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### Authors

Mathew, Daniel

Peigh, Graham

Lima, Joao

et al.

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ORIGINAL RESEARCH

# Associations of Circulating Vascular Cell Adhesion Molecule-1 and Intercellular Adhesion Molecule-1 With Long-Term Cardiac Function

Daniel T. Mathew, MD\*<sup>1</sup>; Graham Peigh , MD, MSc\*<sup>2</sup>; Joao A.C. Lima, MD, MBA; Suzette J. Bielinski , PhD; Nicholas B. Larson , PhD; Matthew A. Allison , MD, MPH; Sanjiv J. Shah , MD; Ravi B. Patel , MD, MSc

**BACKGROUND:** Although VCAM-1 (vascular cell adhesion molecule-1) and ICAM-1 (intercellular adhesion molecule-1) have been associated with incident heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF), the associations of VCAM-1 and ICAM-1 with sensitive measures of cardiac structure/function are unclear. The objective of this study is to evaluate associations between VCAM-1, ICAM-1, and measures of cardiac structure and function as potential pathways through which cellular adhesion molecules promote HFpEF and AF risk.

**METHODS AND RESULTS:** In MESA (Multi-Ethnic Study of Atherosclerosis), we evaluated the associations of circulating VCAM-1 and ICAM-1 at examination 2 (2002–2004) with measures of cardiac structure/function on cardiac magnetic resonance imaging at examination 5 (2010–2011) after multivariable adjustment. Mediation analysis of left atrial (LA) strain on the association between VCAM-1 or ICAM-1 and AF or HFpEF was also performed. Overall, 2304 individuals (63±10 years; 47% men) with VCAM-1 or ICAM-1, cardiac magnetic resonance imaging, and covariate data were included in analysis. Higher VCAM-1 and ICAM-1 were associated with lower LA peak longitudinal strain and worse global circumferential left ventricular strain but were not associated with left ventricular myocardial scar or interstitial fibrosis. Lower LA peak longitudinal strain mediated 8% (95% CI, 2–30) of the relationship between VCAM-1 and HFpEF and 9% (95% CI, 2–21) of the relationship between VCAM-1 and AF.

**CONCLUSIONS:** Higher VCAM-1 and ICAM-1 were associated with lower LA function and left ventricular systolic function but were not associated with myocardial scar or interstitial fibrosis. VCAM-1 and ICAM-1 may promote HFpEF and AF risk through impaired LA reservoir function.

**Key Words:** atrial fibrillation ■ cellular adhesion molecule ■ heart failure ■ interstitial fibrosis ■ left atrial strain ■ myocardial scar

**H**eat failure (HF) with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) commonly coexist, and the presence of AF in HFpEF is independently associated with poor prognosis.<sup>1–4</sup> Furthermore, the prevalence of AF in HFpEF is >50% and appears to be increasing over time.<sup>5</sup> However, despite their common comorbid state, the shared pathobiology driving AF and HFpEF to coexist is not clear.

Endothelial cell activation is characterized by increased expression of CAMs (cellular adhesion molecules), including VCAM-1 (vascular cell adhesion molecule-1) and ICAM-1 (intercellular adhesion molecule-1), on endothelial surfaces, which promote leukocyte infiltration and inflammation and may play a common role in the development of both HFpEF and AF.<sup>6–8</sup> Higher circulating VCAM-1 and ICAM-1 have

Correspondence to: Ravi B. Patel, MD, MSc, Division of Cardiology, Northwestern Memorial Hospital, 676 N St. Clair Suite 600, Chicago, IL 60611. Email: [ravi.patel@northwestern.edu](mailto:ravi.patel@northwestern.edu)

\*D. T. Mathew and G. Peigh contributed equally.

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## CLINICAL PERSPECTIVE

### What Is New?

- In the current analysis of 2304 individuals from the MESA (Multi-Ethnic Study of Atherosclerosis) cohort, higher VCAM-1 (vascular cell adhesion molecule-1) and ICAM-1 (intercellular adhesion molecule-1) were associated with lower left atrial function and left ventricular systolic function but were not associated with myocardial scar or interstitial fibrosis.
- Lower left atrial peak longitudinal strain mediated 8% of the relationship between VCAM-1 and heart failure with preserved ejection fraction and 9% of the relationship between VCAM-1 and atrial fibrillation.
- VCAM-1 and ICAM-1 may promote heart failure with preserved ejection fraction and atrial fibrillation risk through impaired left atrial reservoir function and left ventricular systolic function.

### What Are the Clinical Implications?

- The role of therapies to modulate VCAM-1, ICAM-1, and other indices of microvascular dysfunction on future heart failure with preserved ejection fraction or atrial fibrillation risk warrants investigation.

## Nonstandard Abbreviations and Acronyms

<b>CAM</b>	cellular adhesion molecule
<b>ECV</b>	extracellular volume
<b>GCS</b>	global circumferential strain
<b>HFpEF</b>	heart failure with preserved ejection fraction
<b>ICAM-1</b>	intercellular adhesion molecule-1
<b>MESA</b>	Multi-Ethnic Study of Atherosclerosis
<b>VCAM-1</b>	vascular cell adhesion molecule-1

been associated with future development of AF and HFpEF, suggesting that these cell surface proteins may promote the risk of both AF and HFpEF.<sup>6,7,9,10</sup> VCAM-1 and ICAM-1 are specifically hypothesized to contribute to HFpEF through leukocyte recruitment into the myocardium, leading to myocardial interstitial fibrosis.<sup>11</sup>

There are limited data on the associations between VCAM-1, ICAM-1, and indices of cardiac structure and function. Elucidation of such associations may allow for a better understanding of specific myocardial pathways through which CAMs promote HFpEF and AF risk. We therefore assessed the associations between VCAM-1 or ICAM-1 and sensitive measures of cardiac structure and function on cardiac magnetic

resonance imaging (cMRI) in MESA (Multi-Ethnic Study of Atherosclerosis).

