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Coronary risk correlates with cerebral amyloid deposition

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Abstract

This study investigated the hypothesis that vascular risk factors are amyloidogenic. Participants were 43 persons, most with normal cognition or mild cognitive impairment. Vascular risk was quantified using the Framingham Coronary Risk Profile (FCRP) score. Cerebral amyloid was measured by [^{11}C]Pittsburgh compound B (PIB) positron emission tomography (PET) and quantified with a Global PIB index, which is the average of distribution volume ratios in selected cortical regions of interest. In a bivariate model FCRP accounted for 16% of the variance in PIB index ($p < 0.008$) and the positive association remained significant controlling for age and sex. The effect of FCRP was independent of apolipoprotein E (APOE) genotype, which was also associated as expected with PIB. Carotid intima-media thickness was not associated with PIB index. Effects of individual FCRP component risk factors, cholesterol, and glycemic status on PIB index were all nonsignificant, suggesting an aggregate effect of risk factors. Although this is a correlational observation it may represent a causal relationship as there are multiple, plausible, amyloidogenic mechanisms of vascular risk factors.
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Keywords: Vascular risk factors; Coronary risk factors; Cerebral amyloid; Mild cognitive impairment; Normal aging; Alzheimer's disease

1. Introduction

Epidemiological studies have shown that multiple risk factors for vascular disease, both cerebral and coronary, are corresponding risk factors for Alzheimer's disease (AD) (Decarli, 2004). Among the major cardiovascular risk factors, diabetes has generally been found to confer a relative risk of 1.4–2.4 for AD (Luchsinger, 2010). Midlife hypertension, especially when untreated, substantially elevates the risk of Alzheimer's disease decades later (Launer et al., 1995, 2000), and correlates with neocortical plaque counts at autopsy in aged subjects (Petrovitch et al., 2000). The association between late life hypertension and incident AD is weaker and less clearly established (Feldstein, 2010; Qiu et al., 2003; Skoog et al., 1996). Similarly, studies that measure lipids at midlife have consistently reported elevated late life risk of AD (Kivipelto et al., 2002; Kivipelto and Solomon, 2006; Solomon et al., 2009; Whitmer et al., 2005) whereas studies of late life hyperlipidemia report inconsistent or negative (protective) associations (Mielke et al., 2005; Reitz et al., 2004, 2010). Interestingly, it was recently reported that in middle-aged persons, high total cholesterol was associated with hypometabolism in cortical regions typically affected by AD (Reiman et al., 2010). Although the evidence on smoking is not totally consistent, a number of large, methodologically strong studies have found that midlife smoking increases the risk of AD substantially (Ott et al., 1998; Rusanen et al., 2011). Moreover, a number of studies show that increasing numbers of vas-

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cular risk factors are associated with increasing risk of AD (Luchsinger et al., 2005; Whitmer et al., 2005). The overall pattern of findings in this literature raises the possibility that there may be a common mechanism(s) behind the association between vascular risk and AD, although a particular mechanism has yet to be identified.

One potential such mechanism is that vascular risk factors lead to cerebrovascular disease which then augment the symptomatic expression of AD pathology (Snowdon et al., 1997). Support for this view comes from community-based cohort studies that show high rates of unrecognized cerebrovascular disease in the aged (DeCarli et al., 2005; Longstreth et al., 1998) and also high rates of mixed AD and cerebrovascular pathology in demented cases (Schneider et al., 2007; Neuropathology Group, Medical Research Council Cognitive Function and Aging Study, 2001). Alternatively, it has been proposed that vascular risk factors may promote the deposition of cerebral β-amyloid (Aβ) and thus AD (Altman and Rutledge, 2010; Bhat, 2010; Kalaria, 1999). For example, a variety of molecules important in cholesterol processing also play a role in Aβ processing (Di Paolo and Kim, 2011). There is evidence that insulin resistance can increase plasma levels of Aβ and perhaps increase cerebral deposition or retention of Aβ (Craft, 2009). Conversely, evidence from animal models shows that brain clearance of amyloid occurs along vascular channels; because cerebrovascular disease leads to vascular remodeling, it is plausible that cerebrovascular disease also alters amyloid clearance (Bell and Zlokovic, 2009; Dotti and De Strooper, 2009).

