Vascular risk and A β interact to reduce cortical thickness in AD vulnerable brain regions

Sylvia Villeneuve, PhD
Bruce R. Reed, PhD
Cindee M. Madison, MS
Miranka Wirth, PhD
Natalie L. Marchant, PhD
Stephen Kriger, BS
Wendy J. Mack, PhD
Nerses Sanossian, MD
Charles DeCarli, MD
Helena C. Chui, MD
Michael W. Weiner, MD
William J. Jagust, MD

Correspondence to
Dr. Villeneuve:
sylvia.villeneuve@berkeley.edu

ABSTRACT

Objective: The objective of this study was to define whether vascular risk factors interact with β -amyloid (A β) in producing changes in brain structure that could underlie the increased risk of Alzheimer disease (AD).

Methods: Sixty-six cognitively normal and mildly impaired older individuals with a wide range of vascular risk factors were included in this study. The presence of A β was assessed using [11 C] Pittsburgh compound B-PET imaging, and cortical thickness was measured using 3-tesla MRI. Vascular risk was measured with the Framingham Coronary Risk Profile Index.

Results: Individuals with high levels of vascular risk factors have thinner frontotemporal cortex independent of A β . These frontotemporal regions are also affected in individuals with A β deposition, but the latter show additional thinning in parietal cortices. A β and vascular risk were found to interact in posterior (especially in parietal) brain regions, where A β has its greatest effect. In this way, the negative effect of A β in posterior regions is increased by the presence of vascular risk.

Conclusion: A β and vascular risk interact to enhance cortical thinning in posterior brain regions that are particularly vulnerable to AD. These findings give insight concerning the mechanisms whereby vascular risk increases the likelihood of developing AD and supports the therapeutic intervention of controlling vascular risk for the prevention of AD. *Neurology*® 2014;83:40–47

GLOSSARY

A β = β -amyloid; AD = Alzheimer disease; FCRP = Framingham Coronary Risk Profile; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PiB = Pittsburgh compound B; ROI = region of interest; VBI = vascular brain injury; WMH = white matter hyperintensity.

The prevalence of β -amyloid (A β), the hallmark of Alzheimer disease (AD), is approximately 25% among cognitively normal elderly individuals, indicating that A β alone might not be sufficient to drive brain changes and cognitive decline, and that other factors work with A β to promote disease onset or progression. Vascular risk factors such as hypertension, dyslipidemia, and diabetes are known risk factors for dementia in persons with clinical syndromes suggesting AD pathology.¹ One pathway by which vascular risk increases the likelihood of dementia is by causing vascular brain injury (VBI) (e.g., white matter lesions and infarcts).^{1,2} In vivo studies show that increased vascular risk is related to higher A β burden.^{3–6} Other work suggests that VBI per se is not associated with elevated A β , and that the effects of VBI and A β on brain structure and cognition are independent.^{7,8} Together, these findings suggest that vascular risk factors may have independent effects on A β and VBI, and therefore increase AD risk through multiple pathways.

Integrity of the cerebral cortex is a major determinant of cognitive function.⁹ A better understanding of the interplay between vascular risk and A β pathology in relation to cortical thickness might yield insight into the factors that drive the development of AD. In this study, we assessed how A β and vascular risk, alone and together, affect cerebral cortex, specifically evaluating

Supplemental data
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From the Helen Wills Neuroscience Institute (S.V., C.M.M., M.W., W.J.J.), University of California Berkeley; Department of Neurology (B.R.R., C.D.), University of California Davis; Department of Old Age Psychiatry (N.L.M.), Institute of Psychiatry, King's College London, UK; Center for Imaging of Neurodegenerative Diseases (S.K., M.W.W.), University of California San Francisco; and Departments of Preventive Medicine (W.J.M.) and Neurology (N.S., H.C.C.), University of Southern California, Los Angeles.

