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Effects of vascular risk factors, statins, and antihypertensive drugs on PiB deposition in cognitively normal subjects

Lidia Glodzik[a,b,*], Henry Rusinek[b], Angela Kamer[c], Elizabeth Pirraglia[a], Wai Tsui[a], Lisa Mosconi[a], Yi Li[a], Pauline McHugh[a], John Murray[a], Schantel Williams[d], Ricardo S. Osorio[a], Catherine Randall[a], Tracy Butler[a], Anup Deshpande[a], Shankar Vallabhajolusa[e], Mony de Leon[a]

[a]*Department of Psychiatry, Center for Brain Health, NYU School of Medicine, New York, USA*
[b]*Department of Radiology, NYU School of Medicine, New York, USA*
[c]*Department of Periodontology and Implant Dentistry, College of Dentistry, New York University, New York, USA*
[d]*Renal Research Institute, New York, USA*
[e]*Department of Radiology, Weill Cornell Medical College, New York, USA*

Abstract

Introduction: Hypertension, hypercholesterolemia, and obesity increase the risk of dementia. Although their detection is commonly followed by an introduction of treatment, little is known about how medications frequently used to treat vascular risk affect amyloid deposition.

Methods: A cross-sectional study of 156 subjects who underwent positron emission tomography with PiB. Using linear regression, we tested whether blood pressure, cholesterol, overweight/obese status, angiotensin receptor blockers (ARBs), beta-blockers, diuretics, angiotensin converting enzyme inhibitors, and statins predicted amyloid deposition.

Results: The use of ARBs ($\beta = -.15$, $P = .044$) and diuretics ($\beta = -.20$, $P = .006$) predicted less amyloid accumulation; older age ($\beta = .29$, $P < .001$) and statins ($\beta = .23$, $P = .004$) were related to greater amyloid deposition. Overweight and/or obese women had more cortical amyloid than their peers.

Discussion: Prospective studies should confirm effects of drugs and increased body weight on amyloid accumulation and establish whether they translate into measurable clinical outcomes. Women may be more susceptible to harmful effects of obesity.

Keywords: Amyloid; PET-PiB; Vascular risk factors; Antihypertensive medications; Statins angiotensin receptor blockers; Diuretics; Brain; Healthy elderly

1. Introduction

Alzheimer's disease (AD) and vascular conditions are increasingly common with age. Vascular disease contributes to AD neurodegeneration [1–3] and may even initiate it [4]. This notion is supported both by epidemiologic studies showing that atherosclerosis risk factors like hypertension, high cholesterol, and obesity are associated with higher incidence of cognitive impairment and AD [5], and by neuropathology studies showing that indices of atherosclerosis correlate with AD markers [6].

Amyloid ß deposition in extracellular plaques [7] and vessel walls [4] is a key feature of AD. In animal studies, hypoperfusion and ischemia-activated gamma-secretase [8], increased *BACE1* gene transcription and expression, and augmented Aß accumulation [9]. These observations suggest that the association between vascular disorders and AD could be mediated by changes in amyloid metabolism.

L.M., M.d.L., and W.T. have an imaging patent which belongs to NYU. Other authors report no conflict of interest.

*Corresponding author. Tel.: +1 212 263 5698; Fax: +1 212 263 3270.
E-mail address: Lidia.Glodzik@nyumc.org

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Recent years have brought evidence that higher brain amyloid deposition, measured with Pittsburgh compound B (PET-PiB), is related to high blood pressure [10–12] and abnormal markers of lipid metabolism [13,14]. Interestingly, studies reporting on body mass index (BMI) and PiB found an inverse relationship, with low BMI related to greater PiB uptake [12,15]. Both of these observations were based on subjects in their seventies or older, and the results might have reflected weight loss in preclinical stages of the disease.

The detection of vascular risk is commonly followed by the introduction of appropriate treatment aimed at risk modification. The treatment itself may affect PET measures of brain amyloid accumulation, but this is largely unknown. In a group of cognitively healthy adults and elderly, we examined cross-sectionally the relationships between the most common vascular risk factors: blood pressure, cholesterol, and body weight, as well as frequently used antihypertensive medications and statins, and brain amyloid deposition measured with PET-PiB.

As women are more likely to suffer from AD than men [16], and sex differences in risk factors for conversion to AD [17] and in the associations between lipid levels and dementia [18] have been reported, we also conducted exploratory analyses to examine whether the relationships between vascular risk factors and PiB deposition differed by gender.

2. Methods

2.1. Subjects

We studied 156 cognitively healthy subjects (mean ± standard deviation, age 60.4 ± 10.4 years; education 16.6 ± 2.0 years; 67% women). Eighty-eight percent of the group was Caucasian, 9% African American, 2.5% Asian, and 0.5% Hispanic. All subjects were recruited by the Center for Brain Health at the NYU School of Medicine for longitudinal PET studies of aging, cognitive decline, and AD risk factors. They were volunteers responding to advertisement, subjects interested in research participation or family members of cognitively impaired patients. All signed IRB-approved consent forms and underwent medical, psychiatric, and neurological assessments, blood tests, ECG, MRI, and PET-PiB scans. PET examinations were performed between March 2009 and November 2013. Mild cognitive impairment and dementia were ruled out during a diagnostic interview. All subjects had ≥26 points on the mini mental state examination. Subjects scoring >17 on the 17-item Hamilton Depression Scale [19], subjects with brain tumor, neocortical infarction, and axis I disorders were excluded.

