

## Public Health Focus

# Resistant Hypertension: Risk Factors, Subclinical Atherosclerosis, and Comorbidities Among Adults—The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

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The frequency of resistant hypertension—defined as blood pressure (BP)  $\geq 140/90$  mm Hg with proven use of three antihypertensive medications, or as the use of four antihypertensive drug classes regardless of BP—is unknown in low-middle-income countries. Using data from the Brazilian Longitudinal Study of Adult Health, a cohort of 15,105 civil servants aged 35 to 74 years, the authors identified 4116 patients taking treatment for hypertension, 11% of who had resistant hypertension. These participants were more likely to be older, black, less educated, poorer, and obese. The adjusted prevalence ratios (95% confidence intervals) were

diabetes, 1.44 (1.20–1.72); glomerular filtration rate ( $< 60$  mL/min/1.72 m<sup>2</sup>), 1.95 (1.60–2.38); albumin-to-creatinine ratio ( $> 300$  mg/g), 2.43 (1.70–3.50); carotid-femoral pulse-wave velocity, 1.07 m/s (1.03–1.11 m/s); common carotid intima-media thickness, 2.57 mm (1.64–4.00 mm); left ventricular hypertrophy, 2.08 (1.21–3.57); and atrial fibrillation, 3.55 (2.02–6.25). Thus, the prevalence of resistant hypertension in Brazil is high and associated with subclinical markers of end-organ cardiovascular damage. *J Clin Hypertens (Greenwich)*. 2015;17:74–80. © 2014 Wiley Periodicals, Inc.

High blood pressure (BP) directly impacts mortality, morbidity, disability, and the costs of medical care worldwide.<sup>1</sup> Despite improvements in the detection and treatment of hypertension, the proportion of people with hypertension who do not achieve desirable BP levels with the use of appropriate antihypertensive drugs is relatively high, motivating the American Heart Association to launch guidelines for diagnosing and managing resistant hypertension. In these guidelines, resistant hypertension is defined as systolic BP (SBP)  $\geq 140$  mm Hg or diastolic BP (DBP)  $\geq 90$  mm Hg on current treatment with at least three drugs, one of which is a diuretic and all of which are prescribed at optimal doses.<sup>2</sup>

The reported proportion of resistant hypertensive patients has varied from approximately 11% to 33%, depending on the strictness of the definition and the study population.<sup>3–10</sup> The identification of people with resistant hypertension has been supported by prospective studies revealing a higher risk of major adverse cardiovascular outcomes in approximately 4 years of follow-up varying from 11% to 120%.<sup>8,9,11</sup>

Correct estimation of the prevalence of resistant hypertension and its associated factors is complicated by

the high proportion of pseudoresistance caused by poor BP measurement, poor adherence to antihypertensive drugs, and the white-coat phenomenon of rising BP during examination.<sup>2</sup> Moreover, the definition of resistant hypertension implies to exclude pseudo-hypertension, medication-related causes, secondary causes of hypertension such as renal parenchymal disease, and obstructive sleep disorders<sup>12–17</sup> with a synergic association with high salt intake.<sup>17</sup>

The epidemiology of resistant hypertension across countries, including consideration of demographic, ethnic, social, and medical care access determinants, will be useful for reducing the burden of cardiovascular diseases. For example, Brazil is the country with the highest proportion of disability-adjusted life-years and stroke death rates in the Americas.<sup>18,19</sup> The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)<sup>20,21</sup> is a unique opportunity to investigate the prevalence rates of resistance in a country with high levels of high BP and to identify new factors associated with resistant hypertension.