## METHODS

### Participants

The MESA cohort is composed of community-dwelling adults and was created to further identify risk factors for, and prevalence of, cardiovascular disease. Recruitment strategies and design of the cohort have been previously described.<sup>12</sup> In sum, 6814 participants were recruited among 6 study sites across the United States (Baltimore, Maryland; Chicago, Illinois; St. Paul, Minnesota; Forsyth County, North Carolina; New York, New York; and Los Angeles, California).<sup>12</sup> At the time of enrollment, participants were aged 45 to 84 years and had no history of cardiovascular disease (defined as myocardial infarction, angina, stroke, transient ischemic attack, HF, AF, nitroglycerin use, angioplasty, pacemaker or defibrillator, or prior cardiac surgery). Following enrollment, participants had 6 examinations (1 every 2–5 years) during which study personnel collected updated medical history information. Vital signs, blood tests, and urine tests were obtained during each examination according to study protocol. In addition, participants were contacted yearly to inquire about any recent hospitalizations or changes in health.<sup>9,12</sup>

The current analysis is composed of MESA participants who had serum VCAM-1 and ICAM-1 levels obtained during examination 2 (2002–2004) with available examination 2 covariate data. In MESA, assays for CAMs were drawn from a race-stratified random sample. The MESA protocol was approved by the institutional review board of each participating institution. The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Measurement of Circulating CAMs

VCAM-1 and ICAM-1 were evaluated as part of the MESA Adhesion Ancillary Study from all consenting patients at the 6 MESA sites. All candidates eligible for inclusion in the MESA Adhesion Ancillary study were members of the MESA Candidate Gene cohort. This cohort was a random selection of 2880 MESA subjects who consented for use of DNA and participated in examination 2 (total N=6317 participants). The 2880 MESA subjects in the MESA Candidate Gene cohort consisted of 720 randomly selected subjects from each racial and ethnic group.

Serum VCAM-1 and ICAM-1 levels were measured from blood samples obtained during examination 2 and subsequently stored at –70°C using the Quantlike ELISA kit (R&D Systems, Minneapolis, MN). In sum, 2372 participants have data on VCAM-1, and 2621

participants have data on ICAM-1. The minimum detectable level of the VCAM-1 assay was 0.6 ng/mL, and the coefficient of variation was 3.6%.<sup>9</sup> The minimum detectable level of the ICAM-1 assay was 0.35 ng/mL, and the coefficient of variation was 5%.<sup>13</sup>

## Cardiac Magnetic Resonance Imaging Protocol

Electrocardiographic gated cMRI was completed with 1.5-Tesla magnets (Avanto and Espree, Siemens Healthineers, Malvern, PA; Signa LX, GE Healthcare, Chicago, IL) at all participating MESA centers at examination 5. The MESA cMRI image acquisition technique has been described extensively in the literature and was uniform across study sites.<sup>14,15</sup> The protocol included acquisition of 12 short-axis slices, one 4-chamber view and one 2-chamber view. In addition, short-axis slices at the left ventricular (LV) base, mid-cavity, and apex were obtained. If contraindications were not present, contrast-enhanced cMRI was performed. All eligible participants with estimated glomerular filtration rate  $>60 \text{ mL}/(\text{min} \times 1.72 \text{ m}^2)$  or  $>45 \text{ mL}/(\text{min} \times 1.72 \text{ m}^2)$  (depending on the study site) received 0.15 mmol/kg of gadolinium contrast (Magnevist, Bayer Healthcare Pharmaceuticals, Montville, NJ) for late gadolinium enhanced cMRI sequences.<sup>14</sup>

## cMRI: Cardiac Structure and Function

To measure LV chamber volumes, a semiautomated system (Q-MASS 4.2, Medis, Leiden, The Netherlands) traced endocardial borders on short-axis cine images. Manual correction was completed when appropriate. Ventricular volumes were calculated using the Simpson biplane method. LV volumes were adjusted for body size on the basis of previously documented formulas.<sup>16</sup> Stroke volume was calculated by subtracting end-systolic volume from end-diastolic volume. Using the traced endocardial borders, LV ejection fraction was evaluated using commercial software (CIM version 6.2, Auckland, New Zealand). To obtain LV mass, the epicardial and endocardial areas at end diastole were subtracted and multiplied by the slice thickness and section gap. The resulting product was then multiplied by the myocardial specific gravity (1.05 g/mL).<sup>16,17</sup>

Myocardial scar or replacement fibrosis was defined as present if late gadolinium enhancement was seen in 2 adjacent short-axis slices or in 1 short-axis and a corresponding long-axis slice (Qmass version 7.2; Medis).<sup>18</sup> Interstitial fibrosis was evaluated on 1 short-axis site before contrast injection, then at time periods 12 and 25 minutes following contrast injection, as a percentage of the entire extracellular volume (ECV). ECV was evaluated in T1 myocardial mapping of mid-cavity short-axis sections using a modified Look-Locker inversion recovery protocol and processed

using MASS research software (MASS V2010-EXP; Leiden, the Netherlands).<sup>19</sup>

There were 608 (45.5%) participants who underwent T1 myocardial mapping and had hematocrit measured during examination 5 to calculate ECV. The remainder of participants had a synthetic hematocrit calculated to determine synthetic ECV.<sup>20</sup> Prior analyses have shown a high degree of correlation between ECV and synthetic ECV.<sup>21,22</sup>

LA volumes were calculated from 2- and 4-chamber cine images. End-systolic borders of the LA were measured on endocardial and epicardial surfaces, and tissue-tracking software followed these borders throughout the cardiac cycle to produce volume curves (MTT version 5.0; Toshiba, Tokyo, Japan). Manual correction was completed when appropriate. Minimal and maximal LA volumes were recorded, and LA emptying fraction was calculated by the following formula ( $\text{LA Volume}_{\text{max}} - \text{LA Volume}_{\text{min}} / \text{LA Volume}_{\text{max}}$ ).

