Background: The importance of subclinical cerebrovascular disease in the elderly is increasingly recognized, but its determinants have not been fully explained. Elevated blood pressure (BP) and fluctuation in BP may lead to cerebrovascular disease through ischemic changes and compromised cerebral autoregulation.

Objective: To determine the association of BP and long-term fluctuation in BP with cerebrovascular disease.

Design: A community-based epidemiological study of older adults from northern Manhattan.


Participants: A total of 686 nondemented older adults who had BP measurements during 3 study visits at 24-month intervals and underwent structural magnetic resonance imaging (corresponding temporally with the third assessment). We derived the mean (SD) of the mean BP for each participant during the 3 intervals and divided the participants into 4 groups defined as below or above the group median (≤96.48 or >96.48 mm Hg) and further subdivided them as below or above the median SD (≤7.21 or >7.21 mm Hg). This scheme yielded 4 groups representing the full range of BPs and fluctuations in BP.

Main Outcome Measures: Differences in white matter hyperintensity (WMH) volume and presence of brain infarctions across groups.

Results: White matter hyperintensity volume increased across the 4 groups in a linear manner, with the lowest WMH volume in the lowest mean/lowest SD group and the highest WMH volume in the highest mean/highest SD group (F3,610=3.52, P=.02). Frequency of infarction also increased monotonically across groups (from 22% to 41%, P for trend = .004).

Conclusions: Compared with individuals with low BP and low fluctuations in BP, the risk of cerebrovascular disease increased with higher BP and BP fluctuations. Given that cerebrovascular disease is associated with disability, these findings suggest that interventions should focus on long-term fluctuating BP and elevated BP.

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Large and small vessel cerebrovascular disease (CVD) in the elderly, visualized by structural magnetic resonance imaging (MRI) as infarction and white matter hyperintensities (WMHs), is associated with cognitive decline and disability, but its determinants have not been fully explained. Elevated blood pressure (BP) can cause CVD through a variety of pathways, including atherosclerotic changes, blood-brain barrier dysfunction, lipohyalinosis, carotid stenosis, and hemorrhage. Elevated BP is associated with poorer cognitive function in older adults and has been shown to be a risk factor for Alzheimer disease. Increased BP in midlife and late in life is also related to stroke and, although inconsistently, WMH volume. Studies that examine the association between BP and CVD generally consider BP measurements at 1 time point, limiting the appreciation of the full impact of BP on CVD. In clinical settings, absolute BP is used as a therapeutic target to prevent clinical stroke and heart disease, but BP fluctuation across long periods and its effect on CVD are typically not considered.

The interplay between peripheral vascular systems and cerebrovascular function is complex. In his seminal synthesis of studies using the inert gas method to examine cerebral blood flow, Lassen applied the term “autoregulation” to describe the phenomenon in which brain perfusion remains constant across a wide range of BPs. Through interacting myogenic, neurogenic, and metabolic mechanisms, the cerebrovascular system adapts to changes in BP to maintain the nutri-
tional supply necessary to fuel its high metabolic activity. Thus, in a range of increasing and decreasing BP, brain perfusion remains steady. In the context of hypertension and advancing age, the lower boundary of this so-called autoregulatory “plateau stage” adaptively shifts toward higher BP levels. Although compensatory, this adjustment may enhance the brain’s vulnerability to hypoperfusion at lower BPs. Based on these effects, it is possible that persistently elevated BP and long-term fluctuations in BP can lead to CVD directly through ischemic changes (eg, atherosclerosis) and indirectly through compromised cerebral autoregulation, which may lead to longer periods or high levels of transient hypoperfusion.

We investigated the relation between BP and fluctuations in BP across three 24-month waves on CVD using high-resolution MRI in a large community cohort of older adults. We hypothesized that as BP and long-term fluctuations in BP increased, higher amounts of WMHs and a greater likelihood of having an infarct would be observed.

