Dementia and lower blood pressure in Latin America, India, and China

A 10/66 cross-cohort study

Emiliano Albanese, MD,
PhD
Flavia L. Lombardo, MSc
Martin J. Prince, MD,
PhD
Robert Stewart, MD,
PhD

Correspondence to
Dr. Albanese:
emiliano.albanese@gmail.com

ABSTRACT

Objective: To study the relationship between dementia and blood pressure (BP) in 8 low- and middle-income countries.

Methods: In identical cross-sectional surveys of older adults (aged 65 years and older) conducted in Cuba, Dominican Republic, Peru, Venezuela, Mexico, Puerto Rico, China, and India ($n = 15,746$), we measured systolic and diastolic BP and used the 10/66 prevalidated algorithms to adjudicate dementia diagnosis and quantify dementia severity (Clinical Dementia Rating [CDR]).

Results: BP levels, dementia prevalence, and participants' sociodemographic and health characteristics varied across sites. In fixed-effect meta-analyses of site-specific linear regression coefficients adjusted for potential confounders, dementia and CDR were cross-sectionally associated with lower systolic BP ($\beta = -1.7$, 95% confidence interval [CI]: $-2.8, -0.6$; and $\beta = -1.1$, 95% CI: $-1.5, -0.7$) and diastolic BP ($\beta = -0.4$, 95% CI: $-1.1, 0.2$; and $\beta = -0.4$, 95% CI: $-0.7, -0.2$). Associations were heterogeneous across sites for both dementia ($I^2 < 47\%$) and CDR ($I^2 < 75\%$), and were strongest in Cuba, where prevalence of hypertension was highest. Results were robust to alternative model specifications that accounted for hypertensive status, antihypertensive treatment, and leanness (i.e., smaller waist circumference).

Conclusion: The association between dementia and lower BP was heterogeneous across geographically diverse samples, strongest where prevalent hypertension was highest (in Cuba), and relatively small compared with that found in Western settings. Both the mechanisms and the extent to which different levels of lifetime hypertensive disease explain this heterogeneity remain uncertain. However, because rapid increments in both dementia and hypertension are predicted in low- and middle-income countries, closer monitoring is warranted. *Neurology*® 2013;81:228-235

GLOSSARY

BP = blood pressure; CDR = Clinical Dementia Rating; CI = confidence interval; DBP = diastolic blood pressure; LMIC = low- and middle-income countries; SBP = systolic blood pressure.

The relationship between blood pressure (BP) levels and dementia has important clinical and public health significance but has proven to be complex. In studies with follow-up periods of 10 years or more, higher BP levels predict increased risk of dementia.¹ However, neurodegenerative effects on brain function may cause BP to decrease; hypotension itself might increase risk for dementia in the short-term (e.g., through impaired cerebral perfusion) or it may correlate with other risk factors (e.g., arteriosclerosis caused by earlier hypertensive disease). Relatively low BP is associated with dementia at the point of diagnosis² and over a few years before this,³ particularly in people with no previous antihypertensive treatment.⁴ However, evidence is confined to Western countries, where hypertension prevalence is relatively high, and is scanty from low- and middle-income countries (LMIC), where prevalence of hypertension is increasing but has been low in generations currently at risk of dementia,⁵ although LMIC are where the majority of dementia cases are found and where the steepest increases in numbers affected are anticipated.⁶

Supplemental data at
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From the Laboratory of Epidemiology, Demography, and Biometry (E.A.), National Institute on Aging, National Institutes of Health, Bethesda, MD; National Centre of Epidemiology (F.L.L.), Italian National Institute of Health, Rome, Italy; and Institute of Psychiatry (M.J.P., R.S.), King's College London, UK.