Laboratory tests (in a fasting state) included complete blood count, metabolic and lipid panel, liver function tests, and urinalysis. The clinical evaluation included an interview using the Brief Cognitive Rating Scale and rating on the Global Deterioration Scale (GDS) [20]. All subjects were diagnosed as cognitively healthy: with (GDS = 2) or without (GDS = 1) subjective memory complaints. From a larger pool of potential subjects, we report here on subjects ≥35 years, with technically good PET scans. Diagram in Fig. 1 describes an initial and final study sample.

2.1.1. Neuropsychological assessment

To fully characterize the cognitive status of our participants, we performed cognitive testing. It included the Uniform Data Set Neuropsychological Test Battery as chosen by National Alzheimer's Coordinating Center: Logical memory story A from Wechsler Memory Scale, (I: immediate and II: delayed recall), digits forward and backward, digit symbol substitution test (DSST), Trail Making Test parts A and B (TMT-A,B), Boston Naming Test (BNT), animal and vegetable categories [21]. Subjects also received tests from the Guild Memory Scale assessing immediate and delayed recall of orally presented paragraphs (initial: PARI, and delayed: PARD); and verbal paired associates (initial: PRDI and delayed: PRDD) [22]. Tests results of all tests were converted to age-adjusted, education-adjusted, and gender-adjusted standardized scores (z-scores) based on a normative population [23,24]. We subsequently grouped cognitive tests into memory (logic I and II, PARD, PARI, PRDD, and PRDI), executive function (TMT-B), attention (digits forward and backward), processing speed (DSST and TMT-A), and language (BNT, animals, and vegetables categories) domains. The score for each domain was an average of z scores of all tests combined.

2.1.2. Ascertainment of vascular risk factors

The presence of hypertension (HTN) was determined based on current antihypertensive treatment or blood pressure (BP) ≥140/90 mm Hg [25]. BP was taken in a sitting position, after 5 minutes of rest. Of 50 subjects classified as hypertensive 40 were taking medication, 10 were unmedicated with high blood pressure during in office visit. BMI was calculated as [weight (pounds) × 703]/height^2 (inches). All the subjects were classified as having a normal weight: BMI ≤24.99 or being overweight or obese: BMI ≥25. Subjects currently being treated with cholesterol-lowering medication (statins) or subjects with total cholesterol >200 were considered to have hypercholesterolemia [26].

2.1.2.1. Medication

We separately coded the following groups: angiotensin receptor blockers (ARBs) acting through blocking angiotensin receptor 1; angiotensin converting enzyme inhibitors (ACEi), preventing conversion of angiotensin I to angiotensin II; beta-blockers blocking β-adrenergic receptors in the heart and vascular smooth muscles; diuretics increasing water excretion from the body; statins and antidepressants. We did not analyze calcium channel blockers separately because these were taken only by five subjects.

2.1.2.2. Apolipoprotein E (APOE) genotyping

Genotyping was performed using polymerase chain reaction as previously described [27]. Study subjects were