METHODS

PARTICIPANTS

Data were included from individuals participating in a prospective study of aging in Medicare-eligible northern Manhattan residents 65 years and older (the Washington Heights-Inwood Columbia Aging Project [WHICAP]; N = 2776). The WHICAP cohort represents a combination of continuing members of a cohort originally recruited in 1992 (n = 602) and members of a new cohort recruited between 1999 and 2001 (n = 2174). The sampling and recruitment outcomes of these 2 cohorts have been described elsewhere. The population from which participants were drawn comprises individuals from 3 broadly defined ethnic categories (ie, Hispanic, black, and white). Ethnic group was determined by self-report using the format of the 2000 US Census. Participants have been followed up at approximately 24-month intervals, with similar assessments at each interval. Recruitment, informed consent, and study procedures were approved by the ethics committees at Columbia University and New York State Psychiatric Institute.

Beginning in 2003, participants who did not meet the criteria for dementia at previous evaluations and who did not have contraindications were invited to participate in an MRI study. Image acquisition corresponded temporally with the third assessment wave of the cohort recruited in the 1999-2001 interval. That is, participants recruited at that time had their initial (baseline) evaluations between 1999 and 2001, their second evaluations in the 2002-2004 assessment wave, and their third evaluation, including MRI, in the 2005-2007 wave. Derivation of the WHICAP imaging sample and full sample characteristics are described elsewhere. Briefly, MRI was performed on 769 participants. Participants who refused the MRI study but otherwise met the inclusion criteria for dementia at previous evaluations and who did not meet the criteria for dementia were excluded from the present analyses (but not MRIs). The remaining 686 participants.

MRI ACQUISITION AND ANALYSIS

Detailed procedures and variables for MRI acquisition are included elsewhere. Briefly, standard T1-weighted, T2-weighted fluid-attenuated inversion recovery images and double-echo images were acquired using a 1.5-T scanner (Intera; Royal Philips Electronics, Eindhoven, the Netherlands) at Columbia University. Data from MRI were transferred to the University of California at Davis for morphometric analysis in the Imaging of Dementia and Aging Laboratory. Volumes of WMHs were derived on the fluid-attenuated inversion recovery images following established procedures, and were divided by total cranial volume, and were log transformed to establish a measure of normally distributed relative WMH volume. Determination of the presence, size, and location of cerebral infarct was performed according to previously reported protocols. The presence of brain infarction was determined using all available imaging data. Only lesions 3 mm or larger qualified for consideration as brain infarcts. Infarcts were coded for size (small, >3 mm and <1 cm; large, ≥1 cm), hemisphere, and location. Two raters determined the presence of cerebral infarction on MRI. Previously published k values for agreement among raters have been generally good, ranging from 0.73 to 0.90.

CLINICAL EVALUATION

At each visit, participants underwent an in-person evaluation that included interviews regarding health and functional abilities, a medical history, physical and neurologic examinations, and a neuropsychological battery. As part of the study visit, highly standardized BP measurements were made using the Dinamap Pro 100 (Critikon Co, Tampa, Florida). The BP cuff was placed on the right arm while the individual was seated, and a recording was obtained every 3 minutes across 9 minutes. The third measurement was recorded in the database and was used in the present analyses. The WHICAP study visits usually took place during typical business hours, but precise time of day was not controlled. Thus, we did not explicitly consider circadian variability but did not expect systematic differences across participant groups.

Dementia diagnosis was made based on standard research criteria presented at a consensus conference attended by study physicians and neuropsychologists. Blood pressure and neuromaging data were not considered for diagnosis. Consensus was reached after a review of all available information gathered from initial and follow-up assessments (but not MRIs). Participants were excluded from the present analyses if they met the criteria for dementia.

BP VARIABLES

AND PARTICIPANT GROUPING

As already noted, BP measurements were made at each of the 3 visit waves (ie, 1999-2001, 2002-2004, and 2005-2007), with the third visit corresponding to the time of MRI. We sought to examine the relation of BP and long-term fluctuation in BP with CVD. The exposures of interest were mean and its standard deviation across the 3 visits. Each participant’s mean BP was computed for each of the 3 visits using the following equation: mean BP = (1/3 × systolic BP [SBP]) + (2/3 × diastolic BP [DBP]). For each participant, we then calculated the arithmetic mean (SD) of the mean BP across the 3 follow-up visits. We derived 4 groups based on the median split of the mean BP measurement (median = 96.48 mm Hg) and the median split of the SD (median = 7.21 mm Hg) across the study group. 1 group was defined as mean BP = 96.48 mm Hg and mean SD > 7.21 mm Hg; group 2, mean BP = 96.48 mm Hg and mean SD ≤ 7.21 mm Hg; group...
ease was ascertained by self-report and was coded as present if present, absent if absent. Heart disease history included arrhythmias, coronary artery disease, and congestive heart failure.