This study was designed to test whether vascular risk is associated with cerebral amyloid deposition. For this initial investigation we chose the Framingham Coronary Risk Profile as a summary index of vascular risk factors. The Framingham Coronary Risk Profile (FCRP) score is a weighted combination of the 4 major modifiable risk factors for cardiovascular disease: smoking, hypertension, diabetes, and hyperlipidemia (Wilson et al., 1998). The FCRP is commonly used to quantify 10-year risk of incident coronary disease, is associated with elevated stroke risk (Touboul et al., 2005), and the FCRP predicts both coronary and carotid atherosclerosis (Cho et al., 2011; Touboul et al., 2005). We hypothesized that higher FCRP scores would be associated with elevated cerebral Aβ measured with positron emission tomography (PET) using the tracer [^{11}C]-Pittsburgh compound B (PIB).

2. Methods

2.1. Participants

Participants were 43 persons (31 men), mean age 79, from 2 longitudinal studies that recruit cognitively normal and mild cognitive impairment (MCI) patients at increased risk for vascular disease. Most participants were acquired either through community-based recruitment using a protocol designed to obtain a demographically diverse cohort, or through sources such as stroke clinics and support groups attended by people with high levels of vascular risk factors. Inclusion criteria included age 65 or older, cognitive function in the normal to mild dementia range; exclusion criteria were severe or unstable medical illness, Axis I psychopathology other than depression, head injury with significant loss of consciousness and/or cognitive sequelae, sensory or physical limitations that would preclude cognitive testing, diagnosis of dementia due to causes other than Alzheimer's disease, vascular disease, or the combination thereof. Data from 27 of these participants is included in a related report in this issue (Marchant et al., in press).

Clinical diagnostic evaluations appropriate for memory disorders and dementia were done at the University of California, Davis Alzheimer's Disease Center. The same group of clinicians evaluated all participants using uniform diagnostic criteria and clinical protocols that were highly similar for the 2 studies. Clinical Dementia Rating (CDR) scale (Morris, 1993) scores were 0 (n = 27), 0.5 (n = 12), and 1–2 (n = 4). Table 1 provides more details on participant characteristics.

2.2. Vascular risk measure

The FCRP uses empirically derived age and gender adjusted weighting of categorical variables to predict the 10-year risk of coronary heart disease and is a weighted sum of: smoking, diabetes, hypertension, and high cholesterol. Higher scores indicate greater risk.

2.3. PET imaging

2.3.1. Acquisition

The PIB radiotracer was synthesized at Lawrence Berkeley National Laboratory using a previously published protocol (Mathis et al., 2003). PIB-PET imaging was conducted using a PET in 3-D acquisition mode. PIB (10–15 mCi) was injected as a bolus into an antecubital vein after which dynamic acquisition frames were obtained for a total of 90 minutes: 4 × 15 seconds, 8 × 30 seconds, 9 × 60 seconds, 2 × 180 seconds, 8 × 300 seconds, and 3 × 600 seconds.

Table 1
Characteristcs of the sample

Age	78.9 (6.7)
Years education	14.9 (2.6)
Sex (M:F)	31:12
MMSE	27.9 (2.1)
FCRP	16.1 (7.8)
Global PIB index	1.19 (0.24) (18 PIB-positive)
CIMT (mm)	0.86 (0.14)

Data are mean (SD) except where otherwise noted.
Key: CIMT, carotid artery intima-media thickness; F, female; FCRP, Framingham Coronary Risk Profile; M, male; MMSE, Mini Mental State Examination; PIB, Pittsburgh compound B.

2.3.2. Image analysis

PIB data were preprocessed using Statistical Parametric Mapping 8 (SPM8; www.fil.ion.ucl.ac.uk/spm/). Frames 6 through 34 were realigned to frame 17, and averaged to create a mean frame. The first 5 frames were summed and coregistered to the mean frame, with the coregistration parameters applied to these individual 5 frames. The coregistered frames reflecting the first 20 minutes of acquisition (frames 1–23) were then averaged to create a new image, which was used to guide coregistration with the T1-weighted magnetic resonance image (MRI). Distribution volume ratio (DVR) images were generated from PIB frames corresponding to 35–90 minutes postinjection, and quantified using Logan graphical analysis and the participant's gray matter cerebellar reference region (Logan et al., 1996; Price et al., 2005). The T1-weighted MRI was warped to Montreal Neurological Institute (MNI) space using the statistical parametric mapping (SPM) T1 template, and the warp parameters were applied to the coregistered PIB DVR image. Cerebellar regions of interest (ROI) registration and warped images were visually inspected to ensure alignment.