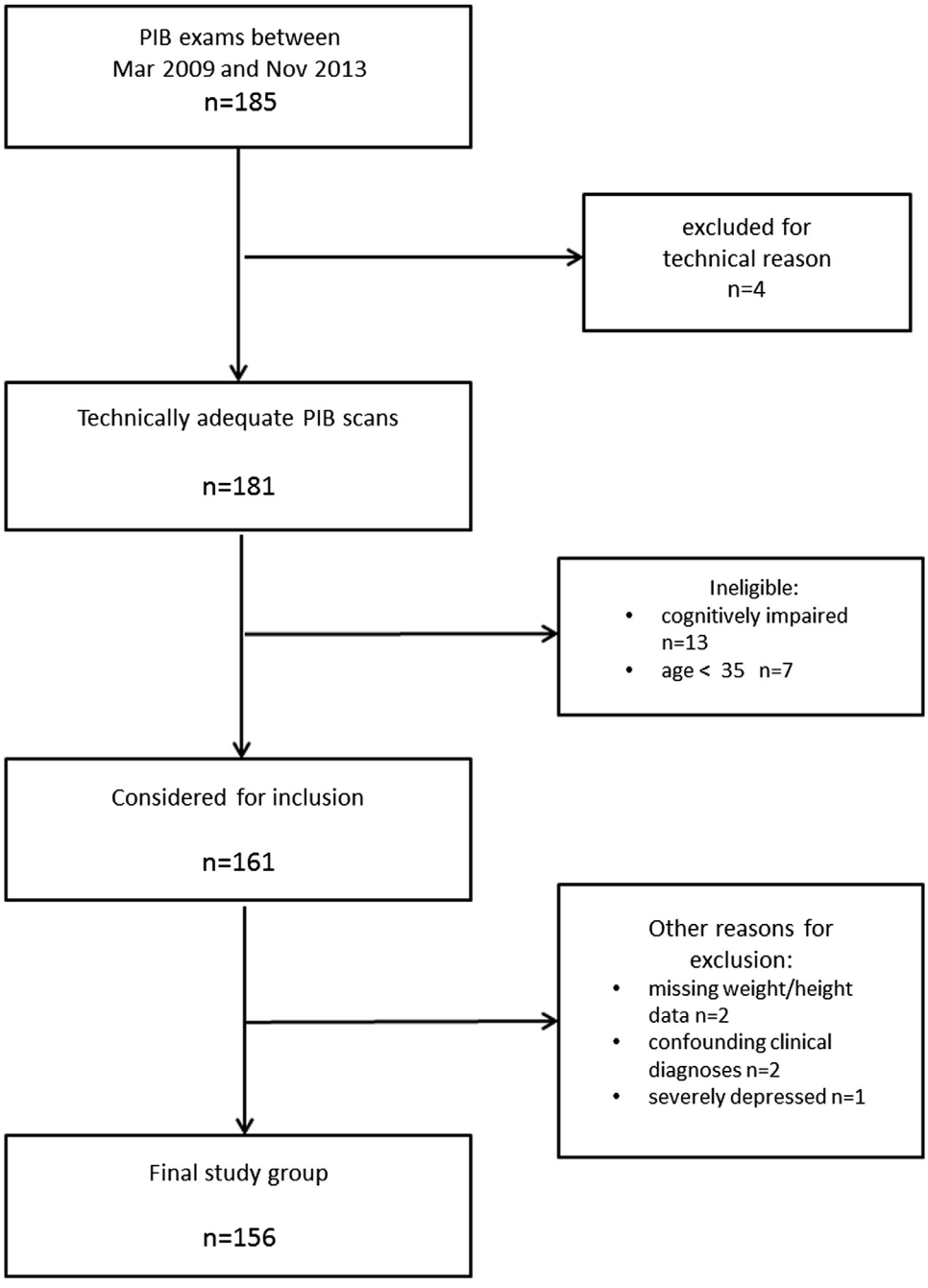

Fig. 1. A diagram representing initial and final study sample.

classified as *APOE* ε4 positive (*APOE* ε4+) if they had one or two ε4 alleles and otherwise negative (*APOE* ε4−). Genotype data were available for 147 of 156 subjects.

2.2. Imaging

2.2.1. MRI acquisition

All magnetic resonance imaging was performed on the same quality-controlled 1.5-T GE scanner (GE, Milwaukee, WI, USA). All participants received coronal T1-weighted and axial FLAIR (fluid attenuation inversion recovery) scans. T1-weighted (gradient echo) scan parameters were repetition time [TR] = 35 ms, time to echo [TE] = 2 ms, flip angle [FA] = 60°, number of excitations [NEX] = 1, slice thickness: 1.6 mm, field of view [FOV] = 200 mm, matrix = 256 × 192 × 124, reconstructed as 256 × 256. FLAIR images were acquired with TR 9279 ms, TE 127 ms, TI 2300 ms, FA 90°, NEX = 1, slice thickness: 3.3 mm, FOV 240 mm, matrix = 256 × 192, as 256 × 256 images.

2.2.2. PiB-PET acquisition

Scans were performed using either an LS Discovery scanner (G.E. Medical Systems, Milwaukee, WI; full width at half maximum (FWHM) = 5.4 mm, FOV = 30 cm) or Bio-Graph PET/CT scanner (Siemens, Knoxville, TN; FWHM = 6.0 mm, FOV = 50 cm). Before scanning, a venous line was inserted in the antecubital vein, and subjects rested in a quiet and dim room. Scanning started 60 minutes after isotope injection and lasted 30 minutes. In each case, 15 mCi (~550 MBq) of N-methyl[11C]2-(4'-methylaminophenyl)-6-hydroxy-benzothiazole (PiB; radiochemical purity >98%) was administered. Before each PET examination, a CT transmission scan was acquired for attenuation correction with the same FOV as PET. All images were corrected for photon attenuation, scatter, and radioactive decay. Each PET-PiB volume was visually screened to assure adequate full brain coverage from the apex to the inferior margin of the cerebellum.

2.2.3. PiB-PET image processing

Images were processed using Multimodal Image Data Analysis System package [28] (MIDAS, version 1.11) and with Statistical Parametric Mapping (SPM, version 8) [29]. The 60–90 minutes PiB data were used to generate summed images. They were co-registered to the corresponding T1-MRI using the normalized mutual information algorithm implemented in SPM. Subsequently, the T1-MRI images were spatially normalized to the SPM T1 brain template in MNI (Montreal Neurologic Institute) space. The same normalization parameters were then applied to the PiB-PET images to resample them into MNI space. An automated cerebellar region of interest (ROI), known to be spared by fibrillary amyloid, was used to extract the cerebellar uptake of PiB [30]. Each PET voxel in 60–90 minutes image was then divided by the cerebellar intensity value. The resulting ratio images were uniformly smoothed with 10-mm Gaussian kernel. Automated ROIs [30] were applied to extract the estimates of PiB deposition. For the purposes of this study, we created a composite of PiB deposition from cortical regions known to be AD-vulnerable: inferior parietal lobe, lateral temporal lobe, medial frontal gyrus, posterior cingulate cortex, and prefrontal cortex.