Thus, the 4 groups represented individuals whose BP was in the normative range with little fluctuation through individuals with higher BP with a greater degree of fluctuation across the 3 evaluations. Participants were considered treated for hypertension if they reported taking diuretics, calcium channel blocking agents, or angiotensin-converting enzyme inhibitors at any point during the 3-visit period. We also examined other medications or medication classes that might affect BP did not differ across groups and in the standard deviations of these measures. The mean (SD) interval between the 1999-2001 and 2002-2004 assessment wave was 2.12 (0.71) years, and between the 2002-2004 and 2005-2007 wave was 2.45 (0.65) years, and between the 1999-2001 and 2005-2007 wave was 4.47 (0.80 years). These intervals did not vary significantly across BP groups. By definition, there were significant group differences in mean BP, mean SBP, and mean DBP across groups and in the standard deviations of these measures. The mean (SD) interval between the 1999-2001 and 2002-2004 assessment wave was 2.12 (0.71) years, and between the 2002-2004 and 2005-2007 wave was 2.45 (0.65) years, and between the 1999-2001 and 2005-2007 wave was 4.47 (0.80 years). These intervals did not vary significantly across BP groups.

The 4 BP groups were similar in age, sex distribution, ethnicity distribution, and number of years of education achieved (Table 1). Participants with the highest BP and the most BP fluctuation were the most likely to have been treated with antihypertensive medications, whereas those with the lowest BP and the least BP fluctuation were the least likely. The distribution of other medications that might affect BP did not differ across groups. By definition, there were significant group differences in mean BP, mean SBP, and mean DBP across groups and in the standard deviations of these measures. The mean (SD) interval between the 1999-2001 and 2002-2004 assessment wave was 2.12 (0.71) years, between the 2002-2004 and 2005-2007 wave was 2.45 (0.65) years, and between the 1999-2001 and 2005-2007 wave was 4.47 (0.80 years). These intervals did not vary significantly across BP groups.

Clinically, participants classified as having a lower BP (groups 1 and 2) had mean, DBPs, and SBPs that were approximately in what is considered the normotensive range, whereas those with a higher BP (groups 3 and 4) were in the prehypertensive or hypertensive range (Table 1). In terms of the degree of long-term BP fluctuation, those with the lowest BP and lowest SD (group 1) fluctuated approximately 5.5% during the 3-year period (SD/mean = 4.90/88.35 mm Hg), BP for those in group 2 with low mean BP but higher SD fluctuated approximately 14.2% (SD/mean = 12.66/89.44 mm Hg) across the 3-year period. Those in the higher BP group but with low

### Table 1. Demographic, Treatment, BP, and Fluctuation (SD) Differences Across BP Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n=176)</th>
<th>Group 2 (n=186)</th>
<th>Group 3 (n=167)</th>
<th>Group 4 (n=177)</th>
<th>Statistics</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>79.25 (5.38)</td>
<td>80.78 (5.61)</td>
<td>79.97 (5.31)</td>
<td>79.98 (5.62)</td>
<td>F&lt;sub&gt;3,683&lt;/sub&gt; = 2.20</td>
<td>.09</td>
</tr>
<tr>
<td>Ethnicity, %</td>
<td>White 28.4</td>
<td>Black 30.7</td>
<td>Hispanic 38.6</td>
<td>Other 2.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education, mean (SD)</td>
<td>10.51 (4.97)</td>
<td>11.02 (4.55)</td>
<td>10.90 (4.62)</td>
<td>10.80 (4.78)</td>
<td>F&lt;sub&gt;3,682&lt;/sub&gt; = 0.37</td>
<td>.78</td>
</tr>
<tr>
<td>Treated with antihypertensive agents, %</td>
<td>57.9</td>
<td>68.4</td>
<td>65.5</td>
<td>73.2</td>
<td>( \chi^2 = 6.03 )</td>
<td>.01</td>
</tr>
<tr>
<td>Treated with other medications that might affect BP, %</td>
<td>23.9</td>
<td>23.8</td>
<td>23.0</td>
<td>21.5</td>
<td>( \chi^2 = 0.37 )</td>
<td>.95</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; DBP, diastolic BP; SBP, systolic BP.