## MATERIALS AND METHODS

### Study Recruitment

ELSA-Brasil addresses the incidence of cardiovascular diseases and major associated risk factors. The design and preliminary findings of this study are available elsewhere.<sup>20,21</sup> Briefly, 15,105 civil servants aged 35 to 74 years from six cities in Brazil (Belo Horizonte, Porto Alegre, Rio de Janeiro, Salvador, Sao Paulo, and Vitoria) were enrolled between August 2008 and

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**Manuscript received:** July 5, 2014; **revised:** September 4, 2014;  
**accepted:** September 14, 2014  
**DOI:** 10.1111/jch.12433

December 2010 for baseline examination. Since then, all participants have reported potential health adverse outcomes in a standardized telephone interview. The second wave of interviews began in September 2012 and will be completed in December 2014. All six participating centers approved the ELSA-Brasil protocol and all participants granted informed consent.

### Data Collection

Interviews and examinations at each site were carried out by trained personnel with strict quality control. The questionnaire addressed sociodemography, lifestyle, morbidity, psychiatric profile, diet, and medications used. Smoking status was defined as never, former, or current. Education was categorized as elementary, high school, or college. Annual household income was converted to US dollars from Brazilian reais. Physical activity at leisure was categorized as little, mild, or vigorous and was ascertained with the International Physical Activity Questionnaire Short Form. Alcohol consumption was assessed via questionnaire and was dichotomized according to the amount ingested per week (men  $\geq 210$  g; women  $\geq 140$  g). All participants described past medical diagnoses of myocardial infarction, stroke, or coronary revascularization. Psychiatric comorbidity was assessed with the Clinical Interview Schedule Revised questionnaire, allowing us to match diagnoses with the *International Classification of Diseases—10th Revision*. We separately analyzed depression, generalized anxiety disorders, mixed anxiety, and depressive disorders.<sup>21</sup> Given the relevance of salt intake to resistant hypertension,<sup>17</sup> we estimated salt intake by measuring an overnight sample of urinary sodium. Further, a 114-item food frequency questionnaire was administered to all participants to reveal daily differences in salt consumption.

All prescription and over-the-counter pill bottles were examined to confirm that medications were taken during the 15-day period preceding the interview. High medication adherence was defined as a score  $\leq 1$  using the four-item Morisky Medication Adherence Scale.<sup>23</sup> We performed an exploratory data analysis of medication prescribed more commonly for participants with resistant hypertension to identify antagonizing substances that may elevate BP or inhibit the effects of antihypertensive drugs.

Trained nurses measured patients' weight, height, sitting height, waist, and hip and neck circumferences and performed standardized physiological examinations. Body mass index (BMI) was calculated by dividing the patients' weight in kilograms by height in meters squared. Although we have no information about sleep apnea, an important factor for resistant hypertension, we used neck circumference as a surrogate for sleep disorders. Resting 12-lead electrocardiography (ECG) was used to identify left ventricular hypertrophy and atrial fibrillation, as determined by the Minnesota Code criteria analyzed electronically (Pyramis ECG Management, Mortara Instrument Inc, Milwaukee,

WI). Carotid-femoral pulse wave velocity was measured using a validated automated device (Complior, Artech Medical, Vincennes, France). The distance from the sternal furcula to the right femoral pulse was measured with a metric tape regardless of abdominal curvature. Pulse sensors were positioned in the right carotid and femoral arteries to record and visualize pulse waves on a computer screen. Intima-media thickness (IMT) was assessed using an Aplio XG device (Toshiba, Tokyo, Japan) with a 7.5-MHz linear transducer. Images of common carotids were acquired over a length of 10 mm, starting 10 mm below the carotid bifurcation. Imaging data from three cardiac cycles were analyzed with an automated computer program (Carotid Analyzer 6 for Research, Medical Imaging Applications, Coralville, IA). IMT measurements are presented as the average value in the right and left arteries of the maximum thickness at the far wall.