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The 10/66 population-based surveys have been conducted in India, China, and 6 countries in Latin America with identical methodology, on large samples of older adults drawn from widely varying source populations. In the present study, we aimed to test the hypothesis that the cross-sectional associations between dementia and low BP would be independent of potential confounders and relevant covariates and consistent across samples with varying hypertension prevalence and treatment levels.⁷

METHODS The 10/66 research program is a multicenter study on aging performed in LMIC. The study protocol has been previously published,⁸ as have data on validation of dementia assessments,⁹ dementia prevalence,¹⁰ and normative data for cognitive assessments.¹¹

Setting. In a series of surveys designed and conducted with identical methodology, data were collected between January 2003 and July 2010 from urban and rural sites in Peru, Mexico, China, and India and from urban sites in Cuba, Dominican Republic, Venezuela, and Puerto Rico. A one-phase survey was conducted of all older adults (aged 65 and older) living within specific geographic catchment areas that were chosen to be broadly representative of the source community. Target samples of 2,000 per country were chosen a priori to allow estimation of a standard error of 0.9% around a typical dementia prevalence of 4.5% with 80% power.

Standard protocol approvals and patient consents. The study received research ethics review and approval from a central committee at King's College London and from the appropriate committees at each participating local institution. Written informed consent or, in case of illiteracy or incapacity, an oral witnessed consent or next-of-kin written agreement was obtained.

Interviews. Interviewers received 1 week of training and applied standard examinations and questionnaires, translated into the local language by clinicians fluent in English, at participants' homes. In Cuba and China, interviewers were medical doctors. Physical examinations, including BP assessments, were performed by doctors in all sites other than Venezuela (medical students), Peru (medical students and nurses), urban India (medical social workers), and rural India (health research workers). The 10/66 team in the London headquarters assisted and supervised the local principal investigators and their teams at all stages of the study and performed field assessments and continuous checks for quality and standardization of procedures and data collection.

Measurements. The 10/66 study protocol consisted of a series of standardized assessments including participant and informant interviews and physical examination. Full details can be found at www.alz.co.uk/1066 and in the published protocol.⁸ All information was corroborated by an informant (usually a relative or a caregiver) if the participant's capacity to provide information was in doubt.

BP and covariate assessment. Resting BP was recorded as the average of 2 readings. Details of antihypertensive agents were noted, and treatment (present/absent) was used as a variable in this analysis (see below). Age and sex were recorded, educational attainment was subdivided into 5 categories equated across countries (no formal education; some formal education but less than primary; primary education; secondary education; and tertiary education), and household

income was based on number of assets and utilities (motor vehicle, television, refrigerator and/or freezer, water, electricity, telephone, and plumbed toilet/bathroom). Information on health status was based on self/informant-reported medical diagnoses of hypertension, myocardial infarction or angina, stroke, and diabetes. Measured waist circumference and smoking status were also included as covariates.

Dementia diagnosis. The procedure for ascertaining dementia in the 10/66 study has been described in detail previously, and followed an extensive prestudy pilot in 26 international centers to confirm cross-cultural validity.⁹ Briefly, 3 component assessments were conducted in all sites: the Community Screening Instrument for Dementia (which comprises both a global cognitive assessment and a structured informant interview),¹² the Geriatric Mental State (a fully structured diagnostic assessment for late-life mental disorder), and a word list recall task (CERAD [Consortium to Establish a Registry for Alzheimer's Disease]).¹³ From the outputs of these measures, a standard algorithm was applied, generating a dementia diagnosis with robust cross-cultural applicability and minimal education bias.⁹ The Clinical Dementia Rating (CDR) scale groups of no, questionable, mild, moderate, and severe dementia were obtained by operationalizing the Washington University CDR criteria combining cognitive and functional information obtained from both informants and patients.¹⁴ Dementia subtypes were determined with an algorithm based on the NINCDS¹⁵ and NINDS-AIREN criteria.¹⁶