## cMRI: Myocardial Strain Analysis

MRI derived LA and LV strain analysis were completed with proprietary tissue-tracking software (MTT version 5.0) that has been validated in numerous prior studies.<sup>15,17,23</sup> Briefly, LV myocardial global circumferential strain (GCS) was analyzed in 4 wall segments (anterior, posterior, lateral, septal) in each of the 3 short-axis slices using the HARM method (MATLAB software or HARP1.15; Diagnosoft, Palo Alto, CA), yielding a total of 12 segments with strain curves. LV GCS was calculated as the average of these 12 strain curves.<sup>18</sup>

Tissue tracking of 2- and 4-chamber views also produced LA strain curves of all LA segments. The LA peak longitudinal strain was calculated as the average of all LA global longitudinal strain curves.<sup>14,18</sup>

All cMRI images were analyzed for structure and function in a core laboratory and at a single image analysis center (Johns Hopkins Medical Center, Baltimore, MD). There was a high degree of interobserver reliability in all MRI-derived values.<sup>24</sup>

## Adjudication of Clinical End Points

All MESA participants were contacted regularly via telephone to screen for clinical events and hospitalizations. If a patient reported a cardiovascular hospitalization, records were obtained and transmitted to the MESA coordinating center for review. In the MESA cohort, hospitalizations for HF were confirmed by an assessment of medical records by a physician review committee composed of 2 study physicians blinded to other study data. All HF events required symptoms including dyspnea or edema. HF events were characterized as “definite” if  $>1$  of the following criteria were met: pulmonary edema on chest radiography, LV dilation, decreased systolic function, or evidence of diastolic

dysfunction. If these definite criteria were not met, the HF event was defined as “probable” on the basis of physician adjudication of presenting symptoms and treatment.<sup>25,26</sup>

HF was further characterized as HFpEF or HF with reduced ejection fraction. HFpEF was defined by ejection fraction  $\geq 45\%$  on echocardiogram or radionuclide study at time of HF hospitalization. Conversely, HF with reduced ejection fraction was defined as ejection fraction  $< 45\%$ .<sup>9</sup>

AF was defined by review of *International Classification of Diseases, Ninth Revision (ICD-9)* or *Tenth Revision (ICD-10)* discharge diagnoses and Medicare claims data, or presence of AF on routine ECG obtained during examination 1 or 5.<sup>27,28</sup> The processes for adjudicating covariates have been reported previously.<sup>9,12,25–28</sup>

## Statistical Analysis

Clinical characteristics at examination 2, stratified by quartile of VCAM-1 and ICAM-1 levels, were compared using  $\chi^2$  tests or Fisher exact tests for categorical variables and univariate general linear models for continuous variables, as appropriate. Numerical results are reported as mean $\pm$ SD, median (interquartile range), or number (percentage). Two-tailed *P* values of  $< 0.05$  were considered statistically significant.

Because of their skewed distributions at baseline (Figures S1 and S2), VCAM-1 and ICAM-1 levels were  $\log_2$ -transformed for multivariable regression models only. We first assessed the potential nonlinear associations of log-transformed CAMs with measures of cardiac structure and function using separate restricted cubic splines with 3 knots. Given the absence of significant departures from linearity, multivariable general linear models were used to evaluate the associations of log-transformed VCAM-1 and ICAM-1 with cMRI derived indices of cardiac structure (LA minimum volume, LV extracellular volume fraction, LV end-diastolic volume, LV mass) and function (LA total emptying fraction, LA active emptying fraction, LA peak longitudinal strain, LV ejection fraction, LV stroke volume, LV global circumferential strain). Models were adjusted for age, sex, race or ethnicity, body mass index, systolic blood pressure, antihypertensive medication use, cigarette use (current/former smokers versus never smokers), diabetes (self-reported diagnosis, fasting glucose  $> 125$  mg/dL, or use of antidiabetic medication), estimated glomerular filtration rate by the 2009 Chronic Kidney Disease Epidemiology Collaboration equation using examination 1 creatinine, total cholesterol, and CRP (C-reactive protein). Covariates were ascertained from the examination closest to CAM measurement (examination 1 for estimated glomerular filtration rate and CRP, examination

2 for all other covariates). Sensitivity analyses adjusting for (1) LV mass on CMR at examination 1 and (2) fibrinogen and interleukin-6 at examination 1, along with all other covariates listed above, were performed to account for asymptomatic cardiovascular disease, and known biomarkers of inflammation, respectively, at baseline. We also evaluated the association of VCAM-1 and ICAM-1 with presence of myocardial scar using multivariable logistic regression models. These models used the same covariates as previously outlined. Given that AF can affect LA functional parameters, we assessed moderation of incident AF by examination 5 on the associations of VCAM-1 and ICAM-1 with LA peak longitudinal strain using an interaction term for AF.

As LA dysfunction is a potential mediator underlying the associations between CAMs and incident AF or HFpEF, we performed formal mediation analyses of LA strain on the association between VCAM-1 or ICAM-1 and AF or HFpEF using the *mediation* package in R (R Foundation for Statistical Computing, Vienna, Austria). Mediation analyses estimate the proportional association of a potential mediator (LA strain at examination 5) on the total effect of exposure (VCAM-1 or ICAM-1) and outcome (AF or HFpEF).<sup>6</sup> For mediation analyses, we excluded participants who experienced a respective end point before the examination 5 cMRI. After exclusions, linear regression models were performed to determine the independent associations between VCAM-1 or ICAM-1 (independent variables) and LA strain, and logistic regression was performed to determine the associations between LA strain (independent variable) and HFpEF or AF that occurred after examination 5 cMRI. If any of these associations were significant, mediation analyses were performed for CAMs and LA strain on the outcome variable (HFpEF or AF). Multivariable-adjusted direct and indirect effects (ie, mediation effect) were reported, with calculation of 95% CIs using bootstrapping with 1000 resamples. Statistically significant mediation was determined if the indirect effect was significantly different from 0.

Statistical analyses were performed in R version 4.0.2 (R Foundation for Statistical Computing).

## RESULTS

### Patient Characteristics

Of the 6814 MESA participants, 4510 were excluded: 4376 did not have VCAM-1 and ICAM-1 measured at examination 2, and an additional 134 were missing covariate data at examination 2. After exclusions, 2304 participants were included in the analysis. Compared with participants in the final analytic cohort, those who were excluded were older; had higher body mass index



and CRP and lower estimated glomerular filtration rate, triglycerides, and glucose; and were more likely to be treated for hypertension (Table S1). In addition, there were differences between race, smoking status, and diabetes status between groups (Table S1).

Baseline characteristics of the analytic cohort, stratified by quartile of VCAM-1 and ICAM-1, are displayed in Table 1 and Table S2, respectively. Within the quartiles of VCAM-1, baseline differences were observed in age, race or ethnicity, sex, glomerular filtration rate, total cholesterol, low-density lipoprotein, and proportions of hypertension. There were baseline differences in sex; body mass index; race or ethnicity; age; blood pressure; cholesterol; blood sugar; CRP; troponin; and rates of diabetes, hypertension, and smoking between

participants in different quartiles of log-transformed ICAM-1.