Diabetes was defined as a report of a previous medical diagnosis of diabetes, the use of medication for diabetes, or meeting a diagnostic cut-off for diabetes according to fasting or 2-hour plasma glucose levels obtained as part of a 75-g oral glucose tolerance test or the glycated hemoglobin test. Glomerular filtration rates were calculated using the equations from the Chronic Kidney Disease Epidemiology consortium without correction for race (has not added useful information for Brazilians)<sup>22</sup> and renal dysfunction was defined as values  $\leq 60$  mL/min/1.72 m<sup>2</sup>. Urine albumin was measured via nephelometry, and an altered albumin-to-creatinine ratio was defined as  $\geq 300$  mg/g.

### Measurement of BP and Definitions of Resistant Hypertension

During the on-site examination, BP was measured with the validated Omron HEM 705CPINT oscillometric device (Omron Co, Kyoto, Japan) after a 5-minute rest with the patient in a sitting position in a quiet, temperature-controlled room (20–24°C). Three measurements were taken at 1-minute intervals. High BP was defined in terms of three criteria: SBP  $\geq 140$  mm Hg, DBP  $\geq 90$  mm Hg, or the use of medication to control hypertension (in the interview: “Are any of the drugs you have taken in the past 2 weeks for high BP?”). We compared a random subsample of 255 ELSA-Brasil participants using 24-hour ABPM (Spacelabs 9075, Spacelabs Healthcare, Snoqualmie, WA) with satisfactory reproducibility between measurements taken in-office.<sup>24</sup> The means of the differences were 4.43 mm Hg for SBP and 3.81 mm Hg for DBP, and we estimated that 4% of ELSA-Brasil patients experienced white-coat hypertension.<sup>24</sup>

On the basis of our review of participants' pill bottles, antihypertensive medications were coded as (1) diuretics, (2)  $\beta$ -blockers, (3) angiotensin-converting enzyme inhibitors, (4) angiotensin receptor blockers, (5) calcium channel blockers, (6) direct vasodilators, (7) central-acting agents, (8) mineralocorticoid receptor antagonists, or (9) renin inhibitors. One-pill combinations

were classified into their respective classes. Medication dosage information was not recorded.

Resistant hypertension was defined as hypertension for which the patient took more than three classes of antihypertensive medication, including at least one diuretic, with SBP  $\geq 140$  mm Hg or DBP  $\geq 90$  mm Hg or the patient taking four classes of antihypertensive medication with SBP  $< 140$  mm Hg and DBP  $< 90$  mm Hg during the preceding 15 days.<sup>2</sup>

### Sampling and Statistical Analysis

A previous baseline description of all members of ELSA-Brasil identified 5402 patients (35.8%) with hypertension, of which 4333 (80.2%) were aware of this condition and 4147 (76.8%) were under drug treatment.<sup>25</sup> Of these 4147 patients, we excluded 31 participants who did not name the antihypertensive under use, resulting in a total of 4116 participants with enough data to define resistant hypertension.

We calculated the proportion of people with resistant hypertension in terms of all persons taking pharmacologic treatment for hypertension.

We sought to investigate factors associated with resistant hypertension such as sex, age, race, annual household income, educational attainment, BMI, neck circumference, previous medical diagnosis of coronary heart disease (myocardial infarction and/or revascularization) or stroke, physical activity, alcohol consumption, cigarette smoking, diagnosis of diabetes and/or depression and/or glomerular filtration rate, albuminuria, pulse wave velocity, common carotid IMT, and alterations in electrocardiography.

Prevalence ratios were estimated with a generalized linear model applying a Poisson regression with a robust estimator. We calculated the ratios for the categories above and adjusted for sex, age, and race. Further, we evaluated three variables associated with the causal pathway of resistant hypertension (family income, body mass index, and neck circumference<sup>26</sup>) to estimate the prevalence ratios associated with resistant hypertension. Waist circumference was not added to the model due to a colinearity effect with BMI (data not shown).