Statistical analyses. We used STATA software version 12 (StataCorp, College Station, TX) for all analyses. Of the 17,031 participants, 15,746 had complete data and formed the analyzed sample. Fewer than 5% of participants had incomplete data in all sites except in Venezuela (39%) and Puerto Rico (26%), mainly because of missing BP measurements ($n = 431$ and $n = 395$, respectively), particularly among those with dementia ($p < 0.001$). There were no other significant differences between those without complete data ($n = 1,285$) and the analytic sample, with the exception of self-reported stroke in the former (11.9%) compared with the latter (7.5%) group in Puerto Rico. We first described the combined sample by presence and stage of dementia severity. Linear regression models were then applied for each site separately, treating systolic BP (SBP) and diastolic BP (DBP) levels as continuously distributed dependent variables and modeling dementia status as the primary independent variable with adjustment for other covariates, adding these sequentially to models in predefined groups. Covariates were selected on the basis of previous findings from the 10/66 surveys¹⁷ and evidence from the literature.¹ CDR score was entered as an independent variable in a second set of analyses, having transformed it into an ordinal measure with one unit between each group and having formally tested departures from linearity (all p values > 0.10). Two regression models were used for the main analysis: model 1 adjusted for age and sex; and model 2 adjusted additionally for education, household assets, the above-mentioned cardiovascular risk factors, and smoking status, constituting the final model for primary analyses. Because the 10/66 dementia algorithm itself takes education into account, this covariate was entered into the second model. We combined site-specific estimates using a fixed-effect method meta-analysis, and between-site heterogeneity was measured using Higgins I^2 . In sensitivity analyses, we checked effect modification in the above associations by hypertensive status and antihypertensive treatment; we repeated fully adjusted models for dementia subtypes, and because antihypertensive treatment and waist circumference might represent causal pathway factors, we also formally tested their mediating effect in the dementia-BP associations using Sobel-Goodman tests,¹⁸ and separately added these 2 variables to the fully adjusted models.

RESULTS Participant sample sizes ranged from 2,944 in Cuba to 539 in rural Peru. Response rates were higher than 80% in all sites except in urban China (74%) and urban India (72%). Mean SBP/DBP levels (mm Hg) by site were as follows: Cuba 146/82, Dominican Republic 136/78, urban Peru 123/71, rural Peru 119/72, Venezuela 137/76, urban Mexico 133/78, rural Mexico 130/77, Puerto Rico 131/74, urban China 137/76, rural China 138/87, urban India 134/90, and rural India 124/82. Prevalence of hypertension and antihypertensive treatment proportions (among those aware of their hypertensive status) ranged from 79% in Venezuela to 42% in rural Peru, and from 95% in urban China to 67% in rural India, respectively.⁷ Dementia prevalence ranged from 5.6% in rural China to 11.7% in the Dominican Republic; samples did not vary in age distribution and have been extensively described in previous publications.¹⁰ The combined analytic sample (n = 15,746) is described by dementia status and severity in table 1. More advanced dementia was associated with older age,

female sex, lower education, stroke and heart disease, diabetes, and smaller waist circumference.

Associations between dementia and SBP levels are reported in table 2. In fully adjusted models, dementia was associated with significantly lower SBP in Cuba, and increasing dementia severity was associated with lower SBP in Cuba, urban Peru, and rural India. Heterogeneity *P* coefficients were moderate for dementia status and high for dementia severity (table 2). Both dementia ($\beta = -1.7$; 95% confidence interval [CI]: $-2.8, -0.6$) and CDR group ($\beta = -1.1$; 95% CI: $-1.5, -0.7$) were associated with lower SBP in the pooled sample (table 2 and figure 1). We found significantly lower DBP in Cuba, rural Mexico, and rural China for dementia, and in Cuba, urban Mexico, and rural India for CDR; only the latter pooled estimate was significant ($\beta = -0.4$; 95% CI: $-0.7, -0.2$) and heterogeneity, although low for dementia, was high for CDR (table 3 and figure 2).

In further analyses, neither reported hypertensive status nor current antihypertensive treatment significantly

Table 1 Characteristics of men and women from Latin America, India, and China by dementia severity in the 10/66 study