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Table 1 Participant characteristics stratified by PiB status

	PiB+ (n = 22)	PiB- (n = 44)	p Value
Age, y	80.1 ± 5.9	77.5 ± 6.9	0.15
Sex, M	19 (86)	29 (66)	0.08
Education, y	15.0 ± 2.8	14.8 ± 3.0	0.82
MMSE score	27.6 ± 2.6	28.4 ± 1.8	0.13
CDR ≥0.5	14 (64)	17 (39)	0.06
PiB binding, DVR	1.5 ± 0.18	1.0 ± 0.06	0.00
FCRP score	17.1 ± 8.6	13.2 ± 6.7	0.06
HDL cholesterol, mg/dL	51.2 ± 17.7	57.0 ± 15.3	0.20
Infarct+	5 (23)	15 (34)	0.34
WMH, mL	0.83 ± 0.81	0.52 ± 0.70	0.12
APO ε4	7 (33)	8 (19)	0.23
Anticholesterol drugs	13 (59)	31 (70)	0.41
Antihypertensive drugs	19 (86)	35 (80)	0.74

Abbreviations: CDR = Clinical Dementia Rating; DVR = distribution volume ratio; FCRP = Framingham Coronary Risk Profile; HDL = high-density lipoprotein; MMSE = Mini-Mental State Examination; PiB = Pittsburgh compound B; WMH = white matter hyperintensity. Data are presented as mean ± SD or number of subjects (%) of the sample. Data for APOE were available for 62 participants. Data for WMH were available for 60 participants. WMH was corrected for intracranial volume. For FCRP, higher scores indicate greater risk.

whether they have an independent and additive effect (as for VBI^{1,2}), or whether the impact of one of these factors varies as a function of the other (i.e., an interaction).

METHODS Design overview. We examined the relationships among Aβ (measured with [¹¹C]Pittsburgh compound B [PiB]-PET), vascular risk, measured with the Framingham Coronary Risk Profile (FCRP), and cortical thickness measured using 3-tesla MRI. The analyses of vascular risk were repeated with low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol because we recently showed that lower HDL and higher LDL levels are associated with higher Aβ burden.³ Only the results related to HDL are presented in this report because the impact of LDL cholesterol on cortical thickness was mild and not present when controlling for vascular risk (FCRP total score).

The primary analyses explored the relationship between Aβ as a continuous variable and cortical thickness and the relationship between vascular risk and cortical thickness on a whole-brain basis. These analyses were conducted separately in persons classified as positive (PiB+) or negative (PiB-) for Aβ burden, and also in the total group. These whole-brain analyses led to statistical cortical maps (representing statistical differences in cortical thickness) from which the mean cortical thickness values were extracted to test the additive and interactive effect of Aβ (as a continuous variable) and vascular risk on these specific cortical regions of interest (ROIs). These last analyses were conducted in all older adults and restricted to these specific ROIs.

Participants. Participants were 66 older adults from the Aging Brain Project, a longitudinal multisite research program recruiting older adults with cognitive ability ranging from normal to very mild dementia with varying risk of vascular disease (details are provided in appendix e-1 on the *Neurology*® Web site at Neurology.org).^{3,4,10} Table 1 contains details on participant characteristics.

Standard protocol approvals, registrations, and patient consents. Written informed consent was obtained from participants or their legal representatives under protocols approved by the institutional review boards at all participating institutions.

Vascular risk. The FCRP represents a weighted sum of age, sex, smoking, diabetes, hypertension, LDL, and HDL cholesterol (appendix e-1).¹¹

Structural MRI. All participants underwent structural MRI on 3-tesla systems using sequences that were harmonized for the set of scanners used in the project (appendix e-1). The FreeSurfer version 5.1 software package (<http://surfer.nmr.mgh.harvard.edu/>) was used to obtain cortical thickness (mm) and to assist PiB-PET processing.¹² We visually examined all images to ensure segmentation accuracy.

