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FULL RESEARCH PAPER
Aging

Association of interleukin-6 and interleukin-18 with cardiovascular disease in older adults: Atherosclerosis Risk in Communities study

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Aims Interleukin-6 (IL-6) and interleukin-18 (IL-18), important cytokines implicated in atherosclerosis and inflammaging, were assessed for associations with global cardiovascular disease (CVD), atrial fibrillation (AF), and death in older adults.

Methods and results Participants from Atherosclerosis Risk in Communities study Visit 5 (mean age 75.4 ± 5.1 years) with IL-6 and IL-18 measurements were included ($n = 5672$). Cox regression models were used to assess associations of IL-6 and IL-18 with coronary heart disease (CHD), ischaemic stroke, heart failure (HF) hospitalization, global CVD (composite of CHD, stroke, and HF), AF, and all-cause death. Over a median follow-up of 7.2 years, there were 1235 global CVD events, 530 AF events, and 1173 deaths. Higher IL-6 [hazard ratio (HR) 1.57, 95% confidence interval (CI) 1.44–1.72 per log unit increase] and IL-18 (HR 1.13, 95% CI 1.01–1.26) were significantly associated with global CVD after adjustment for cardiovascular risk factors. Association between IL-6 and global CVD remained significant after further adjustment for high-sensitivity C-reactive protein (hs-CRP), *N*-terminal pro–B-type natriuretic peptide (NT-proBNP), and high-sensitivity troponin T (hs-TnT) but was no longer significant for IL-18 after further adjustments. Interleukin-6 was also associated with increased risk for CHD, HF, and AF after adjustment for covariates. Both IL-6 and IL-18 were associated with increased risk for all-cause death independent of cardiovascular risk factors and other biomarkers.

Conclusion Among older adults, both IL-6 and IL-18 were associated with global CVD and death. The association between IL-6 with CVD appears to be more robust and was independent of hs-CRP, NT-proBNP, and hs-TnT.

Lay summary In older adults in the Atherosclerosis Risk in Communities study (average age 75 years), higher levels of interleukin-6 and interleukin-18, two proteins implicated in atherosclerosis and increased inflammation that occurs with ageing, significantly increased risk for global cardiovascular disease (including coronary heart disease, stroke, and heart failure) during the next ~7 years; interleukin-6 also increased risk for global cardiovascular disease, coronary heart disease, heart failure, and atrial fibrillation even after adjustment for other biomarkers of inflammation and subclinical myocardial injury, and both interleukin-6 and interleukin-18 were associated with increased risk for all-cause death independent of cardiovascular risk factors and other biomarkers.

- In older adults, higher levels of interleukin-6 and interleukin-18 were both associated with increased risk for global cardiovascular disease (including coronary heart disease, stroke, and heart failure) and death.
- The association between interleukin-6 and global cardiovascular disease appeared to be stronger than that for interleukin-18 and remained significant after adjustment for other biomarkers of inflammation and subclinical myocardial injury.

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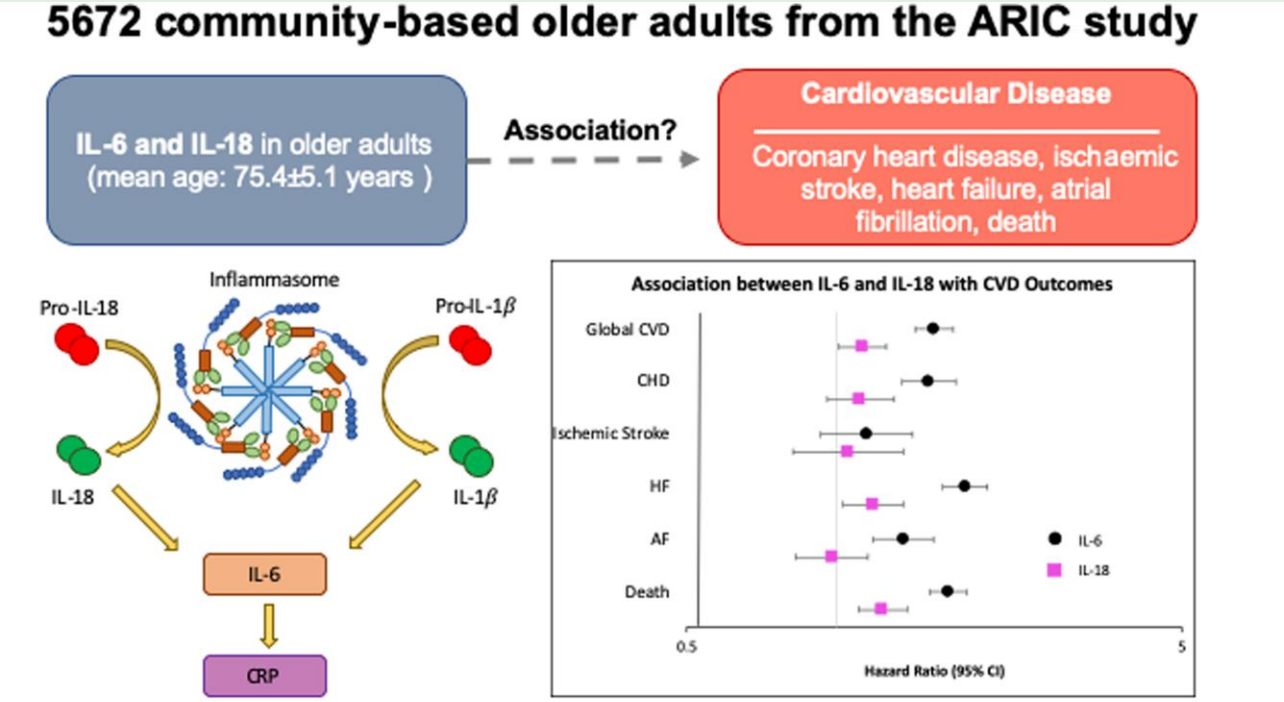
Graphical Abstract



Among older adults in the Atherosclerosis Risk in Communities study, both interleukin-6 and interleukin-18 were associated with global cardiovascular disease (coronary heart disease, ischaemic stroke, and heart failure hospitalization) and death. The association of interleukin-18 with cardiovascular disease appears to be mediated by interleukin-6. *Abbreviations:* AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; CHD, coronary heart disease; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; HF, heart failure; HR, hazard ratio; IL-6, interleukin-6; IL-18, interleukin-18.

