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Association of Coronary Artery Atherosclerosis with Brain White Matter Hyperintensity

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Abstract

Background and Purpose: We aim to determine, in healthy high-risk adults, the association between subclinical coronary artery disease (CAD) and white matter hyperintensity (WMH) volume and location, independent of atherosclerotic risk factors.

Methods: 782 asymptomatic first-degree relatives of index cases with early-onset CAD (<60 years old) from Genetic Study of Atherosclerosis Risk (GeneSTAR) with contemporaneous coronary CTA (C-CTA) and brain MRI were analyzed. Multilevel mixed-effects linear regression models, accounting for family structure, evaluated the association of total WMH volume, and three regions (deep white matter (DWMH), periventricular (PVWMH) or borderzone (cuff)), with markers of CAD. Separate models were created for total WMH, DWMH, PVWMH and cuff volumes, each, as dependent variables, across C-CTA variables, adjusted for covariates.

Results: Mean age was 51years±10, with 58% female and 39% African-American. Participants with any coronary plaque had 52% larger WMH volumes than those without plaque (95%CI 0.24–0.59). Per 1% greater coronary plaque volume, total WMH volumes were 0.07% larger (95%CI 0.04–0.10). Every 1% higher total coronary plaque volume was associated with 5.03% larger DWMH volume (95%CI 4.67–5.38), 5.10% PVWMH larger volume (95%CI 4.72–5.48) and 2.74% larger cuff volume (95%CI 2.38–3.09) with differences in this association when comparing DWMH to PVWMH (P-interaction 0.001) or cuff (P-interaction <0.001) respectively.

Conclusions: In healthy, high-risk individuals, the presence and volume of coronary artery plaque are associated with larger WMH volumes, appearing strongest for PVWMH. These findings in high-risk families suggest a disease relationship in two different vascular beds, beyond traditional risk factors, possibly due to genetic predisposition.

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Introduction:

Coronary artery disease (CAD) is associated with cerebral white matter disease, but the extent to which there is a common mechanism remains unclear. It is possible that shared atherosclerotic risk factors, genetic susceptibility, and yet to be identified novel risk factors are all contributors to disease in both the heart and the brain. Early-onset clinical CAD events clusters strongly in families.[1,2] Additionally, a high prevalence of calcified and non-calcified coronary artery plaque has been found in healthy family members of individuals with manifest CAD at a young age.[3–5]

Besides being causally related to CAD, evidence suggests that traditional vascular risk factors, such as hypertension, are related to cerebral white matter hyperintensities (WMH), and it has been suggested that with targeted treatment of these risk factors, the development of WMH may be stalled, or even reversed.[1–4] A recent genetic analysis of a large cohort of patients with both deep white matter (DWMH) and periventricular (PVWMH) suggest that PVWMH and DWMH have independent genetic underpinnings suggestive of independent etiologies.[6] PVWMH lesions were independently linked to genes with strong previous associations with CAD.[6]

While cerebral blood flow (CBF) is decreased in WMH compared to normal cerebral white matter, there also appears to be a difference in mean CBF between DWMH and PVWMH, with PVWMH having lower exposure to high perfusion pressures compared to DWMH.[7] For example, DWMH is more associated with arteriolosclerosis[8] while PVWMH with chronic hemodynamic insufficiency, leading to watershed infarcts, for example.[9] Given this data, and in light of the knowledge that cerebral vasculature caliber and anastomosis differ depending on location, it is therefore possible that specific areas of the brain are more susceptible to vascular pathology than others.[10]

Our preliminary work has demonstrated an association between the total volume of coronary plaque and total WMH in healthy relatives of persons with early-onset CAD, independent of known vascular risk factors.[11] Given the fact that this cohort has a strong family history of early-onset coronary disease, it is plausible that there is a genetic predisposition to systemic vascular disease in multiple vascular beds at younger ages.[12] The objective for this study is to test, in a high-risk population, the association between the presence and burden of subclinical CAD with WMH volume globally and within 3 different locations of WMH: deep white matter (DWMH), periventricular (PVWMH), and borderzone (cuff), independent of vascular risk factors.