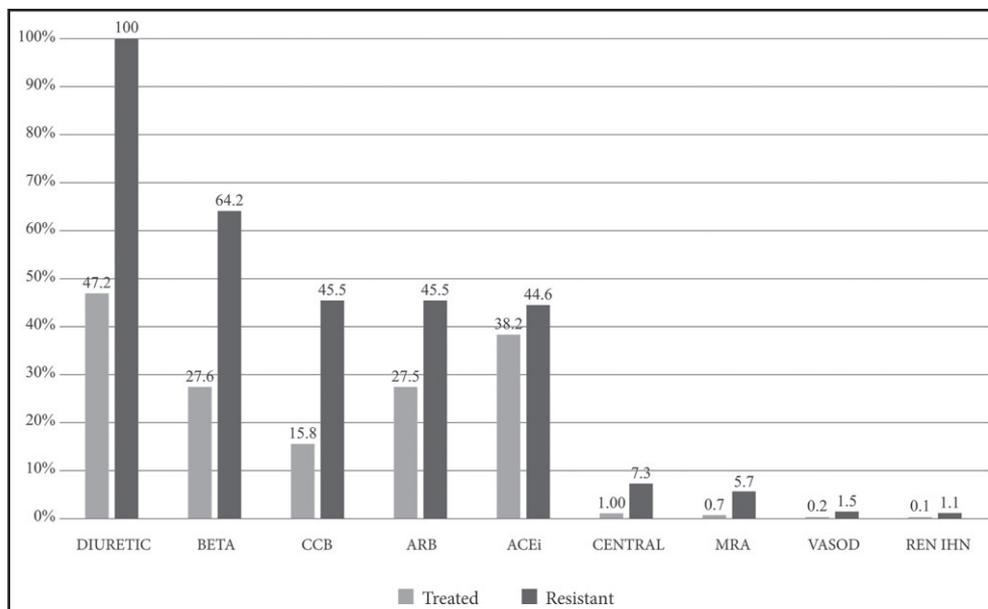
## RESULTS

### Prevalences of Resistant Hypertension

Of the 4116 ELSA-Brasil participants taking antihypertensive medication during the past 2 weeks, 453 had resistant hypertension, yielding an overall prevalence of resistant hypertension of 11%. The compliance with treatment for chronic diseases, as estimated via the Moriski criteria (score  $\leq 1$ ), was 75% for patients with resistant hypertension and 73% for patients taking treatment for hypertension. Extrapolating these findings to participants enrolled at baseline, the prevalence rates were 3% for resistant hypertension.

### Participant Characteristics

In the 453 participants with resistant hypertension, thiazide and thiazide-like diuretics were used for 429 people (94.7%). Hydrochlorothiazide alone or in combination with a potassium-sparing drug was prescribed for 344 participants (75.9%), followed by indapamide for 43 (9.4%) and chlorthalidone for 42 (9.3%). The



**FIGURE.** The use of antihypertensive medication classes by the Brazilian Longitudinal Study of Adult Health participants with resistant hypertension (n=453). ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BETA,  $\beta$ -blocker; CENTRAL, central-acting agent; CCB, calcium channel blocker; VASOD, direct vasodilators; MRA, mineralocorticoid receptor antagonist; REN INH, renin inhibitors.

**TABLE I.** Characteristics of Participants in ELSA-Brasil at Baseline (2008–2010) in Terms of Treated Hypertension, Resistant Hypertension, and Refractory Hypertension