Keywords Cardiovascular disease • Inflammation • Ageing • Interleukin-6 • Interleukin-18

Introduction

Inflammation is increasingly recognized as a risk factor for cardiovascular disease (CVD).[1] Inflammasomes are intracellular sensors of danger-associated molecular patterns that activate interleukin-1β (IL-1β) and interleukin-18 (IL-18), two potent inflammatory cytokines.[2] The nucleotide-binding oligomerization domain–like receptor family pyrin domain containing 3 (NLRP3) inflammasome senses primarily sterile danger signals and may contribute to the pathogenesis of a variety of CVDs.[3] In the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS), targeting IL-1β with the monoclonal antibody canakinumab reduced the risk of atherosclerotic cardiovascular events and, in a secondary analysis, hospitalization for heart failure (HF), among secondary prevention patients with elevated high-sensitivity C-reactive protein (hs-CRP).[4] Interleukin-1β induces the expression of interleukin-6 (IL-6), an important mediator of both local and systemic inflammation.[5,6] Mendelian randomization studies have suggested that IL-6 receptor (IL-6R)–mediated pathways have a causal relationship with coronary heart disease (CHD).[7,8] In contrast, methotrexate did not lower IL-1β or IL-6 levels and failed to reduce the risk for adverse cardiovascular events in stable coronary artery disease patients in the Cardiovascular Inflammation Reduction Trial (CIRT).[9]

Elevation in IL-18, another inflammatory cytokine activated by the NLRP3 inflammasome, has further been shown to be related to atherosclerotic plaque progression and vulnerability as well as increased risk for atherosclerotic CVD (ASCVD) events.[10–12] Interleukin-1β has been found to enhance expression of IL-18 in mononuclear phagocytes and expression of IL-18 receptor (IL-18R) in endothelial, smooth muscle, and monocytic cells of atheromas.[13] Conversely, IL-18 has been found to increase production of IL-1β via CD14+ cell types.[14]

Among older adults, inflammation has been implicated in the progression of chronic diseases and frailty, a process known as inflammaging. This population has increased risk for not only ASCVD but also other cardiac diseases including HF and atrial fibrillation (AF). Studies of the associations of IL-6 and IL-18 with HF and AF, especially in older populations, are limited.[15,16] Similarly, data are lacking on how these cytokines are associated with subclinical CVD, which might improve understanding of how addressing heightened inflammation can limit the progression to clinical disease. Examination of IL-6 and IL-18 in concert will improve understanding of potential differences in associations with CVD, giving insight into their prospective utility as risk markers and therapeutic targets. Indeed, IL-6 blockers have received marketing approval for a variety of inflammatory conditions, and several small-molecule NLRP3 inflammasome inhibitors are in clinical development. In our analysis from the Atherosclerosis Risk in Communities (ARIC) study, we assessed IL-6 and IL-18 with respect to their associations with risk for CVD and mortality among a population of older, community-dwelling adults. As a comparison, we evaluated associations

between hs-CRP, a well-established biomarker for inflammation, and outcome events in this study population. We further assessed associations of these cytokines with subclinical myocardial injury as reflected by cardiac biomarkers [N-terminal pro–B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-TnT)].

Methods

Study population

The Atherosclerosis Risk in Communities study is a prospective population study of CVD incidence in adults aged 45–64 years when recruited from four US communities in 1987–1989 (Visit 1).[17] The study protocol was approved by the institutional review boards of all participating centres, and all participants provided written informed consent. Visit 5 (2011–2013) was the index visit for this study. Of the 6538 participants who attended Visit 5, we excluded those missing IL-6 or IL-18 measurements and, because of small numbers, participants with race other than Black or White or with Black race from the Minneapolis or Washington field centres. After exclusions, a total of 5672 individuals were included in our primary analysis (see Supplementary material online, *Figure S1*).

Quantification of biomarkers

Interleukin-6 and IL-18 measurements were performed on EDTA plasma collected in 2011–2013 at Visit 5 (stored at −70°C), using high-sensitivity enzyme-linked immunosorbent assays (ELISAs) for human IL-6 and IL-18 (R&D Systems, Minneapolis, MN, USA). The interleukins were measured at the same time. The interassay coefficient of variations for the IL-6 and IL-18 ELISAs were 10.9% and 11.7%, respectively. The hs-CRP levels were measured by the immunoturbidimetric CRP-Latex (II) high-sensitivity assay (Denka Seiken, Tokyo, Japan) using a Hitachi 911 analyser (Roche Diagnostics, Indianapolis, IN, USA). N-terminal pro–B-type natriuretic peptide was measured using an electrochemiluminescent immunoassay on an automated Cobas e411 analyser (Roche Diagnostics);[18] the interassay coefficient of variance was 7.4%.[19] High-sensitivity troponin T was measured in EDTA plasma (collected at Visit 5; stored at −70°C) using a highly sensitive assay (Elecsys Troponin T Gen 5 STAT, Roche Diagnostics); the interassay coefficient of variance was 6.4%.[19,20]

Covariates

Sex, race, and age were self-reported. Height and weight were measured by trained personnel and used to calculate body mass index (BMI). Systolic blood pressure and diastolic blood pressure were measured with an automatic sphygmomanometer at Visit 5 by a certified trained technician using an appropriately sized cuff.[19] An enzymatic assay was used to quantify total cholesterol and high-density lipoprotein cholesterol (HDL-C).[21] Diabetes was defined as fasting serum glucose level ≥126 mg/dL or non-fasting serum glucose level ≥200 mg/dL, self-reported diabetes diagnosed by a physician, or use of hypoglycaemic medications. Estimated glomerular filtration rate (eGFR) was calculated based on the creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation.[22] Reduced kidney function was defined as eGFR <60 mL/min/1.73 m^2. Prevalent CHD and stroke were defined as self-reported myocardial infarction or stroke before Visit 1 or ARIC-adjudicated myocardial infarction or stroke, silent myocardial infarction identified by ECG changes, or coronary revascularization between Visits 1 and 5.[23] Prevalent HF was determined by diagnosis code (International Classification of Diseases, Ninth Revision, code 428) or self-reported HF prior to 2005 or by adjudication by an expert panel from 2005 to Visit 5.[24]