2.3. Statistics

Categorical variables were compared with χ^2 test (or Fisher exact when appropriate). T tests were used to compare group means for continuous variables. When covariates were needed, general linear models were used. Correlations were assessed with Pearson coefficient. Nonparametric tests were used to confirm the results.

General characteristics are presented by gender. They were compared using t (Mann–Whitney U when appropriate) or χ^2 tests.

Relationships between vascular risk factors (systolic blood pressure (SBP) and diastolic blood pressure (DBP), cholesterol levels, overweight/obese status) or medication group and PIB deposition were tested using stepwise (backward) linear regression. Age and gender were added to the model. For exploratory purposes, interactions between gender and vascular risk factors were also added. The most parsimonious model was chosen, which was defined as a model including only significant and necessary (main effects when interaction was present) terms. The linear model was checked for violations of the model assumptions (correct distribution of the residuals, correct specification of the variance structure and linear relationship between the response and the linear predictor). The standardized β coefficients are reported for significant independent variables from the linear regression model, after adjusting for other variables which significantly contributed to the model. The variables were centered for the calculation of the higher order terms, to avoid multicollinearity with the main effects and to make the standardized β values more comparable. As log transformation did not render PiB distribution normal, we reexamined the final models created with raw PiB data using rank-transformed PiB data. In two cases with already diagnosed and treated hypertension, SBP or DBP values were missing. They were replaced by means derived from the treated hypertensive group.

Finally, using ANCOVA, we compared PiB deposition between subjects taking different antihypertensive medication, unmedicated hypertensive, and normotensive individuals. The same way we compared PiB binding between statin users, unmedicated subjects with hypercholesterolemia, and individuals with normal cholesterol levels.

Statistical significance was defined as a P value $<.05$. SPSS (version 21; SPSS, Inc., Chicago, IL) software was used for all analyses.

3. Results

3.1. General characteristics

Amyloid deposition was higher in men ($P = .02$), who also had higher triglycerides ($P = .002$), lower total cholesterol ($P = .001$), and lower HDL ($P < .001$) levels. Men were more likely to take statins ($P = .02$) and less likely to take diuretics ($P = .04$) than women. Prevalence of hypertension, being overweight/obese, hypercholesterolemia, *APOE* ε4 status, the use of ARBs, ACEi or beta-blockers, LDL levels, and systolic (SBP) and diastolic (DBP) blood pressure did not differ between genders (Table 1). Table 1 also presents scores in each cognitive domain. Although not used in statistical analyses, they illustrate that our group was indeed cognitively healthy.

3.2. Vascular risk factors, medications, and amyloid deposition

With linear regression, the best fit ($F_{7,149} = 7.2$, $P < .001$) was achieved with a model including age, statins, ARBs,

Table 1
Study variables by gender

Variable	Women (n = 105)	Men (n = 51)	*P* value
Age (years)	60.4 ± 9.7	61.0 ± 11.6	.72
Education[b]	16.6 ± 1.9	16.7 ± 2.0	.69
Cortical PiB deposition (ratio to cerebellum)[b]	1.11 ± .18	1.15 ± .19	**.02**
Overweight/obese (n, %)	51, 48	32, 63	.10
Systolic blood pressure (mmHg)[b]	118.7 ± 15.7	120.0 ± 14.9	.55
Diastolic blood pressure (mmHg)[b]	72.4 ± 11.0	70.9 ± 9.4	.44
Hypertension (n, %)	32, 30	18, 35	.54
Total cholesterol mg/dL	208.1 ± 32.6	188.0 ± 34.7	**.001**
HDL cholesterol mg/dL[b]	70.9 ± 17.0	51.9 ± 16.6	**<.001**
LDL cholesterol mg/dL	119.6 ± 27.3	113.1 ± 31.1	.18
Triglycerides mg/dL[b]	86.3 ± 39.6	115.5 ± 57.4	**.001**
Hypercholesterolemia (n, %)	68, 65	32, 63	.80
Angiotensin receptor blockers (n, %)	8, 8	5, 10	.64
Angiotensin converting enzymes inhibitors (n, %)[a]	6, 6	4, 8	.61
Beta-blockers (n, %)	8, 8	5, 10	.64
Diuretics (n, %)[a]	13, 12	1, 2	**.04**
Antidepressants (n, %)[a]	8, 8	0, 0	.05
Statins (n, %)	17, 16	17, 33	**.02**
APOE ε4 genotype (n, %)*	42, 43	17, 35	.22
Memory†	.14 ± .74	−.04 ± .77	.15
Executive functions	−.14 ± .98	−.14 ± .90	.96
Attention‡	−.05 ± .83	−.17 ± 1.32	.52
Processing speed‡	.05 ± .92	.02 ± .79	.87
Language	.02 ± .77	−.14 ± .63	.21

NOTE. Data presented as mean ± SD, *P* given for comparisons with χ^2 test or Fisher exact test when appropriate (denoted by [a]), *t* test or Mann–Whitney *U* test (denoted by [b]), depending on data distribution.