Characteristic	Treated Hypertension <sup>a</sup>	Resistant Hypertension	P Value
No.	3663	453	
Women, %	52.9	54.5	.274
Age, y	56.6 (±0.1)	58.8 (±0.4)	>.001
Systolic blood pressure, mm Hg	128.8 (±0.3)	138.2 (±1.0)	>.001
Diastolic blood pressure, mm Hg	79.7 (±0.2)	82.8 (±0.6)	>.001
Black race, %	20.7	30.0	>.001
Household income per y <\$20,000, %	52.1	61.0	>.001
Education less than high school, %	16.7	25.6	>.001
Body mass index, kg/m <sup>2</sup>	28.8 (±0.8)	30.6 (±0.3)	>.001
Neck circumference, 10 mm	37.6 (±0.6)	38.4 (±0.2)	>.001
Waist circumference, 10 mm	96.3 (±0.2)	101.0(±0.7)	>.001
Vigorous leisure physical activity, %	7.5	5.1	.036
Current smoker, %	10.8	9.9	.627
Heavy alcohol intake	18.6	15.4	.188
Salt intake, g/d	12.1 (±0.6)	12.7 (±0.6)	>.001
Diabetes mellitus, %	35.0	51.8	>.001
Previous stroke, %	2.8	4.6	>.001
Previous coronary heart disease, %	6.0	12.8	>.001
Pulse wave velocity, m/s	10.0 (±0.4)	10.7 (±0.1)	>.001
Common carotid IMT, mm	0.837 (±0.003)	0.909 (±0.136)	>.001
Left ventricular hypertrophy, %	0.9	2.5	.010
Atrial fibrillation, %	0.4	2.5	>.001
eGFR <60 mL/min/1.72 m <sup>2</sup> , %	11.5	25.4	>.001
Albuminuria (ACR >300 mg/g), %	1.3	4.9	>.001
Medication adherence (%)	72.8	74.7	.218

Abbreviations: ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; ELSA-Brasil, the Brazilian Longitudinal Study of Adult Health. Salt intake was estimated from an overnight urine sample. Values are expressed as mean±standard error or percentage. Diabetes diagnosis followed criteria from the American Diabetes Association.

<sup>a</sup>All treated hypertensive participants except those with resistant hypertension.

other 24 participants (5.3%) were taking furosemide. At least one angiotensin-converting enzyme inhibitor or angiotensin receptor blocker was used by 84.3% of patients with resistant hypertension. Dual therapy blocking of the renin-angiotensin system (angiotensin-converting enzyme inhibitors, angiotensin receptor blocker, or aliskiren) was prescribed for 3.8% of participants with resistant hypertension; spironolactone was used by 5.7% of participants, and at least one central-acting antihypertensive was used by 7.3% of participants (Figure).

Individuals exhibiting resistant hypertension were more frequently older, female, black, and had lower socioeconomic status based on income or education (Table I). We were able to analyze the association of resistant hypertension according to sex, race, body mass index stratified for annual familiar income. No effect modification of ratios was observed for age, sex, and body mass index. However, the prevalence ratios (and 95% confidence interval) of black race compared with white race were significant for people with higher income (1.75; 1.26 to 2.41) but not for those with lower income (1.26; 0.93–1.71).

Indicators of adiposity (BMI and waist/neck circumference) were higher in this population, with a higher

proportion of diabetes, a lower glomerular filtration rate, and a more frequent history of stroke or coronary heart disease (Table I). Further, these participants presented with a higher proportion of hypertension-damaged organs, as indicated by albuminuria and left ventricular hypertrophy.

People with resistant hypertension significantly had a large neck circumference, more frequently confirmed diabetes, reduced glomerular filtration rate, albuminuria, high values of common carotid IMT, and high probabilities of left ventricular hypertrophy, atrial fibrillation, and aortic stiffness (Table II).

Table III shows the prevalence ratios for resistant hypertension adjusted for age, sex, race, body mass index, and neck circumference. Presence of diabetes, reduced glomerular filtration rate, aortic stiffness, previous cardiovascular diseases, ECG abnormalities, and albuminuria were abnormalities related to resistant hypertension independently of these covariates.