	Dementia stage (CDR scale)					p Value ^a
	No dementia (n = 8,714)	Questionable (n = 5,860)	Mild (n = 853)	Moderate (n = 234)	Severe (n = 85)	
Age, mean $\pm$ SD, y	72.8 $\pm$ 6.3	74.4 $\pm$ 6.9	78.3 $\pm$ 7.8	82.1 $\pm$ 8.2	81.6 $\pm$ 7.7	<0.001
Women, n (%)	4,838 (59.1)	3,641 (65.1)	516 (61.6)	179 (70.5)	74 (76.3)	<0.001
Positive family history of dementia, n (%)	596 (7.3)	510 (9.2)	103 (12.5)	43 (17.1)	30 (31.2)	<0.001
Educational level, n (%)						<0.001
None	1,556 (19.0)	1,340 (24.0)	220 (26.5)	68 (27.5)	13 (14.1)	
Did not complete primary	1,885 (23.1)	1,649 (29.5)	279 (33.6)	73 (29.6)	27 (29.3)	
Completed primary	2,532 (31.0)	1,477 (26.4)	187 (22.5)	58 (23.5)	28 (30.4)	
Completed secondary	1,391 (17.0)	734 (13.1)	90 (10.8)	33 (13.4)	15 (16.3)	
Completed tertiary	812 (9.9)	390 (7.0)	54 (6.5)	15 (6.1)	9 (9.8)	
Household assets, n (%)	5.5 (1.4)	5.3 (1.6)	5.3 (1.6)	5.7 (1.2)	5.6 (1.1)	<0.001
Reported hypertension, n (%)	4,000 (45.9)	3,063 (52.3)	445 (52.2)	121 (51.7)	31 (36.5)	<0.001
Reported stroke, n (%)	363 (4.2)	408 (7.0)	154 (18.1)	66 (28.2)	18 (21.2)	<0.001
MI or angina, n (%)	542 (6.2)	397 (6.8)	74 (8.7)	26 (11.1)	3 (3.5)	<0.001
Diabetes, n (%)	1,256 (14.4)	1,057 (18.0)	149 (17.5)	44 (18.8)	9 (10.6)	<0.001
Smoking status, n (%)						<0.001
Never smoked	5,735 (65.8)	3,678 (62.8)	520 (61.0)	160 (68.4)	59 (69.4)	
Ex-smoker	1,594 (18.3)	1,294 (22.1)	209 (24.5)	56 (23.9)	18 (21.2)	
Current smoker	1,385 (15.9)	888 (15.2)	124 (14.5)	18 (7.7)	8 (9.4)	
Waist circumference, mean $\pm$ SD, cm	90.4 $\pm$ 12.6	90.4 $\pm$ 12.3	88.4 $\pm$ 12.9	87.9 $\pm$ 12.4	82.7 $\pm$ 13.0	0.03
Antihypertensive treatment, ^b n (%)	3,803 (94.7)	2,849 (93.1)	413 (92.8)	113 (93.4)	28 (90.3)	<0.001
Systolic blood pressure, mean $\pm$ SD, mm Hg	134.7 $\pm$ 21.5	134.5 $\pm$ 22.5	134.1 $\pm$ 23.8	134.6 $\pm$ 24.5	127.4 $\pm$ 22.4	0.05
Diastolic blood pressure, mean $\pm$ SD, mm Hg	79.2 $\pm$ 13.3	78.3 $\pm$ 12.7	77.2 $\pm$ 12.7	75.4 $\pm$ 12.0	73.7 $\pm$ 11.3	<0.001

Abbreviations: CDR = Clinical Dementia Rating; MI = myocardial infarction.

^aThe p values are from tests for differences between groups: χ^2 for categorical and 1-way analysis of variance for continuous variables.

^bPercentages were calculated among those who were aware of their hypertensive status.

Table 2 Associations of dementia, dementia severity, and SBP in 15,746 older adults from Latin America, India, and China: The 10/66 study