Vascular brain injury. We quantified infarcts on T1-weighted images and white matter hyperintensities (WMH) on fluid-attenuated inversion recovery images (appendix e-1).

PET imaging. All PiB-PET images were processed using a procedure described elsewhere.¹⁰ Briefly, the PiB-PET images were acquired in 3-dimensional acquisition mode. We derived the global measure of PiB binding by averaging the weighted mean distribution volume ratio value from FreeSurfer-derived subjects' native space ROIs in frontal, temporal, parietal, and cingulate cortices, using a gray cerebellar mask as a reference region (appendix e-1). Subjects with high (PiB+) and low (PiB-) levels of Aβ deposition were classified based on a cutoff of 1.16.¹³

Statistical analysis. We examined group differences between PiB+ and PiB- using Student *t* tests for continuous variables and Pearson χ^2 tests for categorical variables. All main analyses were corrected for age and cognitive status (Clinical Dementia Rating 0 vs ≥0.5) and completed using SPSS version 20 (IBM Corp., Armonk, NY). A *p* value ≤0.05 was considered significant. Trends are also presented (*p* value ≤0.08).

Statistical cortical maps. The impact of Aβ (global PiB binding used as a continuous variable) and vascular risk on cortical thickness were explored with whole-brain analyses on a vertex-wise basis in PiB+ subjects, in PiB- subjects, and in the total sample separately. Briefly, each thickness measurement of each vertex of the subject's surface was mapped on a common surface template and smoothed using a gaussian kernel of 15 mm. We used a general linear model to estimate variations in cortical thickness at each vertex of the surface. Right and left hemispheres were tested separately. Statistical surface maps were created using a vertex-wise statistical threshold of *p* < 0.05. Correction for multiple comparisons were performed using Monte Carlo cluster-wise simulation repeated 1,000 times, limited to positive or negative clusters and set at *p* < 0.05.¹⁴

Additive and interactive impact of Aβ and vascular risk on the statistical cortical maps. To test whether Aβ and vascular risk have an additive or an interactive impact on the statistical cortical maps created in PiB+ and PiB- groups and in the total group, the mean cortical thickness value of each significant cluster of each map was extracted for all participants. Cortical values of left and right clusters were then averaged and weighted by the number of vertices to create one ROI for each statistical map (one ROI by vertex-wise analysis). Then, separate linear hierarchical regression analyses were conducted for each ROI with the covariates (age and cognitive status) entered in a first step, Aβ and vascular risk entered in a second step, and their interactive term entered in a third step. These regressions were done in the total group even when looking at the ROIs defined in the PiB+ and the PiB- groups. They were done separately for vascular risk (FCRP total score) and HDL cholesterol.

Figure 1 Relationships among A β , vascular risk (FCRP score), HDL cholesterol, and cortical thickness in elderly individuals with (PiB+) and without (PiB-) A β burden

Statistical cortical maps showing the association among A β , vascular risk (FCRP score), HDL cholesterol, and cortical thickness in PiB+, PiB-, and all older subjects. Cold colors (A-F) suggest that both increased vascular risk and increased A β burden are associated with thinner cortex. Warm colors (G-I) suggest that increased HDL cholesterol levels are associated with thicker cortex. Statistical surface maps were created using a vertex-wise statistical thresholds of $p < 0.05$. The analyses are corrected for age, cognitive status, and multiple comparisons. A β = β -amyloid; FCRP = Framingham Coronary Risk Profile; HDL = high-density lipoprotein; PiB = Pittsburgh compound B.

RESULTS Statistical cortical maps. β -Amyloid. In PiB+ subjects, A β was associated with thinning in the superior and middle frontal cortices, the medial parietal cortex (precuneus), and the medial occipital cortex (figure 1A). When the vertex-wise analysis was conducted in all participants (figure 1C), increased A β was then only associated with thinning in the superior and the middle frontal cortices. As expected, A β was not associated with thinning in PiB- subjects.