3, mean BP >96.48 mm Hg and mean SD ≤7.21 mm Hg; and group 4, mean BP >96.48 mm Hg and mean SD >7.21 mm Hg. Thus, the 4 groups represented individuals whose BP was in the normative range with little fluctuation through individuals with higher BP with a greater degree of fluctuation across the 3 evaluations. Participants were considered treated for hypertension if they reported taking diuretics, calcium channel blocking agents, or angiotensin-converting enzyme inhibitors at any point during the 3-visit period. We also examined other medications or medication classes that might have a secondary effect on BP, including digoxin, nitrates, antiarrhythmics and anginals, and thyroid supplements. Furthermore, history of diabetes mellitus, hypertension, and heart disease was ascertained by self-report and was coded as present or absent. Heart disease history included arrhythmias, coronary artery disease, and congestive heart failure.

**STATISTICAL ANALYSIS**

General linear models were constructed to examine whether WMH volume differed across the 4 BP groups. In addition to comparing each BP group with the low BP/low fluctuation group as a reference, we tested the linear trend in WMH volume across groups. Analyses included age, sex, and treatment status as additional covariates. The proportion of participants with cerebral infarcts was compared across BP groups using logistic regression analysis in which the presence or absence of infarct was the dependent variable and age, sex, and treatment status were additional covariates. This analysis was run first with large and small infarcts combined and then separated by infarct size.

For the WMH and infarct analyses, we also examined whether the primary findings were modified by ethnicity by including it as an additional covariate or by stratification of analysis by ethnic group. We also reran analyses with history of diabetes mellitus, hypertension, and stroke as covariates.

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SD (group 3) fluctuated approximately 5.2% (SD/mean = 5.42/103.75 mm Hg), whereas those with the highest BP and the highest SD (group 4) fluctuated approximately 14.2% (SD/mean = 14.99/105.86 mm Hg) across the 3-year period (Table 1).

Volume of WMHs increased across the 4 BP groups monotonically, with the lowest WMH volume in group 1 and the highest in group 4 (main effect of group: $F_{3,610} = 3.52, P = .02$; test of linear trend $P = .02$ [Figure and Table 2]). Increased age was associated with more severe WMH volume (main effect of age: $F_{1,610} = 27.43$, $P < .001$; no other covariates were associated with WMH volume. Including ethnicity as a covariate or stratifying the analysis by ethnic group did not change the pattern of results. When history of diabetes mellitus, hypertension, and heart disease was included as additional covariates, the findings remained unchanged. Of these additional covariates, only history of hypertension entered into the model significantly ($\beta = 0.24, t = 2.33, P = .02$) such that participants with a self-reported history of hypertension had a significantly higher WMH volume.

Two hundred fifteen of the 686 participants (31.3%) with available data had infarcts. Across the 4 groups, the proportion of individuals with infarcts also increased monotonically (test for linear trend: $\beta = 1.25, P = .004$) (Table 3). Women and those who had received treatment for hypertension were more likely to have infarcts. When stratified by infarct size, the pattern of results was similar. Including ethnicity or stratification by ethnic group yielded similar results as did inclusion of history of diabetes mellitus, hypertension, and heart disease. In the latter case, only self-reported history of heart disease was associated with increased stroke ($\beta = 0.37, P = .045$). When we repeated the analyses separately for DBP and SBP, the general pattern of results was similar.