Study site (n)	Dementia and SBP ^a				CDR stage and SBP ^b			
	Model 1 ^c		Model 2 ^d		Model 1 ^c		Model 2 ^d	
	β -Coefficient (95% CI)	p Value	β -Coefficient (95% CI)	p Value	β -Coefficient (95% CI)	p Value	β -Coefficient (95% CI)	p Value
Cuba (2,884)	-7.1 (-10.3, -3.9)	<0.001	-6.9 (-10.0, -3.7)	<0.001	-3.5 (-4.7, -2.3)	<0.001	-3.5 (-4.6, -2.3)	<0.001
Dominican Republic (1,948)	-1.4 (-4.4, 1.6)	0.37	-1.5 (-4.5, 1.5)	0.33	0.6 (-0.6, 1.8)	0.30	0.4 (-0.8, 1.6)	0.49
Peru urban (1,334)	-1.1 (-4.1, 1.9)	0.46	-1.5 (-4.5, 1.4)	0.30	-0.7 (-1.8, 0.4)	0.21	-1.3 (-2.3, -0.2)	0.02
Peru rural (539)	0.3 (-3.0, 3.6)	0.85	0.6 (-2.7, 4.0)	0.70	0.2 (-1.1, 1.5)	0.73	0.4 (-0.9, 1.7)	0.53
Venezuela (1,414)	5.2 (-0.6, 11.0)	0.08	5.3 (-0.5, 11.1)	0.07	-0.6 (-2.7, 1.5)	0.58	-1.2 (-3.3, 0.9)	0.27
Mexico urban (989)	-1.2 (-6.4, 4.1)	0.66	-1.3 (-6.5, 3.8)	0.61	-1.0 (-3.1, 1.2)	0.38	-1.5 (-3.6, 0.6)	0.17
Mexico rural (985)	-4.8 (-10.1, 0.6)	0.08	-4.4 (-9.7, 0.9)	0.10	-1.5 (-3.8, 0.8)	0.19	-1.9 (-4.1, 0.4)	0.10
Puerto Rico (1,597)	-0.8 (-4.1, 2.5)	0.62	-0.5 (-3.8, 2.8)	0.75	-0.9 (-2.2, 0.4)	0.18	-1.0 (-2.3, 0.3)	0.13
China urban (1,145)	0.2 (-4.4, 4.7)	0.94	-1.9 (-6.3, 2.5)	0.40	1.5 (-0.1, 3.2)	0.07	0.3 (-1.3, 1.9)	0.71
China rural (1,002)	3.2 (-0.9, 7.4)	0.13	-0.3 (-3.7, 3.0)	0.85	2.1 (0.4, 3.7)	0.01	-0.1 (-1.4, 1.2)	0.90
India urban (955)	-2.6 (-8.1, 3.0)	0.37	-2.2 (-7.7, 3.2)	0.43	-0.6 (-3.2, 1.9)	0.61	-0.8 (-3.4, 1.7)	0.51
India rural (954)	-3.8 (-7.7, 0.0)	0.05	-2.7 (-6.4, 1.0)	0.15	-4.2 (-6.0, -2.4)	<0.001	-3.9 (-5.7, -2.2)	<0.001
Pooled effect	-1.5 (-2.6, -0.4)		-1.7 (-2.8, -0.6)		-0.7 (-1.1, -0.3)		-1.1 (-1.5, -0.7)	
Test for heterogeneity, I^2	58.8%	0.01 ^e	46.3%	0.04 ^e	82.1%	<0.001 ^e	74.7%	<0.001 ^e

Abbreviations: CDR = Clinical Dementia Rating; CI = confidence interval; SBP = systolic blood pressure.

^a β -Coefficient representing the difference in SBP (dependent variable) of participants with dementia compared to those without.

^b β -Coefficient representing the difference in SBP (dependent variable) per group increase in CDR score compared with no dementia, assuming constant intervals between CDR categories.

^c Adjusted for age and sex.

^d Further adjusted for education, household assets, reported clinical diagnosis of hypertension, stroke, myocardial infarction or angina, diabetes, smoking status, and family history of dementia.

^e Cochrane Q p value for between-site heterogeneity estimates.

Figure 1 Fully adjusted associations of dementia (A) and dementia severity (B) with systolic blood pressure by study site, and meta-analyzed pooled effect in 15,746 older adults: The 10/66 study

Models were adjusted for age, sex, education, household assets, reported clinical diagnosis of hypertension, stroke, myocardial infarction or angina, diabetes, smoking status, and family history of dementia. CI = confidence interval; fe = fixed-effect method.