ROIs were defined in MNI space using the Automated Anatomic Labeling Atlas (Tzourio-Mazoyer et al., 2002). In order to exclude contamination from white matter and cerebrospinal fluid, ROIs were trimmed using a gray matter mask defined by each participant's segmented MRI (Sun et al., 2007). DVR values were extracted from ROIs vulnerable to early Aβ deposition, which include the frontal cortex (anterior to the precentral gyrus), lateral parietal cortex, lateral temporal cortex, posterior cingulate, and precuneus. A global measure of PIB uptake (Global PIB Index) was generated from the mean DVR of these ROIs (Mormino et al., 2009; Rabinovici et al., 2010). The occipital cortex was also examined due to its susceptibility to cerebral amyloid angiopathy. This Global PIB Index served as the primary dependent variable.

2.3.3. PIB positivity

A secondary, dichotomous variable defined by the presence of abnormal PIB retention was defined as follows. Eleven young adults (mean age = 24.5, SD = 3.4) underwent PIB-PET imaging using the same acquisition and processing procedures described above. PIB uptake was determined using DVR values from the Global PIB Index and the bilateral precuneus/posterior cingulate region (an area most often and earliest affected by amyloid aggregation in AD). Values 2 SDs above the young average for these 2 regions were established as defining values of PIB positivity. Therefore participants with a Global PIB Index $>$ 1.114 or precuneus/posterior cingulate $>$ 1.137 were determined to be PIB-positive.

2.4. Other measures

A structural MRI was obtained under a research protocol. Scans were read and rated clinically for infarcts, degree of generalized and hippocampal atrophy, and for other significant pathology. Apolipoprotein E (APOE) genotyping and carotid ultrasound studies to measure common carotid artery intima-media thickness (CIMT) were performed under standardized research protocols (Selzer et al., 2001). Total-, high-density lipoprotien (HDL)-, and low-density lipoprotein (LDL)-cholesterol, hemoglobin A1C (HbA1c), and glucose were assayed at a central laboratory from fasting blood samples.

3. Results

3.1. PIB and FCRP

Global PIB index values were distributed rather continuously over the range of 0.8 to 1.9, with 18 (42%) cases meeting criteria for being PIB-positive (Fig. 1). PIB index was unrelated to age (R^2 = 0.04; p = 0.22), sex (R^2 = 0.03; p = 0.23), or to CDR (R^2 = 0.03; p = 0.55). In a bivariate model FCRP accounted for 16% of the variance in PIB index (p = 0.0075). In a multivariate model that covaried

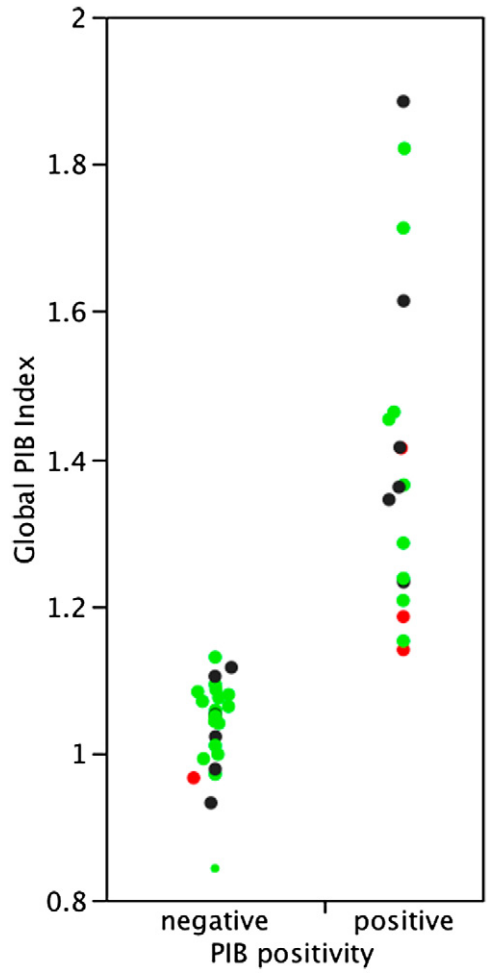

Fig. 1. Distribution of Global Pittsburgh compound B (PIB) index values according to whether the scan was positive or negative with respect to significant PIB retention. Green = cognitively normal; Black = mild cognitive impairment (MCI); Red = demented.