### Table 2. Associations of BP and Long-term BP Fluctuation With Log-transformed Relative WMH Volume

<table>
<thead>
<tr>
<th>Covariate</th>
<th>$\beta$ (SE)</th>
<th>$t$</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.033 (0.006)</td>
<td>5.24</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex (female = 1)</td>
<td>0.123 (0.072)</td>
<td>1.70</td>
<td>.09</td>
</tr>
<tr>
<td>Treated (yes = 1)</td>
<td>0.130 (0.072)</td>
<td>1.81</td>
<td>.07</td>
</tr>
<tr>
<td>BP group$^a$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>[Reference]</td>
<td>1</td>
<td>[Reference]</td>
</tr>
<tr>
<td>2</td>
<td>0.095 (0.096)</td>
<td>0.98</td>
<td>.32</td>
</tr>
<tr>
<td>3</td>
<td>0.245 (0.098)</td>
<td>2.50</td>
<td>.01</td>
</tr>
<tr>
<td>4</td>
<td>0.267 (0.094)</td>
<td>2.83</td>
<td>.005</td>
</tr>
<tr>
<td>$P$ value for trend</td>
<td>NA</td>
<td>NA</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; CI, confidence interval; NA, not applicable.

$^a$Group 1 contains participants with lower mean BP (<96.48 mm Hg) and lower fluctuation (SD <7.21 mm Hg); group 2, lower mean BP (<96.48 mm Hg) and higher fluctuation (SD >7.21 mm Hg); group 3, higher mean BP (>96.48 mm Hg) and lower fluctuation (SD <7.21 mm Hg); and group 4, higher mean BP (>96.48 mm Hg) and higher fluctuation (SD >7.21 mm Hg).

### Table 3. Associations of BP and Long-term BP Fluctuation With the Presence of Stroke

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Infarcts, No./Total No. (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>NA</td>
<td>1.001 (0.969-1.034)</td>
<td>.95</td>
</tr>
<tr>
<td>Sex (female = 1)</td>
<td>NA</td>
<td>0.651 (0.452-0.937)</td>
<td>.02</td>
</tr>
<tr>
<td>Treated (yes = 1)</td>
<td>NA</td>
<td>1.747 (1.192-2.560)</td>
<td>.004</td>
</tr>
<tr>
<td>BP group$^a$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>39/176 (22.2)</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>48/166 (28.9)</td>
<td>1.255 (0.750-2.098)</td>
<td>.39</td>
</tr>
<tr>
<td>3</td>
<td>56/167 (33.5)</td>
<td>1.418 (0.849-2.370)</td>
<td>.18</td>
</tr>
<tr>
<td>4</td>
<td>72/177 (40.7)</td>
<td>2.020 (1.238-3.294)</td>
<td>.005</td>
</tr>
<tr>
<td>$P$ value for trend</td>
<td>NA</td>
<td>NA</td>
<td>.004</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; CI, confidence interval; NA, not applicable.

$^a$Group 1 contains participants with lower mean BP (<96.48 mm Hg) and lower fluctuation (SD <7.21 mm Hg); group 2, lower mean BP (<96.48 mm Hg) and higher fluctuation (SD >7.21 mm Hg); group 3, higher mean BP (>96.48 mm Hg) and lower fluctuation (SD <7.21 mm Hg); and group 4, higher mean BP (>96.48 mm Hg) and higher fluctuation (SD >7.21 mm Hg).

Through the examination of BP characteristics across 3 prospective evaluations separated by intervals of approximately 2 years, we demonstrated that mean BP and long-term fluctuation in BP are associated with CVD in the form of WMHs and infarction in a linear manner. The presence of either factor (elevated mean BP or elevated fluctuations in BP) alone was sufficient to incur a greater burden of WMHs or probability of infarct, although elevated mean BP was associated with more severe CVD. The 2 factors also seem to be additive; those with the higher mean BP and more fluctuation had proportionately more CVD than those with either one alone. Cerebrovascular disease is associated with a constellation of conditions that lead to disability, including cognitive impairment, mood, and movement disorders. Thus, these findings may have important clinical implications.
The association between BP and stroke is a well-replicated finding. Elevated BP is associated with stroke through a variety of avenues, such as atherosclerosis, lipohyalinosis, carotid stenosis, and hemorrhage. Investigators have become interested in identifying the etiology and determinants of WMHs because of their relationship to cognitive dysfunction and disability. White matter hyperintensities are ubiquitous in older adults, and pathological studies suggest an ischemic etiology, including incomplete and total infarction and demyelination, although there is some evidence that WMHs are heterogeneous in etiology. Persistently elevated BP is likely to be related to increased WMH volume and stroke through similar mechanisms. However, elevated BP and increased age also result in a shift in the lower boundary of the autoregulatory curve, which may put areas with relatively low blood supply, including white matter, at risk for ischemic damage due to hypoperfusion.