Salt intake, mental health disorders, and the use of prescription drugs have been linked to resistant hypertension. Salt intake, as estimated by urinary sodium measurements, was high in all categories of participants, at approximately 12 g/d (Table I). We adjusted all models first using sodium-to-potassium excretion ratio

**TABLE II.** Prevalence Ratios (95% Confidence Intervals) for Patients With Resistant Hypertension Compared With Treated Hypertension

	Crude	Adjusted for Sex, Age, Race
Age, y	1.03 (1.02–1.04)	1.03 (1.02–1.04)
Men vs women	1.06 (0.89–1.26)	1.00 (0.84–1.19)
White vs black race	1.62 (1.31–1.99)	1.73 (1.40–2.14)
Education less than high school, %	1.51 (1.26–1.81)	1.37 (1.11–1.68)
Household income per y <\$20,000	1.38 (1.16–1.65)	1.32 (1.08–1.62)
Body mass index, kg/m <sup>2</sup>	1.06 (1.04–1.07)	1.06 (1.05–1.08)
Waist circumference, 10 mm	1.022 (1.016–1.028)	1.025 (1.019–1.031)
Neck circumference, cm	1.05 (1.03–1.07)	1.11 (1.08–1.15)
Vigorous leisure physical activity, %	0.69 (0.46–1.03)	0.71 (0.48–1.07)
Current smoker vs never smoked	0.95 (0.70–1.28)	0.97 (0.72–1.32)
Heavy alcohol intake, yes/no	0.91 (0.61–1.28)	0.88 (0.57–1.31)
Diabetes mellitus, yes/no	1.84 (1.55–2.19)	1.68 (1.41–2.01)
Previous stroke, yes/no	1.58 (1.06–2.35)	1.43 (0.97–2.11)
Previous CHD, yes/no	2.02 (1.58–2.59)	1.78 (1.38–2.29)
Pulse wave velocity, m/s	1.11 (1.08–1.15)	1.08 (1.04–1.12)
Common carotid IMT, mm	4.01 (2.81–5.70)	3.15 (2.09–4.74)
Left ventricular hypertrophy	2.30 (1.33–3.96)	1.94 (1.13–3.33)
Atrial fibrillation	4.01 (2.50–6.45)	3.06 (1.83–5.12)
Glomerular filtration rate <60 mL/min/1.72 m <sup>2</sup> , %	2.27 (1.88–2.75)	1.95 (1.60–2.39)
Albuminuria (albumin-to-creatinine ratio >300 mg/g)	2.97 (2.08–4.24)	2.71 (1.89–3.88)

Abbreviations: CHD, coronary heart disease (self-reported myocardial infarction and/or coronary revascularization); IMT, intima-medial thickness.

**TABLE III.** Prevalence Ratios (95% Confidence Intervals) Adjusted for Age, Sex, Race, Family Income, Body Mass Index, and Neck Circumference of Participants With Resistant Hypertension

	Resistant Hypertension
Diabetes mellitus	1.44 (1.20–1.72)
Glomerular filtration rate <60 mL/min/1.72 m <sup>2</sup>	1.95 (1.60–2.38)
Pulse wave velocity, m/s	1.07 (1.03–1.11)
Common carotid IMT, mm	2.57 (1.64–4.00)
Albumin-to-creatinine ratio >300 mg/g	2.43 (1.70–3.50)
Left ventricular hypertrophy	2.08 (1.21–3.57)
Atrial fibrillation	3.55 (2.02–6.25)
Previous stroke	1.50 (1.01–2.21)
Previous coronary heart disease	1.71 (1.33–2.19)

and further applied only sodium intake for total calories by regressing nutrient intake on total energy intake, but the results did not change substantially. Mental health data obtained via the Clinical Interview Schedule

Revised questionnaire did not reveal any significant associations with anxiety, depression, or common mental disorders. The use of anxiolytics, antidepressants, nonsteroidal anti-inflammatory drugs, oral contraceptives, and appetite inhibitors was similar among the hypertension groups (data not shown).