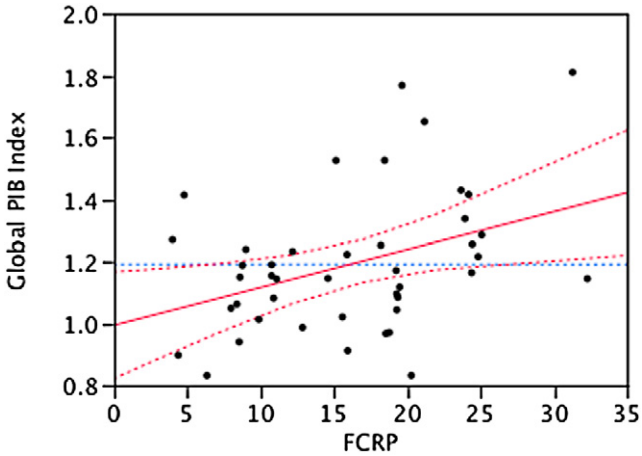

Fig. 2. Leverage (partial regression) plot showing the effect of Framingham Coronary Risk Profile (FCRP) on Global Pittsburgh compound B (PIB) Index controlling for age, gender, and Clinical Dementia Rating (CDR). Solid line indicates the estimated slope and the dotted lines mark the boundaries of the 95% confidence interval around that slope.

age, sex, and CDR the effect of FCRP remained significant ($p = 0.016$) and its parameter estimate was virtually identical to that obtained in the bivariate model. Fig. 2 illustrates this result. Excluding the 4 demented cases did not reduce the size of the FCRP effect.

The regional distribution of PIB was explored in a set of secondary analyses. Table 2 shows mean values for DVRs in selected ROIs. Distributions of DVRs for frontal, parietal, lateral temporal, and occipital cortex, were fairly similar. Highest mean values were obtained in precuneus and posterior cingulate. Table 2 also shows the pattern of correlations between FCRP and regional DVRs. FCRP explained roughly the same proportion of variance in regional PIB in frontal, lateral temporal, and occipital cortex; lowest values were found in parietal cortex and precuneus. The pattern of association between FCRP and PIB was further explored in a voxel-wise correlational analysis (no covariates) using SPM8 with a cluster size of $k > 100$. The results showed a widespread positive association in temporal cortex bilaterally, and also in frontal cortex (Fig. 3).

3.2. APOE

APOE genotyping was available on 42 cases; 10 carried the E4 allele, 10 were 3/2 heterozygotes, 22 were E3 homozygotes. In a model that included age, sex, and CDR, both FCRP and APOE (coded E4 positive/negative) had independent effects in the expected direction on PIB index ($p = 0.023$ for FCRP; $p = 0.040$ for APOE). There was no evidence of an interaction effect between FCRP and APOE but the power of the analysis to detect interaction effects was extremely low. An analogous model found no effect of the E2 allele on Global PIB.

3.3. CIMT

CIMT measurements were available on 34 subjects. CIMT was not associated with Global PIB in either bivariate or demographically adjusted models ($p > 0.30$). When CIMT was added to the demographically adjusted model of FCRP on PIB index, the significance value for FCRP fell to 0.076 but this was due to the loss of power with a smaller n rather than any substantial change in the parameter estimate (analyzing only the 34 cases with CIMT values, the β for FCRP was 0.011 without CIMT in the model, and was 0.010 with CIMT in the model). An analogous model found no effect of the E2 allele on Global PIB.

3.4. Exploratory analyses

In order to test whether the effect of FCRP was mediated by cardiovascular disease, we examined whether a clinical history of either cardiac disease or stroke/transient ischemic attack (TIA) was associated with Global PIB Index. Neither was ($p = 0.15$ for cardiac disease, $p = 0.16$ for stroke/transient ischemic attack) as tested using demographically adjusted models. The effects of individual components of the FCRP on Global PIB Index were also tested. Neither a clinical history of diabetes, hypertension, nor elevated lipids, considered singly, had any effect on Global PIB. History of smoking was too rare to allow testing of its effect. Body mass index (BMI) is a vascular risk factor that correlates with other risk factors but that is not included in the FCRP. BMI did not correlate significantly with FCRP, PIB Index, or any of the covariates. Adding BMI to the primary statistical models did not appreciably alter the effects of FCRP or APOE.