Vascular risk. High vascular risk (FCRP score) was associated with thinner frontal and temporal cortices in both PiB+ and PiB- subjects (figure 1, D and E). In PiB+ cases, thinning was also seen in the lateral parietal

lobes, including the superior parietal lobule, the supramarginal, and the postcentral gyri. When the analysis was conducted across all older adults, vascular risk was associated with widespread cortical thinning (figure 1F).

HDL cholesterol. In both PiB+ and PiB- subjects, lower HDL cholesterol was associated with thinning in lateral and medial frontal cortex (figure 1, G and H). In the PiB+ cases, thinning was also seen in lateral and medial parietal lobes (precuneus), while in the PiB- cases, thinning was seen in anterior temporal lobes. As was the case for vascular risk, when the vertex-wise analysis was conducted in all subjects, thinning associated with low HDL cholesterol was widespread.

Figure 2A shows the impact of vascular risk on cortical thickness when controlling for HDL cholesterol, and figure 2B shows the impact of HDL cholesterol on cortical thickness when controlling for vascular risk.

Medication. To assess whether cholesterol-lowering or antihypertensive drugs modify the above relationships, we repeated the voxel-wise analyses including medication in the models, testing for an interaction between A β , FCRP, or HDL and medication with cortical thickness as the dependent measure. We found that both higher A β and higher FCRP burden were associated with thinner lateral middle frontal cortex in subjects that were not taking cholesterol drugs compared with subjects who were taking cholesterol drugs (appendix e-1, figure e-1). These effects were not present for antihypertensive medication or for the association between HDL cholesterol and cortical thickness. These analyses were conducted in the total sample.

Additional analyses controlling for WMH, infarcts, and APOE. To assess whether white matter lesions (assessed using the WMH volumes), infarcts, or APOE status accounted for the vertex-wise results presented in figure 1, we repeated these analyses including WMH, infarcts, and APOE as covariates. The inclusion of these covariates in the vertex-wise analyses diminished the significance of vascular maps, and maps associated with A β were no longer significant. Because of concerns that effects on vertex-wise analyses reflected reductions of statistical power for whole-brain analyses, we also explored this question by conducting regression analyses on the ROIs corresponding to the vertex-wise statistical maps. The inclusion of WMH, infarcts, or APOE status in these regression models did not attenuate the relationship between amyloid and cortical thickness, or between vascular risk and cortical thickness (table 2).

Additive and interactive associations of A β and vascular risk with cortical thickness. Table 3 shows the additive and interactive effect of A β as a continuous variable and vascular risk on the cortical thickness statistical maps derived from figure 1. Results for the FCRP score are presented on the left part of the table while results for HDL cholesterol are presented on the right. Interactions between A β and vascular risk (when measured using the FCRP total score or only HDL cholesterol) were found for the ROIs defined in the PiB+ group but not for the ROIs defined in the entire group (“Interaction” columns). As expected, no interaction was found for the ROIs defined in the PiB– group, suggesting that A β only increases the negative impact of vascular risk (and/or vice versa) on

Figure 2 Independent effects of vascular risk (FCRP score) and HDL cholesterol on cortical thickness

(A) Statistical cortical maps showing the association between vascular risk (FCRP score) and cortical thickness while controlling for HDL cholesterol. (B) Statistical cortical maps showing the association between HDL cholesterol and cortical thickness while controlling for vascular risk. Cold colors suggest that increased vascular risk is associated with thinner cortex. Warm colors suggest that increased HDL cholesterol levels are associated with thicker cortex. Statistical surface maps were created using a vertex-wise statistical threshold of $p < 0.05$. Correction for multiple comparisons was done using Monte Carlo cluster-wise simulation repeated 1,000 times. FCRP = Framingham Coronary Risk Profile; HDL = high-density lipoprotein.

brain regions vulnerable to A β . Note that these analyses were conducted within the total sample, even when testing the ROIs defined in the PiB+ and the PiB– groups.