modified associations of dementia and dementia severity with SBP or DBP (all p values of interaction terms >0.29). Antihypertensive treatment potentially mediated the association between CDR and SBP (Sobel $p = 0.04$) but not that between CDR and DBP ($p = 0.18$) or those between dementia and SBP ($p = 0.20$) or DBP ($p = 0.29$). Smaller waist circumference potentially mediated the respective associations of both dementia ($p < 0.001$ and $p = 0.006$) and CDR ($p < 0.001$ and $p = 0.01$) with SBP and DBP. However, the main results were identical after additional adjustment for antihypertensive treatment and for waist circumference (data not shown). In investigating dementia subtypes, numbers of cases were a limiting factor (particularly for vascular dementia, with fewer than 10 cases in 5 of the 12 sites). In summary, results from model 2 showed no significant association for SBP with either Alzheimer disease ($p = 0.11$) or vascular dementia ($p = 0.48$), and DBP was significantly reduced in vascular dementia ($\beta = -3.90$; 95% CI: $-6.87, -0.92$) but not in Alzheimer disease ($p = 0.09$).

DISCUSSION In an analysis of data of 15,746 older residents drawn from rural and urban sites in India, China, and 6 countries in Latin America, dementia

Table 3 Associations of dementia, dementia severity, and DBP in 15,746 older adults from Latin America, India, and China: The 10/66 study

Study site (n)	Dementia and DBP ^a				CDR stage and DBP ^b			
	Model 1 ^c		Model 2 ^d		Model 1 ^c		Model 2 ^d	
	β -Coefficient (95% CI)	p Value	β -Coefficient (95% CI)	p Value	β -Coefficient (95% CI)	p Value	β -Coefficient (95% CI)	p Value
Cuba (2,884)	-2.2 (-3.9, -0.6)	0.01	-2.0 (-3.6, -0.4)	0.02	-1.2 (-1.8, -0.6)	<0.001	-1.1 (-1.7, -0.5)	<0.001
Dominican Republic (1,948)	-0.1 (-1.7, 1.4)	0.86	0.0 (-1.5, 1.6)	0.99	-0.5 (-1.1, 0.1)	0.13	-0.4 (-1.0, 0.2)	0.18
Peru urban (1,334)	1.3 (-1.1, 3.7)	0.28	0.4 (-2.0, 2.7)	0.77	1.7 (0.8, 2.5)	<0.001	1.0 (0.1, 1.8)	0.03
Peru rural (539)	1.1 (-2.6, 4.7)	0.57	1.3 (-2.5, 5.0)	0.50	0.9 (-0.5, 2.3)	0.22	0.8 (-0.6, 2.3)	0.26
Venezuela (1,414)	0.8 (-2.1, 3.6)	0.58	0.8 (-2.1, 3.6)	0.60	-0.2 (-1.2, 0.8)	0.72	-0.5 (-1.5, 0.6)	0.36
Mexico urban (989)	-0.6 (-3.4, 2.1)	0.65	-0.8 (-3.6, 1.9)	0.56	-1.1 (-2.2, 0.0)	0.05	-1.2 (-2.3, 0.0)	0.04
Mexico rural (985)	-2.9 (-6.0, 0.1)	0.06	-3.2 (-6.2, -0.1)	0.04	-0.7 (-2.0, 0.5)	0.25	-1.0 (-2.3, 0.3)	0.12
Puerto Rico (1,145)	0.2 (-1.6, 2.0)	0.81	0.4 (-1.4, 2.2)	0.66	-0.2 (-1.0, 0.5)	0.53	-0.2 (-0.9, 0.6)	0.66
China urban (1,002)	1.2 (-1.1, 3.6)	0.30	0.7 (-1.7, 3.1)	0.58	0.7 (-0.1, 1.6)	0.09	0.5 (-0.4, 1.4)	0.26
China rural (955)	-0.9 (-3.2, 1.5)	0.48	-2.7 (-4.8, -0.5)	0.01	0.6 (-0.4, 1.5)	0.25	-0.5 (-1.3, 0.4)	0.30
India urban (954)	1.4 (-3.5, 6.3)	0.58	2.3 (-2.6, 7.2)	0.35	-1.6 (-3.8, 0.6)	0.15	-1.1 (-3.4, 1.1)	0.33
India rural (1,597)	0.8 (-1.8, 3.4)	0.55	1.2 (-1.3, 3.8)	0.35	-2.2 (-3.4, -1.0)	<0.001	-2.1 (-3.3, -0.8)	0.01
Pooled effect	-0.3 (-0.9, 0.4)		-0.4 (-1.1, 0.2)		-0.3 (-0.5, 0.0)		-0.4 (-0.7, -0.2)	
Test for heterogeneity, I^2	24.5%	0.20 ^e	38.2%	0.09 ^e	79.7%	<0.001 ^e	68.8%	0.001 ^e