As might be expected, HbA1c and cholesterol levels were strongly correlated with FCRP: a joint model predicting FCRP with HbA1c and the HDL:LDL ratio had an overall R^2 of 0.51. However, we did not find evidence that these markers mediated the relationship of FCRP to amyloid. Neither HDL-, LDL-, nor total-cholesterol showed a significant relationship to Global PIB ($p > 0.10$). When

Table 2
Regional PIB uptake values and their correlations with FCRP

	Mean DVR left	Mean DVR right	r left	r right
Frontal	1.17	1.16	0.43*	0.39**
Lateral temporal	1.22	1.21	0.45*	0.44*
Parietal	1.21	1.16	0.31**	0.25
Occipital	1.21	1.19	0.40*	0.39**
Precuneus	1.26	1.25	0.30**	0.29
Posterior cingulate	1.38	1.32	0.32**	0.39**
Striatum	1.25	1.27	0.33**	0.32**

The correlation coefficient (r) values represent associations in bivariate, unadjusted regressions of regional PIB DVRs on FCRP.
Key: DVR, distribution volume ratio; FCRP, Framingham Coronary Risk Profile; PIB, Pittsburgh compound B.
* $p < 0.01$.
** $p < 0.05$.

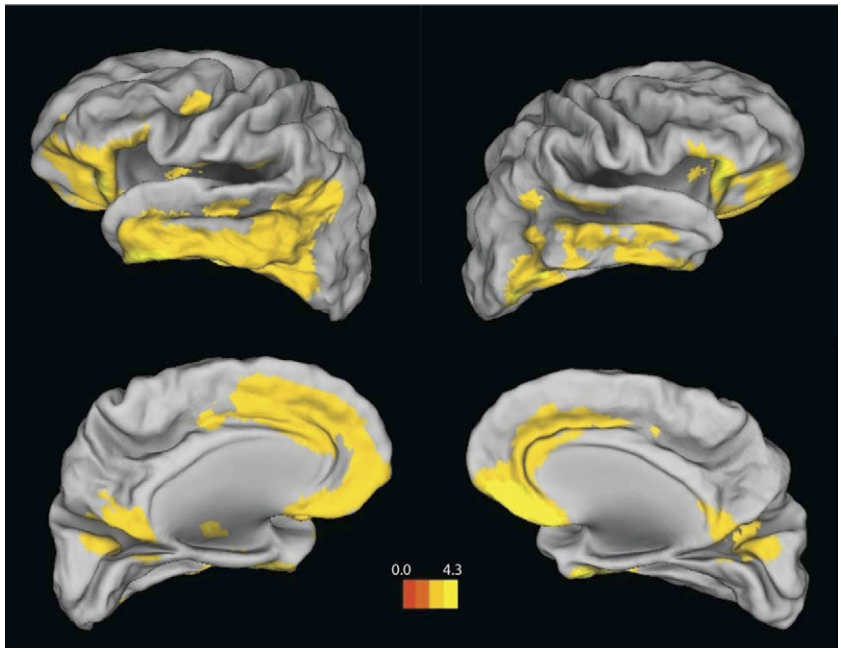

Fig. 3. Regions showing a positive association between Framingham Coronary Risk Profile (FCRP) and Global Pittsburgh compound B (PIB) Index. Threshold at $p < 0.005$ (uncorrected), $k > 100$. The color scale represents T values.

effects of either HDL or the HDL:LDL ratio on PIB were modeled jointly with FCRP, the effect of FCRP on Global PIB remained significant whereas the parameter estimates for cholesterol fell to near 0 and $p > 0.75$. HbA1c and glucose levels were available on 40 and 35 patients respectively, but neither showed a significant association with Global PIB (both p values > 0.30).

4. Discussion

Elevated aggregate coronary risk, quantified by the FCRP, was associated with elevated cerebral amyloid in this elderly, and generally nondemented sample. This association was not explained by APOE, which was independently associated with increased amyloid retention, or by individual risk factors, BMI, or a history of clinical coronary or cerebrovascular disease.