NOTE. All antidepressants belonged to the selective serotonin reuptake inhibitors class.

Significant results are shown in bold.

*Data available for 147 subjects (98 women and 49 men).

†Data available for 155 subjects (104 women and 51 men).

‡Data available for 154 subjects (103 women and 51 men).

diuretics, and gender × overweight/obese interaction (Table 2). Older age and treatment with statins were associated with more amyloid accumulation, whereas ARBs and diuretics were related to less amyloid. Among women, having BMI ≥25 was associated with greater amyloid deposition (median test, $P < .05$), whereas overweight and/or obese men tended to have less amyloid (median test, $P = .07$; Fig. 2).

Table 2
Linear regression model: predicting amyloid deposition with vascular risk factors and medications in the entire group, n = 156

Model term	Standardized β	*P* value	VIF
Main effects*			
Age	**.29**	**<.001**	1.11
Gender	−.03	.67	1.09
Overweight/obese status	.06	.43	1.10
ARBs	**−.15**	**.04**	1.08
Diuretics	**−.20**	**.006**	1.07
Statins	**.23**	**.004**	1.21
2-way interactions			
Gender × overweight/obese	**.24**	**.001**	1.06

Abbreviations: ARBs, angiotensin receptor blockers; VIF, variance inflation factor.

Significant results are shown in bold.

*Values for standardized β shown are before the addition of higher order terms.

Amyloid deposition differed between hypertensive subjects treated with ARBs, diuretics, hypertensive subjects using other antihypertensive medications, untreated hypertensive subjects, and normotensive individuals ($F_{6,148} = 3.2$ $P = .015$, after accounting for age and statin use). Only one subject was treated with both ARBs and diuretics and was excluded from this analysis. *Post hoc* tests revealed the differences between diuretic users and the normotensive group ($P = .01$), between diuretic users and hypertensive subjects treated with other drugs ($P = .02$), between ARBs users and the normotensive group ($P = .02$), and between ARBs users and hypertensive subjects treated with other drugs ($P = .03$; Fig. 3).

Amyloid deposition also differed between subjects treated with statins, subjects with untreated hypercholesterolemia, and subjects with normal cholesterol levels ($F_{5,150} = 4.1$, $P = .02$, after accounting for age, the use of ARBs, and diuretics). *Post hoc* tests showed that treated subjects had higher cortical amyloid than untreated subjects with hypercholesterolemia ($P = .006$) and individuals with normal cholesterol levels ($P = .02$) (Fig. 4). Cortical PiB did not differ between users of hydrophilic (n = 8) vs. lipophilic (n = 26) statins.

We reexamined the relationships between vascular risk factors and amyloid in subjects who were not