Outcomes

Outcome events in our study included incident CHD, ischaemic stroke, HF, global CVD, AF, and all-cause death that occurred after Visit 5. Outcome events were adjudicated by an expert committee. Coronary heart disease included fatal CHD, definite or probable myocardial infarction, silent myocardial infarction as determined by electrocardiography, and coronary revascularization.[25] Ischaemic stroke was defined as definite or probable hospitalized embolic or thrombotic stroke.[26] Heart failure was defined as definite or probable acute decompensated HF based on medical chart review of signs and symptoms, elevation of natriuretic peptides, cardiac function, and HF-specific therapies.[27] Heart failure events were further defined as HF with reduced ejection fraction (HFrEF) for documented LVEF <50% or HF with preserved ejection fraction (HFpEF) for LVEF ≥50%. Global CVD was defined as the composite of CHD, ischaemic stroke, and HF events.[20] Atrial fibrillation events were identified from hospital discharge diagnoses and death certificates.[28] Deaths were ascertained by diagnostic codes from hospital discharge records and from death certificates. The cut-off date for administrative censoring for individuals without events was 31 December 2019, except for participants from the Jackson Field Center, for whom the administrative censoring date was 31 December 2017, because of lack of access to records from 2018 and 2019.

Statistical analysis

Baseline characteristics were tabulated by tertiles of IL-6 and IL-18, with continuous variables expressed as mean ± SD or median (25th percentile, 75th percentile), and categorical variables as percentages. *P*-value for trend was calculated by sum of ranks trend test across ordered groups. Spearman's correlation was assessed among IL-6, IL-18, and hs-CRP. Interleukin-6 and IL-18 were modelled continuously (log-transformed) and categorically (tertiles). Cox regression models were used to evaluate associations between IL-6 or IL-18 and CVD events. Hazard ratios (HRs) were expressed per log unit increase. Model 1 adjusted for age, sex, and race. Model 2 adjusted for model 1 plus systolic blood pressure, antihypertensive medication use, diabetes, total cholesterol, HDL-C, lipid-lowering medication use, BMI, eGFR, current smoking, and prevalent CVD. Model 3 adjusted for model 2 plus either IL-18 if IL-6 was the exposure variable or IL-6 if IL-18 was the exposure variable. Model 4 adjusted for model 2 plus hs-CRP. Model 5 adjusted for model 4 plus NT-proBNP and hs-TnT. For all non-fatal outcomes, we performed competing risk analysis for death using the Fine and Gray approach.[29] To evaluate for any differences by subgroups, we further conducted stratified analysis by sex, race, diabetes status, hypertension status, renal function (eGFR ≥60 mL/min/1.73 m^2 vs. <60 mL/min/1.73 m^2), hs-CRP (≥2 mg/L vs. <2 mg/L), and prevalent CVD status. As a comparison, we further included analyses assessing associations of hs-CRP with outcome events.

To assess associations of IL-6 and IL-18 with subclinical disease, we further excluded patients with prevalent CVD at Visit 5 ($n = 4066$). Linear regression models were used to evaluate associations between IL-6 or IL-18 and cardiac biomarker levels. Adjustment models 1 through 4 similar to the Cox regression analysis were used, though the prevalent CVD covariate was not included. Stata version 16.1 (StataCorp, College Station, TX, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) were used for the statistical analyses.

Results

Among the included study participants, the mean ± SD age was 75.4 ± 5.1 years, 58.0% were women, and 22.2% were Black. The median (25th percentile and 75th percentile) IL-6 level was 3.0 (2.1, 4.7) pg/mL, and the median IL-18 level was 188.1 (137.9, 262.7) pg/mL. Across IL-6 tertiles, participants with higher levels were older, more likely to be Black or male, and had higher hs-CRP, BMI, systolic blood pressure, pulse pressure, heart rate, fasting glucose, and prevalence of current smoking, CVD at baseline, diabetes, hypertension, antihypertensive medication use, and cholesterol-lowering medication use but lower total cholesterol, HDL-C, and eGFR. For IL-18, participants with higher levels were more likely to be White or male and had higher hs-CRP, BMI, heart rate, fasting glucose, and rates of prevalent CHD, prevalent HF, diabetes, and antihypertensive medication use but lower total cholesterol, HDL-C, and eGFR (*Table 1*). Spearman's R was 0.19 between IL-6 and IL-18, 0.45 between IL-6 and hs-CRP, and 0.14 between IL-18 and hs-CRP.

Association between interleukin-6 and cardiovascular disease outcomes

Over a median follow-up period of 7.2 years, there were 638 CHD events, 232 ischaemic strokes, 785 HF hospitalizations, 1235 global

Table 1 Baseline characteristics across interleukin-6 and interleukin-18 tertiles at Atherosclerosis Risk in Communities Visit 5