## DISCUSSION

At baseline, 35.8% of ELSA-Brasil<sup>25</sup> participants had confirmed hypertension. We estimated that resistant hypertension occurred in 11% of participants. Compared with all hypertensive patients under treatment, the most common associations for resistant hypertension were with female sex, black race, obesity, and diabetes. Renal, arterial, and cardiac consequences of high BP occurred significantly more frequently in patients with resistant hypertension. The detected association with diabetes amplifies the cardiovascular risk of patients with resistant hypertension. In contrast to other studies, the frequency of prescription of mineralocorticoid receptor antagonists was very low (<6%) among people with resistant hypertension. To our knowledge, ELSA-Brasil is the first large epidemiological study to uncover associations of resistant hypertension with carotid-femoral pulse wave velocity, common carotid IMT, and neck circumference, which is related to sleep disorders, a potential cause of resistant hypertension.<sup>13–17</sup>

Comparing data from the baseline cohort with other studies with distinct designs must be carried out with caution because of different settings and definitions of resistant hypertension. The National Health and Nutrition Examination Survey (NHANES)<sup>3</sup> did not consider the use of diuretics as a mandatory characteristic of resistant hypertension, as we did here. However, although ELSA-Brasil participants were younger at baseline than NHANES participants, some risk factors for resistant hypertension (albuminuria, reduced renal function, and self-reported coronary heart disease and diabetes) were the same in NHANES. The association of resistant hypertension with diabetes in ELSA-Brasil was confirmed with both the oral glucose tolerance test and the glycated hemoglobin test. The positive relationship between resistant hypertension with previous cardiovascular diseases is in accordance with other studies.<sup>3–9</sup> The impact on the heart, as evidenced by left ventricular hypertrophy, was the same as in the Spanish Ambulatory Blood Pressure Monitoring Registry,<sup>5</sup> a population that was older than that in ELSA-Brasil. The association with atrial fibrillation in the current study confirms the results of studies in Madrid, Spain,<sup>6</sup> by Kaiser Permanente<sup>8</sup> and by the Reduction of Atherothrombosis for Continued Health registry.<sup>9</sup>

Sleep apnea disorder defined via polysomnography has been associated with resistant hypertension. Neck circumference is an important component of obstructive sleep apnea.<sup>15–17</sup> We determined that neck circumference should be considered a risk factor for resistant hypertension independent of BMI and waist

circumference. In addition to a putative role of neck adiposity in the metabolic syndrome and consequently high BP,<sup>26</sup> the most plausible explanation for this association is the mechanic effect of fat at the neck triggering the pathophysiology of obstructive sleep apnea and resistant hypertension. Critically, we simultaneously adjusted our models for BMI and neck circumference to address the associations among hypertension status, obesity, and sleep disturbances.

Here, we demonstrated that both early atherosclerosis and arterial stiffness occur more frequently in a population that is younger than the cohorts of other studies. A high carotid IMT may result from high BP and may not necessarily be an atherosclerotic lesion because IMT may be a consequence of hypertension with hypertrophy of the medial layer of the arterial wall.<sup>27,28</sup> The elevation of carotid-femoral pulse wave velocity observed in our participants should be further considered for new treatments in these patients.<sup>29–31</sup> Aortic stiffness may cause resistant hypertension and may not be a consequence of continuous high BP (proposed by Pickering<sup>29</sup>), as suggested by the Outpatient Quality Improvement Network<sup>30</sup> and demonstrated in the Maine-Syracuse Longitudinal Study.<sup>31</sup> Our data reinforce this putative association between resistant hypertension and arterial stiffness.

The optimal prescription for hypertension control was not applied to ELSA-Brasil participants. Like other studies, we detected a preference for hydrochlorothiazide instead of chlorthalidone, which is much more effective.<sup>32</sup> However, the most relevant finding was a low frequency of mineralocorticoid receptor antagonists prescribed among those who had resistant hypertension despite the results of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)<sup>33</sup> and recommendations from experts.<sup>34</sup> One potential explanation is that only spironolactone is marketed in Brazil, and it is labeled as a drug for heart failure (and refractory ascites) and most physicians avoid it because of the risk of hyperkalemia and side effects caused by estrogenic activity. Another aspect peculiar to our sample is the relatively low frequency of the prescription of calcium channel blockers compared with angiotensin receptor blockers, considering the high proportion of black individuals in our country. The reason for this pattern of prescription cannot be medical therapeutic inertia alone. The National Health System delivers some antihypertensive drugs free of charge (atenolol, captopril, enalapril, losartan, and propranolol) but not chlorthalidone, indapamide, amlodipine, and spironolactone.