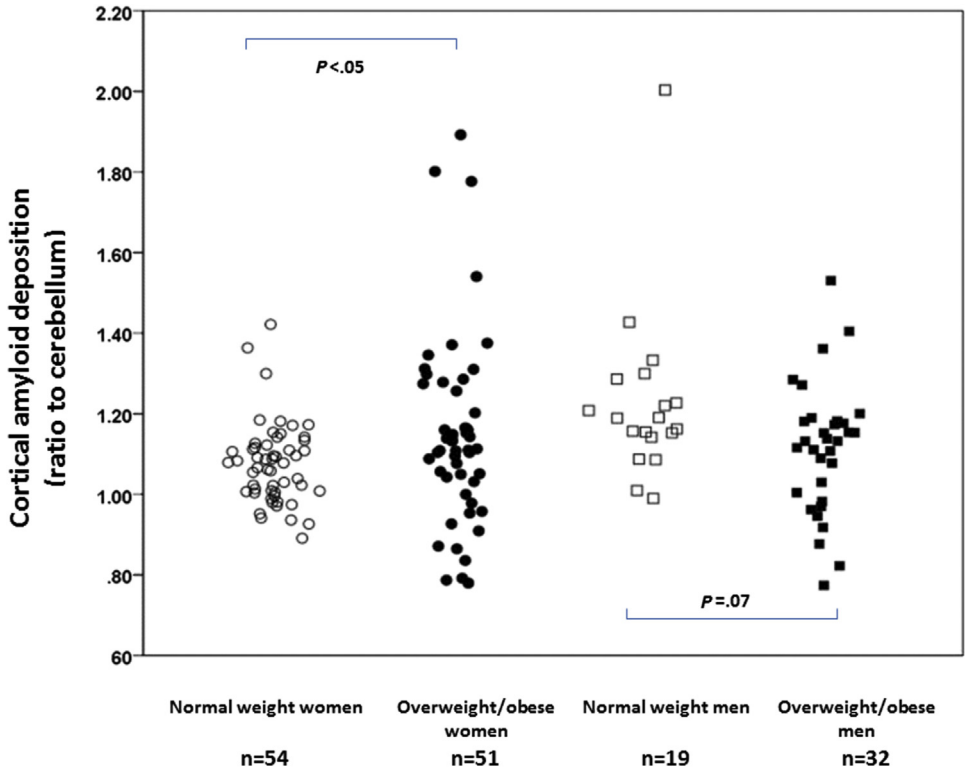

Fig. 2. Distribution of cortical amyloid deposition by gender-overweight/obese groups. Cortical PiB values represent ratio to cerebellum. Circles represent normal-weight women, solid circles represent overweight/obese women, squares represent normal-weight men, and solid squares represent overweight/obese men. With median test differences between: overweight/obese women and normal weight women, $P < .05$; overweight/obese men and normal weight men, $P = .07$.

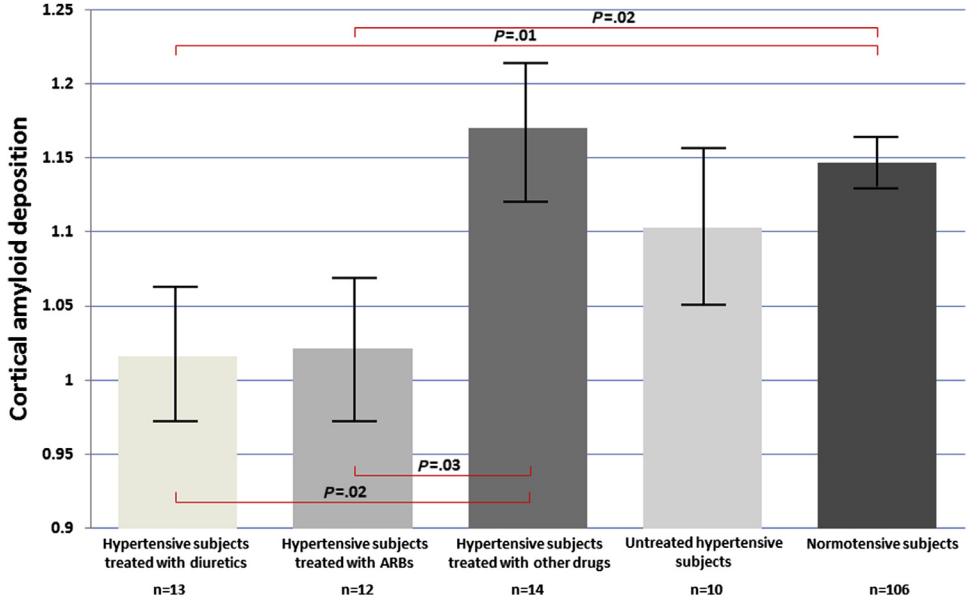

Fig. 3. Cortical amyloid deposition in hypertensive subjects treated with diuretics, ARBs, hypertensive subjects treated with other antihypertensive drugs, untreated hypertensive subjects, and individuals without HTN. Values presented are estimated mean ± standard error after accounting for age and the use of statins. Cortical PiB values represent ratio to cerebellum. Post hoc tests (LSD: least square difference), difference between: diuretic users and hypertensive subjects treated with other drugs, $P = .02$; diuretic users and the normotensive group, $P = .01$; ARBs users and hypertensive subjects treated with other drugs, $P = .03$; ARBs users and the normotensive group, $P = .02$.