Risk factors	Overall ($N = 5672$)	IL-6 (pg/mL) 1st tertile (0.014–2.349, $n = 1892$)	2nd tertile (2.351–3.947, $n = 1891$)	3rd tertile (3.949–75.000, $n = 1889$)	*P* trend	IL-18 (pg/mL) 1st tertile (12.5–154.4, $n = 1894$)	2nd tertile (154.5–232.0, $n = 1890$)	3rd tertile (232.1–2347.1, $n = 1888$)	*P* trend
Age, years	75.4 ± 5.1	74.6 ± 4.8	75.5 ± 5.1	76.2 ± 5.3	<0.001	75.3 ± 5.1	75.4 ± 5.1	75.6 ± 5.2	0.108
Black, %	22.2	19.4	21.9	25.4	<0.001	31.5	19.6	15.5	<0.001
Female, %	58.0	61.0	57.9	55.1	<0.001	67.5	57.1	49.4	<0.001
Prevalent CHD, %	15.7	11.1	15.8	20.2	<0.001	13.4	17.3	16.3	0.015
Prevalent ischaemic stroke, %	3.7	2.8	2.5	5.7	<0.001	3.2	3.9	4.0	0.192
Prevalent HF hospitalization, %	13.6	6.9	11.8	22.0	<0.001	12.0	13.4	15.3	0.004
Prevalent global CVD, %	28.3	19.5	27.4	38.1	<0.001	25.9	29.2	29.9	0.007
BMI, kg/m^2	28.7 ± 5.7	26.7 ± 4.3	29.1 ± 5.3	30.4 ± 6.5	<0.001	28.3 ± 5.7	28.7 ± 5.7	29.2 ± 5.7	<0.001
SBP, mmHg	130.3 ± 18.2	129.4 ± 17.3	130.7 ± 18.4	130.7 ± 18.9	0.049	130.3 ± 18.1	130.3 ± 18.6	130.2 ± 18.0	0.544
DBP, mmHg	66.3 ± 10.8	66.5 ± 10.6	66.4 ± 10.3	65.9 ± 11.4	0.107	66.5 ± 10.6	66.2 ± 10.8	66.1 ± 10.8	0.149
Pulse pressure, mmHg	64.0 ± 14.7	62.9 ± 14.2	64.3 ± 15.1	64.8 ± 14.8	<0.001	63.7 ± 14.7	64.1 ± 15.0	64.2 ± 14.4	0.433
Heart rate, b.p.m.	65.1 ± 10.9	64.0 ± 10.2	64.8 ± 10.9	66.5 ± 11.5	<0.001	64.5 ± 10.7	65.1 ± 11.0	65.7 ± 10.9	0.002
Hypertension, %	74.3	66.3	75.5	81.3	<0.001	73.5	74.5	75.0	0.284
Antihypertensive medication use, %	75.1	65.4	77.0	82.9	<0.001	73.2	74.5	77.7	0.001
Diabetes, %	32.3	24.6	34.3	37.9	<0.001	29.2	31.4	36.2	<0.001
Current smoking, %	5.9	4.8	5.9	7.0	0.003	5.6	6.7	5.4	0.801
Total cholesterol, mg/dL	181.5 ± 42.0	188.2 ± 40.5	181.0 ± 41.8	175.2 ± 42.5	<0.001	185.2 ± 41.7	181.0 ± 41.5	178.3 ± 42.4	<0.001
HDL-C, mg/dL	52.2 ± 13.9	56.1 ± 14.5	51.3 ± 13.4	49.1 ± 12.9	<0.001	56.2 ± 14.9	51.7 ± 12.7	48.6 ± 13.1	<0.001
Fasting glucose, mg/dL	113.3 ± 27.8	109.3 ± 22.8	115.2 ± 29.8	115.4 ± 29.8	<0.001	110.5 ± 25.7	112.9 ± 25.9	116.6 ± 31.2	<0.001
hs-CRP, mg/L	2.0 (1.0, 4.2)	1.1 (0.6, 2.0)	2.0 (1.1, 3.7)	3.9 (1.9, 7.8)	<0.001	1.7 (0.8, 3.5)	2.0 (0.9, 4.1)	2.4 (1.2, 4.9)	<0.001
Lipid-lowering medication use, %	56.5	53.8	58.1	57.5	0.021	57.4	56.5	55.6	0.268
eGFR, mL/min/1.73m^2	69.7 ± 17.2	73.3 ± 14.9	69.6 ± 16.9	66.1 ± 19.0	<0.001	72.1 ± 16.4	69.9 ± 17.0	67.0 ± 17.9	<0.001

Data presented as mean ± SD, median (25th percentile, 75th percentile), or per cent; *P* trend was calculated by sum of ranks trend test across ordered groups.
Abbreviations: BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; IL-18, interleukin-18; SBP, systolic blood pressure.

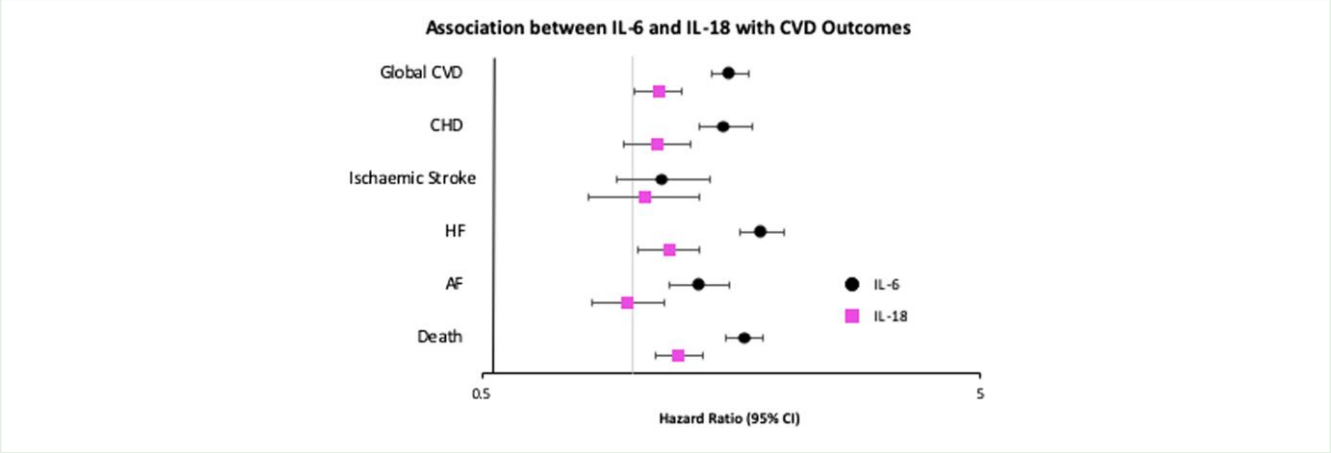


Figure 1 Association of interleukin-6 and interleukin-18 with risk for global cardiovascular disease, atrial fibrillation, and total death in older adults. Cox regression analysis adjusted for age, sex, race, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, antihypertensive medication use, diabetes, current smoking, lipid-lowering medication use, prevalent global cardiovascular disease, body mass index, and estimated glomerular filtration rate. Abbreviations: AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HF, heart failure; IL-6, interleukin-6; IL-18, interleukin-18.