### ICAM-1 and VCAM-1 With Myocardial Structure and Function

In unadjusted analysis, participants with higher VCAM-1 had greater LA volume, along with lower LA total emptying fraction, LV ejection fraction, LV stroke volume, and LA peak longitudinal strain (Table 2). Participants with higher ICAM-1 had higher LA volume along with lower LA total emptying fraction and LA peak longitudinal strain (Table 2).

After adjustment for age, sex, race or ethnicity, body mass index, systolic blood pressure, antihypertensive

**Table 1. Clinical Characteristics by Quartile of VCAM-1 at Examination 2 (Baseline)**

	Quartile 1 (252–591 ng/mL)	Quartile 2 (>591–700 ng/mL)	Quartile 3 (>700–845 ng/mL)	Quartile 4 (>845–2640 ng/mL)	P value
Demographics					
Age, y	58.3±8.6	61.1±9.1	64.7±9.5	68.0±9.9	<0.001
Male sex, n (%)	269 (46.7)	245 (42.5)	274 (47.6)	293 (50.9)	0.043
Race or ethnicity, n (%)					
White	76 (13.2)	149 (25.9)	162 (28.1)	182 (31.6)	<0.001
Chinese	144 (25.0)	150 (26.0)	153 (26.6)	147 (25.5)	
Black	234 (40.6)	118 (20.5)	118 (20.5)	86 (14.9)	
Hispanic	122 (21.2)	159 (27.6)	143 (24.8)	161 (28.0)	
Diabetes status, n (%)					
No diabetes	396 (68.8)	394 (68.4)	379 (65.8)	380 (66.0)	0.61
Impaired fasting glucose	96 (16.7)	100 (17.4)	102 (17.7)	90 (15.6)	
Untreated diabetes	19 (3.3)	14 (2.4)	15 (2.6)	17 (3.0)	
Treated diabetes	65 (11.3)	68 (11.8)	80 (13.9)	89 (15.5)	
Body mass index, kg/m <sup>2</sup>	28.4±5.5	27.9±5.8	27.6±5.2	27.8±5.6	0.09
Hypertension, n (%)	206 (35.8)	236 (41.0)	262 (45.5)	321 (55.7)	<0.001
SBP, mmHg	120.0±19.0	122.1±20.2	125.9±21.7	128.4±20.8	<0.001
DBP, mmHg	71.2±9.8	70.8±10.1	70.5±10.1	69.7±9.5	0.079
Use of antihypertensive medication, n (%)	192 (33.3)	220 (38.2)	224 (38.9)	288 (50.0)	<0.001
Smoking status, n (%)					
Never smoker	292 (50.7)	296 (51.4)	295 (51.2)	283 (49.1)	<0.001
Former smoker	187 (32.5)	203 (35.2)	235 (40.8)	242 (42.0)	
Current smoker	97 (16.8)	77 (13.4)	46 (8.0)	51 (8.9)	
Glomerular filtration rate, mL/min per 1.73m <sup>2</sup>	84.1±14.5	81.1±14.0	77.0±14.7	72.4±17.9	<0.001
Laboratory values					
C-reactive protein, µg/mL	1.85 (0.74–4.19)	1.70 (0.77–3.79)	1.58 (0.74–3.73)	1.64 (0.70–3.81)	0.63
Total cholesterol, mg/dL	195.8±35.0	195.9±36.5	191.0±32.2	185.6±36.2	<0.001
LDL, mg/dL	117.7±30.9	117.0±33.4	113.0±30.1	109.1±31.5	<0.001
Triglycerides, mg/dL	111.0 (79.0, 161.5)	116.5 (84.0, 164.5)	116.0 (77.0, 162.0)	114.0 (83.0, 163.25)	0.28
Glucose, mg/dL	93 (86, 102)	92 (87, 102)	93 (86.8, 104)	93 (86, 104)	0.9

\*Results reported as mean (%) or median (interquartile range). DBP indicates diastolic blood pressure; LDL, low-density lipoprotein; SBP, systolic blood pressure; and VCAM-1, vascular cell adhesion molecule-1.

**Table 2. Cardiac Structure and Function at Examination 5 by Quartiles of CAM Level**

	VCAM-1				ICAM-1			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Quartile 1	Quartile 2	Quartile 3	Quartile 4
LA volume, mL (min)	25.7 (17.1 to 34.8)	24.9 (17.2 to 32.4)	27.4 (19.5 to 38.0)	27.2 (18.5 to 38.0)	23.3 (15.2 to 31.0)	26.8 (19.1 to 37.2)	27.4 (18.4 to 38.6)	28.5 (19.8 to 38.6)
LA total emptying fraction, %	57.3 (50.2 to 64.5)	58.3 (51.2 to 64.8)	55.2 (48.3 to 62.1)	55.5 (46.9 to 62.8)	59.8 (52.9 to 66.1)	56.0 (49.1 to 62.3)	55.3 (47.8 to 63.3)	54.5 (48.3 to 61.2)
LA active emptying fraction, %	42.6 (35.8 to 50.6)	43.7 (37.6 to 51.5)	41.6 (35.8 to 48.3)	43.0 (35.2 to 50.4)	45.5 (37.9 to 52.9)	42.1 (35.4 to 49.8)	41.2 (34.7 to 48.4)	42.0 (36.1 to 49.2)
LV ejection fraction, %	63.1 (58.0 to 67.5)	63.2 (58.3 to 67.7)	63.2 (58.0 to 67.5)	62.0 (56.8 to 67.1)	62.9 (58.3 to 67.8)	63.6 (58.6 to 67.6)	62.2 (57.8 to 66.6)	63.4 (57.1 to 67.6)
LV stroke volume, mL	72.9 (61.4 to 85.8)	69.6 (61.3 to 83.1)	70.2 (60.8 to 80.5)	67.7 (59.0 to 84.1)	68.3 (60.0 to 80.3)	71.1 (60.5 to 86.4)	71.9 (62.1 to 83.1)	69.0 (61.0 to 82.7)
LV extracellular volume, %	26.4 (24.5 to 28.0)	26.9 (24.6 to 29.3)	27.3 (25.7 to 29.2)	26.4 (25.5 to 28.4)	27.0 (25.4 to 28.6)	26.3 (24.4 to 28.1)	26.9 (25.3 to 28.7)	26.9 (25.1 to 28.8)
Presence of myocardial scar, n (%)	10 (3.0)	17 (5.4)	10 (3.6)	8 (3.7)	7 (2.3)	11 (3.7)	19 (6.8)	8 (3.2)
LV end-diastolic volume, mL	115 (100 to 141)	113 (95 to 137)	112 (94 to 134)	112 (93 to 138)	108 (94 to 131)	115 (97 to 141)	116 (101 to 138)	115 (94 to 135)
LV mass, g	121 (99 to 151)	112 (93 to 138)	114 (93 to 138)	117 (95 to 137)	108 (92 to 131)	119 (93 to 143)	119 (98 to 145)	119 (100 to 143)
Tissue-tracking cMRI parameters								
LA peak longitudinal strain, %	31.0 (24.6 to 40.0)	32.6 (24.7 to 40.8)	30.5 (23.7 to 37.4)	28.9 (22.0 to 38.0)	34.2 (26.9 to 43.1)	30.1 (23.9 to 37.0)	30.2 (22.4 to 40.0)	28.2 (22.1 to 35.8)
LV global circumferential strain, %	-18.0 (-19.1 to -17.3)	-18.2 (-19.0 to -17.2)	-17.6 (-19.1 to -16.5)	-17.8 (-19.0 to -16.3)	-17.9 (-18.8 to -17.1)	-18.4 (-19.3 to -17.1)	-17.8 (-18.8 to -16.2)	-18.1 (-18.7 to -16.5)