An additive effect of A β and HDL cholesterol was found in the A β -ROI defined in the total group.

DISCUSSION This study adds 2 principal observations relating to the impact and interaction between A β and vascular risk on cortical thickness. First, vascular risk factors can be associated with frontotemporal thinning independently of A β , VBI, and APOE status. Second, A β and vascular factors interact, particularly in the posterior brain regions known to be

Table 2 Hierarchical regression analyses showing the impact of A β , vascular risk, and HDL cholesterol on the statistical cortical maps defined in figure 1 after controlling for white matter hyperintensity, infarcts, and APOE status

	PiB+ (n = 22)	PiB- (n = 44)	All older adults (n = 66)
Aβ	Figure 1A	Figure 1B	Figure 1C
WMH	0.30 (0.04)	—	0.05 (0.04)
A β	−0.75 (0.09) ^a	—	−0.47 (0.09) ^a
Infarcts	−0.01 (0.04)	—	−0.05 (0.04)
A β	−0.87 (0.09) ^a	—	−0.46 (0.08) ^a
APOE	−0.06 (0.03)	—	0.07 (0.05)
A β	−0.90 (0.09) ^a	—	−0.50 (0.09) ^a
Vascular risk (FCRP score)	Figure 1D	Figure 1E	Figure 1F
WMH	0.17 (0.04)	−0.26 (0.03) ^b	−0.05 (0.03)
Vascular risk	−0.83 (0.00) ^a	−0.56 (0.00) ^a	−0.58 (0.00) ^a
Infarcts	−0.10 (0.05)	−0.16 (0.04)	−0.12 (0.03)
Vascular risk	−0.84 (0.00) ^a	−0.58 (0.00)	−0.58 (0.00) ^a
APOE	−0.06 (0.05)	−0.16 (0.05)	−0.15 (0.03)
Vascular risk	−0.85 (0.00) ^a	−0.66 (0.00) ^a	−0.62 (0.00) ^a
HDL cholesterol	Figure 1G	Figure 1H	Figure 1I
WMH	0.18 (0.05)	−0.24 (0.04)	−0.10 (0.03)
HDL cholesterol	0.77 (0.00) ^a	0.64 (0.00) ^a	0.57 (0.00) ^a
Infarcts	−0.02 (0.05)	−0.19 (0.04)	−0.09 (0.03)
HDL cholesterol	0.83 (0.00) ^a	0.64 (0.00) ^a	0.56 (0.00) ^a
APOE	0.11 (0.05)	−0.09 (0.06)	−0.07 (0.03)
HDL cholesterol	0.85 (0.00) ^a	0.65 (0.00) ^a	0.57 (0.00) ^a

Abbreviations: A β = β -amyloid; FCRP = Framingham Coronary Risk Profile; HDL = high-density lipoprotein cholesterol; WMH = white matter hyperintensity.

Regression models were conducted on the regions of interest defined in figure 1. Shown are standardized regression coefficients (standard error) corrected for age and cognitive status. WMH was corrected for intracranial volume.

^a $p < 0.01$.

^b $p \leq 0.05$.

vulnerable to AD. Thus, the impact of A β on cortical thickness in AD-vulnerable regions is potentiated in the presence of vascular risk (and/or vice versa).

Vascular risk, whether assessed as an aggregate score of risk factors or simply HDL cholesterol, was found to have a widespread effect on cortical thickness (figure 1, F and I). These results are consistent with other reports noting that increased vascular risk^{15–17} and low HDL cholesterol^{18,19} have a detrimental impact on cortical volume and thickness. Because previous in vivo reports have not accounted for A β , it was not known whether A β drove these effects, especially since vascular risk has been found to be associated with higher cerebral A β in older adults without dementia.^{3,4,6} One notable finding of this study is therefore the significant effect of high aggregate vascular risk and low HDL cholesterol on cortical thickness that is not explained by the presence of fibrillar A β (figure 1, E and H). This effect was mainly seen in the anterior parts of temporal cortex