Abbreviations: CDR = Clinical Dementia Rating; CI = confidence interval; DBP = diastolic blood pressure.

^a β -Coefficient representing the difference in DBP (dependent variable) of participants with dementia compared to those without.

^b β -Coefficient representing the difference in DBP (dependent variable) per group increase in CDR score compared with no dementia, assuming constant intervals between CDR categories.

^c Adjusted for age and sex.

^d Further adjusted for education, household assets, reported clinical diagnosis of hypertension, stroke, myocardial infarction or angina, diabetes, smoking status, and family history of dementia.

^e Cochrane Q p value for between-site heterogeneity estimates.

Figure 2 Fully adjusted associations of dementia (A) and dementia severity (B) with diastolic blood pressure by study site, and meta-analyzed pooled effect in 15,746 older adults: The 10/66 study

Models were adjusted for age, sex, education, household assets, reported clinical diagnosis of hypertension, stroke, myocardial infarction or angina, diabetes, smoking status, and family history of dementia. CI = confidence interval; fe = fixed-effect method.

and dementia severity were associated with lower SBP and, to a lesser extent, with DBP. Heterogeneity across sites was higher for dementia severity than for dementia. The most consistent associations of dementia and CDR score with lower levels of both SBP and DBP were found in Cuba. The Cuban sample was also noted to have the highest mean SBP.

As outlined earlier, the relationship between BP and dementia is complex, with higher BP predicting increased risk of dementia 10 to 20 years later, possibly more so for untreated hypertension,¹ but contemporaneous associations between dementia and either lower² or similar BP.¹⁹ These associations tend to be more evident for SBP than DBP and are supported by longitudinal findings of an exaggerated decrease in SBP over 4 to 6 years before the clinical onset of dementia.¹ Our findings are consistent in that lower SBP was found for people with dementia and for those with more severe dementia in the combined samples. However, differences between those with and without dementia were not significant and relatively small in most individual sites. Only the dementia-associated SBP difference in Cuba (6.9 mm Hg, table 2) was comparable to, for example, the 6 mm Hg lower mean SBP in cases of incident dementia compared

with survivors without dementia in wave 6 of the Honolulu-Asia Aging Study (Japanese American men living in Hawaii),⁴ or the 13 mm Hg lower SBP associated with prevalent dementia in the Kungsholmen Study (Swedish older residents).²

Although it is possible that BP decline is purely secondary to the neurodegenerative processes underlying dementia, this does not readily account for the much smaller associations found in these low- and middle-income settings, because the limited neuropathologic research in diverse populations suggests comparable post-mortem findings in dementia among Brazil, Germany, and Japan,²⁰ Mexico,²¹ India,²² and China,²³ as well as between Indian and North American samples.²⁴ Therefore, there is no reason to suppose that dementia has markedly different somatic manifestations in different countries. Supporting this, weight loss, another somatic correlate of dementia that precedes the clinical onset²⁵ and continues afterward,²⁶ has been consistently found across a range of international settings,^{27,28} including within the 10/66 study sites.²⁹ A component of the association between dementia and lower BP might reflect a similar underlying process to that resulting in weight loss, because waist circumference was identified as a significant potential mediator, although results were unchanged when we further adjusted for this covariate.