The FCRP captures the 6 major risk factors for coronary heart disease: age, sex, hypertension, smoking, dyslipidemia, and diabetes. It, and similar predictive indexes, have proven clinically useful in cardiology because risk factors tend to cluster, and have interactive effects that limit the utility of predicting risk based on a single risk factor (D'Agostino et al., 2008). The fact that we found a moderately strong effect of FCRP but no effect of its component measures suggests that the FCRP measures something different from the simple sum of its components. This idea is further emphasized by the fact that at least 2 of the FCRP components, considered individually, appear to be risk factors when elevated in midlife but not in late life (hypertension and dyslipidemia) whereas the relationship found here is a late life association. Other studies have shown an additive effect of vascular risk factors on risk for incident AD (Luchsinger et al., 2005; Whitmer et al., 2005). Together, the literature suggests that it is important to evaluate the combined presence of these risk factors with respect to cerebral amyloid deposition and raises the question of whether they converge to raise cerebral Aβ through a shared pathogenic pathway. However, there are multiple potential explanations for the observed correlation.

If the components of the FCRP together have a direct pathogenic effect on Aβ it would be reasonable to hypothesize that the effect is vascular in nature and that persons with elevated FCRP scores have changes in cerebral vessel structure and/or function that drive amyloid deposition.

An obvious potential vascular mechanism is acceleration of amyloid deposition by cerebral infarcts. Large postmortem studies demonstrate that infarcts are substantially more common in autopsy defined cases with AD than in elderly control cases (Jellinger, 2010) but the interpretation of this correlation is complex. While there is considerable evidence that infarcts play an important comorbid role in causing the dementia associated with AD pathology (Schneider et al., 2007; Neuropathology Group, Medical Research Council Cognitive Function and Aging Study, 2001), studies generally do not find a positive correlation specifically between infarcts and amyloid load. Some pathology-based studies report that vascular pathology is positively correlated with Braak staging of neurofibrillary tangles (Jellinger, 2010), but others do not find this (Strozyk et al., 2010) and amyloid burden is not reported in these studies. There is some human

(Qi et al., 2007) and transgenic mouse (Li et al., 2009) evidence that cerebral ischemia is associated with increased Aβ deposition. The epidemiological evidence actually raises the possibility that amyloid and infarcts may be inversely related, because demented AD cases with infarcts tend to have less AD pathology than similarly impaired cases without infarcts (Petrovitch et al., 2001; Snowdon et al., 1997). If true, such an inverse relationship might reflect a survivor bias effect, such that persons with more severe vascular disease die younger, giving AD pathology less time to accumulate. In a companion article in this issue (Marchant et al. in press) we found no evidence that Global PIB Index was associated with frank cerebrovascular disease. Although it may be counterintuitive to think that vascular risk factors increase Aβ deposition whereas cerebrovascular disease does not, there are several possible explanations for this pattern. Most important is the fact that vascular risk factors may have amyloidogenic effects that are not mediated by infarction.

One such potential mechanism would be risk-factor induced damage to the blood-brain barrier (BBB) (Kalaria, 1999), which could result in reduced clearance of Aβ from brain (Bell and Zlokovic, 2009; Bell et al., 2009), and in increased influx of proinflammatory cytokines and other neurotoxins that could themselves amplify the amyloid cascade (Altman and Rutledge, 2010). Evidence of increased BBB permeability has also been linked to accelerated progression of AD (Bowman et al., 2007). Microvascular damage to vascular smooth muscle cells and the endothelium with degradation of BBB function is commonly observed in AD (Kalaria, 1999) and is generally thought to arise from Aβ mediated effects. However, potential mechanisms by which primary vascular pathology could lead to reduced Aβ clearance have also been investigated. For example, recent evidence suggests that cerebral hypoxia upregulates transcription factors that suppress a low density lipoprotein that is a major transporter of Aβ across the BBB (Bell et al., 2009; Dotti and De Strooper, 2009). In addition, cholesterol in brain, normally produced locally in the endoplasmic reticulum, can be elevated by the addition of cholesterol from plasma if the BBB becomes abnormally permeable (Di Paolo and Kim, 2011). Cholesterol processing and Aβ production are intertwined processes (Altman and Rutledge, 2010), and elevated cholesterol levels appear to increase gamma secretase levels resulting in increased Aβ (Casserly and Topol, 2004; Di Paolo and Kim, 2011).