and the superior frontal gyrus. High aggregate vascular risk was also associated with thinning of the perisylvian regions, a region particularly vulnerable to hypertension¹⁷ and previously found to be thinner in PiB- persons with subcortical vascular dementia.²⁰ Because the impact of vascular risk on cortical thickness remained significant when controlling for APOE status, white matter lesions, and infarcts in addition to A β , it raises the question of what mechanism underlies these effects. Possible explanations include microinfarcts, invisible to magnetic resonance techniques, or neuronal damage through other mechanisms such as breakdown in the blood-brain barrier, chronic hypoperfusion, hypoxia, inflammation, and oxidative stress.^{21–25} While hypothetical, these possible pathways require investigation because they might represent therapeutic targets.

In PiB+ subjects, both vascular risk profile and low HDL were further linked to parietal thinning (figure 1, D and G). This thinning was found in

Table 3 Hierarchical regression analyses showing the additive and interactive impact of A β and vascular risk (or HDL cholesterol) on the statistical cortical maps defined in figure 1

	FCRP models			HDL models		
	Additive impact			Additive impact		
	A β	FCRP	Interaction, A β $\times$ FCRP	A β	HDL	Interaction, A β $\times$ HDL
PiB+ maps						
A β (figure 1A)	−0.24 (0.06) ^c	−0.25 (0.00) ^b	−0.24 (0.01) ^c	−0.26 (0.06) ^b	0.21 (0.00)	0.30 (0.00) ^b
FCRP (figure 1D)	−0.05 (0.07)	−0.46 (0.00) ^a	−0.28 (0.01) ^b	—	—	—
HDL (figure 1G)	—	—	—	−0.14 (0.07)	0.45 (0.00) ^a	0.36 (0.01) ^a
All older-adult maps						
A β (figure 1C)	−0.38 (0.08) ^a	−0.22 (0.00) ^c	−0.06 (0.01)	−0.34 (0.08) ^a	0.36 (0.00) ^a	0.16 (0.01)
FCRP (figure 1F)	−0.04 (0.05)	−0.57 (0.00) ^a	−0.07 (0.01)	—	—	—
HDL (figure 1I)	—	—	—	−0.10 (0.06)	0.53 (0.00) ^a	0.14 (0.00)

Abbreviations: A β = β -amyloid; FCRP = Framingham Coronary Risk Profile; HDL = high-density lipoprotein; PiB = Pittsburgh compound B.

Regression models were conducted among all older adults for the regions of interest defined in the PiB+ maps (figure 1, A, D, G) and all older-adult maps (figure 1, C, F, I). Shown are standardized regression coefficients (standard error) corrected for age and cognitive status.

^a $p < 0.01$.

^b $p \leq 0.05$.

^c $p < 0.08$.

the superior parietal lobule, the supramarginal gyrus, and the postcentral gyrus. The impact of HDL was further extended to the precuneus and the angular gyrus. Thinning in most of these regions has high value in prediction of AD progression when associated with thinning in other specific areas.^{26,27} Among these other brain regions included in the “AD signature,” thinning in the lateral middle frontal lobe and the superior frontal gyrus^{26,27} was also associated with both aggregate vascular risk and low HDL cholesterol in PiB+ subjects. In line with our findings, higher serum total cholesterol in late middle age has previously been associated with reduced glucose metabolism in brain regions affected by AD.²⁸

Given the frequent co-occurrence of A β and vascular risk,¹ an important question is whether vascular risk and A β have an “additive” impact on cortical thickness or whether they “interact.”²⁹ In the first scenario, the impact of both factors on cortical thickness would be no more than the co-occurrence of the 2 factors. In the second scenario, the effect of vascular risk and A β on cortical thickness varies according to A β severity or vice versa, and would be greater than their sum. Autopsy studies mainly suggest that VBI increases the risk of dementia in person with AD pathology via an independent and additive pathway.^{2,29,30} Recent in vivo findings suggest that high vascular risk factors,^{3–6} but not VBI,^{7,8} are associated with higher A β burden. These results propose that even if VBI was not found to interact with AD pathology, vascular risk factors might. This is an important point because outcomes associated with

VBI are often incorrectly assumed to simply reflect vascular risk factors and vice versa.