Methods:

Study Population:

The Genetic Study of Atherosclerosis Risk (GeneSTAR) is an ongoing, prospective cohort study with the overall aim of characterizing biological and genetic risk factors associated with subclinical and incident cardiovascular disease in families with early-onset CAD.[13,14] In 1982, recruitment began of index cases <60 years old, healthy siblings 30–60 years of age of the index case, and healthy adult offspring of either the index case or a sibling of the

index case. Index cases were identified during a hospitalization for acute coronary syndrome with angiographic evidence of disease with or without revascularization. The healthy siblings were identified by index cases at the time of the hospitalization and had no history of CAD, symptoms suggestive of CAD, or stroke/transient ischemic attack. Healthy adult offspring of both the original study siblings and index cases were also enrolled in the study. Family size averaged 1.96 +/− 1.3, ranging from 1 to 8 family members. There were 206 “singlets”, ie, only one participating family member, identified from an index case. Additional inclusion and exclusion criteria have previously been described.[14]

All participants were evaluated contemporaneously for cardiovascular risk factors, medical history, medication use and had a comprehensive cardiovascular physical exam by a cardiologist, a coronary computerized tomography angiography (C-CTA), a maximal graded treadmill test and cerebral magnetic resonance imaging (MRI) between 2009 and 2013. Participants were referred to their own primary care physician for any follow-up. Results were sent to the physician and to the participant with any recommendation for further evaluation and therapies based on their own values and national guidelines. Participants without physicians were given access to care by a federally funded primary care source. Follow-up occurs every 5 years and we do not have final definitive data on coronary interventions from this particular study cohort yet. Written informed consent was obtained from all participants and the study was approved by an ethical standards committee on human experimentation. Data are available to qualified researchers via an application (https://www.hopkinsmedicine.org/gim/research/GeneSTAR/for_researchers) with approval from the GeneSTAR Study Steering Committee.

Measures of White Matter Hyperintensity:

Cerebrovascular imaging was performed on all participants using a Philips 3.0-T MRI scanner to acquire an Axial T1-weighted magnetization prepared rapid gradient echo (repetition time 10 ms, time to echo 6 ms, inversion time voxel size 0.75 × 0.75 × 1.0 mm^3, contiguous slices, with field of view imaging 240 mm, matrix 256 × 256 × 160 mm) and an Axial turbo spin echo fluid attenuation inversion recovery (FLAIR) sequence (repetition time 11,000 ms, inversion time 2,800 ms, time to echo 68 ms, voxel size 0.47 × 0.47 × 3.0 mm^3, contiguous slices, field of view imaging 240 mm, matrix 256 × 256 mm).A MIPAV software package was used to determine WMH volumes with segmentation to determine brain volumes.[15] Total intracranial volume was also calculated using MIPAV, and lesion Lesion-TOpology-preserving Anatomical Segmentation (TOADS)[16] As previously described, PVWMH in GeneSTAR was defined as lesions that were continuous with a lesion voxel within 4mm of a ventricle, while DWMH lesions were those that were not contiguous with the ventricle.[17]

Measures of Coronary Artery Disease:

Coronary CT examinations were performed on 2nd generation dual-source CT scanners (SOMATOM Definition Flash, Siemens Medical Solutions, Forchheim, Germany). Because of the high temporal resolution and excellent image quality of the scanner, pilot data showed that beta-blockade was not necessary for reducing the heart rate.[18,19] The data obtained from this study using this method has been subjected to peer review and published in the

cardiovascular imaging literature.[3] Full details regarding the C-CTA protocol are available (please see https://www.ahajournals.org/journal/str for details).

Covariates:

Blood pressure was measured three times over the course of the day and the average of the three measurements was used to characterize a baseline blood pressure (mmHg). Hypertension was defined as either an average blood pressure of ≥140mmHg systolic and/or 90 mmHg diastolic, or treatment with an antihypertensive agent with a normal blood pressure. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Type 2 diabetes mellitus was defined as a history of type 2 diabetes, fasting glucose level ≥126 mg/dL, and/or use of hypoglycemic medications. Total cholesterol was measured in mg/dL. Age was represented as a continuous variable, race (self-reported) was dichotomized into African-American versus other and smoking status was assessed according to the CDC questionnaire and for this analysis was classified as current versus nonsmoker.

