many health and behavioural risk factors, environmental exposures and genetic predispositions, potentially compounded by healthcare disparities, contributing to higher rates of hypertension and poorer control [11]. Investigating similarities and differences in under-studied groups is important to better understand these relationships and to modify their effects in public health and clinical practice. For example, understanding why younger adults in Latin America and the Caribbean have a higher prevalence of hypertension and subsequent HR of hypertension for dementia could help identify and address factors amongst people of similar decent in other parts of the world. The study by Márquez and colleagues [12] is timely in this context.

The authors examined data from the Study of Latinos-Investigation of Neurocognitive Aging (SOL-INCA), a multi-site ancillary study of the larger Hispanic Community Health Study/Study of Latinos (HCHS/SOL). HCHS/SOL includes community-dwelling middle-aged and older adults of Hispanic or Latino decent living in four metropolitan areas across the continental US (New York, Chicago, Miami and San Diego). A subset of these participants, those aged 45-74 years at baseline (between 2008-2011) were assessed in SOL-INCA, at an average of seven years follow-up (2016-2018), to investigate the effects of hypertension on cognitive function, specifically, decline in cognitive scores over time and prevalent MCI. MCI was defined by National Institute on Aging-Alzheimer's Association (NIA-AA) criteria, though this was not a clinical diagnosis. Instead, as is commonly utilised in secondary analysis of observational longitudinal data, it was based on a bespoke cognitive battery defined by standardised mean z-scores to estimate cognitive impairment relative to the baseline scores of the target population (i.e. -1 to -2 standard deviations from the norm). All participants with MCI self-reported cognitive symptoms. In addition, minimal or no impairment in instrumental activities of daily living (ADL) was required to confirm the absence of functional impairment. Where individuals' cognitive scores suggested more severe impairment (i.e. more than -2 standard deviations), these were excluded to minimise the number with dementia included in the analysis. Change in cognition at follow-up was measured relative to baseline (visit one). However, it is not clear how the researchers handled those with evidence of cognitive impairment at baseline. For example, it is not clear what proportion may have had MCI at baseline or how these were accounted for. While these classification strategies and issues can lead to misclassification bias, the large sample size, subsequent adherence to NIA-AA criteria for visit two and careful statistical analysis allowed for a reasonably credible approximation of MCI to assess cognitive decline and the prevalence of MCI at follow-up.

The diagnosis of hypertension used in this study was arguably more challenging. High BP was characterised using an published definition; i.e. when either a cut-off reading of ≥140/90 mmHg was found and or where participants reported that they currently took antihypertensive mediations [13]. This allowed the authors to generate three subgroups to better examine the effect of patterns of hypertension on cognition, namely those who never met this definition of hypertension ("normotension"), participants who were labelled with hypertension only at the follow-up assessment ("incident hypertension") and persons meeting the definition at both time-points ("persistent hypertension"). A forth subgroup, created by splitting those with "persistent" hypertension into those receiving anti-hypertensive medications at baseline was used in a sensitivity analysis. These are artificial constructs with no way to establish timelines or patterns of treatment but constructed in such a way that they are mutually exclusive categories. These are also prone to misclassification and reporting bias; Isolated readings of high BP ≥140/90 mmHg do not necessarily equate to a diagnosis of hypertension and those with cognitive impairment may not accurately report medication regimens. Visit-visit-variability (VVV) in BP, defined as fluctuations in readings across healthcare visits, was not considered and would have been difficult to assess, given that only two timepoints were available. While observational studies have linked VVV to cognitive decline, findings are inconsistent [14,15].

The final sample of 6,173 participants had a mean age of 63.4 years and near equal proportion with "normotension" (42.4%) and "persistent hypertension" (42.1%); the

remainder had new “incident hypertension” (15.5%). There was a generally high burden of cardiovascular risk factors including diabetes, dyslipidaemia and obesity. The key findings from the covariate-adjusted analysis were that only “persistent hypertension” was statistically significantly associated with cognitive decline across different cognitive domains, albeit these were limited by the battery of assessments available. It more than doubled the adjusted odds of having MCI, while “incident hypertension”, increased it by 1.7 times. Ironically, those with “persistent hypertension” receiving treatment at baseline performed less well on cognitive testing and had higher odds of MCI at follow-up, than though those not reporting treatment. As the authors correctly highlight, this analysis was not able to account for medication compliance or BP control. The associations with prevalent MCI were consistent after adjustment for a range of potential confounders, irrespective of specific Latino or Hispanic background, albeit most (61%) were of Mexican or Cuban decent. Hence, the results may not be generalisable to all individuals of Latino or Hispanic descent in the US.

There are a number of other limitations, some of which the authors have highlighted. Many relate to the observational nature of the data and of inferring causation and conclusions from single assessments over isolated and distant time points with the possibility of reporting and measurement bias. Although the association with MCI remained significant after adjustment, the analysis examining change in the cognitive battery over time showed inconsistent patterns and a trend towards overall non-significance in model 3, which adjusted for cardiovascular risks as possible confounders. This is particularly true for the “incident hypertension” group, which essentially had no significant change in cognitive scores, yet had significant odds of having MCI, which questions the accuracy and reliability of this classification and creates uncertainty over the proportion that may have had MCI at baseline. Understanding the association of hypertension with incident rather than prevalent MCI would have provided greater clarity. It would also have been interesting to examine if there were changes in ADLs over time. Further, given the multiple comparisons performed, there is risk multiplicity. Another challenge is that the assessment instruments used do not reflect clinical practice, limiting their translatability for clinicians. From a epidemiological perspective, this is a challenge too, as common assessment approaches allow comparison and pooling of data. To better examine and draw inferences for such under-researched populations against other studies is important, particularly as these participants are often not included in clinical trials of AD and related dementias, despite representing a increasing proportion of the US population [16]. Overall, this research puts a spotlight on the growing burden of cognitive impairment attributable to hypertension in an important population with relevance for clinicians, epidemiologists and policy-makers. From a public health perspective, MCI can be considered evidence of hypertension-related end organ dysfunction [7], comparable to renovascular kidney disease or hypertensive retinopathy, and hence potentially amenable to early detection using short screening instruments incorporated into two-step screening and assessment pathways [17]. In turn, simple, low cost monitoring of hypertension in primary care and through the use of home BP measurements could increase rates of detection and treatment of hypertension in Latin America and the Caribbean [18] as well as in individuals of these ancestries in other regions. Additional research examining for incident MCI and dementia in this population is now required, particularly among those without known cognitive decline.

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Conflict of Interest
The author is an Editorial Board Member of this journal, but was not involved in the peer-review process nor had access to any information regarding its peer-review. The author reports no other potential conflict of interest.

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