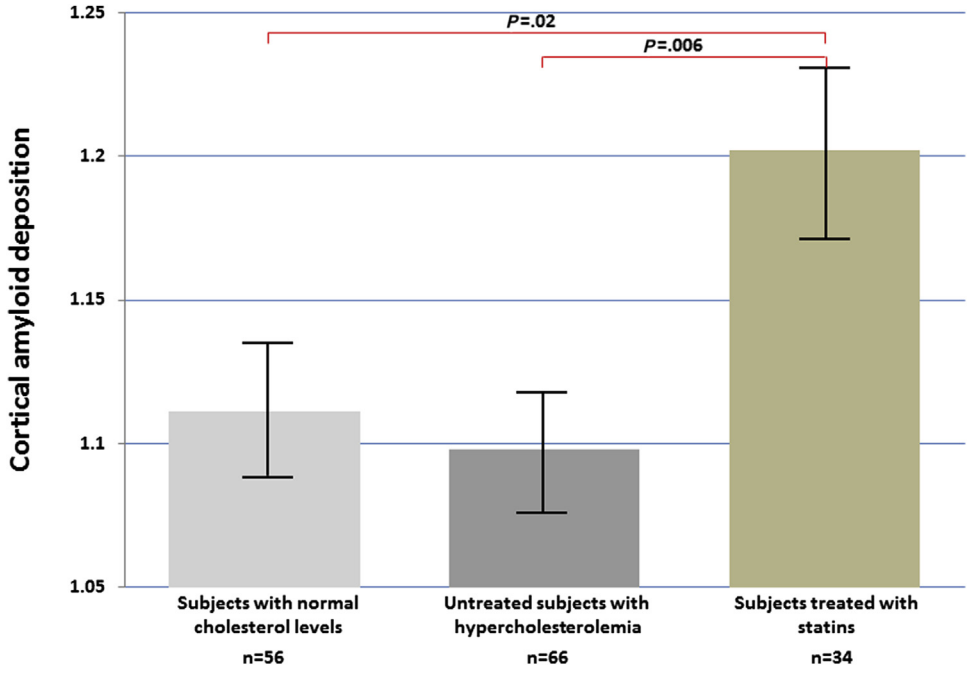

Fig. 4. Cortical amyloid deposition in subjects with normal cholesterol levels, untreated subjects with high cholesterol (above 200 mg/dL), and subjects treated with statins. Values presented are estimated mean ± standard error after accounting for age and the use of ARBs and diuretics. Cortical PiB values represent ratio to cerebellum. Post hoc tests, difference between: subjects with normal cholesterol level and subjects treated with statins, $P = .02$; untreated subjects with high cholesterol and subjects treated with statins, $P = .006$.

pharmacologically treated (n = 96). Using linear regression, the best fit ($F_{6,89} = 5.1$, $P < .001$) included age, as well as gender × overweight/obese and gender × SBP interactions (Table 3). Older age was associated with more amyloid deposition in the entire group. As in the bigger sample, overweight women tended to have more amyloid ($P = .10$), whereas overweight men tended to have less amyloid ($P = .10$) than their respective normal-weight peers. Finally, among women, higher SBP was positively correlated with PiB binding (rho = .30, $P = .02$).

4. Discussion

Our study yielded several important findings. First, besides age, the use of ARBs, diuretics and statins was the strongest predictor of amyloid deposition. Second, having a BMI ≥25 was associated with greater amyloid deposition in women but not in men.

Table 3
Linear regression model: predicting amyloid deposition with vascular risk factors in non-medicated subjects n = 96

Model term	Standardized β	*P* value	VIF
Main effects*			
Age	**.34**	**.002**	1.21
Gender	**−.25**	**.014**	1.06
Overweight/obese status	.07	.52	1.24
SBP	−.12	.26	1.37
2-way interactions			
Gender × overweight/obese	**.23**	**.017**	1.08
Gender × SBP	**.21**	**.033**	1.11

Abbreviations: SBP, systolic blood pressure; VIF, variance inflation factor.
Significant results are shown in bold.
*Values for standardized β shown are before the addition of higher order terms.

Former studies of association between BP and PiB either did not take medications into account [12], adjusted for it [10], or treated it as a homogenous variable (classifying subjects as medicated vs. unmedicated [11]). Our data indicate that effects of medication can differ depending on type. Namely, ARBs or diuretics were related to lower amyloid accumulation, whereas this effect was not observed for other BP-lowering medications. Blood pressure value did not seem to influence these relationships. The finding that ARBs are related to less amyloid pathology corroborates recent human and animal studies. In a large, predominantly male population, the use of ARBs was related to lower rates of incident AD than the use of lisinopril or vascular comparator [31]. A post-mortem study of almost 900 individuals with and without AD showed that those taking ARBs had less amyloid deposition [32]. Animal experiments revealed that ARBs decreased accumulation of amyloid and phosphorylated tau and reduced inflammatory responses in spontaneously hypertensive stroke resistant rats [33]. In contrast, some found that losartan did not alleviate amyloid pathology in transgenic APP mice despite a significant positive effect on cerebrovascular dysfunction and memory consolidation [34]. In the ONTARGET trial, neither ramipril nor telmisartan had any influence on cognitive outcomes [35]. Substantial differences in models of aging and disease, in the case of animal studies, and population characteristics and study design, in the case of human data, likely contributed to these discrepancies. There

are a few possible explanations of the ARBs effect: reduction in amyloid deposition may be related to reduced inflammation, because blocking angiotensin receptor 1 (AT_1) decreases brain inflammatory responses [36]. Similarly, blocking AT_1 reduces reactive oxygen species generation [37] and thus potentially decreases amyloid accumulation. Finally, improved vascular compliance [37] and consequently improved amyloid clearance could also play a role.

The use of diuretics was also related to lower amyloid deposition. An earlier epidemiologic study indicated that treatment with diuretics (especially the potassium sparing type) was associated with a reduced rate of AD 3 years later [38]. Others reported that subjects taking potassium sparing diuretics had better verbal learning and memory than individuals treated with other classes of antihypertensive drugs or medication-free peers [39], and that diuretics decreased the risk of AD by 50%, irrespective of mean SBP (above or below 140) [40]. Although the reasons why diuretics work are not well understood, one study indicated that furosemide prevented amyloid β oligomerization and dissociated pre-aggregated amyloid β42 oligomers [41]. Interactions with renin-angiotensin-aldosterone system were also proposed [38].