Another potential common pathogenic pathway for the FCRP components is arteriosclerosis. The relationship between atherosclerosis ("hardening of the arteries") and Alzheimer's disease is a long running controversy, scientific discussion dating back to the time of Alzheimer (Beach et al., 2007). As coronary risk factors, the FCRP components individually have multiple pathological mechanisms but all also converge on the intermediary pathogenic step of atherosclerosis. Hypertension and hypercholesterolemia are the 2 major risk factors for arteriosclerosis, and smoking and diabetes also are associated with coronary atherosclerosis (Frohlich et al., 2001). All of these factors are also independently associated with the progression of carotid atherosclerosis in older adults (van der Meer et al., 2003), and with CIMT in young adults (Paul et al., 2011). Several studies have reported a positive association between atherosclerosis and the pathology of Alzheimer's disease, including a positive correlation between atherosclerosis and neuritic plaques (Beach et al., 2007; Honig et al., 2005; Roher et al., 2003; Sparks et al., 1990). There are negative reports as well (Dolan et al., 2010).

We did not find direct evidence that atherosclerosis mediates the relationship of FCRP to cerebral amyloid. CIMT had only a weak relationship to Global PIB and did not moderate the effect of FCRP. However, it would be premature to discount the possibility that atherosclerosis-linked mechanisms are involved. Thickness of the vessel wall is but 1 measure of atherosclerosis, and CIMT is essentially a single point sampling of a distributed process. Decades ago autopsy studies demonstrated that the severity of atherosclerosis varies widely throughout the vascular system (Roberts et al., 1959; Wilkins et al., 1959); more recently several large studies have concluded that correlations between CIMT and coronary artery atherosclerosis as measured by angiography are modest, with correlations on the order of 0.3–0.4 (Bots et al., 2007), and AD has been associated with increased intracranial (but not coronary) atherosclerosis (Roher et al., 2011). It may also be that the FCRP components are all amyloidogenic, but through multiple, nonconverging mechanisms. If coronary risk factors increase amyloid levels through multiple pathways one would not necessarily see an association of CIMT and amyloid.

Alternatively, the association of FCRP and cerebral amyloid may reflect the shared effect of a third factor, genetic or environmental, that acts over a lifetime to increase both the FCRP and cerebral amyloid. A high fat diet (a factor beyond the scope of the present study) is an example of 1 such potential factor (Bhat, 2010). Another candidate is APOE, the most important genetic risk factor for late onset AD. The isoforms of APOE have a multiplicity of effects on cardiovascular system, brain, and the neurovasculature. APOE4 is a modest risk factor for coronary disease (Song et al., 2004), while the E2 allele appears to increase the risk of diabetes (Vogelberg and Maucy, 1988; Williams et al., 1993). In addition, APOE plays a role in cholesterol processing which at least partially accounts for the basic observation that the E4 allele is associated with higher levels of amyloid plaques compared with E2 or E3 (Rowe et al., 2007). We also found that the E4 allele was associated with greater cerebral amyloid deposition. However, we found no evidence that the APOE genotype accounts for the effect of coronary risk, as the effect of FCRP was independent of that of APOE genotype.

Finally, there is the possibility that coronary atherosclerosis and cerebral amyloidosis are simply independent disorders that share pathogenic factors. That is, there may be no causal connection between coronary disease or atherosclerosis and AD, but rather these are "convergent" diseases that share risk factors and pathogenic components, such as inflammation (Casserly and Topol, 2004).

The major caveats regarding this study regard sampling issues. The sample is relatively small and was recruited using methods intended to increase the representation of vascular risk factors over that typically found in memory or dementia clinics. The small size limits the extent of statistical modeling that can be done, and a lack of statistical power means that smaller independent effects and, especially, interactions that may in fact exist, might not be detected. Replication of these findings is needed.

To summarize, in this elderly, generally nondemented sample with a relatively high prevalence of vascular risk factors, there was a moderately strong effect of aggregate coronary risk on cerebral amyloid deposition. This effect was independent of age and gender, and was not explained by APOE, or by laboratory measures of cholesterol, glycemic control, or blood pressure, or by clinical history of ischemic events. There are several biologically plausible mechanisms that might account for this correlation, none of which were supported in these analyses. Thus, these findings add to the literature suggesting (but in no way proving) a causal connection between coronary risk and the risk of Alzheimer's disease and they invite further investigation of the mechanism(s) of this association.

Disclosure statement

William Jagust has served as a consultant for GE and Bayer Healthcare, both of which manufacture products that are used in amyloid imaging, and he has also served as a consultant for a number of pharmaceutical and imaging companies. Charles DeCarli has served as a consultant for a number of pharmaceutical and imaging companies. No other authors have potential conflicts of interest.

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