CAM indicates cell adhesion molecule; cMRI, cardiac magnetic resonance imaging; ICAM-1, intercellular cell adhesion molecule-1; LA, left atrial; LV, left ventricular; and VCAM-1, vascular cell adhesion molecule-1.

medication use, cigarette use, diabetes, estimated glomerular filtration rate, total cholesterol, and CRP, higher VCAM-1 and ICAM-1 levels were significantly associated with lower LA peak longitudinal strain (VCAM-1  $\beta$  coefficient,  $-1.10$  [95% CI,  $-2.06$  to  $-0.14$ ];  $P=0.02$ ; ICAM-1  $\beta$  coefficient,  $-1.38$  [95% CI,  $-2.29$  to  $-0.46$ ];  $P=0.003$ ) and LV GCS (VCAM-1  $\beta$  coefficient,  $0.43$  [95% CI,  $0.12$ – $0.74$ ];  $P=0.007$ ; ICAM-1  $\beta$  coefficient,  $0.34$  [95% CI,  $0.03$ – $0.65$ ];  $P=0.03$ ). Sensitivity analyses separately adjusting for LV mass at examination 1, or interleukin-6 and fibrinogen at examination 1, demonstrated consistent associations between higher VCAM-1 and ICAM-1 levels and lower LA peak longitudinal strain (Tables S3 and S4). Adjusted analysis further demonstrated that higher VCAM-1 was associated with lower LV mass ( $\beta$  coefficient,  $-2.01$  [95% CI,  $-3.53$  to  $-0.50$ ];  $P=0.009$ ), and higher ICAM-1 was associated with lower LA total emptying fraction ( $\beta$  coefficient,  $-1.03$  [95% CI,  $-1.74$  to  $-0.33$ ];  $P=0.004$ ), lower LA active emptying fraction ( $\beta$  coefficient,  $-0.85$  [95% CI,  $-1.62$  to  $-0.09$ ];  $P=0.03$ ), and higher LA minimum volume ( $\beta$  coefficient,  $1.48$  [95% CI,  $0.49$ – $2.47$ ];  $P=0.003$ ). There were no associations between VCAM-1 or ICAM-1 with the presence of interstitial myocardial fibrosis as assessed by extracellular volume fraction, LV ejection fraction, LV stroke volume, or LV end-diastolic volume (Table 3). Additionally, there were no significant associations between VCAM-1 and myocardial scar (odds ratio per doubling of VCAM-1,  $1.13$  [95% CI,  $0.98$ – $1.31$ ];

$P=0.10$ ) or ICAM-1 and myocardial scar (odds ratio per doubling of ICAM-1,  $1.10$  [95% CI,  $0.95$ – $1.26$ ];  $P=0.20$ ). While the association between VCAM-1 and LA peak longitudinal strain was stronger among those with AF by examination 5 compared with those without AF by examination 5 ( $P$  interaction= $0.02$ ), the association between ICAM-1 and LA peak longitudinal strain was consistent among those with and without AF by examination 5 ( $P$  interaction= $0.31$ ) (Figure 1).

### Mediation of LA Strain on the Association of CAMs With Clinical Outcomes

Among 2304 participants in our analytic cohort, 140 had an AF event and 33 had a HFpEF event before examination 5 cMRI and were excluded from respective mediation analyses. After examination 5 cMRI, there were 151 AF events and 26 HFpEF events. ICAM-1 was not significantly associated with AF or HFpEF after examination 5 cMRI and was therefore not used in mediation analyses. Results of mediation analyses of VCAM-1, peak LA longitudinal strain, and AF or HFpEF are shown in Figure 2.<sup>29</sup> After multivariable adjustment, VCAM-1 was significantly associated with both the potential mediator (peak LA longitudinal strain) and outcomes of interest (AF and HFpEF). LA strain was a mediator of the relationship between VCAM-1 and both AF and HFpEF. Specifically, peak longitudinal LA strain appeared to mediate 8% (95% CI, 2–30) of

**Table 3. Associations of Log-Transformed VCAM-1 and ICAM-1 at Examination 2 With Cardiac Structure and Function at Examination 5, Respectively**