CVD events, 530 AF events, and 1173 deaths. Risk for global CVD increased significantly with higher IL-6 after adjustment for demographic and cardiovascular risk factors (*Figure 1*). The association persisted after additional adjustments for IL-18, for hs-CRP, and for hs-CRP plus NT-proBNP and hs-TnT (*Table 2*). Furthermore, higher IL-6 level was significantly associated with increased risks for CHD, HF outcomes, and death in all adjustment models. Higher IL-6 was also significantly associated with AF after adjusting for models 1 through 4 covariates, but the association was attenuated with adjustments for NT-proBNP and hs-TnT. Interleukin-6 was not significantly associated with ischaemic stroke beyond model 1 adjustment for demographic covariates (*Table 2*).

Similar associations between IL-6 and global CVD as well as the individual CVD components were observed in sensitivity analyses accounting for competing risk of non-event death as well as when excluding participants with prevalent CHD, stroke, and HF at baseline (see Supplementary material online, *Table S1*). In subgroup analysis, we observed significant interaction by age for the association of IL-6 with HF as well as with global CVD. We also found significant interaction by hs-CRP level for the association between IL-6 and ischaemic stroke and by renal function for the association between IL-6 and all-cause death. No other significant interactions were observed by subgroups including by prevalent CVD (see Supplementary material online, *Figure S2*). In analysis using IL-6 as a categorical variable, the highest tertile was associated with increased risk for global CVD as well as for CHD, HF, and all-cause death compared with the lowest tertile in all adjustment models (*Figure 2A* and Supplementary material online, *Table S2*).

In exploratory analysis, we evaluated the associations of NT-proBNP (log-transformed) and hs-TnT (log-transformed) with CVD outcomes stratified by IL-6 levels less than or greater than or equal to the median (3 pg/mL). We found that IL-6 significantly modified the association of NT-proBNP and hs-TnT with CVD outcomes. The associations of NT-proBNP were more robust among individuals with lower IL-6 compared with higher IL-6 levels for global CVD, HF, AF, and death (see Supplementary material online, *Table S3*). Similarly, the associations of hs-TnT were more robust among individuals with lower IL-6 compared with higher IL-6 levels for HF and ischaemic stroke (see Supplementary material online, *Table S4*).

Association between interleukin-18 and cardiovascular disease outcomes

We observed a significant positive association between IL-18 and global CVD after adjustment for demographic and cardiovascular risk factors. The association was attenuated after adjustment for IL-6, hs-CRP, NT-proBNP, and hs-TnT. Interleukin-18 was also significantly associated with HF hospitalization after adjustment for demographic and cardiovascular risk factors, although as with global CVD, the association was attenuated after further adjustment for hs-CRP and IL-6. The association between IL-18 and HFpEF persisted after adjustments for IL-6, hs-CRP, NT-proBNP, and hs-TnT, whereas the association with HFrEF was no longer significant beyond the basic adjustment model for demographic covariates. Interleukin-18 was not associated with CHD beyond model 1 (demographic factors) adjustment and was not significantly associated with ischaemic stroke or AF. However, IL-18 was significantly associated with all-cause death in all adjustment models (*Table 2*). Findings were similar for competing risk analyses (see Supplementary material online, *Table S5*). Significant interaction by diabetes status was noted for the association between IL-18 and global CVD as well as by prevalent CVD status for death. No other interactions were noted (see Supplementary material online, *Figure S3*).

When IL-18 was assessed as tertiles, the highest tertile was significantly associated with global CVD, CHD, ischaemic stroke, HF hospitalization, and death after model 1 adjustment. However, after further adjustments for cardiovascular risk factors, significance persisted only between IL-18 and death (*Figure 2B*). The association with death persisted after further adjustment for hs-CRP as well as NT-proBNP and hs-TnT but was attenuated after adjustment for IL-6 (see Supplementary material online, *Table S6*).

Association between high-sensitivity C-reactive protein and cardiovascular disease outcomes

By comparison, hs-CRP was significantly associated with global CVD, CHD, HF, and death in older adults after adjustment for demographic and cardiovascular risk factors. The associations with global CVD, CHD, and HF were attenuated after additional adjustment for IL-6

Table 2 Association of log-transformed interleukin-6, interleukin-18 and high-sensitivity C-reactive protein with incident cardiovascular disease events and death after Visit 5