Statistical methods:

For continuous variables, means and standard deviations or medians with interquartile ranges are reported, and for categorical variables, frequencies and percentages are reported. Multilevel mixed-effects linear regression accounting for family structure was used to evaluate the association of WMH volume (dependent variable), in the three specified regions as well as overall, with markers of CAD; specifically plaque volume, type of plaque and Agatston score (independent variables). WMH volumes and continuous CAD variables were log-transformed as they were not normally distributed. In instances where both the dependent and independent variable are log-transformed, the effect estimates are interpreted as the percent increase in the dependent variable for every 1% increase in the independent variable. When only the dependent variable is log-transformed, the coefficient is exponentiated, subtracted from one and multiplied by 100 to give the percent change in the dependent variable for every one-unit increase in the independent variable. Separate models were incorporated for total WMH, DWMH, PVWMH and cuff volumes, each, as dependent variables, across multiple cardiac variables. A final model with different regions within individuals was used to evaluate differential relationships between CAD markers and WMH in different regions. Regressions were adjusted in a step-wise fashion for demographics and vascular risk factors. Specifically, model 1 adjusted for age, sex, race and intracranial volume. Model 2 adjusted for model 1 plus total cholesterol, type 2 diabetes, smoking, body mass index and systolic blood pressure. Due to the potential for multiple comparisons when comparing the three locations of WMH, we also present Bonferroni-corrected results (0.05/3=0.0133). All statistical analyses were performed using Stata v14.1.[20] Two-sided $p<0.05$ was otherwise considered statistically significant.

Results:

A total of 782 participants from 406 hospitalized CAD index cases met inclusion criteria with a mean age of 51±10 years old, with 58% female and 39% African-American race (Table 1). As per the methods, index cases were not included in this study. Participants were comprised of healthy siblings of the index case and healthy offspring of either the index case

or a sibling of the index case, and were thus all family members of the index case. Of this total sample, 545 (70%) participants had white matter disease in the periventricular region, 655 (84%) had WMH in the subcortical region and 669 (85%) in the globoid or cuff region, with overlap between participants. A Spearman's correlation was run to determine the relationship between coronary plaque volume and WMH volume. There was a positive monotonic correlation between total coronary plaque volume and WMH (r_s=0.31, p=<0.0001). This was similarly seen with the correlation between calcified and non-calcified coronary plaque and WMH respectively (calcified r_s=0.28, p= <0.0001; non-calcified r_s=0.30, p=<0.0001).

Associations between subclinical CAD and total WMH volume:

For every 1% greater total coronary plaque volume (log transformed), total WMH volumes (log transformed) were 0.07% larger (95%CI 0.01–0.12; Model 2, Table 2). When looking across type of plaque, higher amounts of calcified plaque (β 0.06, 95%CI 0.01–0.08) or non-calcified plaque (β 0.08, 95%CI 0.04–0.12) were associated with larger WMH volumes in the final adjustment model. Participants with any coronary plaque (calcified or noncalcified) had WMH volumes that were 52% larger (due to log-transformation; see methods) than those without plaque (β 0.42, 95%CI 0.24–0.59). For every 1% increase in Agatston score, WMH total volume was 0.07% higher (95%CI 0.03–0.09). Those with an Agatston score in the highest risk category (>300) had WMH volumes that were 75% larger than those with Agatston scores in the lower categories (β 0.56, 95%CI 0.26–0.89).

Associations between subclinical CAD and WMH by location:

Every 1% higher total coronary plaque volume was associated with 5.03% larger DWMH volume (95%CI 4.67–5.38), 5.10% PVWMH larger volume (95%CI 4.72–5.48) and 2.74% larger cuff volume (95%CI 2.38–3.09) with significant differences in this association when comparing DWMH to PVWMH (P-interaction 0.001) or cuff (P-interaction <0.0001). Participants with any C-CTA plaque had larger WMH lesion volumes in all locations than those without plaque, but differences were seen by region; compared to its association with DWMH (β 5.00, 95% CI 4.70–5.31), C-CTA plaque was associated with more PVWMH (β 5.44, 95%CI 5.08– 5.80, P-interaction 0.009) but less cuff volume (β 2.21, 95%CI 1.88–2.52; P-interaction 0.001). Findings were similar when looking across coronary plaque type. Every 1% higher total calcified plaque volume was associated with 4.88% larger DWMH (95% CI 4.51–5.26), 5.06% PVWMH larger volume (95%CI 4.66– 5.46) and 2.50% larger cuff volume (95% CI 2.12–2.88) with significant differences in this association when comparing DWMH to PVWMH (P-interaction 0.002) or to cuff (P-interaction <0.0001). The direction of the association between non-calcified plaque volume and each location of WMH was similar, with larger effect estimates again seen with PVWMH, with a statistically significant larger percent change in volume seen for PVWMH, and a smaller percent change in cuff when compared to DWMH (Table 3). Per 1% increase in Agatston score, PVWMH total volume was increased by 5.04% (95%CI 4.66–5.43), and cuff volume was increased by 2.50% (95%CI 2.13–2.87), and these changes were significantly different from DWMH (PVWMH p-interaction 0.002; cuff p-interaction 0.001).

Discussion:

White matter hyperintensities of presumed ischemic origin (WMH) represent 40% of all cerebral small vessel disease (SVD) disease burden and are the most prevalent sign of cerebral SVD.[21] Detected as incidental lesions on T2-weighted MRI, they are associated with increased risk for gait disorders, ischemic and hemorrhagic stroke, and cognitive decline.[22–24] We previously reported a relationship between non-calcified coronary plaque volume and total WMH volume.[11] Recently PVWMH and DWMH have been demonstrated as having different independent genetic associations suggesting different underlying causes.[6] PVWMH was shown to have singular and independent associations with many genes previously associated with coronary artery disease as compared to DWMH.[6]

In a large cohort of healthy middle-aged adults with family history of early onset CAD, we now demonstrate that both the presence and volume of coronary plaque measure on C-CTA is associated with larger volumes of WMH, as compared to participants without plaque or individuals with smaller plaque volumes. In our analysis incorporating three anatomically based regions of WMH distribution relative to the lateral ventricles including PVWMH, DWMH, and cuff lesions,[23–28] CAD, as measured in our study, was associated with all three WMH phenotypes. However, we now show differential associations based on location of WMH, with the largest association between coronary plaque and PVWMH. We suggest that these regions may be subject to different types of injury such as small vessel occlusion (DWMH), hypertension (PVWMH) and hypoperfusion (Cuff region or borderzone regions).[7,22,26,29]

DWMH lesions occur in the subcortical areas, primarily supplied by long microvessels, possibly subject to damage secondary to hypertension and potential consequential secondary hypoperfusion.[7,26,29,30] PVWMH are related to alterations in the short penetrating microvessels ending in close approximation to larger arterial blood vessels. They have different vascular architecture, including two leptomeningeal layers and enlarged perivascular spaces.[10,21,25,30] They are hypothesized to be affected more directly by hypertension and traditional risk factors associated with stroke.[7,26,30] It has also been suggested that the white matter disease when located in the periventricular region is different in composition when compared to white matter disease in the deep brain regions.[10,31]

In this study we have also evaluated a region we designated as the cuff region, which is a zone of highly variable WMH lesion volume located on the prominent edges of the anterior and posterior prominences of the periventricular lesions in areas thought to be potentially subject to border zone infarcts. Thus, this cuff region may represent an area subject to distinct processes, including chronic hypoperfusion secondary to vascular injury.[22] The cuff lesion lying in the border zone region also had the smallest association with CAD of all the phenotypes analyzed.

Ischemia may play an important role in the longitudinal development of WMH. The primary initiating event is described as endothelial activation secondary to vascular damage with many consequential after effects leading to increased blood brain barrier permeability and prominent T2 / FLAIR signaling and eventual SVD phenotypes.[21] There is strong evidence

that vascular risk factors are associated with increased prevalence of WMH (both behavioral risk factors like smoking, as well as some more genetically influenced like hypertension).[32–34] Additionally, it appears that there is variability of the importance of different vascular risk factors at different ages, and that this interaction (risk factor and age) also influences the development of WMH.[21]

Determining how these risk factors are causal in development of WMH is not well understood. Additionally, there may be a different hierarchy of risk factors when considering small versus large vessel disease. One may postulate that if WMH is a manifestation of atherosclerotic disease, statin usage may show a beneficial effect, which has been suggested by others.[35–39] While WMH is primarily a disease of the small cerebral vasculature, it is interesting to consider that the positive effect of statins on WMH and CAD may potentially suggest similar vascular disease mechanisms.