International heterogeneity in associations between dementia and lower BP may have other explanations. As mentioned earlier, SBP decline associated with dementia in the Honolulu-Asia Aging Study was also not homogeneous but was confined to people who had not received antihypertensive treatment.⁴ In discussing this, the authors proposed that this BP decline might reflect previous hypertensive disease—either because of arterial stiffness causing cognitive decline³⁰ or through watershed ischemia and disturbed cerebral autoregulation, white matter damage, and Alzheimer pathology.^{31,32} The fact that associations between dementia and BP were relatively small and did not differ by hypertensive history or antihypertensive treatment might reflect that mean BPs in all sites were relatively low compared with what would be expected in higher-income populations.³³ Thus, some lack of association between dementia and lower BP may simply reflect populations where hypertension has been uncommon. In keeping with this, the associations that were most prominent and consistent were those in Cuba, where mean BP levels were closest to higher-income setting norms.⁷

Strengths of this study included the large samples, high response rates, and consistencies in measurement among sites. Resting BP was measured according to a standard protocol and dementia was ascertained in an identical manner following a procedure that had been extensively validated.⁹ Measurement error (in BP or dementia) cannot be excluded absolutely and may have diluted our results. However, procedures were

highly standardized and quality control was thorough, and there have been no difficulties identifying other associations with BP in the same samples.⁷ Limitations also include the cross-sectional design and the sampling procedure, and missing BP measurements might have altered results in Venezuela and Puerto Rico. However, because dementia prevalence was higher among those without compared to those with complete data, our results may be an underestimate. Participants' BP measurements before inclusion were not available, and BP levels rather than BP changes were thus analyzed. However, reported clinical diagnosis of hypertension previous to study inception did not significantly modify associations. The 10/66 protocols preserved internal validity so that comparisons among study sites were appropriate.⁸ Findings were near identical for CDR score analyses, but heterogeneity due to differences in dementia severity cannot be excluded, and wider issues of differential survival might have accounted for differences from higher-income settings, although most international life-expectancy differences are driven by mortality in childhood and survival through mid- and late-life is much less variable.³⁴ The impact of those covariates included in the models was modest, suggesting that confounding was not a major issue. However, residual confounding needs consideration (for example, life-long diet and physical activity). The nature of the study also precluded measurements such as *APOE* genotype and vascular biomarkers, and information on vitamin supplementation was limited (although unlikely to have a substantial influence in these settings). Brain structure is influenced by both genetic and environmental factors,³⁵ and both BP and cerebral pathophysiology have strong genetic influences.^{36,37} Adjustment for reported family history of dementia made little difference to the associations of interest, but this does not preclude familial influences.

Overall, these findings from large community samples in low- and middle-income settings suggest that contemporaneous associations between dementia and lower BP are not universally strong. Lifetime hypertensive disease may be key to dementia-associated SBP decline and a reason why the latter is more marked in source populations with higher cardiovascular risk. However, LMIC are predicted to experience rapid increments in both dementia⁶ and hypertension prevalence,⁵ so closer monitoring of such associations across populations undergoing these epidemiologic transitions is warranted. Clinicians should be aware that BP may be relatively low in patients by the time they develop dementia but this does not rule out effects of earlier hypertensive disease. Whether early antihypertensive use might reduce the extent of this decline remains uncertain, but our data suggest

caution in BP lowering, particularly when the disease is more advanced.

AUTHOR CONTRIBUTIONS

Emiliano Albanese and Robert Stewart conceived the study and drafted the manuscript, and had access to all the data and take responsibility for the data, accuracy of the data analysis, and the conduct of the research; they have the right to publish all data, separate and apart from the guidance of any sponsor of the research; and take responsibility for listing coinvestigators (see the *Neurology*[®] Web site at www.neurology.org). Emiliano Albanese and Flavia L. Lombardo analyzed the data and performed the meta-analyses. Martin J. Prince was responsible for study concept and design, study coordination, obtaining funding, and revising the manuscript.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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Development and validation of a clinical guideline for diagnosing blepharospasm (See p. 236)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the July 16, 2013, issue of *Neurology*. In the second segment, Dr. Binit Shah talks with Dr. Giovanni Defazio about his paper on development and validation of a clinical guideline for diagnosing blepharospasm. Dr. Roy Strowd then reads the e-Pearl of the week about iatrogenic botulism. In the next part of the podcast, Dr. Alberto Espay focuses his interview with Dr. Salvatore DiMauro on The

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