Event	IL-6		IL-18		hs-CRP	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
CHD (638/5672, 11.25%)						
Model 1	1.81 (1.63–2.02)	<0.001	1.29 (1.11–1.50)	0.001	1.30 (1.21–1.40)	<0.001
Model 2	1.53 (1.36–1.74)	<0.001	1.12 (0.96–1.31)	0.158	1.20 (1.11–1.29)	<0.001
Model 3[a]	1.53 (1.35–1.73)	<0.001	1.05 (0.90–1.24)	0.519	1.08 (1.00–1.18)	0.061
Model 4[a]	1.44 (1.25–1.66)	<0.001	1.08 (0.92–1.26)	0.363	1.20 (1.11–1.29)	<0.001
Model 5	1.24 (1.07–1.44)	0.003	1.08 (0.92–1.27)	0.331	—	—
Ischaemic stroke (232/5672, 4.09%)						
Model 1	1.36 (1.12–1.65)	0.002	1.26 (0.98–1.62)	0.067	1.17 (1.04–1.32)	0.011
Model 2	1.15 (0.93–1.43)	0.191	1.06 (0.82–1.37)	0.645	1.04 (0.92–1.19)	0.512
Model 3[a]	1.15 (0.93–1.42)	0.208	1.04 (0.80–1.35)	0.763	1.01 (0.87–1.16)	0.929
Model 4[a]	1.15 (0.90–1.46)	0.260	1.05 (0.81–1.36)	0.700	1.04 (0.91–1.18)	0.543
Model 5	1.03 (0.81–1.31)	0.800	1.06 (0.82–1.37)	0.661	—	—
HF hospitalization (785/5672, 13.84%)						
Model 1	2.10 (1.91–2.31)	<0.001	1.36 (1.19–1.56)	<0.001	1.35 (1.27–1.44)	<0.001
Model 2	1.82 (1.64–2.02)	<0.001	1.19 (1.03–1.37)	0.017	1.23 (1.15–1.32)	<0.001
Model 3[a]	1.81 (1.62–2.01)	<0.001	1.09 (0.94–1.25)	0.247	1.06 (0.98–1.14)	0.145
Model 4[a]	1.75 (1.55–1.97)	<0.001	1.14 (0.99–1.31)	0.080	1.22 (1.14–1.31)	<0.001
Model 5	1.37 (1.20–1.56)	<0.001	1.16 (1.00–1.34)	0.043	—	—
HFpEF (518/5672, 9.13%)						
Model 1	2.00 (1.78–2.25)	<0.001	1.42 (1.21–1.68)	<0.001	1.37 (1.27–1.48)	<0.001
Model 2	1.71 (1.50–1.96)	<0.001	1.28 (1.07–1.52)	0.006	1.24 (1.14–1.35)	<0.001
Model 3[a]	1.69 (1.47–1.93)	<0.001	1.19 (1.00–1.42)	0.049	1.09 (1.00–1.20)	0.055
Model 4[a]	1.60 (1.38–1.87)	<0.001	1.22 (1.03–1.45)	0.024	1.23 (1.13–1.34)	<0.001
Model 5	1.35 (1.15–1.59)	<0.001	1.23 (1.03–1.46)	0.019	—	—
HFrEF (376/5672, 6.63%)						
Model 1	1.99 (1.73–2.28)	<0.001	1.29 (1.06–1.57)	0.011	1.36 (1.24–1.49)	<0.001
Model 2	1.79 (1.53–2.09)	<0.001	1.13 (0.93–1.39)	0.226	1.27 (1.16–1.40)	<0.001
Model 3[a]	1.78 (1.53–2.08)	<0.001	1.03 (0.84–1.26)	0.771	1.11 (1.00–1.23)	0.061
Model 4[a]	1.66 (1.39–1.98)	<0.001	1.07 (0.87–1.31)	0.512	1.27 (1.15–1.40)	<0.001
Model 5	1.23 (1.02–1.48)	0.030	1.13 (0.92–1.40)	0.250	—	—
Global CVD (1235/5672, 21.77%)						
Model 1	1.81 (1.67–1.96)	<0.001	1.29 (1.16–1.44)	<0.001	1.29 (1.22–1.35)	<0.001
Model 2	1.57 (1.44–1.72)	<0.001	1.13 (1.01–1.26)	0.036	1.18 (1.12–1.25)	<0.001
Model 3[a]	1.57 (1.43–1.71)	<0.001	1.05 (0.94–1.18)	0.367	1.06 (0.99–1.12)	0.076
Model 4[a]	1.51 (1.37–1.67)	<0.001	1.08 (0.97–1.21)	0.158	1.18 (1.12–1.24)	<0.001
Model 5	1.26 (1.14–1.40)	<0.001	1.11 (0.99–1.24)	0.086	—	—
AF (530/5084, 10.42%)						
Model 1	1.48 (1.31–1.68)	<0.001	1.04 (0.88–1.23)	0.638	1.13 (1.04–1.22)	0.003
Model 2	1.37 (1.19–1.57)	<0.001	0.98 (0.83–1.16)	0.825	1.07 (0.99–1.17)	0.102
Model 3[a]	1.38 (1.20–1.58)	<0.001	0.93 (0.79–1.11)	0.434	0.98 (0.90–1.08)	0.726
Model 4[a]	1.38 (1.19–1.61)	<0.001	0.96 (0.81–1.14)	0.671	1.08 (0.99–1.17)	0.094
Model 5	1.17 (0.99–1.37)	0.059	0.95 (0.80–1.13)	0.577	—	—
Total mortality (1173/5672, 20.68%)						
Model 1	1.77 (1.63–1.92)	<0.001	1.35 (1.21–1.51)	<0.001	1.26 (1.20–1.33)	<0.001
Model 2	1.68 (1.54–1.83)	<0.001	1.24 (1.11–1.39)	<0.001	1.24 (1.17–1.31)	<0.001
Model 3[a]	1.66 (1.52–1.81)	<0.001	1.15 (1.02–1.29)	0.022	1.09 (1.03–1.16)	0.004
Model 4[a]	1.58 (1.43–1.74)	<0.001	1.19 (1.06–1.33)	0.004	1.23 (1.16–1.30)	<0.001
Model 5	1.39 (1.25–1.54)	<0.001	1.19 (1.06–1.34)	0.003	—	—

Data presented as *n*/*N* and hazard ratio with 95% CI; model 1, adjusted by age, sex, and race; model 2, model 1 plus total cholesterol, HDL-C, SBP, antihypertensive medication use, diabetes, current smoking, lipid-lowering medication use, prevalent CVD, BMI, and eGFR; model 3, model 2 plus IL-18 (in IL-6 analysis) or IL-6 (in IL-18 analysis); model 4, model 2 plus log(hs-CRP). model 5: model 4 plus log(NT-proBNP) and log(hs-TnT). Global CVD includes CHD, ischaemic stroke, and HF.

[a]For hs-CRP analysis: model 3, adjusted by model 2 plus IL-6; model 4, model 2 plus IL-18.

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hs-CRP, high-sensitivity C-reactive protein; hs-TnT, high-sensitivity troponin T; IL-6, interleukin-6; IL-18, interleukin-18; NT-proBNP, N-terminal pro–B-type natriuretic peptide; SBP, systolic blood pressure.