Our ROI analyses provided converging evidence of interactions between A β and vascular risk in regions characteristic of A β -related thinning (table 3). It is important to note that these synergistic effects were restricted to the ROIs extracted from PiB+ maps even if the analyses were conducted across all older adults. Taken together, these results show that the interaction effect of both factors is mainly constrained to superior and posterior (parietal) brain regions. When anterior regions such as the temporal poles are included in the analyses, the interactions disappear. The predominant presence of A β in posterior regions³¹ and the fact that posterior regions are vulnerable to AD^{27,32} might not be a coincidence for the site of this interaction. These findings are important because they suggest that one mechanism by which vascular risk might increase the likelihood of developing the clinical syndrome of AD is by potentiating the negative effect of A β on cortical thickness in particularly vulnerable regions.

These findings have implications for the current models of AD pathology, which propose that A β starts a cascade of neurotoxic events leading to neuronal impairment and eventually cognitive deficits and dementia.^{33,34} The association found between A β and cortical thickness supports the idea that A β might lead to synaptic and neuronal loss. The interaction between A β and vascular factors on cortical thickness, however, underscores that other factors work with A β to drive the progression of brain changes in AD-vulnerable regions.

Finally, these results reinforce the idea that treating vascular risk factors could prevent, or at least postpone, the clinical expression of AD. These treatments should probably be started in middle life, when vascular risk starts to impair brain integrity³⁵ and when A β is absent, or at its earliest stages of accumulation. Because our findings suggest that low HDL presented an overlap with A β in the posterior cortical regions, increasing HDL cholesterol could have promising outcomes.

Despite its multisite nature, the sample size is relatively small and included fewer PiB+ than PiB− participants. However, this is a multimodal study, which has the clear advantage of exploring the interactions between several biomarkers. In addition, because cortical thickness measurements are complex and influenced by methodologic differences in data acquisition, we carefully only included study participants with similar imaging methods. One of the major strengths of the aging brain project is the inclusion of persons with a spectrum of vascular risk. Because cardiovascular risks are frequent in the US population,³⁶ we believed this sample is representative of a large proportion of the US population. Finally, it is important to highlight the fact that some of the results associated with aggregate vascular risk (figure 1) may be driven by HDL cholesterol.

Together, these findings highlight the negative impact of vascular risk on cortical thickness in the presence, but also independently of A β . They further show that vascular risk, particularly low HDL cholesterol, targets brain regions vulnerable to AD. Finally, A β and vascular risk had a synergistic negative impact in brain regions characteristic of PiB+ thinning. These findings provide insight about the mechanisms by which vascular risk increases the risk of developing AD and support the idea that controlling vascular risk factors or modulating HDL cholesterol might be an effective target for AD prevention.

AUTHOR CONTRIBUTIONS

Dr. Villeneuve: study concept or design, data analysis and data interpretation, drafting/revising the manuscript for content. Dr. Reed: acquisition of data, study concept or design, critical revision of the manuscript for important intellectual content. Mrs. Madison: data analysis and programming. Dr. Wirth: data analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. Marchant: critical revision of the manuscript for important intellectual content. Mr. Kriger: data analysis. Dr. Mack: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Sanossian: data analysis, critical revision of the manuscript for important intellectual content. Dr. DeCarli, Dr. Chui, and Dr. Weiner: acquisition of data, study concept or design, critical revision of the manuscript for important intellectual content. Dr. Jagust: acquisition of data, study concept or design, critical revision of the manuscript for important intellectual content, study supervision.

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DISCLOSURE

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