The terms BP variability and fluctuation typically refer to modulation in DBP or SBP on the order of minutes to hours or in response to experimental manipulation. In the present study, we were interested in determining whether long-term fluctuation in BP is associated with CVD. To this end, the study design paralleled routine clinical medical follow-up. The BP information in this study is similar to that available to any physician using standard BP measurements and can be computed easily. Consistent with the hypothesis, long-term fluctuation in BP was associated with small and larger vessel vascular disease, even when mean BP was low. Typically, physicians examine absolute levels of BP but do not consider fluctuations across visits. The findings highlight the potential clinical importance of monitoring, and perhaps treating, persistent fluctuation in BP across months and years, although future studies need to establish more definitively a causal link between BP fluctuation and CVD. Furthermore, CVD may lead to hippocampal dysfunction, places individuals at increased risk for dementia, and is associated with an increased rate of decline in individuals with mild cognitive impairment or dementia. Thus, proper risk factor management is essential for reducing risk of cerebrovascular-related cognitive decline in aging and dementia. Participants in the present study who had the highest BP and highest fluctuation levels were most likely to have been treated with antihypertensive agents, which suggests that intermittent lack of compliance may be one source of long-term BP fluctuation and further highlights the potential clinical importance of maintaining a consistently normotensive BP.

White matter is particularly susceptible to fluctuations, or inconsistent perfusion. With consistent with this notion, the present findings show that fluctuation in BP is related to a higher WMH volume. We also found that fluctuation in BP was more informative in addition to BP status than each variable alone. This finding is particularly important in a population with a high prevalence of hypertension, relatively homogeneous in BP level, but heterogeneous in BP variability. Hypertension treatment has been shown to restore BP regulation in addition to treating BP levels in the elderly. Thus, fluctuation in BP may be important as an exposure in epidemiological research in the elderly and as a clinical variable.

Whether long-term fluctuation in BP is a reflection of the degree of BP variability across shorter intervals remains to be tested empirically. Nevertheless, much as with persistently elevated BP, the association between fluctuations in BP, across any interval, and CVD could reflect age-associated autoregulatory dysfunction. Even in normotensive individuals, high variability in BP could cause ischemic damage due to hypoperfusion during periods of particularly low BP. This possibility is particularly evident in the present study in individuals with low mean BP but higher fluctuation who had increased CVD compared with those with low BP and less variability.

The present study has several strengths. The WHICAP cohort is a large and ethnically diverse community-based elderly cohort with quantitative neuroimaging. The neuroimaging protocol and morphometric analysis was standardized across participants. These strengths must be appreciated in the context of some weaknesses. Although we characterized participants based on reliable longitudinal BP data, MRI data were acquired at only one point in time, and, thus, analyses were correlational. It is unlikely that structural brain changes caused hypertension or fluctuations in BP; however, the time course of the relationship between the 2 remains to be elucidated. Future studies should examine incidents and change in CVD as they relate to BP characteristics.

These results demonstrate a strong association of BP and fluctuations in BP with measures of CVD. Although the control of elevated BP or the treatment of hypertension is an obvious and well-replicated conclusion, these findings suggest that management of BP fluctuations, even in normotensive older adults, may be beneficial in reducing the risk of CVD and in maximizing healthy cognitive aging.

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Author Contributions: Drs Brickman and Reitz contributed equally to this article. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Schupf, and DeCarli. Analysis and interpretation of data: Brickman, Reitz, Luchsinger, Schupf, Muraskin, Brown, and Mayeux. Drafting of the manuscript: Brickman, Reitz, Luchsinger, Schupf, and Mayeux. Critical revision of the manuscript for important intellectual content: Brickman, Manly, Schupf, Muraskin, DeCarli, Brown, and Mayeux. Statistical analysis: Brickman and Schupf. Obtained funding: Brickman, Luchsinger, Manly, and Mayeux. Administrative, technical, and material support: Manly, Schupf, Muraskin, DeCarli, and Brown.

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