There is data to suggest that proximal aortic stiffening transmits pressure into the carotid circulation, and this combined with co-occurring flow pulsatility triggers microvascular damage, leading to microvascular ischemia and cerebral tissue damage.[40] We did not specifically consider aortic stiffness, and our population is relatively young as aortic stiffness normally increases with age, but it represents another interesting mechanism to consider in light of our results.[41]

Very few, if any prior studies, have examined the WMH/preclinical CAD link in healthy persons at higher than usual risk for vascular disease. The GeneSTAR cohort represents a unique environment in which to address the answers to these questions as well as examine the potentially shared and unique aspects of atherosclerotic disease in different vascular beds. Traditional risk factors were accounted for in our analysis, and our participants were free of symptomatic disease, and relatively young. Our results suggest that one manifestation of preclinical CAD, specifically coronary plaque, is not only associated with larger WMH volumes, but that there is a difference in the strength of the association with WMH volume depending on the location of the disease. PVWMH was specifically compared to DWMH, given the interest in both of these locations and the possibility, as alluded to earlier, that the pathology behind disease in each area differs. We cautiously suggest that a shared genetic predisposition to CAD may be the reason for some of the contributions of CAD to WMH and that these contributions may differ by location of disease (with different regions sharing underlying pathophysiology more with CAD than others).

We readily acknowledge that there are limitations in our work. We have described associations, and cannot provide conclusive evidence that cardiovascular plaque is a risk factor for WMH, and it is possible that they share a common cause that is not identified in the known risk factors for both diseases. Specifically, we understand that our work is cross-sectional in nature and does not imply causation. Longitudinal lifetime exposure to risk factors and their relative severity over time are not accounted for in this study, therefore raising the possibility that residual confounding could account for an even greater proportion of the shared co-existence of WMH and CAD in our participants. However, this does not differ from other similarly structured studies of cerebral small vessel disease and CAD. It is possible that conditions beyond vascular disease might represent a confounder, such as

multiple sclerosis, or neurodegenerative diseases, although participants were carefully screened for such potentially confounding brain pathology, with only 5 participants across the entire cohort excluded for this reason.

In conclusion, we have demonstrated in a unique higher risk family-based cohort that preclinical CAD is associated with WMH and that the burden of asymptomatic CAD, specifically coronary plaque, differs based on location of cerebrovascular white matter disease. These findings suggest that there might be novel risk factors and/or genetic susceptibility that influences this relationship and supports recent associations of the cause of PVWMH with genetic risk for CAD. Ongoing prospective work plans to evaluate our results in light of cognitive function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-standard Abbreviations and Acronyms:

DWMH	Deep white matter hyperintensities
PVWMH	Periventricular white matter hyperintensities
WMH	White matter hyperintensities
C-CTA	Coronary computerized tomography angiography
SVD	Cerebral small vessel disease

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Table 1:

Participant characteristics (N=782)

Mean (SD)	
Age, years	51 (10.6)
Systolic blood pressure, mmHg	124 (14.8)
Body mass index, kg/m^2	30 (5.9)
Total cholesterol, mg/dL	193 (40)
N (%)	
Female sex	457 (58.4)
African-American race	305 (39.0)
Current smoker	149 (19.1)
Type 2 Diabetes	92 (11.8)
Median (IQR)	
Total coronary plaque volume, mm^3	0 (0–163.4)
Total calcified coronary plaque volume, mm^3	0 (0–23.1)
Total non-calcified coronary plaque volume, mm^3	0 (0–117.1)
Low attenuated coronary plaque volume, mm^3	0 (0–20)
Agatston score, Hounsfield units	0 (0–22)
Total WMH volume, mm^3	971.5 (353–2610)
PVWMH volume, mm^3	439 (0–1646)
DWMH volume, mm^3	273.5 (79–665)
Cuff volume, mm^3	18 (4–50)