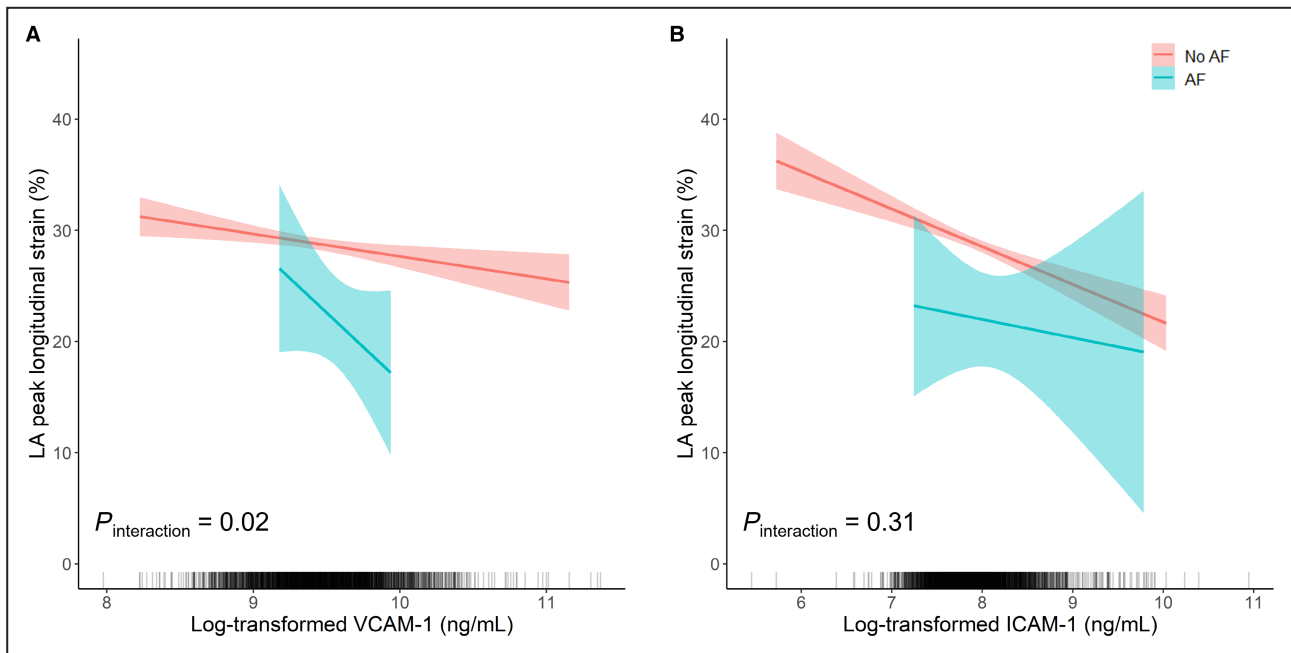
cMRI variable	Log <sub>2</sub> VCAM-1		Log <sub>2</sub> ICAM-1	
	$\beta$ Coefficient* per SD increase (95% CI)	P Value*	$\beta$ Coefficient per SD increase (95% CI)	P value*
LA function				
Peak longitudinal strain, %	$-1.10$ ( $-2.06$ to $-0.14$ )	0.02	$-1.38$ ( $-2.29$ to $-0.46$ )	0.003
LA total emptying fraction, %	$-0.67$ ( $-1.41$ to $0.07$ )	0.08	$-1.03$ ( $-1.74$ to $-0.33$ )	0.004
LA active emptying fraction, %	$-0.79$ ( $-1.60$ to $0.01$ )	0.05	$-0.85$ ( $-1.62$ to $-0.09$ )	0.03
LV function				
Ejection fraction, %	$-0.25$ ( $-0.70$ to $0.21$ )	0.29	$-0.22$ ( $-0.65$ to $0.22$ )	0.33
Global circumferential strain, %	$0.43$ ( $0.12$ to $0.74$ )	0.007	$0.34$ ( $0.03$ to $0.65$ )	0.03
Stroke volume, mL	$-0.58$ ( $-1.68$ to $0.52$ )	0.30	$-0.81$ ( $-1.86$ to $0.24$ )	0.13
LA structure				
LA minimum volume, mL	$0.72$ ( $-0.32$ to $1.76$ )	0.17	$1.48$ ( $0.49$ to $2.47$ )	0.003
LV structure				
End-diastolic volume, mL	$-0.46$ ( $-2.24$ to $1.33$ )	0.62	$-0.61$ ( $-2.32$ to $1.09$ )	0.48
Mass, g	$-2.01$ ( $-3.53$ to $-0.50$ )	0.009	$0.38$ ( $-1.07$ to $1.82$ )	0.61
Extracellular volume fraction, %	$0.15$ ( $-0.16$ to $0.45$ )	0.35	$-0.02$ ( $-0.29$ to $0.26$ )	0.90

More impaired cardiac function is indicated by greater (less negative) LV global circumferential strain and lower LA peak longitudinal strain.

cMRI indicates cardiac magnetic resonance imaging; ICAM-1, intercellular cell adhesion molecule-1; LA, left atrial; LV, left ventricular; and VCAM-1, vascular cell adhesion molecule-1.

\*Adjusted for age, sex, race or ethnicity, body mass index, systolic blood pressure, antihypertensive medication use, cigarette use, diabetes, glomerular filtration rate, total cholesterol, and C-reactive protein.





**Figure 1. Associations of VCAM-1 and ICAM-1 with LA peak longitudinal strain by AF status during follow-up.**

**A**, Linear model displaying the associations of log-transformed VCAM-1 and LA peak longitudinal strain. The rug plot shows the distribution of log-transformed VCAM-1. **B**, Linear model displaying the associations of log-transformed ICAM-1 and LA peak longitudinal strain. The rug plot shows the distribution of log-transformed ICAM-1. AF indicates atrial fibrillation; ICAM-1, intercellular cell adhesion molecule-1; LA, left atrial; and VCAM-1, vascular cell adhesion molecule-1.