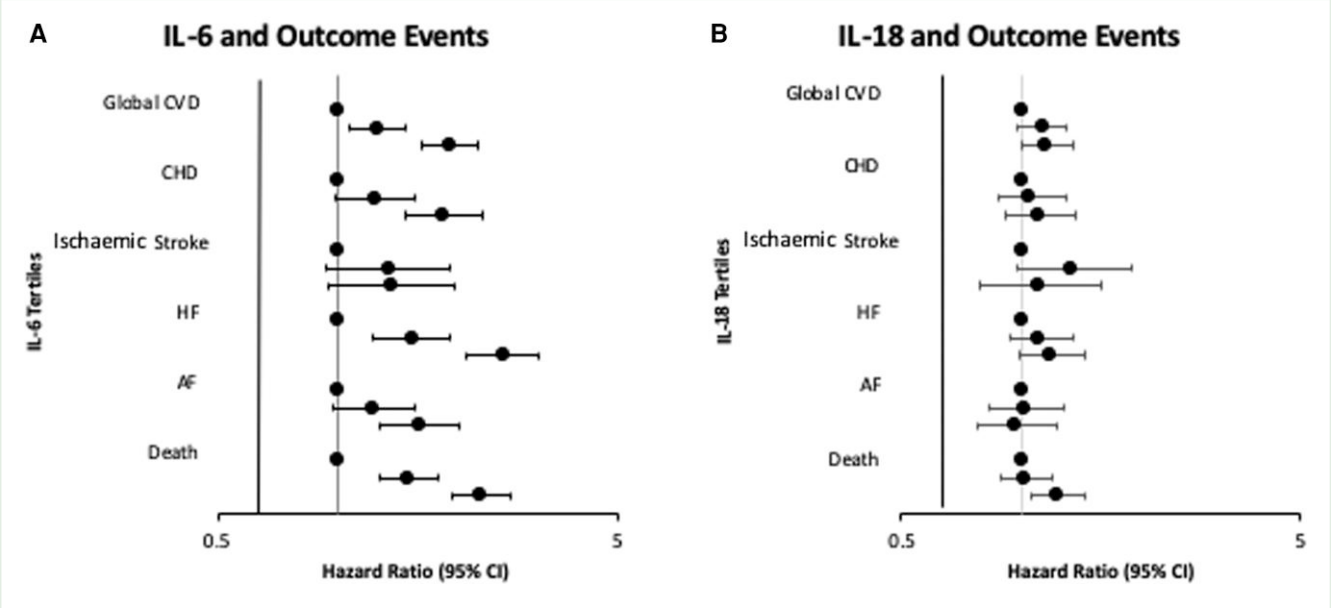


Figure 2 Associations of (*A*) tertiles of interleukin-6 and (*B*) tertiles of interleukin-18 with incident cardiovascular outcome events after Visit 5. Cox regression analysis adjusted for age, sex, race, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, antihypertensive medication use, diabetes, current smoking, lipid-lowering medication use, prevalent global cardiovascular disease, body mass index, and estimated glomerular filtration rate. Abbreviations: AF, atrial fibrillation; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HF, heart failure; IL-6, interleukin-6; IL-18, interleukin-18.

but not IL-18 (*Table 2* and Supplementary material online, *Table S7*). In categorical analysis, the highest tertile of hs-CRP was associated with increased risk for global CVD, CHD, HF, and all-cause death compared with the lowest tertile in all adjustment models (see Supplementary material online, *Table S8*).

Associations of interleukin-6 and interleukin-18 with subclinical disease

In linear regression analysis assessing associations of IL-6 and IL-18 with cardiac biomarkers, we found significant associations of higher IL-6 with higher hs-TnT and NT-proBNP in all adjustment models among participants without prevalent CVD. Associations of IL-18 with cardiac biomarkers were significant only with the base model adjusting for demographic factors and were no longer significant with further adjustments (*Table 3*).

Discussion

Among older, community-dwelling adults, we found that higher IL-6 levels had robust associations with increased risk for global CVD, as well as for CHD, HF, and death, independent of cardiovascular risk factors and IL-18 as well as hs-CRP, NT-proBNP, and hs-TnT. Interleukin-6 modified the association of NT-proBNP and hs-TnT with CVD outcomes. Interleukin-18 was also found to be associated with global CVD, HF, and death independent of cardiovascular risk factors, but the association with global CVD and HF was not independent of IL-6 or hs-CRP. Higher IL-6 but not IL-18 was further associated with markers of subclinical CVD reflected by higher hs-TnT and NT-proBNP among patients without prevalent CVD.

The chronic proinflammatory state observed in many older individuals, so-called inflammaging, is associated with increased frailty as

Table 3 Linear regression analysis assessing the associations of interleukin-6 and interleukin-18 with high-sensitivity troponin T and N-terminal pro–B-type natriuretic peptide among older adults without prevalent global cardiovascular disease

	IL-6		IL-18	
	Beta coefficient	*P*-value	Beta coefficient	*P*-value
hs-TnT				
Model 1	0.123	<0.001	0.065	<0.001
Model 2	0.071	<0.001	0.014	0.416
Model 3	0.088	<0.001	0.014	0.411
Model 4	0.071	<0.001	0.003	0.885
NT-proBNP				
Model 1	0.211	<0.001	0.008	0.786
Model 2	0.204	<0.001	−0.016	0.553
Model 3	0.186	<0.001	−0.033	0.225
Model 4	0.210	<0.001	−0.050	0.065

Model 1: adjusted by age, sex, and race; model 2, model 1 plus total cholesterol, HDL-C, SBP, antihypertensive medication use, diabetes, current smoking, lipid-lowering medication use, BMI, and eGFR; model 3: model 2 plus hs-CRP; model 4, model 2 plus log(IL-18) or log(IL-6). All biomarker values were log-transformed. Abbreviations: BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; hs-TnT, high-sensitivity troponin T; IL-6, interleukin-6; IL-18, interleukin-18; NT-proBNP, N-terminal pro–B-type natriuretic peptide; SBP, systolic blood pressure.

well as increased risk for CVD and other age-related chronic diseases.[30,31] It is important to recognize that heightened inflammation in older individuals is a risk factor not only for ASCVD. Indeed, we found that IL-6 was significantly associated with CHD but also with HF, AF, and death. These findings are in line with prior studies that showed that IL-6 is an important risk marker contributing to inflammaging and the development of CVD, in particular HF, in older adults.[15,32–34] The association between IL-6 and AF has been described in select patient subgroups, including those with coronary artery disease and chronic kidney disease;[35,36] we showed in our study that the association extends to older adults in the general population.