Table 2:

Multilevel mixed-effects linear regression of white matter hyperintensity volume* versus cardiac variables, accounting for family structure (N=782)

Cardiac variable	β (Model 1)	95% CI	β (Model 2)	95% CI
Total coronary plaque volume*	0.07	0.02–0.11	0.07	0.01–0.12
Total calcified coronary plaque volume*	0.06	0.01–0.09	0.06	0.01–0.08
Total non-calcified coronary plaque volume*	0.08	0.01–0.14	0.08	0.04–0.12
Low attenuated coronary plaque volume*	0.06	0.01–0.10	0.06	0.03–0.10
Agatston score* (per 1% higher volume)	0.07	0.01–0.10	0.07	0.03–0.09
Any coronary plaque (versus no plaque)	0.41	0.10–0.70	0.42	0.24–0.59
Agatston score >300 (versus score ≤300)	0.67	0.04–1.04	0.56	0.26–0.89

*Log transformed, units are per 1 natural log unit unless otherwise noted (original units: white matter hyperintensity $1mm^3$, plaque volume $0.01mm^3$)

Abbreviations: β=Beta coefficient, CI=Confidence Interval; Model 1: Age, sex, race, total intracranial volume (TIV); Model 2: Model 1 +total cholesterol (mg/dL), type 2 diabetes (history of type 2 diabetes, fasting glucose level ≥126 mg/dL, and/or use of hypoglycemic medications), smoker (current vs. non), body mass index (kg/m^2), systolic blood pressure (mmHg).

Table 3:

Multilevel mixed-effects linear regression of white matter hyperintensity volume[+] versus cardiac variables accounting for family structure, stratified by location (N=782)

Cardiac variable	DWMH[*] β (1)	95% CI	PVWMH[*] β (2)	95%CI	Cuff[*] β (3)	95%CI	p-interaction (1):(2)	p-interaction (1):(3)
Total coronary plaque volume[*]	5.03	4.67–5.38	5.10	4.72–5.48	2.74	2.38–3.09	0.001[*]	<0.0001[*]
Total calcified coronary plaque volume[*]	4.88	4.51–5.26	5.06	4.66–5.46	2.50	2.12–2.88	0.002[*]	<0.0001[*]
Total non-calcified coronary plaque volume[*]	5.29	4.85–5.79	5.45	4.98–5.91	2.95	2.49–3.40	0.001[*]	0.001[*]
Low attenuated coronary plaque volume[*]	5.29	4.80– 5.77	5.67	5.14–6.22	3.52	2.92–4.12	0.003[*]	<0.0001[*]
Agatston Score[*] (per 1% higher volume)	4.88	4.52–5.26	5.04	4.66–5.43	2.50	2.13–2.87	0.002[*]	0.001[*]
Any coronary plaque (versus no plaque)	5.00	4.70–5.31	5.44	5.08– 5.80	2.21	1.88–2.52	0.009[*]	0.001[*]
Agatston score >300 (versus score ≤300)	5.04	4.46–5.62	6.22	5.50–6.94	1.52	0.92–2.12	0.003[*]	0.001[*]

[+]Log transformed, units are per 1 natural log unit unless otherwise noted (original units: white matter hyperintensity $1mm^3$, plaque volume $0.01mm^3$)

Abbreviations: β=Beta coefficient CI=Confidence Interval DWMH=Deep White Matter Hyperintensity (WMH), PVWMH=Periventricular WMH

Adjusted for Model 2: age, sex, race, total cholesterol (mg/dL), type 2 diabetes (history of type 2 diabetes, fasting glucose level ≥126 mg/dL, and/or use of hypoglycemic medications), smoker (current vs. non), body mass index (kg/m^2), systolic blood pressure (mmHg), total intracranial volume (TIV).

P-interactions (1):(2) between DWMH & PVWMH, (1):(3) between DWMH & Cuff.

[*]Indicates associations that retain significance after adjusting for multiple comparisons (Bonferroni correction).