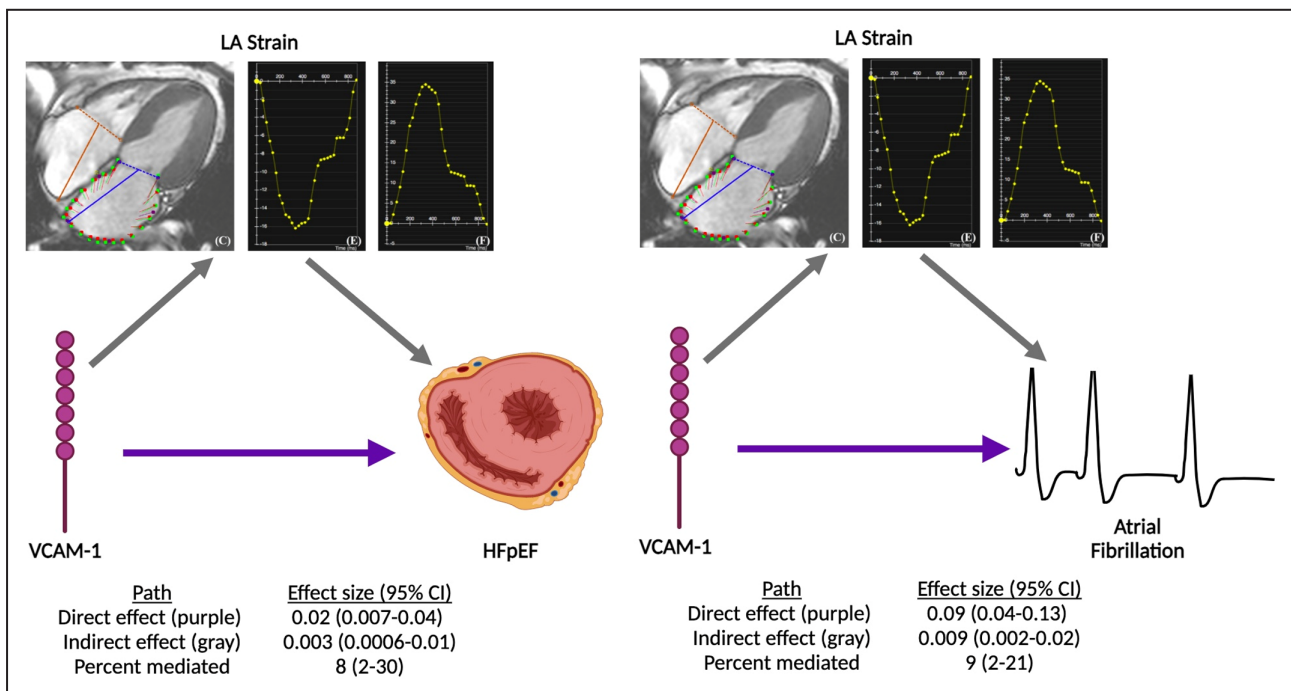
the relationship between VCAM-1 and HFpEF and 9% (95% CI, 2–21) of the relationship between VCAM-1 and AF (Figure 2).

## DISCUSSION

In this multiethnic cohort of community-dwelling adults, we evaluated associations of circulating VCAM-1 and ICAM-1 with indices of cardiac structure and function on cMRI. We demonstrated that, after adjustment for clinical and laboratory covariates, higher VCAM-1 and ICAM-1 were associated with lower LA peak longitudinal strain. These results were consistent in sensitivity analyses adjusting for baseline cardiac structure and biomarkers of inflammation. In addition, higher ICAM-1 was associated with lower LA total emptying fraction, LA active emptying fraction, and higher LA minimum volume. Mediation analysis further demonstrated that LA peak longitudinal strain appeared to be a mediator of the relationship between VCAM-1 and both AF and HFpEF. Notably, neither VCAM-1 nor ICAM-1 were associated with myocardial scar or interstitial fibrosis on cMRI. Taken together, these findings suggest that VCAM-1 and ICAM-1 may promote HFpEF and AF risk through impaired LA reservoir function and LV systolic function. Indeed, the current analysis provides mechanistic data regarding the pathways connecting initiation of AF and HFpEF with LA and LV dysfunction.<sup>30</sup>

Accumulating evidence suggests that specific markers of endothelial activation and subsequent CAM up-regulation are implicated in the pathogenesis of HFpEF and AF.<sup>6,7,9,10</sup> Specifically, VCAM-1 and ICAM-1 have been shown to participate in the rolling, adhesion, and transmigration of infiltrating leukocytes across the endothelial cell barrier. This transmigration promotes vascular and myocardial interstitial collagen deposition, decreased nitric oxide bioavailability, and increased production of reactive oxidative species.<sup>11</sup> These intersecting processes may ultimately lead to microvascular dysfunction and subsequently play an important role in the pathogenesis of HFpEF and AF in at-risk populations. Indeed, recent studies from both MESA and external cohorts have demonstrated associations of VCAM-1 with incident HFpEF and AF, further emphasizing the role of systemic inflammation in these heterogeneous syndromes.<sup>9,10,31,32</sup> Despite current knowledge of systemic inflammation, and resultant endothelial activation in pathogenesis of HFpEF and AF, the relationships between CAMs and myocardial structure and function have been less clear. Through evaluation of sensitive measures on cMRI in MESA, the current study further describes that the pathways in which CAMs promote HFpEF and AF risk may act through decreased LA reservoir function and LV systolic function.

In the current analysis, increased levels of VCAM-1 and ICAM-1 were both independently associated with decreased LA peak longitudinal strain. Furthermore,



**Figure 2. Mediation analysis of VCAM-1, peak longitudinal LA strain, and clinical outcomes (AF or HFpEF).** Mediation analysis demonstrates that lower LA peak longitudinal strain mediated 8% (95% CI, 2–30) of the relationship between VCAM-1 and HFpEF and 9% (95% CI, 2–21) of the relationship between VCAM-1 and AF. Portions of this figure were reproduced from Qu et al<sup>29</sup> under the terms of and conditions of the Creative Commons Attribution (CC-BY) license (<https://creativecommons.org/licenses/by/2.0/>). The composite figure was created using BioRender.com. AF indicates atrial fibrillation; HFpEF, heart failure with preserved ejection fraction; ICAM-1, intercellular cell adhesion molecule-1; LA, left atrial; and VCAM-1, vascular cell adhesion molecule-1.