We further demonstrated that associations of IL-6 with CHD, HF, and death were independent of hs-CRP, NT-proBNP, and hs-TnT. Thus, IL-6 may provide additional information on CVD risk assessment beyond more traditional biomarkers and highlights the strong association between inflammation and CVD in older adults. With respect to biomarkers for inflammation, IL-6 appears to be more robust in risk assessment for CVD in older adults compared with hs-CRP. We found that although the association between IL-6 and CVD risk persisted after adjustment for hs-CRP, the association between hs-CRP and CVD risk was attenuated after adjustment for IL-6. A recent investigation into clonal hematopoiesis of indeterminate potential (CHIP) showed that the association between CHIP and CVD events is mediated by IL-6, providing a potential mechanism of the relationship between inflammaging and CVD.[37] Moreover, among individuals without prevalent CVD, those with higher IL-6 were noted to have higher cardiac biomarkers of myocardial injury suggesting an association with subclinical CVD. Therefore, measuring IL-6 in older individuals without prevalent CVD may offer an opportunity for earlier intervention to prevent progression to clinical disease.

An important distinction between IL-6 and biomarkers of end organ damage such as NT-proBNP and hs-TnT is that IL-6 level may be directly modifiable. In the Trial to Evaluate Reduction in Inflammation in Patients with Advanced Chronic Renal Disease Utilizing Antibody Mediated IL-6 Inhibition (RESCUE), ziltivekimab, a fully human monoclonal antibody against IL-6, significantly reduced hs-CRP (the primary endpoint) as well as other biomarkers of inflammation and thrombosis in patients with chronic kidney disease and hs-CRP $\geq$2 mg/L.[38] The Ziltivekimab Cardiovascular Outcomes Study (ZEUS) is ongoing to determine whether IL-6 reduction with ziltivekimab reduces ASCVD events in ~6200 patients with ASCVD, stages 3–4 chronic kidney disease, and elevated hs-CRP.[39] Several direct inhibitors of the NLRP3 inflammasome have entered clinical development, including compounds studied in patients with HFrEF.[40] Should these trials demonstrate clinical efficacy, IL-6 has the potential to aid in prognostication as well as guide treatment strategies for CVD risk reduction in older adults. Although hs-CRP is an inexpensive test that provides information on aspects of the inflammatory response, IL-6 provides additional information as a prognostic marker and may be helpful for identification of patients who have the greatest benefit-to-risk ratio for therapies that target the IL-6 pathway. The establishment of an international standard for human IL-6 by the World Health Organization and availability of proficiency testing programs for IL-6 offered by laboratory accreditation agencies such as the College of American Pathologists should aid the implementation of IL-6 measurement in both clinical research and potentially clinical practice.

The association between IL-18 and CVD in older age, on the other hand, is less clear. We found that IL-18 was significantly associated with global CVD in older adults, as previously reported.[10,41–43] However, we noted only modest association with CHD, which was attenuated after adjustment for cardiovascular risk factors, whereas IL-18 appeared to be more strongly associated with HF, in particular HFpEF, and with death. Unlike IL-6, IL-18 was not significantly associated with cardiac biomarkers of subclinical disease. Analyses from CANTOS have shown that residual risk from inflammation remains after treatment with canakinumab; despite IL-6 reduction with IL-1β antagonism, the magnitude of residual risk from IL-6 was greater than that from IL-18, although IL-18 levels were not affected by canakinumab.[44] Taken together, although IL-6 and IL-18 are both integral parts of the NLRP3 inflammasome pathway, circulating IL-6 appears to have stronger association with subclinical and clinical cardiac disease in older adults, whereas the association of circulating IL-18 with CVD is less consistent.

Our study had several strengths. The Atherosclerosis Risk in Communities study is a large, well-established prospective cohort study with long follow-up time and rigorous adjudication of outcome events. We included not only ASCVD outcomes but also HF events, AF, and death, which allowed for an assessment of the relationships of IL-6 and IL-18 with more comprehensive CVD risk in an older population. Moreover, we quantified both IL-6 and IL-18, which allowed a unique opportunity to analyse these inflammatory markers together with respect to association with cardiovascular risk. Our study also had several limitations. We did not measure IL-1β and therefore could not assess how IL-1β modulated the effects of IL-6 and IL-18 with CVD. Lastly, given the observational nature of our study, significant associations demonstrated between inflammatory markers and global CVD cannot be established as causal.

Conclusion

Among older adults, higher IL-6 and IL-18 levels were both associated with increased risk for global CVD and death after adjustment for cardiovascular risk factors. The magnitude of association was higher for IL-6 than IL-18 and was independent of hs-CRP, NT-proBNP, and hs-TnT, whereas the association between IL-18 and CVD appeared to be dependent on IL-6. Our study supports IL-6 as a target along the inflammasome signalling pathway and provides further insight into the relationship between inflammaging and development of CVD.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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Authors contribution

X.J., L.B., A.M.S., and C.M.B. contributed to the conception or design of the work. X.J., L.B., C.S., E.S., R.C.H., J.C., A.M.S., and C.M.B. contributed to the acquisition, analysis, or interpretation of data for the work. X.J., L.B., and C.M.B. drafted the manuscript. X.J., L.B., M.A.R., B.Y., V.N., S.S.V., E.S., K.M., R.C.H., J.C., A.M.S., and C.M.B. critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

X.J., (conceptualization: equal; investigation: lead; methodology: equal; writing—original draft: lead; writing—review and editing: lead), L.B., (investigation: equal; writing—review and editing: supporting), C.S., (formal analysis: lead; writing—review and editing: supporting), M.A.R., (writing—review and editing: supporting), B.Y. (writing—review and editing: supporting), V.N., (writing—review and editing: supporting), S.S.V., (writing—review and editing: supporting), E.S., (writing—review and editing: supporting), K.M., (writing—review and editing: supporting), R.C.H., (investigation: equal; resources: lead; writing—review and editing: supporting), J.C., (writing—review and editing: supporting), A.M.S., (investigation: equal;

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

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