A relevant problem concerning resistant hypertension is related to patient adherence to antihypertensive drugs and to the therapeutic inertia of physicians. This problem was more marked in patients with apparent treatment of resistant hypertension. The Spanish Ambulatory Blood Pressure Monitoring Registry<sup>35</sup> identified 12.2% of participants with resistant hypertension according to office BP, but one third of these cases were considered to be white-coat resistant hypertension

because the high value in the office was not repeated during ambulatory blood pressure monitoring. However, the Spanish registry<sup>35</sup> identified a rate of white-coat hypertension of nearly 20%, in contrast to the rate of 4% in ELSA-Brasil.<sup>24</sup> This discordance may be the result of different examination settings (a regular outpatient clinic vs a clinical research environment). We do not think this difference is caused by the effects of other medicines or compliance with antihypertensive treatment, since these variables were similar in our sample and other studies.

## STUDY LIMITATIONS

Our findings may overestimate the true prevalence rates of resistance in the current Brazilian cohort, as in other large epidemiological studies. First, neither in ELSA-Brasil nor in a large cohort in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study<sup>36</sup> was it possible to identify participants who consistently take their medication, only those who took their medication during the 2 weeks before the examination. Second, we were not able to quantify the dosages for each antihypertensive drug, and so we cannot assess the degree to which an inadequate dosage contributed to apparent treatment failure. Third, we did not ascertain possible causes of secondary hypertension. Regarding generalization, the ELSA-Brasil cohort has an ethnic background that approximates the entire Brazilian population, but our patients significantly differed from the overall population in terms of socioeconomic status and education.

## CONCLUSIONS

Our findings confirm the importance of physicians to provide their patients with dietary counseling for low-salt intake, to shift the preference from hydrochlorothiazide to chlorthalidone as the diuretic, and encourage the use of mineralocorticoid receptor antagonists as the fourth antihypertensive drug. From a public health perspective, the diagnosis and management of resistant hypertension is a priority given the relatively high prevalence of uncontrolled hypertension and the high risk of events and premature deaths. In addition to primary prevention strategies such as salt regulation, body weight control, and limitation of alcohol intake, countries with a high prevalence of hypertension must consider the treatment of resistant hypertension as secondary prevention and expand the portfolio of free-of-charge cardiovascular medications.

*Acknowledgments:* The authors thank the ELSA-Brasil participants who agreed to collaborate in this study. The authors also thank the ELSA-Brasil research team for their contributions.

*Funding Sources:* The ELSA-Brasil baseline study was supported by the Brazilian Ministry of Health (Science and Technology Department) and the Brazilian Ministry of Science and Technology (Financiadora de Estudos e Projetos and CNPq National Research Council grants 01 06 0010.00 RS, 01 06 0212.00 BA, 01 06 0300.00 ES, 01 06 0278.00 MG, 01 06 0115.00 SP, and 01 06 0071.00RJ).

*Conflicts of Interest/Disclosures:* Drs Bensenor, Lotufo, and Mill are the recipients of an established investigator award from CNPq, Brasilia, Brazil. Drs

Benseñor, Lotufo, and Mill are co-chairs of the Estudo Longitudinal de Saúde do Adulto (ELSA-Brasil). Dr Lotufo received grants from GlaxoSmithKline and Takeda to enroll participants for clinical trials addressing acute coronary syndrome and atrial fibrillation, respectively.

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