higher ICAM-1 was associated with lower LA total emptying fraction and higher LA minimum volume. Prior investigations demonstrated that in both AF and HFpEF, reactive collagen fibers deposit in the LA myocardial wall and result in significant fibrosis and remodeling.<sup>30,33,34</sup> The resulting increases in LA stiffness are reflected in decreased LA peak longitudinal strain, lower LA emptying fraction, and higher LA minimum volume. Given the independent associations of higher VCAM-1 and ICAM-1 with lower LA peak longitudinal strain and higher ICAM-1 with lower LA total and active emptying fractions, our findings suggest that endothelial activation is strongly associated with LA myocardial dysfunction. Of note, levels of VCAM-1 and ICAM-1 did not correlate with interstitial fibrosis in the current analysis. While the timing of CAM assays may have impacted the measured values, we believe that this is due to a unique impact of VCAM-1 and ICAM-1 on the LA substrate, as demonstrated by the association between higher levels of VCAM-1 and ICAM-1 and impaired LA peak longitudinal strain. Nonetheless, it is also possible that the difference in timing between circulating VCAM-1 and ICAM-1 measurement and cMRI may have masked potential associations between CAMs and ECV. In addition, through mediation

analysis, we demonstrated potential direct and indirect relationships between VCAM-1, abnormal cardiac mechanics, and incident HFpEF or AF. Indeed, the associations between VCAM-1 with both incident HFpEF and AF were partly mediated by LA peak longitudinal strain. As such, our findings provide evidence for the role of impaired LA function as a mediator in the relationship between VCAM-1 and incident HFpEF or AF in at-risk populations. Furthermore, based on differential integrin counter-receptors on leukocytes that bind VCAM-1 and ICAM-1, these results could potentially suggest that particular inflammatory cells that are more specific to VCAM-1 may be involved in the processes that impact peak LA longitudinal strain.<sup>35,36</sup> Further investigations are required to understand immune cell subtypes that are associated with LA dysfunction.

VCAM-1 and ICAM-1 appear to capture pathways of inflammation that are independent of traditional inflammatory biomarkers. In the current analyses, associations between CAMs and LA and LV dysfunction persisted after adjustment for variables including CRP. These findings demonstrate that the pathways of inflammation captured through VCAM-1 and ICAM-1 are likely distinct from those of CRP and uniquely associated with myocardial dysfunction. These results speak

to the complex inflammatory substrate that underlie both AF and HFpEF and encourage further research into the pathophysiologic processes that can contribute to both conditions. In addition, preclinical studies to assess the impact of VCAM-1 or ICAM-1 modulation on LA function would be of particular interest.

Our findings additionally suggest that CAMs are associated with LV systolic dysfunction, but such associations may not be driven by LV interstitial fibrosis or LV scar. In the current study, higher levels of VCAM-1 and ICAM-1 were independently associated with lower LV GCS, a sensitive measure of LV circumferential deformation.<sup>37</sup> While there were significant associations between VCAM-1 and ICAM-1 and lower LV GCS, there were no significant associations between CAMs and the presence of myocardial scar or interstitial fibrosis as quantified by ECV. Overarching hypotheses surrounding the role of endothelial activation and CAMs in HFpEF have suggested that upregulation of CAMs on endothelial surfaces of the heart leads to leukocyte transmigration, collagen formation, and, ultimately, LV interstitial myocardial fibrosis.<sup>32,38</sup> By leveraging cMRI data in MESA, we demonstrate a lack of associations between CAMs and LV scar or LV interstitial fibrosis. In concert with the overall findings of the study, these data suggest that VCAM-1 and ICAM-1 may promote AF or HFpEF risk through LA and LV systolic dysfunction through pathways independent of LV interstitial fibrosis.

## Limitations

The results from this study should be viewed in the appropriate context. Indeed, several participants were excluded from the current analysis because of lack of VCAM-1 or ICAM-1 measurement. Participants excluded from this analysis represented a somewhat higher-risk group with increased age, comorbidities, and cardiovascular risk factors. As a result, their exclusion potentially biases our results. VCAM-1 and ICAM-1 measurements, along with indices of cardiac structure and function, were obtained only once at examinations 2 and 5, respectively. Serial measurements would have better accounted for fluctuations in endothelial activity and myocardial function over time. Additionally, it remains uncertain if serum VCAM-1 and ICAM-1 levels are reflective of activity at the level of the coronary microvasculature. While ICAM-1 was associated with LA dysfunction on cMRI, it was not associated with AF or HFpEF by examination 5. It is possible that our power to detect associations between ICAM-1 and clinical outcomes was limited given the sample size of our study. Although we adjusted for various demographic, clinical, and laboratory covariates, our findings remain subject to potential residual confounding or additional mediating variables. Given the differences

in CAM levels by race or ethnicity,<sup>8</sup> future investigations in larger populations are required to understand effect modification by race or ethnicity on associations of CAMs with cardiac function. Furthermore, the authors acknowledge that identification of AF depends, at least partly, on access to health care, that the mechanism of categorizing the presence of AF via ECGs and diagnosis codes may underestimate the true prevalence of AF, and that multiple testing may have increased the risk of type I error. Despite independent physician adjudication, it is possible that some “probable” heart failure events were mischaracterized, thereby impacting results. Finally, LA fibrosis was not able to be quantified on MESA cMRI. Mediation analyses assume no unmeasured confounding, but we cannot rule out the possibility of residual confounding in our models. Although CAMs (exposures) were measured before measurement of the mediator (LA strain), we cannot rule out the possibility of reverse causation in mediation models.

## CONCLUSIONS

In a multiethnic community-based cohort, higher levels of VCAM-1 and ICAM-1 were independently associated with lower indices of LA function and LV systolic function, as measured by LA peak longitudinal strain and LV GCS. Lower LA peak longitudinal strain appeared to significantly mediate the associations of VCAM-1 with incident HFpEF and AF, further suggesting that increased VCAM-1 may drive incident HFpEF and AF through impaired myocardial function. Neither VCAM-1 nor ICAM-1 were associated with myocardial scar or interstitial fibrosis on cMRI. In aggregate, these findings suggest that VCAM-1 and ICAM-1 may promote the risk of HFpEF and AF through associations with adverse LA and LV function but not through LV interstitial fibrosis. Further investigations are required to understand the molecular and cellular effects of circulating VCAM-1 and ICAM-1 that may drive the associations with LA and LV dysfunction.

## ARTICLE INFORMATION

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### Affiliations

Northwestern University Feinberg School of Medicine, Chicago, IL (D.T.M.) and Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL (G.P., S.J.S., R.B.P.); Division of Cardiology, Department of Medicine, Johns Hopkins University, Baltimore, MD (J.A.L.); Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN (S.J.B., N.B.L.); Division of Preventive Medicine, Department of Family Medicine, University of California, La Jolla, CA (M.A.A.); and Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL (S.J.S., R.B.P.).

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### Supplemental Material

Data S1

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