Epidemiologic studies showed that midlife use of statins may reduce the risk of AD [42], but in our cross-sectional observation, statin users had more cortical amyloid than nonusers. Neither hypercholesterolemia status nor lipophilic or hydrophilic nature of the drug affected the amyloid accumulation. Our results differ from a previous study by Reed et al., who did not find any effects of statins on PiB-PET [14] and from an earlier report showing that statins were related to less amyloid in postmortem examination [43]. Considerably older age and more vascular comorbidities in subjects in both of these studies at least partly explain these differences. Cholesterol homeostasis is crucial for the central nervous system [44]. Despite the beneficial influence of statins on cardiovascular morbidity and mortality, some have postulated that long-term statin use may have negative effects on the brain. Reduction in cholesterol is related to increased risk of hemorrhage and small vessels disease [45]. In addition, statin use increases the risk of diabetes [46], which in turn can alter amyloid metabolism and clearance. In postmortem examination, the prevalence of cerebral amyloid angiopathy was greater in the poststatin era than the prestatin era [45]. Clinical studies failed to find benefits of statins on cognitive decline in AD patients [47,48], and some observed that statin discontinuation improved cognition in AD [49]. Finally, in line with our finding, a recent retrospective study of nearly 1 million nondemented statin users and nonusers found a relationship between acute memory loss and the initiation of therapy with statins or other lipid-lowering drugs [50]. Overall, our results contribute to the ongoing debate about the effects of statins on the brain.

We observed that in women, being overweight/obese was related to an increased amyloid deposition. The opposite trend was observed in men. Obesity has been consistently linked to increased levels of pro-inflammatory markers (cytokines and c-reactive protein [51]). We suggest that chronic systemic inflammation may facilitate amyloid deposition by intensifying brain inflammatory responses. Although it is unclear why positive high BMI–amyloid association was observed only among women, some precedents exist for such differences. There are sex differences in body fat distribution, metabolic and hormonal regulation of fat deposition, and adipocytes function [52]. They could affect putative obesity–amyloid pathways. Among men, overweight/obese subjects tended to have less amyloid deposition. While former studies found an inverse association between BMI and PiB binding [12,15], we believe our result should be treated with caution as highly skewed amyloid distribution in men could contribute to our findings.

There was a significant positive correlation between higher SBP and amyloid deposition among nonmedicated women. This observation supports a previous study where a similar relationship was reported [10] and also highlights the fact that medication may obscure or modify relationships between AD markers and vascular risk factors.

There are several limitations of our report. Study participants were rather young (mean age around 60). Among older individuals with more risk factors, the relationships could be more robust. However, studying the younger age group is especially important, as preventive therapies should be initiated early in the process, before brain damage becomes irreversible. Second, our group was predominantly Caucasian with low levels of vascular comorbidity, so generalizability is uncertain. Although reexaminations of relationships between vascular risk and PiB in a medication-free subgroup revealed a new amyloid-SBP association, medication-free subjects were by definition healthier, so lower levels of pathology might have prevented us from discovering more meaningful relationships. One can argue that because statin users are more often overweight, body mass might have been the driver behind statin–amyloid relationship. However, statin use was a significant predictor of PiB retention even when the BMI status was entered in the regression model.

It is possible that clinical characteristics dictating prescription of specific classes of medication, for which we were not able to account, could themselves affect amyloid deposition. Moreover, information about treatment duration was not available and that could introduce a bias. Ideally, one should consider both short and long effects of treatment, which may differentially affect vascular risk factors and core features of AD pathology. We used single measurement of blood pressure in the office setting, whereas it has been showed that multiple measurements or 24-hour blood pressure monitoring better correlates with brain pathology [53]. Finally, the reported associations are only cross-sectional and causality cannot be determined.

There are several implications of our study: First, while assessing relationships between vascular risk factors and brain measures, modifying effects of treatment must be taken into account. Women may be particularly sensitive

to detrimental effects of obesity on the aging brain. This must be taken into consideration when planning future interventions. Finally, our findings add to mounting evidence that some classes of medication may impact AD pathology. However, prospective studies should confirm this effect and establish whether such modifications translate into measurable clinical outcomes.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.dadm.2016.02.007.

RESEARCH IN CONTEXT

1. Systematic review: We conducted a review of articles focusing on the relationship between vascular risk factors and cortical amyloid accumulation in normal elderly. While the possibility that vascular conditions may affect hallmarks of AD pathology and risk for clinical presentation is widely acknowledged, there are almost no studies investigating how commonly prescribed antihypertensive and lipid-lowering medications affect amyloid deposition measured in vivo with PET-PiB.
2. We showed that the use of ARBs and diuretics was related to less amyloid accumulation, while statin users had more cortical amyloid. Drug treatment was a stronger predictor of PiB binding than vascular risk factors.
3. Future directions: Prospective, longitudinal studies should confirm observed cross-sectional relationships between certain classes of drugs and amyloid deposition. Moreover, we offer that while assessing relationships between vascular risk factors and brain measures, modifying effects of treatment must be taken into account.

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